2024-2025

Compendium of Research Publications

GOVERNMENT MEDICAL COLLEGE, THRISSUR





Foreward

It gives me great pleasure to present this Research Compendium of Publications from Government Medical College, Thrissur, an important milestone not only for the institution but for the Directorate of Medical Education, Kerala. This is the first time such a consolidated body of research work is being systematically documented and shared across our academic community, and it stands as a testament to Kerala's commitment to strengthening evidence-based medical practice and fostering a culture of inquiry.

Government Medical College, Thrissur has long been recognized for its clinical excellence and public service. What this compendium highlights is the parallel tradition of rigorous scientific investigation undertaken by its faculty, residents, and students—work that often continues quietly behind the scenes but significantly shapes our understanding of disease, patient care, and evolving health systems. Bringing together these publications in a single volume not only celebrates these achievements but also creates a valuable reference for future researchers, clinicians, and policymakers.

In a time when healthcare faces complex and rapidly changing challenges, research emerging from our medical colleges plays a crucial role in guiding clinical decisions, informing policy, and improving the quality of care delivered across Kerala. Initiatives like this compendium reinforce the importance of cultivating strong academic environments, encouraging interdisciplinary collaboration, and ensuring that our healthcare workforce continues to innovate.

I congratulate Government Medical College, Thrissur, the Directorate of Medical Education, and all contributors who have made this compendium possible. May this initiative inspire similar efforts across our medical institutions and further strengthen Kerala's leadership in medical education and public health.

Dr Rajan Kobragade IAS
Additional Chief Secretary
Health & Family Welfare Department
Government of Kerala



Foreward

It gives me immense pleasure to present the consolidated booklet of research publications from Government Medical College, Thrissur for the academic year 2024–2025. This compilation reflects not only the intellectual vibrancy of the institution but also our unwavering commitment to advancing medical science through rigorous inquiry and innovation. In an era where evidence-based practice forms the backbone of quality healthcare, such an effort stands as a testament to the academic strength and evolving culture of research within the college.

I deeply appreciate the intent behind this initiative. Documenting and showcasing the diverse research output of our faculty, postgraduate residents, and students reinforces the importance of scientific thinking and continuous learning. It provides a platform for recognising excellence, encourages cross-disciplinary dialogue, and inspires young clinicians and researchers to pursue meaningful questions that impact patient care, public health, and scientific understanding.

This compilation also highlights the persistent effort invested by every individual and team whose work is featured here. Research demands perseverance, curiosity, and a commitment to ethical and methodologically sound practices. I commend the dedication of the authors, the mentorship provided by the faculty, and the institutional support that has enabled these studies to be conceptualised, executed, and brought to publication. Their collective contributions enhance the reputation of Thrissur Medical College as a center of academic distinction.

I congratulate the editorial team for taking up this much-needed initiative to present our annual research achievements in a unified format. This booklet will serve as a valuable reference, inspire further scholarly pursuits, and strengthen our vision of fostering a robust research ecosystem within the institution. I extend my best wishes to all contributors and look forward to seeing the continued growth of high-quality research from our college in the years ahead.

Dr Viswanathan K.V
Director of medical education



PREFACE

It gives me great pleasure to present the *Department-wise Compilation of Publications for the Academic Year 2024–2025* of Government Medical College, Thrissur. This volume highlights the academic vibrancy and research culture that our institution continues to foster. The contributions included here reflect the dedication, perseverance, and intellectual curiosity of our faculty, postgraduate students, and researchers across various specialties.

In an era where evidence-based practice forms the backbone of quality healthcare, research assumes an increasingly significant role. The studies and publications compiled in this document not only advance scientific understanding but also contribute meaningfully to patient care, clinical innovation, and public health. It is heartening to see the breadth and depth of work emerging from our departments, demonstrating both individual effort and collaborative spirit.

This compilation serves as an important record of our institutional progress and provides inspiration for future scholarly pursuits. I extend my sincere appreciation to all contributors for their commitment to academic excellence. I also acknowledge the coordinated efforts of those involved in organizing and preparing this volume.

I am confident that this report will encourage continued participation in research activities and strengthen our collective resolve to uphold the highest standards in medical education and scientific inquiry.

Dr Indu . P.S

Principal
Government Medical College, Thrissur



MESSAGE

It is the bounden duty of an evolving nation to keep it's younger generation research - enabled. 'Catch them young' is the watch-word. All our universities and institutions of national repute, and the Government are meticulously following this dictum in letter and spirit. Government Medical College, Thrissur is no exception.

It is important that the Institutional Review Board (IRB) serves this principle in all earnestness. This publication is an evidence to this effect. By providing the much deserved appreciation and recognition to the young researchers, the IRB is contributing to the larger cause of subserving the national interest.

I take this occasion to congratulate Prof. Dr. Ravindran. C, the Member Secretary of IRB who has taken meticulous efforts to get this document ready in no time.

I hope this will benefit the young researchers, who have put in huge efforts to get their work ready and print- ready in the stipulated time.

Best wishes to all, and for the wonderfully brought out volume.

Dr. V. V. Unnikrishnan
Chairman, IRB, GMCTSR.
Director, KUHS Academic Staff College, Thrissur.



NOTE FROM THE INSTITUTIONAL ETHICS COMMITTEE

It is with great pride and satisfaction that I present this *Department-wise Compilation of Publications for the Academic Year 2024–2025* of Government Medical College, Thrissur. This volume is a reflection of the academic strength and research enthusiasm that continues to grow across our institution.

As the Institutional Ethics Committee, we have the privilege of witnessing the evolution of research ideas—from initial concepts to scientifically sound, ethically responsible studies that contribute meaningfully to medical knowledge. The publications featured here highlight not only the intellectual capability of our faculty and postgraduate students but also their commitment to maintaining the highest ethical standards in research.

The preparation of this compilation has been a journey of careful coordination, documentation, and verification. It has reaffirmed the remarkable efforts taken by various departments to encourage responsible research practices. I am grateful to all investigators for their cooperation and timely submissions, which have made this compilation possible.

I extend my sincere appreciation to the Principal and institutional leadership for their support, and to all committee members for their unwavering dedication to safeguarding ethical principles in research. It is my hope that this document will motivate continued academic inquiry, interdisciplinary collaboration, and adherence to ethical integrity in all future research endeavors.



Dr Ravindran C

Member Secretary
Institutional Ethics Committee
Government Medical College, Thrissur

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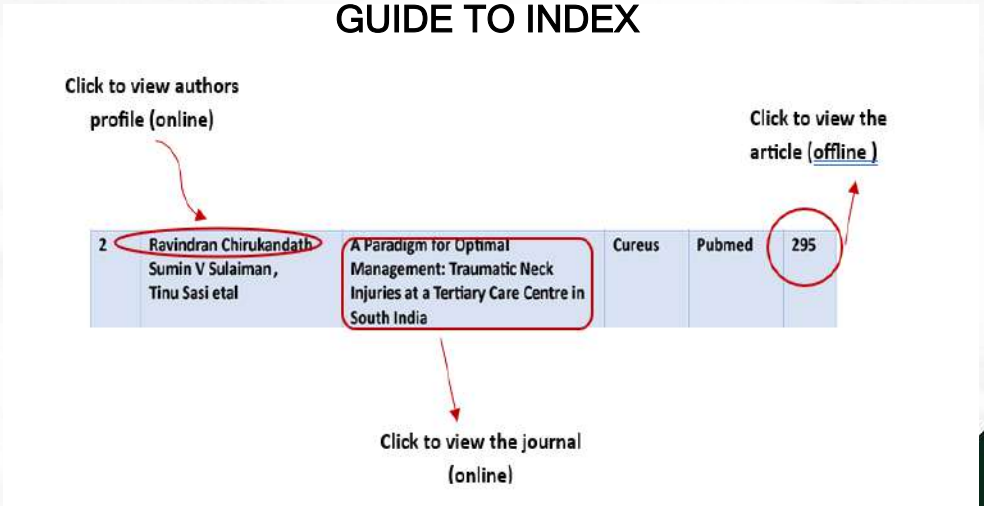
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Original Research Article

Intraoperative Hyperglycemia in Patients Undergoing Emergency Craniotomy for Traumatic Brain Injury

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ABSTRACT

INTRODUCTION

Hyperglycemia following TBI is linked to poor outcomes. But studies on intraoperative hyperglycemia in adult TBI (Traumatic Brain Injury) were fewer in number. In this study, conducted at Govt. Medical College, Thrissur, we examined blood glucose value variability and risk factors for hyperglycemia during craniotomy in persons with TBI.

OBJECTIVES

The primary objective was to study the prevalence of intraoperative hyperglycemia during an emergency craniotomy for traumatic brain injury. The secondary objective was to identify the risk factors for intraoperative hyperglycemia during an emergency craniotomy for traumatic brain injury.

METHODS

This was a prospective observational study conducted in the Department of Anaesthesiology, Government Medical College, Thrissur for an 18-month period after approval from the Institutional Ethics Committee on 214 patients meeting the inclusion criteria who had provided consent and were undergoing emergency craniotomies for traumatic brain injury. The sampling method was continuous sampling. Hyperglycemia was defined as a GRBS (General Random Blood Sugar) value >140 mg/dl (preoperative or intraoperative first hour or second hour GRBS value). Hyperglycemia was treated with either an insulin bolus or an infusion when the GRBS value exceeded 180–190 mg/dl.

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RESULTS
Intraoperative hyperglycemia was common in our study population. It was observed that the prevalence of intraoperative hyperglycemia was higher in older adults, aged 65 years and older. The prevalence of intraoperative hyperglycemia was higher in the diabetic population. There was no significant association between intraoperative hyperglycemia and EDH. The prevalence of intraoperative hyperglycemia was high in patients with SDH. There was no significant association between intraoperative hyperglycemia and SAH. Both preoperative GCS and GCS at discharge from the ICU were lower in patients who had intraoperative hyperglycemia. Patients with preoperative hyperglycemia had a higher chance of developing intraoperative hyperglycemia. The following were independent risk factors for intraoperative hyperglycemia: age ≥ 65 years, SDH, preoperative GCS ≤ 9, and preoperative hyperglycemia.

CONCLUSION
Intraoperative hyperglycemia was common during an emergency craniotomy for a traumatic brain injury. The following were independent risk factors for intraoperative hyperglycemia: age ≥ 65 years, SDH, preoperative GCS ≤ 9, and preoperative hyperglycemia.

KEYWORDS
Traumatic Brain Injury, Craniotomy, Intraoperative Hyperglycemia, GCS.

INTRODUCTION

In India and across the globe, the burden of diabetes has steadily increased over the past 25 years, with India contributing a major part of the global burden. The number of people with diabetes in India rose from 26 million in 1990 to 65 million in 2016. The prevalence of diabetes in adults aged 20 years or older in India increased from 5.5% in 1990 to 7.7% in 2016, with an increase in every state of India. This prevalence was highest in the more developed states, such as Tamil Nadu and Kerala.[1]

Traumatic brain injury, defined as an alteration in brain function or other evidence of brain pathology, caused by an external force, is a leading cause of death among adults.[2]

TBI induces a variety of basic and functional changes that exacerbate the patient's condition. Associated injuries produce remarkably varied outcomes. Individuals seem to react differently to the stress caused by trauma. Since there is little that medical professionals can do to ameliorate the symptoms of a primary brain injury, the main focus of head injury treatment is on preventing further injuries.[3]

A retrospective cohort study conducted in 185 patients >18 years old at Harborview Medical Centre, who underwent emergency craniotomy for traumatic brain injury showed that intraoperative hyperglycemia was common and in-hospital mortality was higher in patients with intraoperative hyperglycemia.[4]

Aims and Objectives

To study the prevalence of intraoperative hyperglycemia during emergency craniotomy for traumatic brain injury and to identify the risk factors for intraoperative hyperglycemia during emergency craniotomy for traumatic brain injury.

MATERIALS AND METHODS

It was a prospective observational study done at the department of anesthesiology at Government Medical College Hospital, Thrissur. Adults > 18 years old undergoing emergency craniotomy for traumatic brain injury at Govt. Medical College, Thrissur, who are consenting

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to be part of the study. Patients not consenting to be part of the study, age <18 years, pregnant patients, repeat craniotomies, and patients on steroids were excluded.

Study Procedure

After obtaining ethical committee clearance, 240 patients who presented with TBI for emergency craniotomy in the EOT were screened, out of which 26 patients were excluded from the study based on the exclusion criteria. The study was then conducted on 214 patients undergoing emergency craniotomies for traumatic brain injuries. After explaining the anesthetic procedure, written informed consent for participation in the study was obtained from the caregivers of the patients, since the majority of the study population had poor GCS scores with which they couldn't provide consent. A preanaesthetic evaluation was done, and a detailed history and physical examination were conducted. Pre-operative GCS and pre-operative blood glucose values were noted.

The first- and second-hour intraoperative capillary blood glucose values were obtained. Hyperglycemia was defined as a GRBS value >140 mg/dl (preoperative/intraoperative first hour or second hour GRBS value). Hyperglycemia was treated with either an insulin bolus or an infusion when the GRBS value exceeded 180–190 mg/dl. All cases were managed intraoperatively as per the institutional treatment protocol. The decision to treat hyperglycemia. (i.e., the level of intraoperative glucose to give insulin, whether to give a bolus injection of insulin or an insulin infusion, and the amount of insulin given) was made by the attending anesthesiologist in charge of the table and was observed by the principal investigator. The patient was prospectively followed up, i.e., the length of stay in the ICU and GCS at the time of discharge from the ICU to the ward were noted. The data procured was analyzed using appropriate statistical methods.

Statistical Analysis

Data are presented as mean and standard deviation for continuous variables and as frequency for categorical variables. Analysis was carried out using the Student's *t*-test, $\chi 2$ test, or Fisher's exact test. A univariate analysis of factors associated with mortality and ICU length of stay was carried out using logistic regression analysis. Interaction and confounding were assessed through stratification and relevant expansion covariates. Factors with a p-value <.20 in the univariate analysis were entered in a multivariable logistic regression analysis. *P*-values of ≤.05 were considered statistically significant.

RESULTS

A total of 240 patients who presented to the EOT with TBI for emergency craniotomies were enrolled. 214 patients who fulfilled the inclusion criteria and consented to be part of the study were included. 26 patients were excluded based on the exclusion criteria.

		Frequency	Percent
Age Group	Young adults (18-25)	38	17.8
	Adults (26-64)	129	60.3
	Older adults (65 and above)	47	22.0
Gender	Male	161	75.2
	Female	53	24.8
Presence of DM	No	182	85.0
	Yes	32	15.0

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Treatment of DM	Diet control	1	3.125
	Insulin	8	25
	OHA	23	71.875
GCS score	Severe TBI:≤ 8	117	54.7
	Moderate TBI: 912	91	42.5
	Mild TBI:13-15	6	2.8
	Total	214	100.0
GCS score on discharge	**GCS Score**	**Frequency**	**Percent**
	≤ 8	0	0
	9-12	47	22.7
	13-15	160	77.3
	Total	207	100.0

Table 1: Age, Sex, Presence of Diabetes Mellitus and Treatment, Pre-Operative GCS Score, GCS Score on Discharge

Patients in the age group 26–64 years (adults) contributed to 60.3% of the study population. 22% of the patients were in the age group 65 years and older (older adults), and young adults (18–25 years) constituted 17.8% of the study population.

15% of the study population were those with diagnosed diabetes mellitus, while the majority were nondiabetic (85%). In the diabetic individuals of the study population (32 out of 214), 71.875% were on treatment with OHA, 25% were on insulin, and 3.125% were on diet control.

Distribution Based on Mode of TBI Sustained

Injury	Frequency	Percent
EDH	78	36.4
SDH	73	34.1
SAH	1	.5
EDH, SDH	57	26.6
SDH, EDH, SAH	1	.5
Total	214	100.0

Table 2: Mode of Traumatic Brain Injury

In the study population, the most common injury sustained was EDH (36.4%), followed by SDH (34.1%). 26.6% of the study population had sustained a combination of EDH and SDH. 0.5% of the study population had SAH and a combination injury of SDH, EDH, and SAH each. 54.7% of the study population had a preoperative GCS of ≤ 8. For 42.5% of individuals, preoperative GCS was in the range of 9-12. 2.8% of the study population had a preoperative GCS of 13-15**.**

After surgery, the mortality rate was 3.3%. Out of 214 study participants, 7 expired after surgery.

Time	N	Minimum	Maximum	Mean	Std. Deviation
Pre-operative	214	3	13	8.52	2.06
At ICU discharge	207	11	15	13.78	1.30
Length of ICU stay	214	1	14	3.18	2.10

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GRBS Values					
Before start of surgery	214	85	412	182.60	63.06
First hour intra operative	214	102	385	183.36	61.86
Second hour intra operative	214	109	358	170.78	48.06
Before start of surgery	214	85	412	182.60	63.06

Table 3. Descriptive Statistics Regarding GCS before Start of the Surgery and at ICU Discharge

In Table 4, the mean preoperative GCS of the study population was 8.52 with a standard deviation of 2.06. The mean GCS at discharge from the ICU to the ward was 13.78, with a standard deviation of 1.3**.** In the study population, the minimum length of ICU stay was one day, and the maximum length of stay in ICU was 14. The mean length of stay in the ICU was 3.18, and the standard deviation was 2.1. Intraoperative hyperglycemia was common in our study population. Out of the 214 study participants, 171 had a GRBS value >140 mg/dl in either the first or second hour (79.9%). The GRBS value was less than 140 mg/dl in both the first and second hours in 43 participants (20.09%).

In the study population, the minimum preoperative GRBS value noted was 85 mg/dl, and the maximum was 412 mg/dl. The mean preoperative GRBS was 182.6, and the standard deviation was 63.06. The minimum first-hour GRBS value noted was 102 mg/dl; the maximum value was 385 mg/dl. The mean first hour GRBS was 183.36, and the standard deviation was 61.86. The minimum second-hour GRBS value noted was 109 mg/dl; the maximum value was 358 mg/dl. The mean second-hour GRBS was 170.78, and the standard deviation was 48.06. In the study population, 69.6% had preoperative GRBS >140 mg/dl. 72% had first-hour GRBS >140 mg/dl. And 64.5% had a second-hour GRBS >140 mg/dl.

Age Group	**No Hyperglycaemia**		**Hyperglycaemia**		**Total**
	Freq.	**Percent**	**Freq.**	**Percent**	
Young adults (18-25)	21	55.3	17	44.7	38
Adults (26-64)	27	20.9	102	79.1	129
Older adults (65 and above)	1	2.1	46	97.9	47
Total	49	22.9	165	77.1	214
χ^2 value = 34.315**; P-value <0.001					
Gender	**No Hyperglycaemia**		**Hyperglycaemia**		**Total**
	Freq.	**Percent**	**Freq.**	**Percent**	
Male	43	26.7	118	73.3	161
Female	6	11.3	47	88.7	53
Total	49	22.9	165	77.1	214
χ^2 value = 5.348*; P-value = 0.021					
History of DM	**No Hyperglycaemia**		**Hyperglycaemia**		**Total**
	Freq.	**Percent**	**Freq.**	**Percent**	
No	49	26.9	133	73.1	182
Yes	0	0	32	100	32
Total	49	22.9	165	77.1	214
χ^2 value = 11.174**; P-value = 0.001					
EDH	**No Hyperglycaemia**		**Hyperglycaemia**		**Total**
	Freq.	**Percent**	**Freq.**	**Percent**	

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No	15	19.2	63	80.8	78
Yes	34	25.9	102	75.0	136
Total	49	22.9	165	77.1	214
χ^2 value = 0.935^{ns}; P-value = 0.334					
SDH	**No Hyperglycaemia**		**Hyperglycaemia**		**Total**
	Freq.	**Percent**	**Freq.**	**Percent**	
No	28	33.7	55	66.3	83
Yes	21	16.0	110	84.0	131
Total	49	22.9	165	77.1	214
χ^2 value = 9.021**; P-value = 0.003					

Table 4. Association of Intraoperative Hyperglycemia with Age, Gender, History of DM, EH and SDH of the Patients

** Significant at 0.01 level

A significant chi-square value indicates that intraoperative hyperglycemia is significantly associated with increasing age. Percentage analysis shows that among the young adults, 44.7% had intraoperative hyperglycemia. Among the adult population, it was 79.1%, and among older adults, the chance of having intraoperative hyperglycemia was 97.9%. Thus, it was observed that the prevalence of intraoperative hyperglycemia was higher in older adults, aged 65 years and older.

Percentage analysis shows that in females with TBI, 88.7% had intraoperative hyperglycemia. Among males, it was 73.3%. Thus, it was observed that the prevalence of intraoperative hyperglycemia was higher in females.

Intraoperative hyperglycemia is strongly associated with the presence of diabetes mellitus. Percentage analysis shows that in diabetic individuals, 100% had intraoperative hyperglycemia. It was observed that the prevalence of intraoperative hyperglycemia was higher in the diabetic population.

Here the p-value was 0.334, hence the chi square value was found to be nonsignificant. This indicates that there is no significant association between intraoperative hyperglycemia and EDH.

Intraoperative hyperglycemia is significantly associated with SDH. Percentage analysis shows that 84% of the patients who sustained SDH had intraoperative hyperglycemia. Thus, the prevalence of intraoperative hyperglycemia is high in patients with SDH. There is no significant association between intraoperative hyperglycemia and SAH.

GCS Score	**No Hyperglycaemia**		**Hyperglycaemia**		**Z-Value**	**P-Value**
	Median	**Range**	**Median**	**Range**		
Pre-operative	9	7-13	8	5-13	4.154**	<0.001
At ICU discharge	15	13-15	13	11-15	4.295**	<0.001
Variable	**No Hyperglycaemia**		**Hyperglycaemia**		**T-Value**	**P-Value**
	Mean	**SD**	**Mean**	**SD**		
Pre-operative GRBS	131.51	14.67	197.77	63.96	7.185**	<0.001

Table 5. Comparison of GCS among Patients with and without Intraoperative Hyperglycemia

When preoperative GRBS was compared in patients with and without intraoperative hyperglycemia, it was observed that patients with preoperative hyperglycemia had a higher

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chance of developing intraoperative hyperglycemia. A comparison of the GCS score among patients with and without intraoperative hyperglycemia was done using the Mann-Whitney U test. A comparison of the preoperative GRBS value among patients with and without intraoperative hyperglycemia was done using an independent t-test.

Factors	Odds Ratio	95% CL	P-Value
Age ≥ 65	18.555	2.49 - 138.38	0.004
SDH	2.667	1.39-5.12	0.003
Pre GCS ≤ 9	2.903	1.497-5.629	0.002
Pre-operative hyperglycemia	17.657	8.032-38.814	<0.001

Table 6: Odds Ratio for the Independent Risk Factors

Binary linear logistic regression was fitted with each risk factor as an independent variable to find out the odds ratio corresponding to each risk factor.

Thus, it was observed that the following were independent risk factors for intraoperative hyperglycemia: age ≥ 65; BMI ≥ 25; SDH; preoperative GCS ≤ 9; preoperative hyperglycemia.

DISCUSSION

It is estimated that by 2025, India will be the world's "diabetes capital," with 69.9 million diabetics. Diabetes is more severe in low- and middle-income countries.[4]

In our study, the age of the patients ranges from 18 to 76 years, with a mean age of 45.27 and a standard deviation of 17.443. Patients in the age group 26–64 years (adults) contributed to 60.3% of the study population. 22% of the patients were in the age group 65 years and older (older adults), and young adults (18–25 years) constituted 17.8% of the study population.

In our study population, 75% were males and 25% were females. In a cross-sectional longitudinal study by Joseph J. J. et al. at Trivandrum Medical College, out of the 658 patients included in the study, the majority of the subjects belonged to the age group of 30–60 years. About 80% of the subjects were males.[5] In a prospective observational study by Bhattacharjee et al. on the perioperative glycemic status of adult TBI patients undergoing a craniotomy, the mean age of the included patients was 33.9 ± 8.6 years (n = 200), with a male-to-female ratio of 9:2.[6] The age and gender distribution of our study population is consistent with other published data.[5,6,7]

Fifteen percent of the study population were those with diagnosed diabetes mellitus, while the majority were nondiabetic (85%). In the diabetic individuals of the study population, (32 out of 214), 71.875% were on treatment with OHA, 25% were on insulin, and 3.125% were on diet control. Studies from developed nations showed a slightly lower incidence of diagnosed diabetes mellitus. In a retrospective review study in a level 1 trauma center at the University of Alabama at Birmingham, 7.2% of the total patient population had diabetes, which approximates the estimates seen by Kerby et al. when evaluating trauma patients (8.7% of the study population) and the estimates of DM in the United States (9.3% of the population) from the Center for Disease Control and Prevention.[8,9,10]

In our study population, the most common injury sustained was EDH (36.4%), followed by SDH (34.1%). In our study population, 26.6% had sustained a combination of EDH and SDH. 0.5% of the study population had SAH and a combination injury of SDH, EDH, and SAH each. In a prospective observational study by Bhattacharjee et al., extradural hemorrhage had

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the highest frequency (44%), followed by an equal incidence of intracerebral hemorrhage and acute subdural hemorrhage (28% each).[5]

More than half of the study population (54.7%) had a preoperative GCS of ≤ 8. For 42.5% of individuals, preoperative GCS was in the range of 9–12. 2.8% of the study population had a preoperative GCS of 13–15.

After surgery, the mortality rate was 3.3%. Out of 214 study participants, seven expired after surgery. During discharge from the ICU to the ward, the GCS score of 77.3% of live patients was in the range of 13–15. The GCS score of 22.7% of live patients was in the range of 9–12.

The mean preoperative GCS of the study population was 8.52, with a standard deviation of 2.06. The mean GCS at discharge from the ICU to the ward was 13.78, with a standard deviation of 1.3. In a cross-sectional, non-interventional manuscript study of the "Pennsylvania Trauma Outcome Study Database" by Chalouhi N. et al., the proportion of patients who had a GCS score of 3 to 5 (vs. a GCS of 6-8) was significantly higher in level I trauma centers (78.7%, n = 2021) than level II trauma centers (74.4%, n = 1051, p = 0.002). The mean GCS score on admission was significantly lower in level I (3.9±1.6) than in level II centers (4.2±1.7).[11]

In a retrospective cohort study by Herou E. et al., surgically treated patients: median age was 76 years', and their 30-day overall mortality rate was 36%. Higher mortality was seen with a lower level of consciousness, high energy trauma, one pupil fixed and dilated, and more extensive intracranial pathology. Mortality for patients with GCS (Glasgow Coma Scale) 10–15 was 6%, GCS 6–9 67%, and GCS 3–5 100%.[12]

In the study population, the minimum length of ICU stay was one day, and the maximum length of stay in ICU was 14. The mean length of stay in the ICU was 3.18, and the standard deviation was 2.1. In a retrospective multicenter cohort study by P.A. Tardif et al., the average length of the ICU and total hospital stay were 9.1 and 15.8 days, respectively. The median GCS at 24 hours was 10, with 67% improving to GCS 15 by the time of discharge.[13]

Intraoperative hyperglycemia was common in our study population. Out of the 214 study participants, 171 had a GRBS value > 140 mg/dl in either the first or second hour (79.9%). The GRBS value was less than 140 mg/dl in both the first and second hours in 43 participants (20.09%).

In the study population, the minimum preoperative GRBS value noted was 85 mg/dl, and the maximum was 412 mg/dl. The mean preoperative GRBS was 182.6, and the standard deviation was 63.06. The minimum first-hour GRBS value noted was 102 mg/dl; the maximum value was 385 mg/dl. The mean first hour GRBS was 1183.36, and the standard deviation was 61.86. The minimum second-hour GRBS value noted was 109 mg/dl; the maximum value was 358 mg/dl. The mean second-hour GRBS was 170.78, and the standard deviation was 48.06.

In our study population, 69.6% had preoperative GRBS >140 mg/dl. 72% had first-hour GRBS >140 mg/dl. And 64.5% had second-hour GRBS >140 mg/dl. In the study by Bhattacharjee et al. on the perioperative glycemic status of adult TBI patients undergoing a craniotomy, the preoperative capillary blood glucose value was 136.8±11.9 mg/dL, and the one-hour postoperative value was 166.7±11.4 mg/dL.[5]

In our study, we observed that the prevalence of intraoperative hyperglycemia was higher in older adults, aged 65 years and older. It was observed that the prevalence of intraoperative hyperglycemia was higher in the diabetic population. It was also observed from our study that the prevalence of intraoperative hyperglycemia was high in patients with SDH. There was no significant association between intraoperative hyperglycemia and EDH.

There was no significant association between intraoperative hyperglycemia and SAH. It was observed that both preoperative GCS and GCS at discharge from the ICU were lower in

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patients who had intraoperative hyperglycemia. It was observed from our study that patients with preoperative hyperglycemia had a higher chance of developing intraoperative hyperglycemia. These observations were in concurrence with the retrospective cohort study by Travis Pecha et al.[14]

CONCLUSION

The study concluded that intraoperative hyperglycemia was common during emergency craniotomies for traumatic brain injuries. These were independent risk factors for intraoperative hyperglycemia: age ≥ 65 years, SDH, preoperative GCS ≤ 9, pre-operative hyperglycemia.

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Anesth Pain Med. 2014 August; 4(3): e20030. DOI: 10.5812/aapm.20030
Published online 2014 August 13. **Research Article**

Comparison of the Incidence of Sore Throat After Rapid Sequence Intubation With Succinylcholine and Cisatracurium

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Background: Postoperative sore throat is a common complication of endotracheal intubation and can lead to dissatisfaction after surgery. Airway management has the strongest influence on the incidence of sore throat and improving endotracheal intubating conditions can reduce this complaint. Type of induction agent used during anesthesia can contribute to variances in the degree of post-operative sore throat.
Objectives: We aimed to compare the incidence of postoperative sore throat after rapid sequence induction with Succinylcholine and high dose Cisatracurium.
Patients and Methods: The study was carried out on patients admitted to Shohada-e-Tajrish hospital for emergent abdominal surgery. Of the 80 patients who were enrolled in the study, 40 were randomly assigned to receive Succinylcholine while the remaining patients received Cistracurium during induction. Sore throat, muscle ache, hoarseness, dry throat and pain were assessed in each patient at baseline in recovery and at 2, 4, 12 and 24 hours post-operation.
Results: Number of patients who developed sore throat was significantly higher in the Succinylcholine group (75%) compared to Cisatracurium group (27.5%) at the time of entrance to the recovery room ($P = 0.001$). These numbers decreased at 2 hours post-operation (42% versus 17.5%) but the difference was still statistically significant ($P < 0.05$). At 12 ($P = 0.062$) and 24 ($P = 0.14$) hours post operation, the difference was no longer significant.
Conclusions: Use of high dose Cisatracurium for induction during rapid sequence intubation carries a lower chance of developing sore throat compared to Succinylcholine. Studies comparing other adverse effects of these two agents are required to guide physician's choice of induction agent.

Keywords: Cisatracurium; Intratracheal Intubation; Pharyngitis; Succinylcholine

1. Background

Sore throat is a common postoperative complaint occurring most often as a complication of endotracheal intubation with an incidence ranging from 14 to 50% (1, 2). The symptom usually lasts for about 12-24 hours post-operation. Among the causative factors airway management has the strongest influence on the incidence of sore throat (3); therefore improving endotracheal intubating conditions can reduce post operative sore throat. Several methods have been proposed to minimize this side effect: application of smaller size ETT (4), use of cuffed ETT (5), minimizing ETT cuff pressure (6), application of Lidocain gel on ETT (7), spraying the endotracheal tube cuff with benzydamine hydrochloride (8), adminisration of beclomethasone spray (9), postponing intubation until achieving complete muscle relaxation (10), mild suctioning of mouth and pharynx before extubation, and withholding extubation until the cuff is completely empty.

Factors such as Succinylcholine administration also contribute to the occurrence of postoperative sore throat (11), even though use of muscle relaxants during anesthesia has been shown to reduce post-intubation symptoms (12). It has been proposed that the type of induction agent used during anesthesia can affect the incidence of post operative sore throat. Currently, succinylcholine is the muscle relaxant of choice for rapid sequence intubation in emergency situations, but Cisatracurium administered at high doses can also be used for induction and studies comparing these two agents show that some of the adverse effects of Succinylcholine such as hyperkalemia and malignant hyperthermia are rarely seen with Cisatracurium (13). Most of the currently available literature on postoperative sore throat revolve around Succinylcholine's effect on this complication, and so far no study has been carried out to compare the incidence of sore throat after with these two agents.

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2. Objectives

We aimed to compare the incidence of postoperative sore throat after rapid sequence induction with Succinylcholine and high dose Cisatracurium.

3. Patients and Methods

We conducted a randomized double blind clinical trial on patients admitted to Shohada-e-Tajrish hospital for emergent abdominal surgery. Patients with ASA PS (American Society of Anesthesiologists Physical Status) class I-II and aged 20 to 60 years old undergoing emergent abdominal surgery were included in the study. Exclusion criteria consisted of history of previous sore throat, cigarette smoking, history of addiction, history of heart or lung disease, previous neck surgery, mallampati score 3 or 4, difficult intubation and decline in oxygen saturation to less than 95% during induction due to difficult intubation. Consort flowchart of the study is depicted in Figure 1.

80 patients were enrolled in the study and were randomly assigned to receive either Succinylcholine or Cisatracurium. Sore throat, muscle ache, hoarseness, dry throat and pain were assessed in each patient at baseline in recovery and at 2, 4, 12, and 24 hours post-operation. Presence of sore throat, muscle ache, hoarseness and dry throat were evaluated using a simple yes/no question. Post-operative sore throat was also scaled according to visual analogue score (VAS). Patients were observed for the development of fasciculation.

General anesthesia was administered with patients in supine position. For premedication, 2 μg/kg Fentanyl and 0.02 mg/kg Midazolam was administered. For induction, 5 mg/kg Thiopental was administered. After 60-90 seconds when TOF (Train of Four) = 0 patients received either 1.5 mg/kg Succinylcholine or 0.4 mg/kg Cisatracurium, and were intubated. All intubations were performed by a single anesthesiologist. Endotracheal tubes used in the study were made in Germany and their size was selected by the anesthesiologist after direct laryngoscopy. If intubation was difficult or was attempted more than once, patient was excluded from the study. Endotracheal tube cuff was inflated until no exhalation sounds or leak were heard. Besides, inflated cuffs were measured using a standard gage at 20-30 cm H_2O. Anesthesia was maintained using Isofluorane and Atracurium. 2 μg/kg Fentayl was repeated 1 hour after the start of the surgery. No additional analgesics were administered during the operation and patients who required this intervention were excluded from the study. Extubation was performed post-operatively using the same method in both groups. When TOF > 0.7 and the patient were fully awake, neuromuscular block was reversed using Neostigmin 0.05 mg/kg and Atropin 0.02 mg/kg, and patient was extubated. While in recovery, patients received oxygen at a rate of 5 liters/minute. If VAS ≥ 4 at any time, then analgesics were administered.

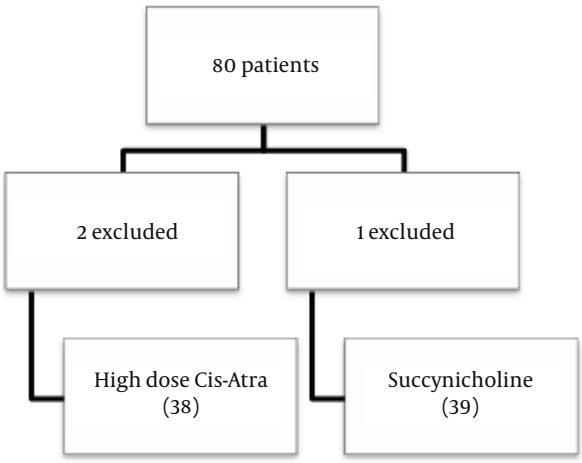


Figure 1. Consort Flow Diagram of the Trial

The study was reviewed and approved by the university's Ethics Committee. Comprehensive information about the trial was provided to the patients both orally and in written form. Patient enrollment was voluntary. Informed consent was obtained from all patients prior to inclusion in the study.

Sample size was calculated based on a confidence of 5% and desired power of 80% and desired ratio of 30%. In our study, based on reduction of 3 scores of VAS in postoperative sore throat the difference between Cisatracurium and Succinylcholine was calculated about 30%. Sample size calculation used the normal approximation to the Binomial distribution.

Data analysis was conducted using SPSS v.18. The parametric variables were presented as mean ± SD and were analyzed by student t-test or ANOVA and Pearson correlation test as appropriate. Statistical analysis was performed using Chi-Square or Mann-Whitney U-test and Spearman correlation coefficients for non-parametric samples. $P < 0.05$ was considered as statistically significant. Sample size was estimated using sample size calculator software with 95% confidence interval and $P < 0.05$.

4. Results

40 patients received Succinylcholine and 40 received Cisatracurium. There were no significant differences in the distribution of age, sex, and BMI between the two arms (Table 1). Duration of surgery was not significantly different as well (P value = 0.32).

The incidence of sore throat and its variants (sore throat, dry throat, and hoarseness) was significantly higher in the Succinylcholine group (75%) compared to Cisatracurium group (27.5%) at baseline in the recovery room (P = 0.001).

Number of patients who developed sore throat was significantly higher in the Succinylcholine group (51%) compared to Cisatracurium group (25%) at the time of entrance to the recovery room (P = 0.001). These numbers decreased at 2 hours post–operation (42% in the Succinylcholine group and 17.5% in the Cisatracurium group) but

the difference was still statistically significant (P = 0.027). At 12 and 24 hours post operation, the difference was no longer significant (Figure 2).

Number of patients who developed hoarseness was significantly higher in the Succinylcholine group compared to Cisatracurium group at the time of entrance to the recovery room (37.5% versus 17.5% with P = 0.015) and 2 hours post-operation (15% versus 12.5% with P = 0.046) and the difference was statistically significant. At 12 and 24 hours post operation, the difference was no longer significant (P = 0.35 and P = 0.19 respectively) (Figure 3).

Number of patients who experienced dryness of the throat was significantly higher in the Succinylcholine group (57.5%) compared to Cisatracurium group (17.5%) at baseline (57.5% compared to 17.5%) and at 2 hour post-operation (22% compared to 12.5% with P = 0.041). The difference was no longer significant at 12 (P = 0.22) and 24 (P = 0.063) hours post-operation (Figure 4).

Number of patients with VAS > 3 was significantly higher in the Succinylcholine group (67.5%) compared to Cisatracurium group (27.5%) at the time of entrance to the recovery room. These numbers decreased at 2 hours post-operation (35.5% in the succinylcholine group and 12.5% in the Cisatracurium group) but the difference was still statistically significant (P = 0.039). At 12 (P = 0.077) and 24 (P = 0.14) hours post operation, the difference was no longer significant (Figure 5). 97.5% of the patients who had received Succinylcholine developed fasciculation, while none of the patients in the Cisatraciruim arm showed similar problem (P < 0.001).

Muscle ache and fasciculation was experienced in 85% of the patients in Succinylcholine group and 27.5% of the Cisatracurium group (P = 0.002). In order to determine the frequency of sore throat in relation to muscle ache, both arms were further divided into those who had developed muscle ache and those who didn't, and the incidence of sore throat was calculated in each group. In the Succinylcholine arm, 29.3% of patients who developed muscle ache and 28.2% of those who didn't experienced accompanying sore throat; while in the Cisatracurium arm, these numbers were 18.5% and 14.5%, respectively (Figure 5). Number of patients with sore throat was significantly lower in the Cisatracurium arm, whether they had (P = 0.025) or had not (P = 0.01) accompanying muscle.

Table 1. Demographic Characteristics of Patients in the Two Arms [a]

	Succinylcholine	Cisatracurium	P Value
Age, y	35.5 ± 12.4	36.2 ± 14.1	0.22
Gender			> 0.05
Male	31	28	
Female	19	22	
Weight, kg	65.6 ± 21.2	71.8 ± 25.5	0.14
BMI, kg/m²	22.6 ± 3.5	23.5 ± 4.3	0.65
Duration of surgery, min	185 ± 45.3	192 ± 51.3	0.32

[a] Data are presented as mean ± SD.

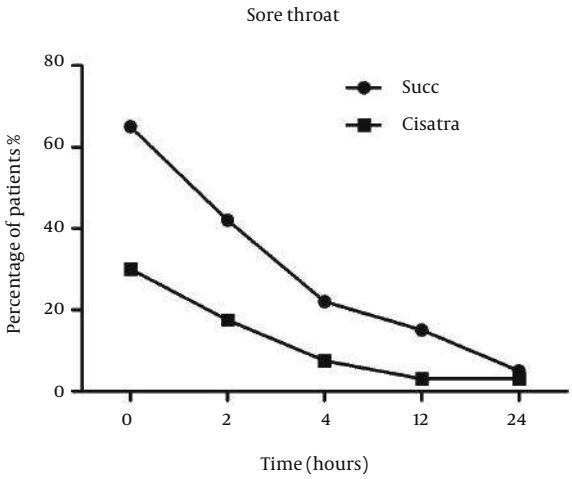


Figure 2. Sore Throat Incidence After Induction With Succinylcholine or Cisatracurium at Baseline, 2, 4, 12 and 24 Hours Post Operation.

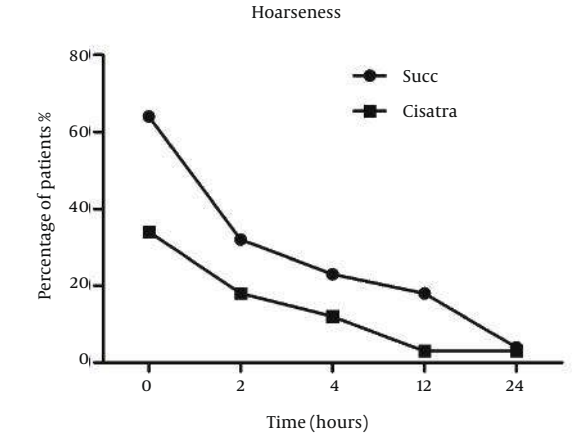


Figure 3. Hoarseness Incidence After Induction With Succinylcholine or Cisatracurium at Baseline, 2, 4, 12 and 24 Hours Post Operation.

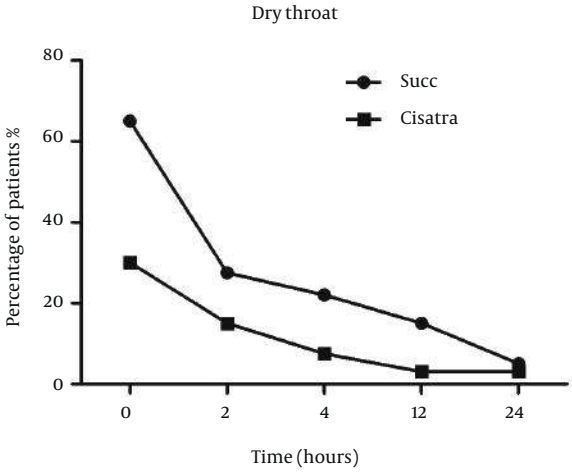


Figure 4. Dry Throat Incidence After Induction With Succinylcholine or Cisatracurium at Baseline, 2, 4, 12 and 24 Hours Post Operation.

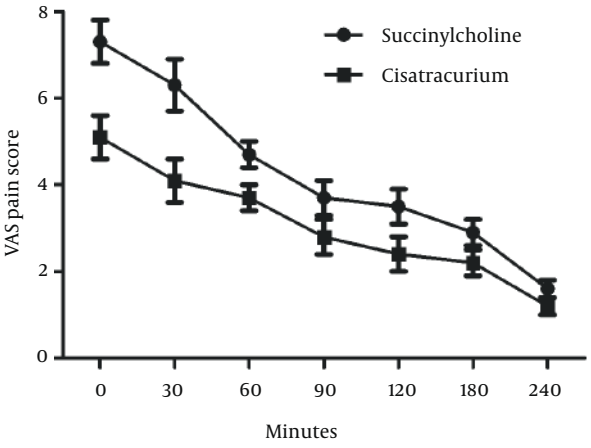


Figure 5. Percentage of Patients Who Experienced Pain With Visual Analogue Scale (VAS) > 3 After Induction With Succinylcholine or Cisatracurium at Baseline, 2, 4, 12 and 24 Hours Post Operation.

5. Discussion

As mentioned earlier, postoperative sore throat is a common complication of endotracheal intubation and can lead to dissatisfaction after surgery. Type of induction agent used for airway management has a considerable influence on the incidence of sore throat. Succinylcholine is the most commonly used type of muscle relaxant. Not many studies have evaluated the effect of Succinylcholine on postoperative sore throat, and contradictory data exists among them. A study by Capan et al. (11) published in 1983 on 83 patients undergoing dilation and curettage examined the incidence of post operative sore throat (6-10 hours post operation) after induction with different doses of Succinylcholine while avoiding perioperative intubation. According to their results, sore throat was experienced in 0% of patients who had not received Succinylcholine, 9% of patients who had received 1 mg/kg Succinylcholine and 10% of those who had received the medication at a dose of 1.5 mg/kg. The authors concluded that intravenous administration of Succinylcholine may cause postoperative sore throat (11). However, another study by Joorgensen et al. conducted on 60 patients in 1987 did not show an increase in the incidence or severity of sore throat 20 to 30 hours post operation (14). The difference can be attributed to the fact that sore throat was evaluated at different times after surgery. Our results show that the difference between the incidence of sore throat caused by Succinylcholine and Cisatracurium reduced as time went by, reaching an insignificant level 24 hours post operation. As previously stated, no study has been carried out to compare the incidence of sore throat after induction with Succinylcholine and Cisatracurium. Our results show that the number of patients who developed sore throat was significantly higher in the Succinylcholine group (75%) compared to Cisatracurium group (27.5%) at the time of entrance to the recovery room and 2 hours post-operation (42% in the Succinylcholine group and 17.5% in the Cisatracurium group) (P = 0.027).

Fasiculation has been proposed as the main cause of post-induction sore throat. Interestingly, our study showed that patients with or without fasciculation had almost equal chances of developing sore throat and the incidence varied only based on the type of muscle relaxant used: In the Succinylcholine arm 29.3% of patients who developed muscle ache and 28.2% of those who didn't, experienced accompanying sore throat; while in the Cisatracurium arm, these numbers were 18.5% and 14.5%, respectively.

We demonstrated that high dose Cisatracurium can provide a muscle relaxant effect without increasing rates of post-operative sore throat and its use during rapid sequence intubation carries a lower chance of developing sore throat compared to Succinylcholine. Studies comparing other adverse effects of these two agents are required to decide which one is generally a more suitable option for induction and to guide physicians' choices of induction agent.

Authors' Contributions

Study concept and design: Teymourin, Solatpour, Mohajerani. Acquisition of data: Solatpour, Hoseinzadegan. Analysis and interpretation of data: Hoseinzadegan, Lotfollahzadeh. Drafting of the manuscript: Lotfollahzadeh, Baikpour, Amraei. Critical revision of the manuscript for important intellectual content: Teymourian, Solatpour, Mohajerani. Statistical analysis: Hoseinzadegan, Lotfollahzadeh. Administrative, technical, and material support: Baikpour, Amraei. Study supervision: Teymourian.

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Research Article

Ease Of Intubation and Hemodynamic Response to Laryngoscopy and Endotracheal Intubation with Macintosh and Hugemed Video Laryngoscope

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Abstract: **Objectives**: The aim of this study is to compare the Ease of intubation and changes in hemodynamic parameters during endotracheal intubation using McIntosh & Hugemed laryngoscope in a patients who are ASA grade I and II.. **Methods**: A total of 70 patients who are ASA grade I and II belonging to the age group 18 to 60 years posted for elective surgeries under general anesthesia in Government Medical College, Thrissur were studied. 35 of them were intubated using McIntosh laryngoscope while the rest were intubated using Hugemed video laryngoscope. The time taken to perform endotracheal intubation and changes in hemodynamic parameters during the initial five minutes following intubation were recorded and compared between the 2 groups. **Results**: The 2 groups were similar with respect to demographic data and airway examination. The duration of laryngoscopy and intubation was significantly longer in group B (Hugemed laryngoscopy) when compared to group A patients with p value = 0.000. However, haemodynamic changes did not show any significant differences between the groups. **Conclusion**: The study found that, as compared to traditional laryngoscope (McIntosh), Hugemed video laryngoscopy did not provide any benefits for patient hemodynamic response to laryngoscopy and intubation, but the time required for intubation was significantly longer in the video laryngoscope group.

Keywords: McIntosh, Endotracheal intubation, Haemodynamic changes, Duration of laryngoscopy, Hugemed Video laryngoscopy

INTRODUCTION

Laryngoscopy and endotracheal intubation is an integral part of general anesthesia. Direct laryngoscopy and passage of endotracheal tube through the larynx is a noxious stimulus, which can provoke untoward response in the cardiovascular, respiratory and other physiological systems. (1) . Significant tachycardia and hypertension can occur with tracheal intubation under light anaesthesia. Hypertension, tachycardia and arrhythmia caused by endotracheal intubation can be deleterious in patients with poor cardiovascular reserve. The magnitude of hemodynamic response increases with the force and duration of laryngoscopy (DOL) and can also be influenced by prolonged intubation time (10). Because it may lead to rare, but serious complications such as myocardial infarction or brain hemorrhage, Anesthesiologists should be careful to minimize the incidence of hypertension during tracheal intubation. Thus, use of different types of laryngoscope blades can help decreasing these responses

The Macintosh laryngoscope (MCL) has been the "gold standard" device for direct laryngoscopy and tracheal intubation since its invention by Foregger and Foregger in 1940s. Direct laryngoscopy (DL) does not always allow optimal viewing of the glottis, especially in those patients with anatomical characteristics which can make tracheal intubation difficult. (2)

The videolaryngoscope(VLS) (HugeMed, Shenzhen) is a portable device designed to perform indirect laryngoscopy in both routine and difficult airway intubations, in elective or in emergency settings(3). The main advantage is the visualization of the target, as the operator's "eye" is now located at the tip of the blade 2 or 3 cm. The alignment of the oral-pharyngeal-laryngeal axis, crucial to DL, is thus rendered nonessential in VLS. The number of attempts, and consequently the trauma to the airway, is also reduced.

The study was designed with the objective to assess the hemodynamic changes that occur during and after endotracheal intubation with HugeMed video laryngoscope and comparing those changes with conventional laryngoscopy (Macintosh). We are also comparing the time taken to perform the endotracheal intubation in both groups.

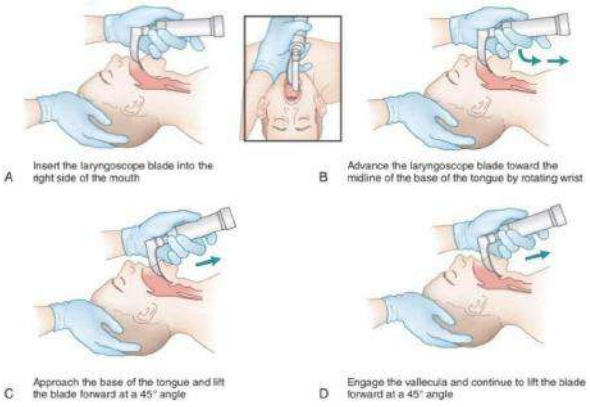


Figure 1: Conventional laryngoscopy using a curved Macintosh blade



Figure.2
The VL3 video laryngoscope.

1. 3.5" high-resolution display;
2. handle with recording button for pictures and videos;
3. Reusable blade with a 66° field angle;
4. 2- megapixel camera with an antifog lens

METHODS:

After receiving approval from the institutional ethics committee and signed informed consent from the study participants, a comparative- cross sectional study based in a hospital was carried out among 70 patients(35 in each groups) who underwent surgical, gynaecological and orthopaedic procedure under general anaesthesia at the Department of Anaesthesiology, Government Medical College, Thrissur, between October 2021 and October 2022.70 patients will be divided into two equal groups –35 of them were intubated using McIntosh laryngoscope while the rest were intubated using Hugemed videolaryngoscope. The time taken to perform endotracheal intubation and changes in hemodynamic parameters during the initial five minutes following intubation were recorded and compared between the 2 groups.

Inclusion Criteria:
Patients of either sex ASA Grade 1&2
Age between 18& 60year
Patients undergoing elective surgeries

Exclusion Criteria:
Patient refusal Pregnant women
Patients undergoing emergency surgery Those with airway abnormalities
Anticipated difficult airway (Mallampati class lll and IV, thyromental distance <6cm , inter-incisor distance <3cm, and cervical instability)
Active smoking Chronic hypertension In addition, the patient in whom laryngoscopy lasted for more than 30sec and if more than one intubation attempt was needed were also excluded.

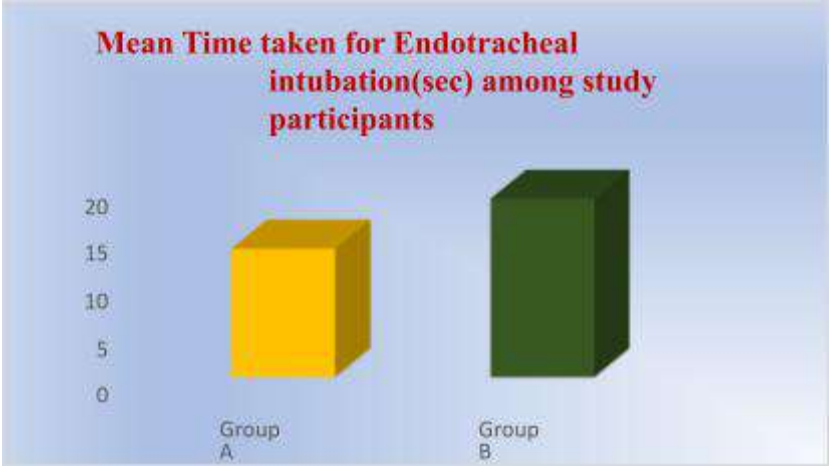
Statistical Method:
This was the appropriate statistical technique used to meet the study objective. The Quantitative variables like HR, BP (SBP, DBP, MAP) were compared in 2 groups with unpaired T-test. If any non-normal data exists for comparison Mann-Whitney test was used. 'p' value less than 0.05 was considered statistically significant.

RESULTS AND OBSERVATIONS

The study was conducted in the Department of Anaesthesiology, Govt. Medical College Thrissur from October 2021 - October 2022.The study population consisted of 70 patients undergoing elective surgery requiring endotracheal intubation. Patients satisfying the inclusion criteria were included into 2 groups of 35 each. Group A - patients undergoing intubation with Macintosh laryngoscope. Group B
- patients undergoing intubation with Hugemed video laryngoscope. Data were entered in Microsoft Excel Software

and analysed using SPSS version 21.The continuous variables like age, weight, heart rate at different time points, blood pressures at different time points were summarized as mean and standard deviation or median depending on distribution. Categorical variable like sex was summarized as frequencies and proportions. Unpaired t-test were used for comparing continuous variables between the groups at different time points. Chi square test or fishers exact test based on cell counts were used for comparing categorical variables between the two groups.

Figure 3: Mean duration of intubation among the study groups (N=70)



The mean time taken for endotracheal intubation in Group A and Group B are 13.343 seconds and 18.543 seconds respectively. There is significant difference between mean time taken for endotracheal intubation in Group A and Group B with a p value of 0.000.

***Group B takes more time for endotracheal intubation than Group A.*

Table 1: Comparison of Mean duration of intubation among study groups (N=70)

Variable	Group	Mean	Standard deviation	P value
Time taken for Endotracheal intubation(sec)	A	13.343	3.865	0.000
	B	18.543	2.715	

**This result is significant at 0.05 level of significance. The mean duration of intubation in group A and group B is 13.343 and 18.543 respectively.

Table 2: Patient demography and other details

Variables	Group A	Group B	P value
Age(years)	**44.886 ± 12.061**	**43.314 ± 10.868**	**0.569**
Weight(kg)	**65.171 ± 10.063**	**65.429 ± 8.759**	**0.910**
Sex(male/female)*	**9/26**	**10/25**	
Teeth Abnormality	**None**	**None**	
Anticipated Difficulty	**None**	**None**	××××××××××
Time taken for Endotracheal intubation(sec)	**13.343 ± 3.865**	**18.543 ± 2.715**	**0.000**

The mean age of the group A and group B patients were 44.886 and 43.314 respectively.The mean weight of the group A and group B patients were 65.171 and 65.429 respectively.Out of 35 study patients in group A 9 were males and 26 were females. And out of 35 study patients in group B 10 were males and 25 were females.

Figure 4: Line graph showing the mean Heart rate of the patients during the procedure at different points among the study groups. (N=70)

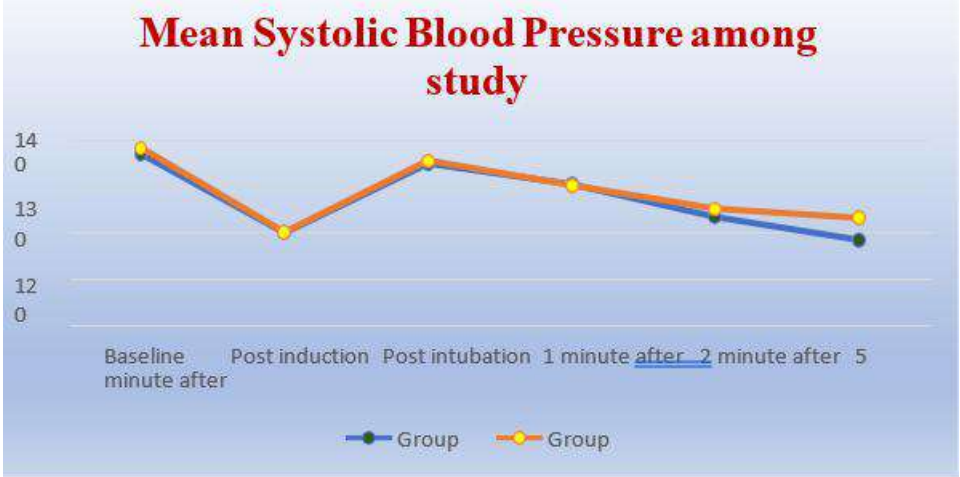


At all points, the heart rate was similar in both groups with p value >0.05.

Table 3: Heart Rate during the procedure at different time points

Variable	Group	Mean	Standard deviation	P value
T1	A	82.543	10.856	0.658
	B	83.743	11.738	
T2	A	70.714	8.995	0.524
	B	72.200	10.344	
T3	A	87.857	9.997	0.108
	B	83.457	12.460	
T4	A	72.200	9.074	0.722
	B	78.314	11.550	
T5	A	73.857	8.603	0.770
	B	74.514	10.092	
T6	A	68.771	6.151	0.086
	B	72.200	9.866	

Figure 5: Systolic blood pressure of the patients during the procedure at different time points



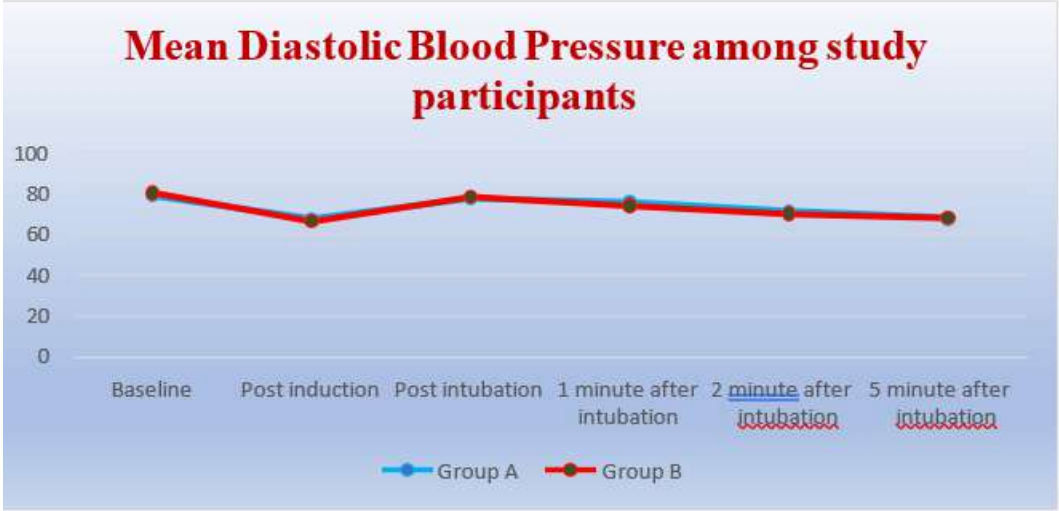
At all points, the systolic blood pressure was similar in both groups with p value >0.05.

Table 4: Systolic blood pressure during the procedure at different time points

Variable	Group	Mean	Standard deviation	P value
T1	A	**136.771**	**9.290**	
	B	**138.057**	**9.133**	**0.561**
T2	A	**119.714**	**9.342**	
	B	**119.886**	**9.408**	**0.939**
T3	A	**134.629**	**9.350**	
	B	**135.286**	**8.411**	**0.758**
T4	A	**130.143**	**8.416**	
	B	**129.943**	**8.415**	**0.921**

T5	A	**123.143**	**8.339**	
	B	**124.914**	**7.559**	**0.355**
T6	A	**118.171**	**8.956**	
	B	**122.886**	**8.116**	**0.240**

Figure 6: Diastolic blood pressure of the patients during the procedure at different time points (N=70)

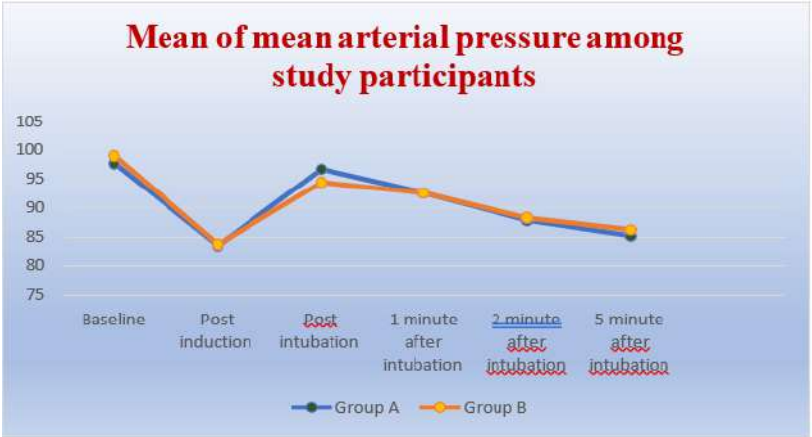


At all points, the diastolic blood pressure was similar in both groups with p value >0.05.

Table 5: Diastolic blood pressure during the procedure at different time points (N=70)

Variable	Group	Mean	Standard deviation	P value
T1	A	**78.543**	**6.405**	**0.439**
	B	**79.886**	**7.959**	
T2	A	**66.914**	**7.781**	**0.618**
	B	**65.971**	**7.943**	
T3	A B	**77.229** **77.914**	**14.134** **7.434**	**0.800**
T4	A	**75.486**	**7.500**	**0.291**
	B	**73.571**	**7.547**	
T5	A	**70.886**	**7.190**	**0.438**
	B	**69.571**	**6.895**	
T6	A	**67.371**	**6.899**	**0.817**
	B	**67.771**	**7.468**	

Figure 7: Mean arterial pressure of the patients during the procedure at different time points (N=70)



At all points, the mean arterial blood pressure was similar in both groups with p value >0.05

Table 6: Mean arterial pressure during the procedure at different time points (N=70)

Variable	Group	Mean	Standard deviation	P value
T1	A	**97.657**	**7.284**	**0.444**
	B	**99.057**	**7.918**	
T2	A	**83.428**	**8.118**	**0.881**
	B	**83.714**	**7.827**	
T3	A	**96.686**	**7.981**	**0.463**
	B	**94.457**	**15.980**	
T4	A	**92.543**	**7.671**	**0.975**
	B	**92.600**	**7.429**	
T5	A	**87.800**	**7.407**	
	B	**88.257**	**6.887**	**0.790**
T6	A	**85.114**	**7.411**	
	B	**86.286**	**7.430**	**0.511**

DISCUSSION:

Laryngoscopy and endotracheal intubation results in sympathetic stimulation that leads to hypertension and tachycardia. Direct laryngoscopy involves stretching the oropharyngeal tissues in an attempt to straighten the angle between the mouth and the glottic opening, and this stretch can cause pain and trigger a stress response (4). Both laryngoscopy and intubation separately result in sympathetic stimulation, but the catecholamine rise with intubation exceeds that with laryngoscopy alone(5) .Various anaesthetic agents, adjuvants and analgesics have been used to blunt the level of stimulation and the stress response to the manipulation and stimulation of airway during laryngoscopy and intubation. Fentanyl, beta adrenergic receptors blockers, and lignocaine have all been used with varying results(6).Newer airway aids have always been a part of the evolution of anaesthetic equipment and have been used either to facilitate laryngoscopy and intubation so as to avoid major sympathetic stimulation or to aid in a scenario of difficult intubation. These airway aids are compared with the current standard practice of using a direct laryngoscopy and endotracheal intubation. The fibreoptic bronchoscope, McCoy laryngoscope, and more recently the style scope have been studied and the haemodynamic changes have been found to be lesser. In this study, 70 ASA PS class 1 and 2 patients who underwent surgical, gynaecological and orthopaedic procedure under general anaesthesia, requiring endotracheal intubation were observed in Government Medical College, Thrissur. The patients were included in group A(Mcintosh) and group B(Hugemed video laryngoscopy) based on the laryngoscope blade used for intubation. The heart rate, blood pressure (systolic, diastolic and mean) were recorded at six specified intervals, namely, T1= baseline, prior to

anaesthetic induction; T2= post induction, prior to relaxant administration; T3= post intubation; T4= 1 min after endotracheal intubation; T5= 2 min after endotracheal intubation; T6= 5 min after endotracheal intubation. The time taken to perform endotracheal intubation was also noted in both the groups by which ease of intubation was compared. Hemodynamic parameters like heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure at different time points during the procedure were similar in both groups. No statistically significant difference was observed

between hemodynamic responses to laryngoscopy and tracheal intubation with Mcintosh and Hugemed laryngoscopes. However, this finding of ours is in contrast to a study by **Altun et al** which compared hemodynamic responses to four different laryngoscopes – McGrath, McCoy, Macintosh and C-mac – in patients with normal airway. The study showed that McGrath videolaryngoscope caused fewer hemodynamic fluctuations compared to the other three devices during laryngoscopy and tracheal intubation.(7).However, in studies conducted by **Han et al. and Shimoda et al**. regarding hemodynamic effect during laryngoscopy with McCoy and Macintosh laryngoscopes there was no significant difference in the hemodynamic response with the two blades.(8).In a study conducted by **kamewad et al** which included regarding hemodynamic response and ease of intubation during laryngoscopy with conventional and pentax video laryngoscope did not provide any benefit in terms of haemodynamic response to laryngoscopy and intubation in patients. However The duration of laryngoscopy and intubation was significantly longer in group of patients who was intubated with video laryngoscopy when compared to other group patients.(9).From our study, it can be concluded that while comparing Macintosh and Hugemed laryngoscope, there is no definite advantage of one over the other in reducing the stress response to laryngoscopy and intubation. However, the duration of laryngoscopy and intubation was significantly lower in those for whom Mcintosh laryngoscope was used.

CONCLUSION:

The time taken to perform endotracheal intubation and haemodynamic changes associated with intubation were noted in both the groups at different time points. The duration of laryngoscopy and intubation was significantly longer in group B (Hugemed video laryngoscopy) when compared to group A patients (Mcintosh). However, haemodynamic changes were not different between the groups. Video laryngoscopy did not provide any benefit in terms of haemodynamic response to laryngoscopy and intubation in patients.

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Perfusion Index as a Predictor of Hypotension Following Propofol Induction - A Prospective Observational Study

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Abstract: ***Background*:** This study was conducted to determine the baseline perfusion index value that can predict hypotension at 5 minutes post-induction. ***Methods:***This was a hospital-based prospective observational study conducted among forty-two adults aged between 18 and 65 years belonging to the ASA (American Society of Anesthesiologists) physical status I and II undergoing elective surgery under general anaesthesia at the Department of Anaesthesiology, Government Medical College, Thrissur, Kerala, India, over a period of one year from January 2019-January 2020 after obtaining clearance from the institutional ethics committee and written informed consent from the study participants. ***Results:***Out of the 42 participants, 26 (62%) developed hypotension within 5 minutes and 13 (31%) developed hypotension after 15 minutes. ROC analysis was conducted to identify a cut off for predicting hypotension. The area under the ROC curve was 0.98, 95% CI [0.95 to 1.0]. Hypotension was predicted with a baseline PI < 1.86, showing 92.3% sensitivity and 93.75% specificity. There was a 96% positive predictive value and an 88.2% negative predictive value. The baseline perfusion index is an accurate predictor of hypotension within 5 minutes. ***Conclusion:***The perfusion index was found to be a significant predictor of hypotension following propofol induction and a cut off value (baseline PI<1.86) was obtained to predict the same, from this study.

Keywords: Perfusion Index, Predictor, Hypotension. Propofol Induction.

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INTRODUCTION

General anaesthesia indiuction using general anaesthetic agents and opioid analgesics induces significant changes in peripheral vascular physiology and sympathetic or parasympathetic tone, thereby affecting peripheral perfusion, as observed by changes in the pulse oximetry plethysmographic waveform. PI (Perfusion Index) is a relatively new parameter estimating the pulsatility of blood in the extremities, calculated using the infrared spectrum as part of plethysmography waveform processing. It is the ratio of pulsatile to non-pulsatile blood flow in the extremities. It's an easy, non-invasive way to check peripheral perfusion. PI, then, is a measurement of peripheral perfusion that may be obtained constantly from

a pulse oximeter without requiring any intrusive procedures. Opioid analgesics and general anesthetics like propofol, desflurane, and isoflurane raise the vasodilation threshold by suppressing the sympathetic nervous system, lowering the vasoconstriction threshold. Following the administration of opioid analgesics and general anesthetics, a reduction in peripheral sympathetic tone dilates peripheral arteries, boosts peripheral perfusion, and lowers arterial blood pressure. As a result, these medications may increase the patients' chances of experiencing hypotension brought on by general anesthesia. Pre-existing heart dysfunction or underlying volume depletion may exacerbate this hypotensive reaction. Clinicians may be better able to recognize and treat hypotension brought on by general anesthesia if they have a continuous, noninvasive way to gauge a patient's sympathetic or parasympathetic reaction to the induction of general anesthesia. Conventional pulse oximetry uses two light wavelengths-red and infrared-transmitted through the finger and detected by a photodetector. The LED's (Light Emitting Diode) nonabsorbed light is detected by the sensor's photodetector. An inverting operational amplifier reverses this signal. This signal, which is separated into DC (Direct Current) and AC (Alternating Current) components, indicates the light that has been absorbed by the finger. The tissue's absorption of light, venous blood, and non-pulsatile arterial blood is represented by the DC component, while the pulsatile arterial blood is represented by the AC component. Hence, PI is defined as AC/DC * 100% of the plethysmograph waveform. It reflects the peripheral vasomotor tone. A low PI suggests peripheral vasoconstriction, while a high PI suggests vasodilation. In addition, vasoactive medications, stroke volume, sympathetic activity (pain, anxiety), and finger temperature can all affect PI. A variety of circumstances influence the condition of the sympathetic nervous system-intense microcirculation, causing the microvasculature to dilate or constrict.[1] It also serves as an indicator of SVR (Systemic Vascular Resistance). Though not linearly, the relationship between the vascular tone and the value of PI is inverse. Propofol-induced hypotension is caused by the autonomic nervous system, which affects both the sympathetic and parasympathetic branches.[2] Additionally, there is proof that propofol has a direct impact via both endothelium-dependent and independent mechanisms. Both lead to vasodilatation at the end. The patient is more prone to experience hypotension if they have low peripheral PI, or substantial peripheral vasoconstriction. Similarly, there is less chance of hypotension if the patient already has low vascular tone, which is indicated by a greater PI and is vasodilated and relatively compensated blood volume. The baseline SVR is responsible for a considerable amount of the hypotension that occurs during the induction of anesthesia with propofol. Therefore, based on a person's pre-induction SVR, it might be possible to set a threshold value of PI that indicates hypotension. When life-threatening problems such as abrupt hypotension, rapid hypertension, arrhythmias, and cardiovascular collapse occur, especially in high-risk patients, the induction of anesthesia is an essential component of therapeutic management. Consequently, it is preferable to employ a safe induction agent with a negligible impact on hemodynamics. The most widely used induction drug is propofol (2, 6 diisopropylphenol), which has the advantages of a smooth and quick induction and recovery as well as a lower rate of nausea and vomiting. However, there is a strong correlation with hypotension. One common issue during propofol induction is hypotension. The goal of this study is to determine the pre-anaesthesia PI cut-off value, which may be helpful in predicting hypotension that occurs after propofol induction of anesthesia. If the anesthesiologist can predict which patients are most at risk of severe hypotension, they may be able to individualize treatment.[3]

AIMS AND OBJECTIVES

To obtain a cut-off value for the baseline perfusion index that predicts hypotension following induction using propofol.

MATERIALS AND METHODS

This was a hospital based prospective observational study conducted among forty-two adults aged between 18 and 65 years belonging to the ASA (American Society of Anesthesiologists) physical status I and II undergoing elective surgery under general anaesthesia at the Department of Anaesthesiology, Government Medical College, Thrissur, Kerala, India, over a period of one year from January 2019-January 2020 after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

Inclusion Criteria

Patients belonging to American Society of Anaesthesiologists physical status 1 and 2 aged between 18 and 65 years undergoing elective surgery under GA.

Exclusion Criteria

1. Patients with hypertension, on vasoactive medications.
2. Patients with difficult airways.
3. Pregnancy.

Statistical Methods

The data of the study was entered in Microsoft Excel sheet and statistical analysis was done using SPSS software version 16.

Sample Size

Sample size is calculated using the formula

$n \geq \{[Z_{1-\alpha/2} + Z_{1-\beta}] / 1/2 \log e^{(1+r/1-r)}\}^2 + 3$

α=0.01

β=0.2

r=0.503

α=α error

β=β error

n=sample size

r=correlation coefficient

Substituting the values in the equation, sample size, n=42.

Study Procedure

With approval from the institutional ethical committee, a prospective observational study was carried out at the hospital affiliated with Thrissur Medical College. After obtaining written informed consent, 42 adults between the ages of 18 and 65 who were undergoing elective surgery under general anesthesia and fit into physical status I and II of the American Society of Anesthesiologists were enrolled.

On reception in the Operation Theatre

1. With the Mindray Multipara iMEC 12 Monitor, baseline readings (heart rate [HR], PI, systolic [SBP], diastolic [DBP], and mean BPs [MAP]) were recorded. An electrocardiograph, a non-invasive blood pressure monitor, and a pulse oximeter were attached.
2. Ringer's lactate intravenous infusion was started at a rate of 100 ml/h.
3. The patient was given vecuronium intravenously (IV) at a dose of 0.1 mg/kg after a senior anesthesia care provider titrated the patient's intravenous propofol injection at a rate of 2-3 mg/kg until the patient no longer responded to vocal communication. Up to five minutes, the hemodynamic parameters were recorded every two minutes.
4. A senior anaesthesia care provider used a suitable sized endotracheal tube to intubate the patient after the patient's lungs were ventilated with 100% oxygen for three minutes.
5. The maintenance of anesthesia was established using 0.6% isoflurane and 50% N2O in oxygen. At one minute, three minutes (after induction), five minutes, ten minutes, and fifteen minutes (after intubation), hemodynamic data were measured. A decrease in SBP to <20% of baseline or an absolute mean arterial pressure of <60 mmHg was considered hypotension. Severe hypotension with a MAP <55 mmHg was promptly treated with IV boluses of injectable mephenteramine (6 mg) and fast intravenous fluid administration (10 ml/kg). IV boluses of Inj. Atropine (0.6 mg) were used to treat bradycardia, which was defined as a heart rate less than 50 bpm.

The incidence of hypotension was computed in two sets: the first 15 minutes following induction (impact of the induction process and endotracheal intubation) and the first 5 minutes following anesthesia induction (effect of induction drug). The result was a baseline PI cut-off value below which hypotension was predicted five minutes after introduction.

Continuous variables like age and BMI were summarized as mean and SD. Categorical variables like gender and ASA were summarized as proportions. Perfusion index, heart rate, blood pressure and SpO_2 at different time points were summarized as mean ± SD.

The incidence of hypotension was defined as mean arterial pressure < 60 mmHg or SBP less than 80% of the baseline value.

ROC analysis was done to identify the baseline perfusion index cut off to predict the incidence of hypotension within 5 minutes. Sensitivity, specificity, positive predictive value and negative predictive value were calculated based on the cut off identified in ROC analysis.

The incidence of hypotension at 15 minutes was summarized as a proportion.

RESULTS

Parameter	Mean (SD)
Heart Rate	88.8 (8.3)
Systolic BP	133.2 (15.6)
Diastolic BP	81.0 (7.2)
Mean Arterial Pressure	97.1 (9.2)
Perfusion Index	2.1 (1.2)

Table 1: Baseline Haemodynamic Parameters of Patients in the Study

	1 Minute	3 Minutes	5 Minutes	10 Minutes	15 Minutes
HR	84.7 (8.1)	84.1 (7.2)	81.6 (7.9)	80.0 (8.9)	77.7 (7.8)
SBP	121.9 (13.2)	109.0 (10.7)	105.7 (11.9)	110.1 (11.8)	116.0 (10.8)
DBP	76.3 (6.8)	69.3 (6.7)	66.7 (6.6)	70.4 (7.6)	71.5 (5.5)
MAP	90.3 (7.9)	82.0 (6.7)	80.3 (7.6)	83.5 (8.4)	85.2 (6.3)
PI	3.3 (1.1)	6.0 (12.5)	4.3 (1.4)	3.7 (1.3)	3.2 (1.1)
Table 2. Mean Values of Haemodynamic Parameters Over Time					

Hypotension Incidence

The incidence of hypotension is defined as mean arterial pressure < 60 mmHg or SBP less than 80% of the baseline value.

Out of the 42 participants, 26 (62%) developed hypotension within 5 minutes.

Hypotension and Baseline Perfusion Index

ROC analysis was conducted to identify a cut off for predicting hypotension.

The area under the ROC curve was 0.98, 95% CI [0.95 to 1.0]. The baseline perfusion index is an accurate predictor of hypotension within 5 minutes.

Baseline PI < 1.86 predicted hypotension with a sensitivity of 92.3% and a specificity of 93.75%. The positive predictive value was 96% and the negative predictive value was 88.2%.

Perfusion Index	Hypotension	No Hypotension
< 1.86	24	1
≥ 1.86	2	15
Table 3. Baseline Perfusion Index with Identified Cut Off and Incidence of Hypotension		
Sensitivity = 92.3, Specificity = 93.75, PPV = 96%, NPV = 88.2		

	Baseline	1 Minute	3 Minutes	5 Minutes	10 Minutes	15 Minutes
SpO_2	99.9 (0.3)	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)
Table 4. Mean SpO_2 at Different Time Points						

SpO_2 was maintained at 100% for all patients post intubation.

DISCUSSION

The study evaluated 42 adults between 18 and 60 years old, with a with a BMI between 19 and 29 $kg/m^2$and ASA physical status I and II, who underwent elective surgeries under general anaesthesia in Government Medical College, Thrissur.

Hypotension was defined as a reduction in systolic arterial pressure, to less than 100 mm of Hg or a reduction of 20% below baseline. For the purpose of this study, hypotension was defined as a reduction of systolic blood pressure to less than 20% of the baseline pressure or MAP less than 60 mmHg.

The age of the patients in the study ranged from 19 to 58 years. The mean age of the participants was 37.8 ± 10.5 years. Out of the 42 participants, 25 (60%) were males and 17 (40%) were females.

The study's patients' BMI ranged from 19.5 to 28.2 kg/m^2. The mean BMI of the participants was 24.0 ± 2.2 kg/m^2.

Out of the 42 participants, 27 (64%) were in the ASA 1 category and the rest belonged to the ASA 2 category.

Out of the 42 participants, 26 (62%) developed hypotension within 5 minutes and 13 (31%) developed hypotension after 15 minutes.

In this study, severe hypotension necessitating rescue with mephenteramine and bradycardia necessitating atropine administration were not observed.

Our hypothesis was that a baseline prognostic index would be helpful in anticipating hypotension after propofol induction. Our results support this theory by demonstrating a relationship between PI and the prevalence of hypotension. The SBP criterion showed a link with baseline PI, but the absolute MAP criterion did not show a connection with hypotension. In this case, it makes more sense to define hypotension as a function of baseline SBP since PI is based on the vascular contractile state and absolute MAP only looks at the patient's pre-operative vasomotor tone.

ROC analysis was conducted to identify a cut off for predicting hypotension. The area under the ROC curve was 0.98, 95% CI [0.95 to 1.0].

Hypotension was predicted with a baseline PI < 1.86, showing 92.3% sensitivity and 93.75% specificity. There was a 96% positive predictive value and an 88.2% negative predictive value.

Therefore, we could infer from the study that the baseline perfusion index is an accurate predictor of hypotension within 5 minutes.

Loss of pulsatility is a simple explanation for low PI and low SBP. Hypovolemia and the use of vasopressors are associated with it. On the other hand, concurrent increases in the non-pulsatile component may be the cause of high SBP and low PI.

Low PI levels may be the consequence of compensatory vasoconstriction brought on by relative hypovolemia, and propofol, through vasodilatation, may induce hypotension in these patients. The intubation stress likely caused blood pressure to return to normal, which decreased the incidence of hypotension at 15 minutes, as seen by the difference in the size of the correlation between the hypotension that occurred at the first 5 minutes and that at 15 minutes.

Propofol administration causes mild reductions in systolic, mean, and diastolic arterial blood pressure without a corresponding increase in heart rate.

Selective premedicants substantially modify this typical response. Billard V et al. concluded that premedication with fentanyl reduced hypertension after intubation but increased the incidence of hypotension after propofol induction.[4]

Propofol induction can cause severe hypotension in patients who are hypovolemic or have a low cardiac reserve. We excluded patients with a severely contracted state or cardiovascular compromise from the study, and restricted it to adequately optimized patients scheduled for elective procedures.

Studies have shown that the perfusion index and pleth variability index, obtained from non-invasive pulse oximetry can be useful parameters in predicting the hypotensive response to anaesthetic agents like propofol.

Mehandale SG et al. came to the conclusion that the Perfusion Index had a very high negative predictive value and may predict hypotension after propofol induction, particularly prior to endotracheal intubation.[5]

Tsuchiya M. et al. concluded that pre-anesthesia PVI can predict a decrease in MAP during anesthesia induction with propofol.[6]

Propofol, a unique sedative hypnotic medication with anesthetic properties, enables safe and efficient induction and maintenance of anesthesia. Propofol's favorable recovery profile makes it a better option than standard anesthetics in clinical settings where a quick recovery is essential. Combining a sedative or analgesic with propofol to maintain anesthesia enhances both the quality of the anesthesia and the ease of titration. As a result, practitioners can employ intravenous anesthetic techniques more effectively in their clinical practice.[7,8]

CONCLUSION

The study was conducted to determine whether the perfusion index could predict hypotension after anesthetic induction with propofol. The perfusion index was found to be a significant predictor of hypotension following propofol induction and a cut off value (baseline PI<1.86) was obtained to predict the same in this study.

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COMPARATIVE STUDY BETWEEN DEXMEDETOMIDINE AND FENTANYL AS ADJUVANT TO BUPIVACAINE IN SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK

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Abstract

Background: This study was conducted to evaluate the effects of fentanyl and dexmedetomidine as adjuvants to bupivacaine used for supraclavicular brachial plexus block in terms of analgesia, duration of motor block, and sensory and motor block onset times.

Methods: This was a hospital-based prospective comparative study conducted among 70 patients aged 18-60 years belonging to ASA 1 or 2 undergoing upper limb orthopaedic surgeries under supraclavicular brachial plexus block at the Department of Anesthesiology, Government Medical College, Thrissur, Kerala, India, from January 2021 to December 2022 after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

Results: The statistically significant times for the onset of sensory block were 6.43 ± 1.22 min for the dexmedetomidine group and 10.3 ± 1.25 min for the fentanyl group. The statistically significant motor block onset times were 9.7 ± 0.95 minutes for the dexmedetomidine group and 12.93 ± 1.82 minutes for the fentanyl group. A statistically significant duration of motor block was seen in the dexmedetomidine group (528 ± 48.02 min) and the fentanyl group (460 ± 34.74 min). The duration of sensory block was 538.67 ± 48.62 min in the dexmedetomidine group and 487.33 ± 48.28 min in the fentanyl group, which was statistically significant. The duration of analgesia was 734 ± 34.40 min in the dexmedetomidine group and 650 ± 23.38 min in the fentanyl group, which was statistically significant.

Conclusion: Addition of dexmedetomidine to 0.5% bupivacaine in supraclavicular brachial plexus block significantly reduces the onset of sensory and motor block and prolongs the duration of sensory and motor block and the duration of analgesia compared to fentanyl with 0.5% bupivacaine.

Keywords: Supraclavicular Brachial Plexus Block, Bupivacaine, Dexmedetomidine, Fentanyl.

INTRODUCTION

Peripheral nerve blockade has several benefits, including avoiding the side effects of anaesthetics used during general anaesthesia, helping patients with a variety of cardiorespiratory comorbidities, lowering the risk of pulmonary and thromboembolic complications, and lowering the use of opioids.[1] in addition to less discomfort, a quicker discharge timeline, and an improved quality of life during the first few days following surgery. The growing use of regional anaesthesia has led to technological and equipment advancements. From employing paresthesia to localise nerves, the technique has progressed to electrical nerve stimulation and, more recently, ultrasonography.

In order to produce a block with a quick onset, the supraclavicular technique blocks the plexus where it is most compactly organised, at the level of the nerve trunks. The improved quality of anaesthesia results from the brachial plexus's trunks and divisions passing relatively close together when they cross the first rib. At this location, the brachial plexus is in close proximity to the chest cavity and pleura, which is a major concern while giving block. However, using ultrasound (US) guidance to evaluate the plexus, ribs, pleura, and subclavian artery improves safety by enabling better anatomical surveillance and needle placement.[2]

Many local anaesthetics have been used to produce brachial plexus block. The most common among them being bupivacaine, because of its higher potency and prolonged duration of action. Local anesthetics generally block the generation of an action potential in nerve cells by increasing the threshold for electrical excitation. The progression of anesthesia is dependent on factors such as the diameter, degree of myelination, and conduction velocity of the nerve fiber. The length of time a local anaesthetic lasts is correlated with its solubility in lipids. This is because the medication has a higher affinity for lipid membranes and is consequently closer to its areas of action. The drug's effect on the membrane's Na+ channel lasts longer the longer it is present in the region of the membrane as opposed to being absorbed.

To extend the duration of block and postoperative analgesia, a variety of adjuvants have been added to local anaesthetics, including opioids, midazolam, magnesium sulphate, dexamethasone, neostigmine, and clonidine. In intensive care units, patients who are intubated and on mechanical ventilation are given intravenous (IV) sedation and analgesia with dexmedetomidine, an α2 receptor agonist.[3] Peripheral nerve blocks have been reported to utilise it recently. It is around eight times more powerful than clonidine, has a quick onset time, is said to extend the duration of local anaesthetics, and is safe and effective for peripheral nerve blocks.[4]

The analgesic effect is mediated through stimulation of the α_{2C} and α_{2A} receptors in the dorsal horn, which directly suppresses pain transmission by reducing the release of pronociceptive transmitters, substance P and glutamate, and hyperpolarization of interneurons. It is commonly recognised that opioids have analgesic properties at the spinal cord and brain levels. On the other hand, peripheral opioid receptor activation can start an opioid analgesic response.[5]

To increase the length and quality of regional nerve plexus blocks, opioids like fentanyl have been used. Opioids administered peripherally produce a more potent and prolonged analgesic without producing central side effects.

Therefore, improving analgesia by targeting peripheral receptors can prevent crippling centrally mediated side effects such as respiratory depression, altered consciousness, and addiction. Research has indicated that the inclusion of fentanyl improves the success rate and block duration of brachial plexus block. Fentanyl, a synthetic opioid agonist, is more potent and has a quicker beginning of effect than morphine, the naturally occurring parent opioid.

Fentanyl causes superior intraoperative and postoperative analgesia when administered intrathecally without causing hemodynamic instability. When compared to other opioids, the medication's superior safety profile has made it a popular option.[6] The duration of sensory and motor blockade is extended when local anaesthetics are administered in conjunction with dexmedetomidine or fentanyl in neuraxial and peripheral nerve blocks, according to several clinical investigations.

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Aims and Objectives

To compare the impact of dexmedetomidine and fentanyl as adjuvants to bupivacaine used for supraclavicular brachial plexus block with regard to onset time of sensory block, onset time of motor block, duration of sensory block, duration of motor block and duration of analgesia.

METHODS

This was a hospital-based prospective comparative study conducted among 70 patients aged 18-60 years belonging to ASA 1 or 2 undergoing upper limb orthopaedic surgeries under supraclavicular brachial plexus block at the Department of Anesthesiology, Government Medical College, Thrissur, Kerala, India, from January 2021 to December 2022 after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

Study Procedure

A total of 70 patients belonging to ASAPS (American Society of Anesthesiologists Physical Status) classes I and II, aged 18–60 years, underwent upper limb, orthopaedic and plastic surgeries under supraclavicular brachial plexus block.

Sample Size Calculation

Sample size (n) was calculated by the formula.

$n = (Z\alpha+Z\beta)2\ (S12+S22)$

d2

Where,

Zα: 1.96 (significant level α)

Zβ: 0.84 (significant level β)

S1: 37.2(standard deviation of dexmedetomidine group)

S2: 36.8 (standard of fentanyl group)

d: 26.3 (mean difference)

As per the statistical calculation the minimum sample size was 31 in each group.

Total sample size: 70

Sample size is calculated for 5% type 1 error (p-value <0.05) and 80% power of study. Values are selected from a previous study by Hamed et al.[4] at Fayoum University, published in Anaesthesia Essays and Researches, April 2018.

Inclusion Criteria

Age 18–60 yrs., weight 50–85, ASA classes 1 and 2 for upper limb surgeries not exceeding 2 hours as orthopaedic and plastic surgeries

Exclusion Criteria

1. Local infection at the site of the puncture
2. Patient with a neurological defect in the upper limb
3. Patient having hematological disorders, including coagulation abnormality
4. Patients with severe hepatic impairment
5. Known case of allergy to study drug or adjuvant

Statistical Methods

Mann-Whitney U test and independent sample T tests have been selected and conducted based on the distribution of the data to find out any statistically significant differences in onset of sensory block, onset of motor block, duration of sensory block, duration of motor block and duration of analgesia between the two drug groups and the results revealed that there were statistically highly significant differences in all the variables between the drug groups as p-values were <0.005.

RESULTS

Variables	DRUG. Group A		DRUG. Group B		P-Value
	Mean	S.D	Mean	S.D	
Onset of Sensory Block (minutes)	6.43	1.22	10.03	1.25	*<0.001
Comparison of Onset of Sensory Block in Each Group					
Variables	**DRUG. Group A**		**DRUG. Group B**		**P-Value**
	Mean	**S.D**	**Mean**	**S.D**	
Onset of Motor Block (minutes)	9.7	0.95	12.93	1.82	*<0.001
Comparison of Onset of Motor Block in Each Group					
Table 1					

Group B observed a mean onset time of 10.03 ± 1.25 min, with a p-value of < 0.001, while group A experienced a quicker 6.43 ± 1.22 min.
Hence, the two groups were statistically significant.
Group A had a faster mean time to motor block onset of 9.7 ± 0.95 min, whereas group B had a mean time of 12.93 ± 1.82 min, with a p-value of < 0.001. Therefore, there was a statistically significant difference.

Variables	DRUG. Group A		DRUG. Group B		P-Value
	Mean	S.D	Mean	S.D	
Duration of Sensory Block (minutes)	538.67	48.6	487.33	48.28	*0.001
Comparison of Duration of Sensory Block in Each Group)					
Variables	**DRUG. Group A**		**DRUG. Group B**		**P-Value**
	Mean	**S.D**	**Mean**	**S.D**	
Duration of Motor Block (minutes)	528	48.02	460	34.74	*<0.001
Comparison of Duration of Motor Block in Each Group					
Table 2					

Group A had a longer mean time of sensory block (538.67 ± 48.6 min), whereas group B had a shorter mean duration of 487.33 ± 48.28 min (p < 0.001). Hence, the difference was statistically significant.
The mean duration of motor block in group A was 528 ± 48.02 min, which was longer and group B was 460 ± 34.74 min, which was found to be shorter with a p-value of < 0.001. Hence, the difference was statistically significant.

Variables	DRUG. Group A		DRUG. Group A		P-Value
	Mean	S.D	Mean	S.D	
Duration of Analgesia (minutes)	734	34.40	650	23.34	*<0.001
Table 3: Comparison of Duration of Analgesia in Each Group (minutes)					

The mean duration of analgesia in group A was 734 ± 34.4 min, which was longer and group B was 650 ± 23.34 min, which was found to be shorter with a p-value of < 0.001. Hence, the difference was statistically significant.

DISCUSSION

At Government Medical College in Thrissur, 70 patients had upper limb orthopaedic procedures under supraclavicular brachial plexus block. Patients were divided into two groups: Group A underwent supraclavicular brachial plexus block with 0.5% bupivacaine 20 ml and 1 mcg/kg of dexmedetomidine, whereas Group B received the same treatment but with 0.5% bupivacaine 20 ml and 1 mcg/kg of fentanyl. The purpose of the study was to compare the effectiveness of fentanyl against dexmedetomidine as a brachial plexus block adjuvant to bupivacaine.

The demographic information for Groups A and B was similar. Within the study group, the average age was 36.82 ± 12.18. The mean height among the study group was 166.26 ± 7.88. The mean weight was 65.27 ± 8.17.

40% of the study group consisted of females and 60% of males. The distribution of ASA PS classes 1 and 2 among the study group was 55% and 45% respectively.

Sensory blocks were compared between the two groups. Onset of sensory block was 6.43 ± 1.1.22 min in group A and 10.03 ± 1.25 min in group B. the p-value was < 0.001 and the result was statistically significant.

The length of the sensory block was 487.33 ± 48.28 minutes for group B and 538.67 ± 48.62 minutes for group A. The p-value was less than 0.001, indicating the statistical significance of the outcome.

The onset of the motor block was 9.7 ± 0.97 min in group A and 12.93 ± 1.82 min in group B. The p-value was < 0.001, and the result was statistically significant.

In group A, the motor block lasted 528 ± 48.02 minutes, while in group B, it lasted 460 ± 34.74 minutes. The p-value was less than 0.001, indicating the statistical significance of the outcome.

In group A, analgesia lasted 734 ± 34.4 minutes, while in group B, it lasted 650 ± 23.34 minutes. The outcome was statistically significant, with a p-value of less than 0.001. Renuka Holyachi *et al.* in 2017[7] conducted a comparative study between dexmedetomidine and fentanyl as adjuvants to ropivacaine. Eighty patients who were scheduled for elective upper limb procedures and had American Society of Anesthesiologists grade I/II status were divided into two groups at random. Patients in group A were given 30 mL of 0.5% ropivacaine mixed with 1 μg kg−1 dexmedetomidine for a supraclavicular brachial block guided by USG. Patients in group B were given 30 mL of 0.5% ropivacaine mixed with 1 μg kg−1 fentanyl. Notable were the beginning and length of the sensory and motor block, the need for rescue analgesia, and any unfavourable events that occurred during the perioperative phase.

They discovered that the dexmedetomidine group had sensory blocking at 13.95 ± 1.34 minutes, whereas the fentanyl group experienced it at 14.18 ± 1.41 minutes. Regarding the length of the sensory blockage, there was a statistically significant difference (p<0.0001): 801.75 ± 46.07 min with dexmedetomidine versus 590.25 ± 40.41 min with fentanyl. Compared to group B, which experienced motor blockage for 456.75 ± 32.93 minutes, group A experienced it for 649.56 ± 42.73 minutes, a very statistically significant difference.

They found that when added to ropivacaine in supraclavicular brachial plexus block, dexmedetomidine makes the sensory and motor block last longer than fentanyl and doesn't cause any major side effects. Furthermore, it provides better pain relief after surgery. The results were comparable to our study.

Swastika Swaro et al., Daisy Kurian et al., and Swarna Nanerjee et al. on a comparative study between dexmedetomidine and fentanyl as adjuvants to bupivacaine in supraclavicular brachial plexus block: a randomized double blind prospective study.

In a randomised, double-blinded procedure, fifty Physical Status I and II patients, according to the American Society of Anesthesiologists were scheduled for elective upper limb procedures under supraclavicular brachial plexus block. The patients were split into two equal groups. Patients in groups BF and BD were given 30 millilitres of bupivacaine mixed with 50 Î¼g of fentanyl and 50 Î¼g of dexmedetomidine, respectively. Both groups' anaesthesia and analgesia characteristics were evaluated.

They discovered that the length of the motor and sensory blocks was 441.52 ± 48.46 minutes and 452.96 ± 77.12 minutes in Group BD, respectively, whereas it was 363.4Â ± 38.36 minutes and 357Â ± 36.77 minutes in Group BF. Between the two groups, there was a statistically significant difference in the start of sensory and motor blocks. Group BD experienced a longer duration of analgesia (time to require rescue analgesia) (471.44 ± 65.88 minutes vs. 366.48 ± 38.02 minutes) with statistical significance (p < 0.0001). With the exception of a grade 3 sedation score that was higher in group BD, there were very few hemodynamic disruptions and adverse effects in either group.

They came to the conclusion that adding dexmedetomidine to bupivacaine in supraclavicular brachial plexus block prolonged both the duration of analgesia and the sensory and motor block more than adding fentanyl. In our study, we also observed similar findings.

In upper extremity orthopaedic surgery, Sane et al evaluated the impact of dexmedetomidine with bupivacaine vs. bupivacaine alone on sensory and motor block duration, pain score, and hemodynamic fluctuations in the supraclavicular block. Sixty individuals, ages 20 to 60, participated in the study.

Patients in the dexmedetomidine group (intervention group) received 39 ml of bupivacaine (0.25%) + 0.75 μg/kg dexmedetomidine (total volume 40 ml). Patients in the control group received 39 ml of 0.25% bupivacaine + 1 ml of normal saline (total volume 40 ml). In patients receiving just bupivacaine, the mean start time of sensory and motor block was 31.03 ± 9.65 min and 24.66 ± 9.2 min, respectively. In the group receiving dexmedetomidine, the mean onset times were around 21.36 ± 8.34 min and 15.93 ± 6.36 minutes. Both groups saw comparable changes in mean arterial blood pressure and heart rate. In the intervention group, sensory and motor block durations, as well as the initial analgesia request time, were greater. For a whole day, the intervention group experienced less postoperative discomfort.

They came to the conclusion that bupivacaine and dexmedetomidine lengthened the period of numbness and immobility and slowed the development of sensory and motor blocks. Dexmedetomidine also considerably decreased postoperative pain when supraclavicular blocks were performed with bupivacaine.

Mohamed Ahmed Hamed et al.[4] at Fayoum University Hospital, about the comparison between dexmedetomidine and fentanyl as adjuvants to 0.5% bupivacaine in a prospective randomised controlled double-blinded clinical study.

Sixty patients, between 18 and 50 years old, who were scheduled for upper limb surgery and had physical status classes I and II on the American Society of Anesthesiologists were randomly assigned to three research groups, each with twenty patients: C Group: up to a 40 mL volume limit, get 0.5 mL/kg. The bupivacaine dosage was 1.5 mg/kg. D Group: 1 mcg/kg of dexmedetomidine plus bupivacaine as the control group. F Group: 1 mcg/kg of fentanyl plus bupivacaine as the control group. Patients were monitored for side effects, postoperative pain, duration of analgesia, and onset and duration of sensory and motor blockage.

They discovered that in the D group ($p < 0.001$) and F group ($p < 0.001$), the duration of the block was considerably prolonged and the start time of sensory and motor blockade was decreased. Additionally, the D group's postoperative analgesia lasted 13.5 hours longer than that of the F group (8.3 hours) and the C group (7.5 hours). Two patients in the D group experienced bradycardia and hypotension, whereas the F group experienced vomiting and nausea.

With an α2:α1 binding selectivity ratio of 1620:1, which is lower than clonidine's 220:1 ratio, dexmedetomidine, the pharmacologically active d-isomer of medetomidine, is a highly selective and specific α2 adrenoceptor agonist that reduces the undesirable side effects of α1 receptors. The central nervous system (CNS) releases less norepinephrine when α2 adrenoceptors are postsynaptically activated, which stops the transmission of pain signals. This also reduces heart rate and blood pressure (HR and BP).[8]

CONCLUSION

Based on the onset and duration of sensory block, motor block, and duration of analgesia, we examined the effects of adding dexmedetomidine vs. fentanyl as adjuvants to 0.5% Bupivacaine in supraclavicular brachial plexus block for upper limb orthopaedic procedures. The study concludes that, in comparison to 1 mcg/kg of fentanyl, the addition of 1 mcg/kg of dexmedetomidine to 0.5% Bupivacaine greatly reduces the onset of sensory and motor block, as well as lengthens the duration of both.

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RESEARCH ARTICLE
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A COMPARISON OF EFFICACY OF BETAMETHASONE GEL V/S LIGNOCAINE JELLY APPLIED OVER ENDOTRACHEAL TUBE CUFF AS PROPHYLAXIS AGAINST INTUBATION ASSOCIATED THROAT COMPLICATIONS

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ABSTRACT

BACKGROUND: This study was undertaken to compare the effectiveness of application of an endotracheal tube cuff with betamethasone gel and lignocaine jelly in reducing the incidence and severity of postoperative sore throat,hoarseness and cough.

METHODS: After receiving approval from the institutional ethics committee and signed informed consent from the study participants, a prospective comparative study based in a hospital was carried out among 100 patients (50 in each groups) who underwent for elective chest, limb & abdominal surgeries under general anesthesia at the Department of Anaesthesiology, Government Medical College, Thrissur, between January 2021 and January 2022.100 patients will be divided into two equal groups – group B is betamethasone group, who will receive betamethasone 0.05% water miscible gel applied over ETT and group D is lignocaine group,who will receive lignocaine 2% water miscible jelly applied on ETT & In the post-anaesthesia care unit, a blinded anaesthesiologist will interview all patients on postoperative sore throat, cough, and hoarseness of voice at 1, 6, 12, and 24 hours after operation using the four point scales.

RESULTS: The severity of post-operative sore throat, severity of hoarseness and post extubation cough among the two groups showed Group D and Group B had most of them in minimal sore throat at 1-hour post op, but moderately sore throat was higher in group D. Similar pattern was seen in 6 hours, 12 hours and 24 hours; this was statistically significant.Hence Betamethasone (group B) usage for endotracheal intubation showed to be better than Lignocaine (group D) when compared to severity of post-operative sore throat, severity of hoarseness and post extubation cough.

CONCLUSION: The study's findings also show that, Betamethasone (group B) usage for endotracheal intubation showed to be better than Lignocaine (group D) when compared to severity of post-operative sore throat, severity of hoarseness and post extubation cough.

KEYWORDS: Intubation associated throat complications,Betamethasone, Lignocaine, ETT cuff.

INTRODUCTION

Tracheal intubation is often required during general anaesthesia to secure the airway and facilitate ventilation. Tracheal intubation is associated with an increase of polymorphonuclear cells in the tracheal tissue and plasma levels of interleukin-6, suggesting an inflammatory response to the presence of the endotracheal tube itself or to some aspect of the intubation process.The process of laryngoscopy and placement of tracheal tube is associated with postoperative throat complications such as sore throat, cough and hoarseness of voice. 1,2,3 The incidence of these throat complications vary between 15% and 94%.Although not typically incapacitating, these sequelae can be very discomforting and often a major source of patients' dissatisfaction post-operatively.Postoperative sore throat, cough, and hoarseness of voice is common,uncomfortable, distressing sequelae after tracheal intubation. It was postulated that these effects are because of irritation and inflammation of the airway.3 Although local anaesthetic jelly along with its lubricating properties limits the potential damage to the tracheal mucosa by suppressing bucking on the tracheal tube, its role in prevention of postoperative sore throat is inconclusive as it does not possess any intrinsic anti-inflammatory action.4,5

Postoperative throat complications following tracheal intubation are thought to result from a number of events. One mechanism is trauma to the pharyngotracheal mucosa following laryngoscopy and placement of endotracheal tube (ETT). Prolonged contact of the ETT with the vocal cords and posterior pharyngeal wall may also result in pathological changes such as epithelial loss,glottis haematoma and/or oedema, submucosal tear and contact granuloma. These,in addition to neuropraxia of the recurrent laryngeal nerve due to compression from excessive intracuff pressure have been implicated in the pathogenesis of postoperative hoarseness.

Several medications and non-pharmacological methods have shown to reduce the incidence of airway symptoms with variable success rate.These inconsistent results suggest the likelihood of multiple factors associated with these symptoms like endotracheal tube size, cuff design, duration of surgery, etc.Whatever the cause, the main mechanism postulated is irritation and inflammation of the airway.6,7 Although lidocaine is used for airway anaesthesia, its use for postoperative airway symptoms have shown variable results .8,9,10 Steroids are known for their anti-inflammatory action. Betamethasone gel is a long acting water soluble glucocorticoid that has been used topically for the treatment of inflammatory lesions of the oral mucosa. It should, thus, provide lubrication as well as anti-inflammatory effect if used for lubrication of the endotracheal tube.

Betamethasone is a synthetic glucocorticoid with metabolic,immunosuppressive and anti inflammatory activities. Betamethasone binds to specific intracellular glucocorticoid receptors and subsequently binds to DNA to modify gene expression. The synthesis of anti-inflammatory proteins is induced while the synthesis of certain inflammatory mediators is inhibited. As a result, there is an overall reduction in chronic inflammation and autoimmune reactions

Lignocaine is a synthetic amino-ethylamide with local anaesthetic property.Lignocaine stabilizes the neuronal membrane by binding to and inhibiting voltage gated sodium channels, thereby inhibiting the ionic fluxes required for the initiation and conduction of impulses and effecting local anaesthesia. The present study was undertaken to compare the effectiveness of application of an endotracheal tube with betamethasone gel and lignocaine jelly with using an unlubricated endotracheal tube in reducing the incidence and severity of postoperative sore throat, hoarseness and cough.

OBJECTIVES

Betamethasone gel or lignocaine jelly applied over ETT cuff are commonly used prophylactic methods for intubation assosciated throat complications in Govt medical college, Thrissur. The Present study aims to compare the effects of betamethasone gel and lignocaine jelly applied over endotracheal tube cuff as prophylaxis against intubation associated throat complications.

METHODS

After receiving approval from the institutional ethics committee and signed informed consent from the study participants, a prospective comparative study based in a hospital was carried out among 100 patients (50 in each groups) who underwent posted for elective chest, limb & abdominal surgeries under general anesthesia at the Department of Anaesthesiology, Government Medical College, Thrissur, between January 2021 and January 2022.100 patients will be divided into two equal groups – group B is betamethasone group, who will receive betamethasone 0.05% water miscible gel applied over ETT and group D is lignocaine group,who will receive lignocaine 2% water miscible jelly applied on ETT & In the post-anaesthesia care unit, a blinded anaesthesiologist will interview all patients on postoperative sore throat, cough, and hoarseness of voice at 1, 6, 12, and 24 hours after operation using the four point scales.

Inclusion Criteria

1. Patients of either sex ASA Grade l & ll
2. MMPC 1&2
3. Age between 20 & 60 years.
4. Body weight between 40 – 80 kg.
5. Intubated in a single attempt.
6. Patients undergoing elective general surgery,orthopaedic surgery& gynaecological surgeries
7. Duration of mechanical ventilation < 3hrs.

Exclusion Criteria

1. Patients not willing to participate in the study
2. Patients with history of drug allergy
3. Patient with an anticipated difficult airway
4. Patients with hypertension, cardiac, renal, hepatic, cerebral disease; peripheral vascular disease; bradycardia; patients on beta blockers; and obese, pregnant and nursing mothers.
5. Duration of mechanical ventilation > 3 hours

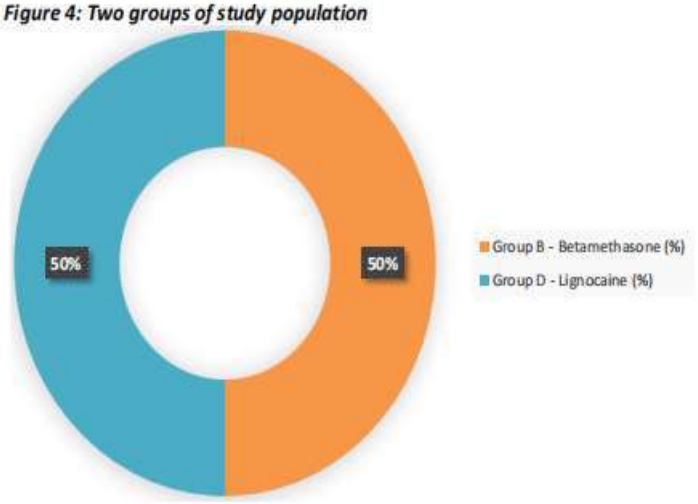
Statistical Methods

The data of study subjects and the outcome will be statistically analyzed and the appropriate statistical test, will be applied using the latest version of SPSS software. ‘p’ value less than 0.01 will be considered significant.

RESULTS

In this study the patients posted for elective chest, limb & abdominal surgeries under general anaesthesia. In total 50 each were included in 2 groups with betamethasone (Group B) and lignocaine (Group D). The results are as follows:

Figure 4: Two groups of study population



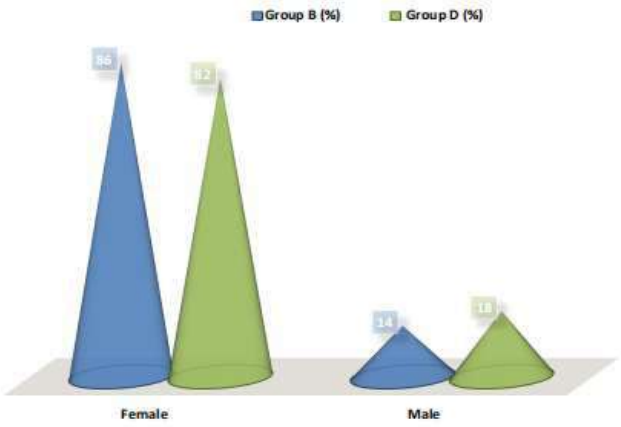
Gender distribution among the two groups

The gender distribution among the two groups showed females were higher in group B and males were higher in group D. As this difference was not statistically significant, hence gender is same in both groups

Table 1: Gender distribution among the two groups

Gender	Group B (n)	(%)	Group D (n)	(%)
Female	43	86.0	41	82.0
Male	7	14.0	9	18.0
Chi-square test value 0.298, d.f 1; p value 0.585				

Figure 5: Gender distribution among the two groups



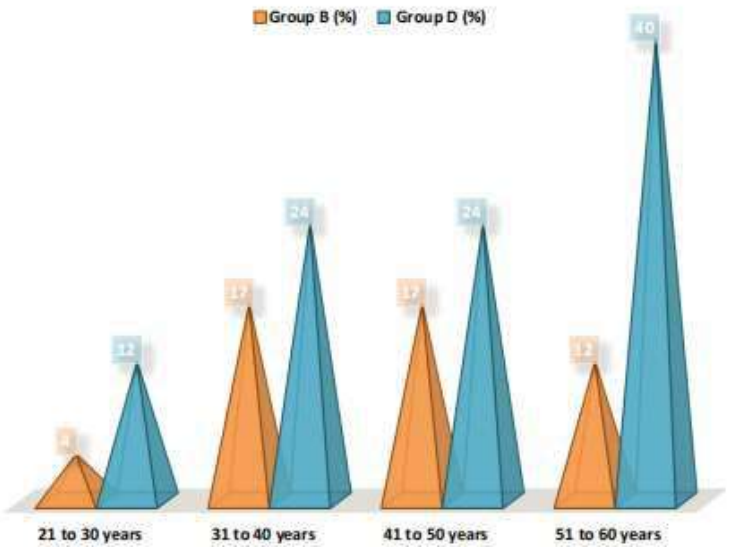
Age wise distribution among the two groups

The age distribution showed group B had higher number of people in 31 to 40 years and 41 to 50 years. The Group D had majority of the patients in the age group 51 to 60 years. As this differencewas not statistically significant, hence age groups are same in both groups.

Table 2: Age wise distribution among the two groups

Age groups (years)	Group B (n)	(%)	Group D (n)	(%)
21 to 30 years	4	8.0	6	12.0
31 to 40 years	17	34.0	12	24.0
41 to 50 years	17	34.0	12	24.0
51 to 60 years	12	24.0	20	40.0
Chi-square test value 4.124, d/f 3; p value 0.248				

Figure 6: Age wise distribution among the two groups



ASA classification among the two groups

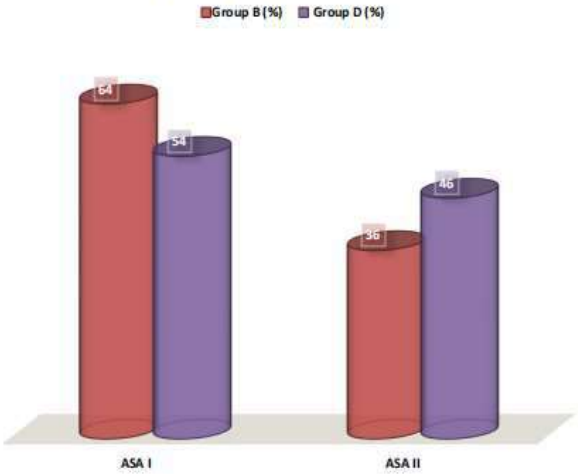
The ASA classification was studied and ASA I was higher in Group B and similarly group D also had higher numbers than ASA II in both groups. As this difference was not statistically significant, hence ASA classification is same in both groups.

Table 3: ASA classification among the two groups

ASA classification	Group B (n)	(%)	Group D (n)	(%)
ASA I	32	64.0	27	54.0
ASA II	18	36.0	23	46.0
Chi-square test value 1.033, d.f 1; p value 0.309				

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Figure 7: Age wise distribution among the two groups



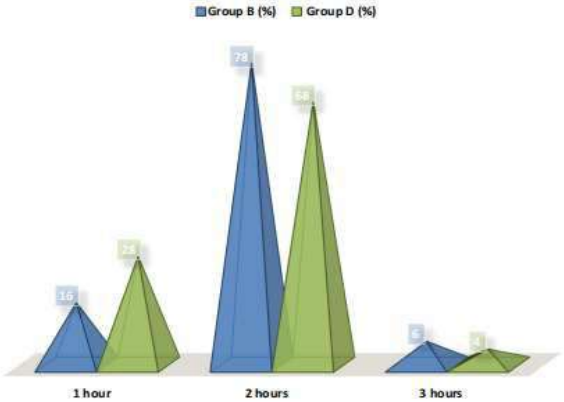
Duration of surgery among the two groups

The duration of surgery showed in both the groups nearly three forth had 2 hours of surgery, and only very few patients in both groups had 3 hours or more duration of surgery. As this difference was not statistically significant, hence age duration of surgery is same in both groups.

Table 4: Duration of surgery among the two groups

Duration of surgery	Group B (n)	(%)	Group D (n)	(%)
1 hour	8	16.0	14	28.0
2 hours	39	78.0	34	68.0
3 hours	03	06.0	02	04.0
Chi-square test value 2.179, d.f 2; p value 0.336				

Figure 8: Duration of surgery among the two groups



Patient weight among the two groups

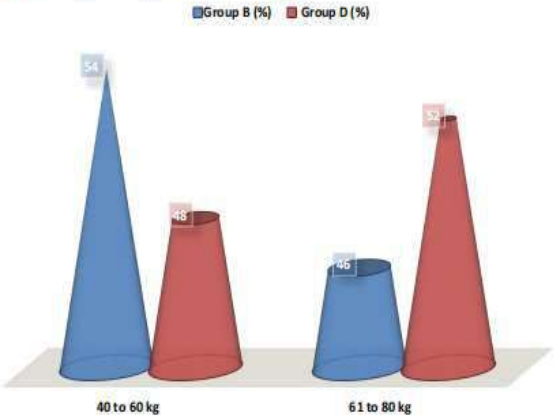
The patient weights showed equal or similar number of patients in group B and group D with 40 to 60 kg and 61 to 80 kg. As this difference was not statistically significant, hence patient's weight is same in both groups

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Table 5: Patient weight among the two groups

Patient weight	Group B (n)	(%)	Group D (n)	(%)
40 to 60 kg	27	54.0	24	48.0
61 to 80 kg	23	46.0	26	52.0
Chi-square test value 360, d.f 1; p value 0.548				

Figure 9: Patient weight among the two groups



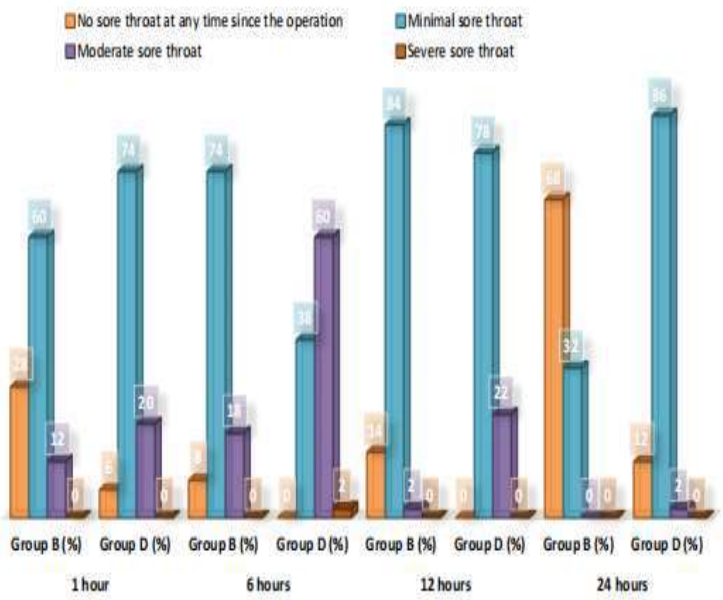
Severity of post-operative sore throat among the two groups

The severity of post-operative sore throat among the two groups showed Group D and Group B had most of them in minimal sore throat at 1-hour post op,but moderately sore throat was higher in group D. Similar pattern was seen in 6 hours, 12 hours and 24 hours; this was statistically significant.

Table 6: Severity of post-operative sore throat among the two groups

Severity of post-operative sore throat 1 hour	Group B (n)	(%)	Group D (n)	(%)	Fischer's exact
No sore throat at any time since the operation	14	28.0	3	6.0	
Minimal sore throat	30	60.0	37	74.0	*<0.001*
Moderate sore throat	6	12.0	10	20.0	
Severity of post-operative sore throat 6 hours	**Group B (n)**	**(%)**	**Group D (n)**	**(%)**	**Fischer's exact**
No sore throat at any time since the operation	4	8.0	0	0	
Minimal sore throat	37	74.0	19	38.0	*<0.001*
Moderate sore throat	9	18.0	30	60.0	
Severe sore throat	0	0	1	2.0	
Severity of post-operative sore throat 12 hours	**Group B (n)**	**(%)**	**Group D (n)**	**(%)**	**Fischer's exact**
No sore throat at any time since the operation	7	14.0	0	0	
Minimal sore throat	42	84.0	39	78.0	*<0.001*
Moderate sore throat	1	2.0	11	22.0	
No sore throat at any time since the operation	34	68.0	6	12.0	
Minimal sore throat	16	32.0	43	86.0	*<0.001*
Moderate sore throat	0	0	1	2.0	

Figure 10: Severity of post-operative sore throat among the two groups



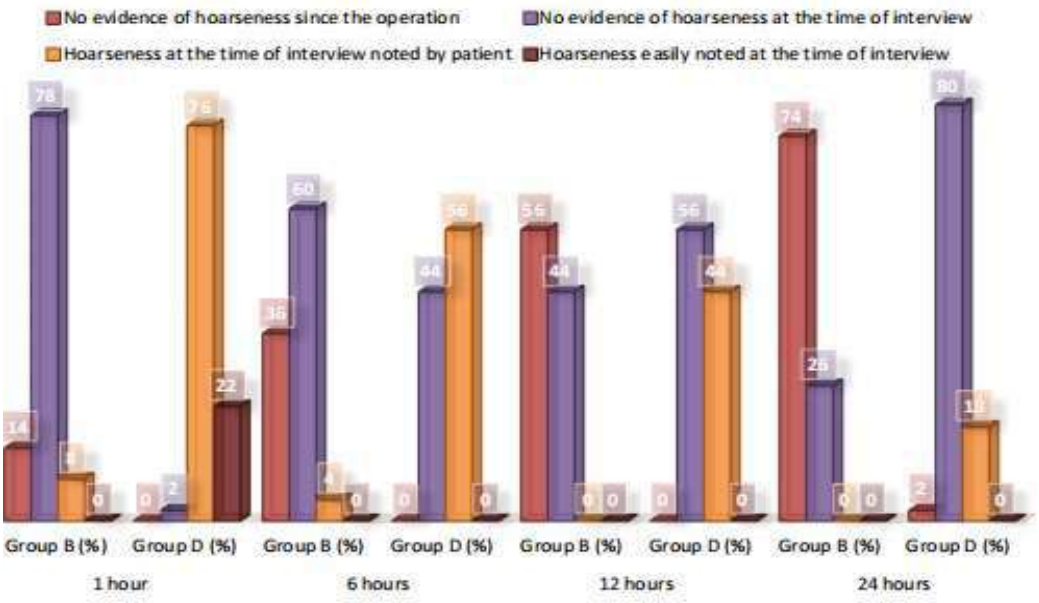
Severity of hoarseness among the two groups

The severity of hoarseness among the Group B and Group D showed at 1-hour group D had hoarseness at the time of interview noted by patient and group B had more patients with no evidence of hoarseness at the time of interview; this difference was statistically significant. At 6 hours, 12 hours and 24 hours a similar picture was noted, and this difference was statistically significant.

Table 7: Severity of hoarseness among the two groups

Severity of hoarseness 1 hour	Group B (n)	(%)	Group D (n)	(%)	Fischer's exact
No evidence of hoarseness since the operation	7	14.0	0	0	<0.001
No evidence of hoarseness at the time of interview	39	78.0	1	2.0	
Hoarseness at the time of interview noted by patient	4	8.0	38	76.0	
Hoarseness easily noted at the time of interview	0	0	11	22.0	
Severity of hoarseness 6 hours	**Group B (n)**	**(%)**	**Group D (n)**	**(%)**	**Fischer's exact**
No evidence of hoarseness since the operation	18	36	0	0	<0.001
No evidence of hoarseness at the time of interview	30	60	22	44	
Hoarseness at the time of interview noted by patient	2	4	28	56	
Severity of hoarseness 12 hours	**Group B (n)**	**(%)**	**Group D (n)**	**(%)**	**Fischer's exact**
No evidence of hoarseness since the operation	28	56.0	0	0	<0.001
No evidence of hoarseness at the time of interview	22	44.0	28	56.0	
Hoarseness at the time of interview noted by patient	0	0	22	44.0	
Severity of hoarseness 24 hours	**Group B (n)**	**(%)**	**Group D (n)**	**(%)**	**Fischer's exact**
No evidence of hoarseness since the operation	37	74.0	1	2.0	<0.001
No evidence of hoarseness at the time of interview	13	26.0	40	80.0	
Hoarseness at the time of interview noted by patient	0	0	9	18.0	

Figure 11: Severity of hoarseness among the two groups



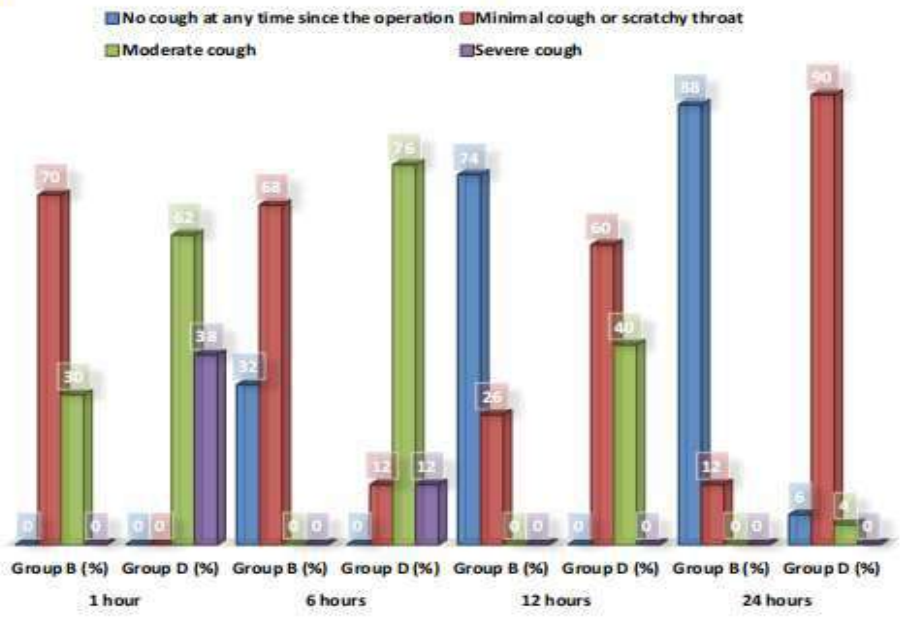
Post extubation cough among the two groups

The post extubation cough among the two groups showed the post extubation cough at 1 hour the group B had minimal cough & moderate cough however the Group D had more patients with moderate & severe cough; this difference was statistically significant. There was similar pattern see for post extubation cough at 6 hours, 12 hours and 24 hours which was statistically significant among the two groups.

Table 8: Post extubation cough among the two groups

Post extubation cough 1 hour	**Group B (n)**	**(%)**	**Group D (n)**	**(%)**	**Fischer's exact**
Minimal cough or scratchy throat	35	70.0	0	0	*<0.001*
Moderate cough	15	30.0	31	62.0	
Severe cough	0	0	19	38.0	
Post extubation cough 6 hours	**Group B (n)**	**(%)**	**Group D (n)**	**(%)**	**Fischer's exact**
No cough at any time since the operation	16	32.0	0	0	*<0.001*
Minimal cough or scratchy throat	34	68.0	6	12.0	
Moderate cough	0	0	38	76.0	
Severe cough	0	0	6	12.0	
Post extubation cough 12 hours	**Group B (n)**	**(%)**	**Group D (n)**	**(%)**	**Fischer's exact**
No cough at any time since the operation	37	74.0	0	0	*<0.001*
Minimal cough or scratchy throat	13	26.0	30	60.0	
Moderate cough	0	0	20	40.0	
Post extubation cough 24 hours	**Group B (n)**	**(%)**	**Group D (n)**	**(%)**	**Fischer's exact**
No cough at any time since the operation	44	88.0	3	6.0	*<0.001*
Minimal cough or scratchy throat	6	12.0	45	90.0	
Moderate cough	0	0	2	4.0	

Figure 12: Post extubation cough among the two groups



DISCUSSION

In this study the patients posted for elective chest, limb & abdominal surgeries under general anaesthesia. In total 50 each were included in 2 groups with betamethasone (Group B) and lignocaine (Group D). In our study the gender distribution, age distribution, ASA classification, duration of surgery and the patient weights showed equal or similar number of patients in group B and group D and was statistically non-significant, hence both groups had similar baseline characteristics. In the reviewed studies by P. A. Sumathi et al.67 had similar baseline characteristics which were similar in both groups. Parineeta Thapa et al.68 had a similar prospective, randomized, single-blind comparative study carried out among 120 ASA I and II patients aged 18–65 years undergoing elective surgery under general anaesthesia with endotracheal intubation. Adamu Muhammad Sarki et al.69 also had similar baseline characteristics.

In our study the severity of post-operative sore throat among the two groups showed Group D and Group B had most of them in minimal sore throat at 1-hour post op, but moderately sore throat was higher in group D. Similar pattern was seen in 6 hours, 12 hours and 24 hours; this was statistically significant. In this study the severity of hoarseness among the Group B and Group D showed at 1-hour group D had hoarseness at the time of interview noted by patient and group B had more patients with no evidence of hoarseness at the time of interview; this difference was statistically significant. At 6 hours, 12 hours and 24 hours a similar picture was noted, and this difference was statistically significant. In our study the post extubation cough among the two groups showed the post extubation cough at 1 hour the group B had minimal cough & moderate cough however the Group D had more patients with moderate & severe cough; this difference was statistically significant. There was similar pattern see for post extubation cough at 6 hours, 12 hours and 24 hours which was statistically significant among the two groups.

Similar pattern was seen in the reviewed studies by P. A. Sumathi et al.67 results showed in the first 24 h after surgery, the incidence of postoperative sore throat was 40, 100, and 100%; cough was 6, 40, and 28%; and hoarseness of voice was 4.1, 32.9, and 50%, for the betamethasone, lidocaine and control groups, respectively.

The incidence of postoperative sore throat, cough, and hoarseness of voice was significantly lower in the betamethasone group compared with the other two groups (P,0.05). It Concluded that a wide spread application of betamethasone gel on the tracheal tube decreases the incidence and severity of postoperative sore throat, cough, and hoarseness of voice. Another study by Parineeta Thapa et al.68 . At 24 hr following extubation, group B had the lowest incidence of postoperative sore throat among

the three groups (group B: 12.5% vs group L: 37.5% vs group C: 25%; p = 0.036). Severity of postoperative sore throat at 24 h was less with betamethasone (score 0: 87.5%, 1: 10%) compared with lidocaine (score 0: 62.5%, 1: 37.5%) and control (score 0:75%, 1: 20%) (p = 0.006). Observations at other times and of other variables were comparable. It concluded that Wide spread application of 0.05% betamethasone gel to lubricate the endotracheal tube significantly reduces the incidence and severity of sore throat at 24 h of extubation but not of hoarseness or cough. Adamu Muhammad Sarki et al.69 showed that the incidence and severity of sore throat, cough and hoarseness were then assessed by a blinded interviewer at the 6th, 24th and 48th h postoperative. Results were as follows**.** The highest incidence of throat complaints was recorded during the first evaluation at the 6th h postoperative. The incidence of sore throat was 36.7%, 66.7% and 80%; cough was 13.3%, 26.7% and 43.3%; and hoarseness was 23.3%, 30% and 46.7%, for the betamethasone, lidocaine and KY jelly groups, respectively.

Betamethasone gel demonstrated significant superiority over lidocaine and KY jellies in the prevention of sore throat (P = 0.002), cough (P = 0.03) and hoarseness (P = 0.03) throughout the study. Duration of tracheal intubation longer than 2 h was associated with significant increase in the incidence of throat complaints (P < 0.001). Another study showed a different results by Mahnaz Narimani et al.70 showed patients were assessed for postoperative sore throat, cough, and hoarseness at 1, 6, and 24 hours after surgery. Results were as follows. In the first hour after surgery, the patients who received lidocaine or betamethasone had a significantly greater incidence of sore throat than the patients who received distilled water (RR = 2.9). In the sixth hour after surgery, there was a better effect of distilled water on reducing the incidence of sore throat, but no significant differences between the three groups were seen 24 hours after surgery. The incidence of cough was significantly lower in the distilled water group (P < .02) except at the first and 24 hours postoperative when the incidence of cough was similar. The incidence of hoarseness was similar between the three groups at 1, 6, and 24 hours after surgery.

Another related study by Aatir Fayyaz et al.71 showed of the 120 patients, there were 60(50%) each in the two groups. The mean intubation time was 5.58+-1.31 hours in group 1and 5.43+-1.21 hours in group 2. Besides, 7(11.7%) patients developed mild sore throat and 3(5.0%) moderate sore throat in group 1,whereas 13(21.7%) patients developed mild sore throat, 7(11.6%) moderate and 2(3.3%) severe sore throat after one hour of extubation (p=0.04). After 6 hours, there were 2(3.3%) patients with moderate and 1(1.7%) with severe sore throat in group 1 compared to 8(13.3%) with moderate and 4(6.7%) with severe sore throat in group 2. After 24 hours,5(8.3%) patients developed mild and 2(3.3%) moderate sore throat in group 1 compared to 14(23.7%) patients with mild sore throat, 5(8.5%) with moderate and 1(1.7%) with severe throat in group 2. Generalized estimating equation analysis showed a significant positive association between application of lidocaine gel on endotracheal tube and severity of sore throat (p<0.001).

It concluded that local application of betamethasone gel was associated with reduced risk of post-operative sore throat as compared to local application of lidocaine gel on the endotracheal tube. Reviewed studies by Dr M. Raja et al.72 that in the post-anaesthesia care unit, all patients were interviewed on postoperative sore throat, cough, and hoarseness of voice at 0, 6, and 24 h after surgery. A wide spread application of betamethasone gel (B) on the endotracheal tube decreases the incidence and severity of postoperative sore throat, cough, and hoarseness of voice as compared to lignocaine group(L) and control group (c).

CONCLUSION

In our study the gender distribution, age distribution, ASA classification, duration of surgery and the patient weights showed equal or similar number of patients in group B and group D and was statistically nonsignificant, hence both groups had similar baseline characteristics.In this study the severity of post-operative sore throat, severity of hoarseness and post extubation cough among the two groups showed Group D and Group B had most of them in minimal sore throat at 1-hour post op, but moderately sore throat was higher in group D. Similar pattern was seen in 6 hours, 12 hours and

24 hours; this was statistically significant.Hence Betamethasone (group B) usage for endotracheal intubation showed to be better than Lignocaine (group D) when compared to severity of post-operative sore throat, severity of hoarseness and post extubation cough.

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Research Article

Effect of Low-Dose Dexmedetomidine Infusion on Hemodynamic Response and Postoperative Analgesia in Laparoscopic Cholecystectomy

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Abstract: ***Background***: Laparoscopic cholecystectomy is a widely performed surgical procedure, favored for its minimally invasive nature and faster recovery. However, the physiological stress response triggered by surgery and anesthesia can impact hemodynamic stability. Dexmedetomidine, a selective alpha-2 adrenergic agonist, has shown efficacy in attenuating the perioperative stress response by reducing serum catecholamine levels. This study evaluates the effect of two different low-dose dexmedetomidine infusions on intraoperative hemodynamics and postoperative analgesia. ***Methods***: Fifty ASA Physical Status I and II patients undergoing elective laparoscopic cholecystectomy were randomized into two groups. Group A received dexmedetomidine infusion at 0.2 mcg/kg/hr, while Group B received 0.4 mcg/kg/hr. No loading dose was given. Hemodynamic parameters, including heart rate and MAP (Mean Arterial Pressure) were recorded at baseline, 15 minutes after infusion initiation, post-induction, post-intubation, post-pneumoperitoneum creation, and post-extubation. Postoperative pain was assessed using the VAS (Visual Analogue Scale), and time to first rescue analgesia (tramadol) and total 24-hour analgesic requirement were documented. ***Results***: Both dexmedetomidine infusion rates maintained stable intraoperative hemodynamics. However, the 0.4 mcg/kg/hr group showed better control of heart rate and MAP at key surgical milestones. Additionally, patients in this group experienced prolonged pain relief and required significantly less cumulative analgesia in the first 24 hours postoperatively. ***Conclusion***: Continuous low-dose dexmedetomidine infusion without a bolus effectively blunts the perioperative stress response during laparoscopic cholecystectomy. A higher infusion rate of 0.4 mcg/kg/hr provides superior intraoperative hemodynamic control and enhanced postoperative analgesia compared to 0.2 mcg/kg/hr.

Keywords: Dexmedetomidine, Laparoscopic Cholecystectomy, Hemodynamic Response, Postoperative Analgesia, Alpha-2 Agonist.

INTRODUCTION

Laparoscopic cholecystectomy is among the most frequently performed surgeries today, offering benefits such as a shorter hospital stay, minimal incisions, reduced postoperative pain, and quicker recovery. Despite these advantages, it still triggers a stress response due to surgical and anesthetic stimuli.[1]

Modern anesthetic practices aim to suppress sympathetic discharge and maintain perioperative hemodynamic stability. Various pharmacologic agents-opioids, beta-blockers, and centrally acting sympatholytics-have been employed to attenuate this stress response. Among these, alpha-2 adrenergic agonists are notable for their anxiolytic, sedative, sympatholytic, and analgesic-sparing properties.[1]

Inadequately controlled postoperative pain can lead to significant physiological and psychological morbidity, delayed recovery, prolonged hospitalization, and even the development of chronic pain.[2] Effective pain control improves patient satisfaction and recovery. Preemptive analgesia has been proposed to reduce overall analgesic needs and enhance pain outcomes.[3]

Dexmedetomidine, a selective alpha-2 agonist, has eight times greater affinity for alpha-2 receptors compared to clonidine. Its intravenous use has been shown to reduce serum catecholamine levels by up to 90%, thereby blunting the hemodynamic stress responses to laryngoscopy, intubation, pneumoperitoneum, and extubation. It also provides sedation without respiratory depression and lowers postoperative analgesic requirements.[1] Approved by the FDA in 1999 for short-term sedation and analgesia in ICU settings, dexmedetomidine acts via alpha-2A, 2B, and 2C receptors, mediating hypotension, bradycardia, sedation, and analgesia through central and spinal pathways.

This study aims to compare the effects of two maintenance infusion doses-0.2 mcg/kg/hr and 0.4 mcg/kg/hr-of dexmedetomidine in patients undergoing laparoscopic cholecystectomy, focusing on perioperative hemodynamic response and 24-hour postoperative analgesic requirements.

Aims and Objectives

This study aims to compare the perioperative hemodynamic responses, specifically mean arterial pressure and heart rate, between two groups of patients undergoing laparoscopic cholecystectomy who receive different maintenance infusion doses of dexmedetomidine (0.2 mcg/kg/hr and 0.4 mcg/kg/hr). Additionally, the study aims to evaluate the timing of the first requirement for

postoperative analgesia and the total analgesic consumption within the first 24 hours after surgery.

MATERIALS AND METHODS

Study Design

This prospective observational study was conducted in the Department of Anesthesiology at Government Medical College, Thrissur, over a period of one year from January 2020 to December 2020. The study population comprised patients undergoing elective laparoscopic cholecystectomy at the institution, with the objective of evaluating perioperative hemodynamic responses and postoperative analgesic requirements associated with two different doses of dexmedetomidine infusion.

Inclusion and Exclusion Criteria

The study included patients aged between 18 and 60 years of both genders, classified as ASA (American Society of Anesthesiologists) physical status I or II, who were scheduled to undergo elective laparoscopic cholecystectomy at Government Medical College, Thrissur. Patients who were unwilling to undergo surgery were excluded from the study.

Sample Size Calculation

d =|x1—x2|

$$n = \frac{(\sigma 1^2 + \sigma 2^2)(Z_\alpha + Z_\beta)^2}{d^2}$$

Power (beta) = 80% Alpha error = 5% mean BP after extubation was highest between two groups in the study done by Manne et al., in 2014 on low dose dexmeditomedine in patients undergoing laparoscopic cholecystectomy.[1]

X1 = 106.35, X2 = 98.30, σ1 = 12.45, σ2 = 6.82

Sample size = 25 each in both groups.

Data Collection Tools

Data were collected using a self-designed proforma to document patient demographics, pre-anesthetic evaluation, intraoperative hemodynamic parameters, and postoperative analgesic requirements. Monitoring equipment included multiparameter monitors, pulse oximeters, ECGs, and a cuff pressure monitor, used as required throughout the perioperative period.

Data Collection Procedure

After obtaining informed written consent and ethical clearance, patients were divided into two groups based on the dexmedetomidine infusion dose (0.2 mcg/kg/hr for Group 1 and 0.4 mcg/kg/hr for Group 2). Standard preoperative medications and fasting guidelines were followed. Dexmedetomidine infusion was prepared and administered by a senior anesthesia provider, and patients were monitored using standard protocols. Baseline and perioperative hemodynamic parameters (pulse rate, mean arterial pressure, and oxygen saturation) were recorded at defined intervals, along with intraoperative observations for bradycardia, tachycardia, hypotension, or hypertension. Anesthesia was induced and maintained using standard drugs and techniques. Time to extubation was noted. Postoperatively, patients were monitored for pain using the VAS, and the time to first rescue analgesia (tramadol) and total 24-hour analgesic requirement were recorded.

Statistical Analysis

Data were entered using Microsoft Excel and analyzed with SPSS software version 16. Continuous variables such as age, height, and weight were summarized using mean and SD (Standard Deviation), while categorical variables like gender and ASA physical status were expressed as proportions and compared between the two groups. Hemodynamic parameters, including SBP (Systolic Blood Pressure), DBP (Diastolic Blood Pressure), MAP (Mean Arterial Pressure), and HR (Heart Rate) were recorded at various predefined intraoperative time points. These parameters, along with the timing and dose of rescue analgesia, were summarized as mean ± SD. Comparisons between the two groups were made using independent (unpaired) t-tests. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Variable	Group 1 (n = 25)	Group 2 (n = 25)	P-Value
Age (Mean ± SD)	45.7 ± 2.6	43.1 ± 2.1	0.44
Gender (M/F)	10 / 15	11 / 14	0.77
ASA I / II (%)	72% / 28%	76% / 24%	0.74
Weight (kg)	59.2 ± 7.1	61.6 ± 5.4	0.18
Height (cm)	159.0 ± 6.8	157.8 ± 6.2	0.52

Table 1: Demographic and Baseline Characteristics of Participants

Table 1 summarizes the baseline demographic and physical parameters of the participants. Both groups were statistically comparable in terms of age, gender distribution, ASA classification, weight, and height.

Parameter	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	P-Value
Heart Rate (bpm)	95.4 ± 5.3	95.0 ± 5.5	0.84
Systolic BP (mmHg)	145.1 ± 7.6	144.9 ± 7.6	0.91
Diastolic BP (mmHg)	94.4 ± 4.8	92.2 ± 5.6	0.13
Mean Arterial Pressure	111.3 ± 5.0	109.7 ± 5.2	0.28

Table 2: Baseline Haemodynamic Parameters

Table 2 reveals no statistically significant differences in baseline haemodynamic parameters between the two groups, confirming physiological comparability before intervention.

Parameter	Group 1	Group 2	P-Value
Duration of Surgery (min)	94.3 ± 12.3	95.0 ± 11.4	0.83
Bradycardia Incidence	0 (0%)	8 (32%)	0.004
Hypotension Incidence	0 (0%)	18 (72%)	<0.001
Table 3: Duration of Surgery and Perioperative Events			

Table 3 illustrates equal duration of surgery in both groups. However, Group 2 showed a significantly higher incidence of bradycardia and hypotension post-infusion, indicating greater haemodynamic depression.

Time Point	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	P-Value
15 min after infusion	85.8 ± 4.7	74.8 ± 4.2	<0.001
1 min after induction	83.2 ± 5.3	75.7 ± 5.1	<0.001
1 min after laryngoscopy/intubation	88.2 ± 4.2	80.2 ± 4.5	<0.001
1 min of pneumoperitoneum	92.1 ± 3.1	85.1 ± 3.7	<0.001
15 min of pneumoperitoneum	94.4 ± 3.2	88.5 ± 2.5	<0.001
30 min of pneumoperitoneum	94.6 ± 3.5	90.2 ± 1.7	<0.001
45 min of pneumoperitoneum	94.9 ± 3.4	91.4 ± 2.1	<0.001
60 min of pneumoperitoneum	94.9 ± 3.5	92.6 ± 2.6	0.01
1 min after pneumoperitoneum	91.2 ± 2.7	92.2 ± 2.2	0.14
1 min after extubation	91.0 ± 3.6	89.4 ± 2.7	0.08
Table 4: Heart Rate at Different Time Points			

Table 4 tracks intraoperative heart rate trends. Group 2 consistently maintained lower heart rates up to 60 minutes of pneumoperitoneum, supporting the hypothesis of better sympathetic control.

Time Point	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	P-Value
15 min after infusion	99.6 ± 4.9	87.2 ± 4.7	<0.001
1 min after induction	94.9 ± 5.3	81.2 ± 4.7	<0.001
1 min after laryngoscopy/intubation	104.1 ± 5.5	87.8 ± 4.9	<0.001
1 min of pneumoperitoneum	107.5 ± 4.3	92.8 ± 4.3	<0.001
15 min of pneumoperitoneum	109.3 ± 4.9	95.6 ± 2.9	<0.001
30 min of pneumoperitoneum	108.5 ± 4.6	97.2 ± 2.8	<0.001
45 min of pneumoperitoneum	108.3 ± 2.8	99.0 ± 1.9	<0.001
60 min of pneumoperitoneum	107.5 ± 4.8	100.4 ± 2.3	<0.001
1 min after pneumoperitoneum	104.2 ± 4.4	98.3 ± 2.9	<0.001
1 min after extubation	106.8 ± 3.9	96.4 ± 3.6	<0.001
Table 5: MAP (Mean Arterial Pressure) at Different Time Points			

Table 5 highlights MAP trends across intraoperative phases. Group 2 maintained significantly lower MAP throughout, which aligns with their higher incidence of hypotension.

Parameter	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	P-Value
Time to first analgesia (min)	136 ± 30.1	361.2 ± 63.9	<0.001
Dose of rescue analgesia (mg)	236 ± 51.1	106 ± 16.5	<0.001
Table 6: Rescue Analgesia – Time and Dose			

Table 6 reveals that Group 2 required rescue analgesia much later and in a significantly lower dose, indicating better postoperative pain control.

Adverse Event	Group 1	Group 2	P-Value
Bradycardia	0 (0%)	8 (32%)	0.004
Hypotension	0 (0%)	18 (72%)	<0.001
Tachycardia	0 (0%)	0 (0%)	—
Hypertension	0 (0%)	0 (0%)	—
Table 7: Summary of Adverse Events			

Table 7 aggregates adverse event occurrences. Group 2 was more prone to bradycardia and hypotension, suggesting a need for vigilant intraoperative monitoring when using the same regimen.

DISCUSSION

Laparoscopic cholecystectomy has become the preferred surgical technique for treating gallstone disease, replacing the open approach due to its advantages, such as faster recovery, reduced postoperative pain, earlier return of bowel function, shorter hospital stay, and better cosmetic outcomes. However, despite its minimally invasive nature, it is still associated with significant postoperative pain-visceral, somatic, and shoulder pain due to diaphragmatic irritation. Visceral pain, most prominent in the first 24 hours postoperatively, is typically short-lived and unaffected by movement but aggravated by coughing. Shoulder pain, likely due to phrenic nerve irritation, can persist for up to three days.

Dexmedetomidine is a highly selective α2-adrenergic receptor agonist that provides sedation, anxiolysis, analgesia, and sympatholysis through action on α2A, α2B, and α2C receptors located in the brain and spinal cord. Activation of α2A receptors in the brainstem vasomotor center results in inhibition of norepinephrine release, leading to hypotension and bradycardia. Sedation is mediated via α2A and α2C receptors in the locus ceruleus, while analgesia results from suppression of substance P release in the spinal cord through α2A and α2C receptor activation.

Previous studies have highlighted the effectiveness of dexmedetomidine in controlling perioperative hemodynamic responses. Hall et al. demonstrated its dose-dependent sedative effects along with minimal respiratory depression.[4] Bakhamees et al. observed that dexmedetomidine reduced anesthetic and opioid requirements while maintaining stable heart rate and MAP in morbidly obese patients undergoing laparoscopic bariatric surgery.[5] Bhattacharjee et al. also reported superior intraoperative and postoperative hemodynamic control in patients undergoing laparoscopic cholecystectomy with dexmedetomidine.[6]

Shamim et al. compared different dexmedetomidine dosing strategies and found improved hemodynamic stability in both loading and maintenance infusion groups.[7] Similarly, Masoori Tahir et al. found better suppression of the hemodynamic stress response using a higher maintenance dose of 0.6 µg/kg/hr in laparoscopic cholecystectomy.[8] In contrast, Shefali Gautam et al. found that both 0.5 and 0.7 µg/kg/hr doses were equally effective in hypertensive patients.[9] Vora et al. demonstrated stable hemodynamics and stress attenuation during intubation and extubation with a loading dose followed by maintenance infusion.[10]

Dexmedetomidine can be administered with or without a loading dose, and infusion rates ranging from 0.1 to 10 µg/kg/hr have been studied. High-dose infusions are associated with increased cardiovascular side effects. A biphasic blood pressure response is often seen with a bolus dose-initial hypertension due to α2B receptor stimulation followed by hypotension-especially in young, healthy individuals.[1]

In our study, we compared maintenance doses of 0.2 µg/kg/hr and 0.4 µg/kg/hr without administering a loading dose. Both groups exhibited stable intraoperative hemodynamics, with no significant episodes of hypertension or tachycardia. However, in the 0.4 µg/kg/hr group (Group 2), hypotension was observed in 18 patients, occurring 15 minutes after starting the infusion and shortly after induction. These episodes were managed effectively with intravenous fluids. Bradycardia was noted in 8 patients in the same group, reflecting the known sympatholytic action of dexmedetomidine.

Postoperative analgesia was significantly better in the higher-dose group. Venn et al. reported that dexmedetomidine reduces the need for rescue analgesia for up to 24 hours postoperatively.[11] Manne et al. also observed delayed onset of first rescue analgesia and reduced total analgesic requirement within 24 hours.[1] In our study, the mean time to first rescue analgesia was longer in Group 2 (236 minutes) compared to Group 1 (136 minutes), and the total dose of tramadol required in 24 hours was lower in Group 2, supporting the analgesia-sparing effect of higher-dose dexmedetomidine.

These findings align with existing literature and reinforce the efficacy of dexmedetomidine, particularly at 0.4 µg/kg/hr, in providing better hemodynamic control and reducing postoperative analgesic needs in laparoscopic cholecystectomy patients.

CONCLUSION

A low-dose infusion of dexmedetomidine at 0.4 mcg/kg/hr without a bolus has proven to be an effective adjuvant for attenuating the hemodynamic stress response during critical perioperative events such as intubation, pneumoperitoneum, and extubation in patients undergoing laparoscopic cholecystectomy. This dosage not only contributes to intraoperative hemodynamic stability but also reduces the requirement for anesthetic agents, particularly opioids. Furthermore, it provides effective postoperative analgesia with minimal adverse effects, making it a safe and valuable component of balanced anesthesia in laparoscopic procedures.

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Original Research Article

Association between Abdominal Circumference and Incidence of Hypotension Following Spinal Anaesthesia in Elective Caesarean Sections: A Prospective Observational Study

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Abstract:

Background: Spinal anaesthesia is the preferred technique for elective caesarean sections due to reduced maternal risks compared to general anaesthesia. However, it often leads to hypotension resulting from sympathetic blockade, which can adversely affect both mother and fetus. Identifying predictors of hypotension is crucial for improving maternal safety. This study aimed to evaluate the association between AC (Abdominal Circumference) and the incidence of hypotension following spinal anaesthesia.

Methods: A prospective observational study was conducted in the Department of Anaesthesiology, Government Medical College, Thrissur, after obtaining ethical approval. A total of 240 patients undergoing elective caesarean sections under spinal anaesthesia were enrolled using convenient sampling. Patients were grouped based on abdominal circumference (larger AC vs. smaller AC). Baseline parameters, including height, weight, and AC were recorded. MAP (Mean Arterial Pressure) was monitored at 1-, 5-, and 10-minutes post spinal anaesthesia. The incidence of hypotension, sensory blockade levels, and vasopressor use were also documented. Data were analysed using SPSS version 22.

Results: The overall incidence of hypotension was 37.9%. Patients with larger AC had a significantly greater fall in MAP at 1-, 5-, and 10-minutes post spinal anaesthesia ($p < 0.05$). A significant association was also found between larger AC and the occurrence of hypotensive symptoms, higher sensory blockade levels, and increased vasopressor requirements.

Conclusion: Abdominal circumference is significantly associated with post-spinal hypotension and can serve as a useful preoperative screening tool to predict the risk of hypotension in patients undergoing spinal anaesthesia for caesarean section.

Keywords: Abdominal Circumference, Spinal Anaesthesia, Caesarean Section, Hypotension, Mean Arterial Pressure, Vasopressors.

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Introduction

Spinal anaesthesia is the preferred technique for caesarean sections due to its rapid onset, effective sensory and motor blockade, and minimal fetal effects.[1] It avoids maternal complications associated with general anaesthesia, such as aspiration and airway management difficulties.[1] However, a major limitation of spinal anaesthesia is hypotension caused by sympathetic blockade, which can negatively affect both mother and fetus.[2,3]

Hypotension may lead to reduced uteroplacental perfusion, fetal hypoxia, acidosis, and maternal symptoms like nausea, vomiting, and altered consciousness.[1] Its incidence in obstetric patients ranges from 20–100%, significantly higher than the 15–33% seen in the general population.[3] This is due to several pregnancy-induced physiological changes that enhance the effect of local anaesthetics.[4,5] Despite fluid preloading or co-loading, spinal hypotension remains prevalent in up to 80% of parturients.[4]

Vasopressors, particularly sympathomimetic agents like ephedrine, are more effective than fluids in managing spinal-induced hypotension.[6] Supine hypotensive syndrome-caused by a gravid uterus compressing major vessels-also contributes to hypotension in pregnant women.[3]

Various factors, including height, weight, BMI, and fetal weight, may influence the spread of spinal block, though their roles remain debated. [7,8] Obesity, a growing global concern, adds complexity to obstetric anaesthesia due to altered physiology, increased comorbidities, and anatomical challenges.[9] It also increases the risk of prenatal complications and adverse anaesthetic outcomes.

Maternal hypotension can result in serious fetal complications, including low APGAR scores, delayed respiration, prolonged acidosis, poor breastfeeding reflexes, and long-term neurological damage. [10-13] Therefore, identifying predictors of hypotension is critical to improving outcomes.

Studies suggest that larger AC (Abdominal Circumference) correlates with increased intra-abdominal pressure and higher sensory block levels, both of which are associated with a higher risk of hypotension in obstetric patients.[12] This study explores the role of AC as a predictor of post-spinal hypotension in caesarean sections.

Aims and Objectives

This study aims to investigate the relationship between abdominal circumference and the incidence of post-spinal hypotension, a potentially life-threatening complication. Specifically, the objectives are to compare the fall in MAP (Mean Arterial Pressure) from baseline between groups with larger and smaller abdominal circumferences following spinal anesthesia and to assess the occurrence of symptoms associated with severe hypotension in these two groups.

Materials and Methods

Study Design: After obtaining clearance from the Institutional Ethical Committee and informed written consent from participants, a prospective observational study titled "Association between Abdominal Circumference and Post-Spinal Hypotension in Patients Undergoing Caesarean Section under Subarachnoid Block" was conducted over a period of one year. The study was carried out in the elective obstetric operation theatre of the Department of Anesthesiology, Government Medical College, Thrissur. A total of 240 patients scheduled for elective caesarean section under lumbar subarachnoid block were recruited for the study.

Inclusion and Exclusion Criteria: The study included pregnant women aged 18 to 35 years, classified as ASA physical status II, who were scheduled for elective caesarean section and provided written informed consent. Patients were excluded if they were unwilling to give consent, had overt or gestational hypertension, had absolute contraindications to spinal anesthesia, or had other co-morbid conditions such as diabetes.

Sample Size Calculation

Sample size was calculated using the formula

$$N = (Z\alpha + Z\beta)^2(S_1^2+S_2^2)/ d^2$$

According to a study conducted in Surat by Hiren B. Andani, Malti J. Pandya and Divyang V. Shah using MAP.[3]

S_1- SD of group 1 (larger AC group) = 11.84 S_2-SD of group 2 (smaller AC group) = 10.25 Zα- 1.96

Zβ- 0.84

d_1-Mean difference between SD of group 1 = 88.25
d_2 - Mean difference between SD of group 2 = 92.3
n = 7.84 x (140.19 + 105.06) / 16.65 = 116.

Sample size: 120 in each group

Total: 240.

Data Collection Tools: Data were collected using a structured proforma designed to record socio-demographic and clinical details such as age, height, weight, abdominal circumference, and BMI. Blood pressure measurements were systematically documented at specific time intervals-5, 10, 15, 30, 45, and 60 minutes following the administration of spinal anesthesia. A standard measuring tape was used to measure abdominal circumference at the level of the umbilicus in the supine position. All clinical and physiological data were obtained and recorded consistently by the investigators using standardized tools and techniques.

Data Collection Procedure: After obtaining Institutional Ethical Committee approval and informed written consent, 240 ASA class II parturients aged 18–35 years, weighing between 55–65 kg and with a height between 150–160 cm, scheduled for elective caesarean section under spinal anesthesia were enrolled in this prospective observational study conducted at Government Medical College, Thrissur. Each participant underwent a thorough pre-anesthetic evaluation, including medical history, physical examination, and relevant lab investigations. Patients were kept nil per oral (NPO) for 8 hours for solids and 2 hours for clear fluids and were premedicated with T. Ranitidine 150 mg and T. Metoclopramide 10 mg. Abdominal circumference was measured in the operating room by the same investigator prior to anesthesia. Patients were divided into two groups based on abdominal circumference (<101 cm and ≥101 cm). Baseline vital signs were recorded, and standard monitoring was instituted. Following IV fluid preloading, spinal anesthesia was administered using 2 ml of 0.5% hyperbaric bupivacaine via a 25G Quincke spinal needle in the lateral position, targeting a T4 sensory level. Intraoperative hemodynamic parameters, including MAP and heart rate, were recorded at baseline and at regular intervals (T1, T5, T10, T15, T20, T30, T40, T50,

T60, and every 10 minutes thereafter). Hypotension was defined as systolic BP <90 mmHg or MAP <65 mmHg, with significant hypotension considered as a ≥20% drop in MAP from baseline. Mephentermine was administered as required to maintain MAP ≥65 mmHg, and the total dosage used was recorded.

Statistical Analysis: The collected data were entered into a Microsoft Excel spreadsheet and subsequently analyzed using SPSS version 22 software. Statistical analysis was performed to interpret the findings and assess the association between abdominal circumference and the incidence of post-spinal hypotension in the study population.

Results

Table 1: Distribution of Study Participants Based on Demographics

Variable	Group	Mean ± SD	95% CI	P-Value	Frequency (%)
Age (in years)	Large AC	25.74 ± 3.69	24.81–26.63	0.195	
	Small AC	26.40 ± 3.60	25.86–26.96		
Gravidity	Large AC	2.75 ± 1.22	2.46–3.04	0.404	
	Small AC	2.62 ± 1.09	2.45–2.79		
Weight (kg)	Large AC	69.25 ± 9.55	67.15–71.47	0.127	
	Small AC	67.40 ± 8.16	66.14–68.72		
BMI (kg/m²)	Large AC	27.91 ± 3.19	27.18–28.69	0.301	
	Small AC	27.44 ± 3.24	26.95–27.95		
Heart Rate (bpm)	Large AC	77.28 ± 12.80	74.47–80.25	0.310	
	Small AC	79.11 ± 12.73	77.22–81.02		
Weight Gain (kg)	Large AC	10.26 ± 1.91	9.81–10.69	0.270	
	Small AC	9.99 ± 1.65	9.75–10.24		
Volume Pre-loading (ml)	Large AC	551.39 ± 115.67	523.65–579.22	0.573	
	Small AC	541.62 ± 125.59	521.61–561.18		

Table 1 shows the baseline demographic and clinical characteristics between large and small AC groups. None of the parameters differed significantly (p > 0.05).

Table 2: Distribution of Study Participants Based on General Characteristics

Variable	Category	Frequency	Percentage
Abdominal Circumference	Large AC	73	30.4%
	Small AC	167	69.6%
Gravidity	1	34	14.2%
	2	87	36.3%
	3	66	27.5%
	4	34	14.2%
	5	19	7.9%
BMI Class	Pre-obese	140	58.3%
	Obese type 1	57	23.8%
	Overweight	43	17.9%
Socioeconomic Status	APL	140	58.3%
	BPL	100	41.7%
Education	Illiterate	50	20.8%
	Primary	36	15.0%
	High School	71	29.6%
	Graduate	83	34.6%

Table 2 observes the general distribution of abdominal circumference, gravidity, BMI classes, socioeconomic status, and educational qualification. Most participants were in the smaller AC group, pre-obese, from APL families, and graduates

Table 3: Distribution of Sensory Level Attained

Sensory Level	Large AC (>101 cm)	Small AC (<101 cm)	Total	P-Value
Below T4	27 (15.9%)	143 (84.1%)	170	0.000
Above T4	46 (65.7%)	24 (34.3%)	70	
Total	73 (30.4%)	167 (69.6%)	240	

Table 3 illustrates that a significantly higher proportion of patients with large AC attained sensory levels above T4 compared to smaller AC ($p < 0.001$).

Table 4: Occurrence of Hypotension and Symptoms

Variable	Large AC (>101 cm)	Small AC (<101 cm)	Total	P-Value
Hypotension (Yes)	28 (38.4%)	63 (37.7%)	91	NS
Symptoms (Yes)	38 (58.5%)	27 (41.5%)	65	0.000

Table 4 shows that while the occurrence of hypotension was similar across groups, symptoms of hypotension were significantly more frequent in the large AC group.

Table 5: Vasopressor Administration

Vasopressor Use	Large AC (>101 cm)	Small AC (<101 cm)	Total	P-Value
No	35 (20.6%)	136 (79.4%)	170	0.000
Yes	38 (54.3%)	32 (45.7%)	70	

Table 5 observes that vasopressor requirement was significantly higher among patients with large AC compared to smaller AC ($p < 0.001$).

Table 6: Distribution of MAP Over Time

Time Point	Large AC (Mean ± SD)	Small AC (Mean ± SD)	P-Value
Baseline	77.00 ± 5.14	76.58 ± 4.69	0.535
1 min	65.47 ± 3.41	66.72 ± 3.71	0.014
5 min	57.93 ± 3.41	59.40 ± 3.51	0.003
10 min	59.51 ± 3.46	60.52 ± 3.04	0.024
15 min	62.71 ± 2.35	63.17 ± 2.37	0.165
20 min	65.03 ± 2.68	65.33 ± 2.69	0.421
30 min	66.88 ± 2.64	67.51 ± 2.55	0.083
40 min	69.51 ± 2.19	70.30 ± 2.35	0.015
50 min	72.64 ± 2.36	73.10 ± 2.49	0.189
60 min	76.10 ± 3.67	75.96 ± 3.48	0.781

Table 6 demonstrates fluctuations in MAP across time. Significant differences were observed at 1, 5, 10, and 40 minutes, with smaller AC patients maintaining higher MAP.

Table 7: Summary of Outcomes Based on Abdominal Circumference

Outcome	Large AC (>101 cm)	Small AC (<101 cm)	Significant Difference
Sensory Level Above T4	65.7%	34.3%	Yes (p=0.000)
Symptoms of Hypotension	58.5%	41.5%	Yes (p=0.000)
Vasopressor Requirement	54.3%	45.7%	Yes (p=0.000)
Hypotension (Overall)	38.4%	37.7%	No (NS)
MAP Drop (1–10 min, 40 min)	Lower	Higher	Yes

Table 7 consolidates the main findings, indicating that large AC patients had a higher risk of high sensory block, more hypotension symptoms, and greater vasopressor need, though the overall incidence of hypotension was similar between groups.

Discussion

This study was conducted on 240 patients undergoing elective caesarean sections under spinal anaesthesia at Government Medical College, Thrissur. Preoperative parameters including BMI, AC, and volume of fluid preloading were assessed, and intraoperative outcomes such as hypotension, sensory blockade, and vasopressor requirements, were carefully monitored.

The mean age of participants was comparable between the two groups (25.74 years in the larger AC group and 26.40 years in the smaller AC group). Most participants were in the 26–30 years age range, with the majority classified as pre-obese based on BMI. These demographic trends are in line with earlier reports on parturients undergoing caesarean sections.

Incidence of Hypotension: In the present study, the overall incidence of hypotension following spinal anaesthesia was 37.9%, which is relatively lower compared to other studies. Somboonviboon et al. reported an incidence of 60%,[14] while In Ae Song et al. observed 65%.[15] The reduced incidence in the current study may be attributed to improved preoperative hydration and fluid optimization protocols adopted in this population.

Abdominal Circumference and Blood Pressure Changes: Pattaraleeya Thomard demonstrated that the incidence of hypotension did not differ significantly between women with larger and smaller AC, though the larger AC group showed a greater fall in MAP from baseline.[16] Similarly, our study revealed a significant decline in MAP at 1, 5, and 10 minutes after subarachnoid block in the larger AC group, highlighting the impact of abdominal circumference on hemodynamic changes.

Hartmann et al. analysed risk factors for hypotension in the general population, reporting that high BMI, hypertension, and chronic alcohol intake were associated with increased risk.[17] However, since their study excluded obstetric cases, it emphasizes the relevance of specifically evaluating pregnant women, as we have done.

Vasopressor Requirement: In this study, 29.2% of parturients required vasopressors to manage hypotension, which is slightly lower than the 40–60% reported by Gupta et al. [18] This again may reflect differences in fluid management strategies and baseline patient characteristics.

Sensory Block Height and Hypotension: Our findings showed that 65.7% of the larger AC group attained a sensory level above T4, compared to 34.3% of the smaller AC group. A higher block level was strongly associated with hypotension, corroborating the findings of Somboonviboon et al., who reported that sensory block above T4 increases the risk of hypotension.[14] The underlying mechanism involves sympathetic blockade extending to the upper thoracic region, reducing compensatory vasoconstriction in the upper extremities and thereby predisposing to hemodynamic instability.[19]

Role of Abdominal Circumference as a Predictor: In Ae Song et al. concluded that abdominal circumference, body weight, and BMI (but not height) were significantly associated with hypotension incidence. They further noted that severe hypotension requiring vasopressors and associated with nausea was strongly related to larger AC. [15] Our study supports these findings, as participants with larger AC experienced more frequent symptoms of hypotension and required vasopressor support more often than those with smaller AC.

Limitations: This study had certain limitations. Firstly, there was a potential for bias as blinding of the anesthesiologist was not feasible. Additionally, the majority of participants had smaller abdominal circumferences, resulting in an underrepresentation of individuals with larger abdominal circumferences, which may have introduced bias in the comparative analysis. The classification of abdominal circumference groups, with <101 cm defined as smaller and ≥101 cm as larger, may also have influenced the study outcomes. These factors should be considered when interpreting the results, and we recommend that future research further explore this association with a more balanced sample and refined grouping criteria.

Conclusion

The study found that the overall incidence of post-spinal hypotension at the study center was 37.9%. The findings suggest that abdominal circumference can serve as a useful screening parameter for predicting post-spinal hypotension in parturients undergoing caesarean section under spinal anesthesia. Being cost-effective, non-invasive, quick to measure, and patient-friendly, abdominal circumference offers a practical tool for routine preoperative evaluation. The study recommends incorporating abdominal circumference measurement into the preoperative assessment to help anticipate and promptly manage this potentially serious complication.

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Original Research Article

Comparing Analgesic Effectiveness of Ultrasound Guided Femoral Nerve Block versus Fascia Iliaca Block for Positioning During Spinal Anaesthesia in Adult Patients Undergoing Femoral Fracture Surgery

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Abstract:

Background: Femoral fractures are highly painful and commonly require surgical fixation, typically performed under SAB (Subarachnoid Block). However, severe pain can hinder proper positioning for SAB. PNB (Peripheral Nerve Blocks), such as FNB (Femoral Nerve Block) and FICB (Fascia Iliaca Compartment Block) offer effective analgesia in these cases.

Methods: This prospective observational study included 70 patients undergoing femur fracture surgery, divided into two groups: Group 1 (n=35) received ultrasound-guided FNB (15 ml of 0.25% bupivacaine), and Group 2 (n=35) received FICB before SAB. Parameters assessed included VAS during positioning, ease of interspinous space palpation, number of dural puncture attempts, patient satisfaction, and haemodynamic/respiratory changes.

Results: Both blocks effectively reduced pain during positioning, but Group 2 (FICB) showed significantly lower VAS scores ($p < 0.05$), indicating superior analgesia. Both techniques had a similar onset of analgesia, achieving pain relief within 15 minutes ($p < 0.05$). Patient satisfaction was higher in the FICB group ($p < 0.05$). Quality of positioning, assessed by fewer spinal attempts, was also better in the FICB group ($p < 0.05$). No significant differences were observed between groups regarding interspinous palpation, haemodynamic, or respiratory changes.

Conclusion: Preoperative FICB provides superior analgesia compared to FNB for SAB positioning in femur fracture surgeries, evidenced by lower VAS scores, better positioning, and higher patient satisfaction. Both techniques were safe with no significant impact on haemodynamics or respiration during positioning.

Keywords: Femoral Nerve Block, Fascia Iliaca Compartment Block, Spinal Anaesthesia, Bupivacaine, Visual Analogue Scale, Patient Satisfaction.

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Introduction

Femur fractures are the most common fractures globally, with approximately 2.9 million cases annually. The highest incidence occurs between ages 15 and 44, followed by 5–14 years and those over 60, accounting for 29% and 21% of cases, respectively.[1]

The periosteum, one of the body's most pain-sensitive tissues, contributes to the severe pain in femoral shaft fractures. It receives innervation from surrounding nerves, while the deeper periosteum is supplied by motor branches of muscles attached to the bone. In the femoral shaft, the femoral nerve, which innervates the quadriceps femoris muscle, is the primary source of periosteal innervation.

SAB (Subarachnoid Block) is the most widely used anaesthetic technique for femur fracture fixation, typically performed in sitting or lateral positions. However, positioning patients with femur fractures for SAB is challenging due to severe pain caused by fracture movement, often requiring high doses of opioids.[2] This poses risks, especially in elderly patients with comorbidities, such as respiratory depression.

Effective pre-procedure analgesia can greatly ease patient positioning and reduce opioid needs. FICB (Fascia Iliaca Compartment Block) and FNB (Femoral Nerve Block) are simple, safe, and effective regional blocks with few contraindications.[3] FICB is especially useful in

prehospital care due to its safety, ease, and high success rate.[4]

Ultrasound guidance improves the accuracy, reduces local anaesthetic dosage, enhances sensory block quality, and lowers complication rates compared to landmark or nerve stimulator techniques.[5] Ultrasound-guided FNB offers rapid, long-lasting, opioid-sparing analgesia, especially beneficial in elderly patients with hip fractures.[6]

Pain assessment using the VAS (Visual Analogue Scale) involves marking a 100-mm line from "no pain" to "worst pain possible," providing a simple yet effective pain quantification method.[7]

Aims and Objectives

The study aimed to compare the analgesic efficacy of ultrasound-guided FNB and FICB in patients with femur fractures to facilitate optimal positioning for spinal anaesthesia. The study evaluates the effectiveness and quality of analgesia using the VAS 20 minutes post-block, the ease of patient positioning assessed by the number of spinal attempts, and monitors for any intervention-related complications.

Materials and Methods

Study Design: This prospective observational study was conducted in the Department of Anaesthesiology at Government Medical College, Thrissur, Kerala, India, after obtaining approval from the Institutional Research and Ethics Committees. The study included patients aged between 18 and 80 years who were scheduled for surgical management of femur fractures.

Inclusion and Exclusion Criteria: The study included patients aged 18 to 80 years with ASA physical status I or II who were scheduled for proximal femur fracture surgeries. Patients were excluded if they had any of the following: refusal to participate, cardiovascular or cerebrovascular disease, raised intracranial pressure, psychiatric illness, agitation or anxiety, vertebral column deformity, bleeding disorders, local infection or malignancy at the injection site, sepsis, history of seizures, or known allergy to local anaesthetics or study drugs.

Sample Size Calculation: As per the study conducted by Jain N, Mathur PR, Patodi V, and Singh S.A comparative study of ultrasound-guided femoral nerve block versus fascia iliaca compartment block in patients with fractured femurs for reducing pain associated with positioning for subarachnoid block. Indian J Pain 2018; 32:150-4.[6]

The mean VAS score in 20 minutes in group A-femoral nerve block (μ1) = 1.88 The mean VAS score in 20 minutes in group B-fascia iliaca block (μ2) = 2.40 d = mean difference.

SD1 (standard deviation in group A) = 0.83 Sd2 (standard deviation in group B) = 0.52 Zα at 0.05 significance = 1.96

Zβat 80% power = 0.84

Sample size (N) can be calculated by substituting values in the formula.

$$\frac{(Z_{\alpha}+Z_{\beta}^{2})\,x\,(S_{1}^{2}+S_{2}^{2})}{d^{2}}$$

Final sample size (N) = 70 (35 in each group)

Data Collection Procedures

Seventy patients with proximal femur fractures who met the inclusion criteria were enrolled and divided into two groups of 35 each: Group 1 received ultrasound-guided FNB, and Group 2 received FICB, both with 20 ml of 0.25% bupivacaine, 20 minutes prior to spinal anaesthesia. All patients received standard premedication, fasting instructions, IV access, and baseline monitoring, along with oxygen supplementation and pre-procedure sedation using IV midazolam (0.01–0.05 mg/kg) and fentanyl (1 mcg/kg). Under ultrasound guidance, nerve blocks were administered in the supine position using a high-frequency linear probe. Spinal anaesthesia was performed in the lateral position with the fractured side down using a 25G spinal needle at the L3–L4 interspace under aseptic precautions. Pain during positioning was assessed using the VAS, and other parameters recorded included ease of palpating interspinous space (graded 1–5), number of dural puncture attempts, MAP, respiratory rate, heart rate, and patient satisfaction (satisfied/not satisfied).

Statistical Analysis: Data were entered in Microsoft Excel and analyzed using SPSS version 20, with graphs generated using Excel or SPSS. Continuous variables were expressed as mean ± standard deviation based on their distribution, while categorical variables were presented as frequencies and percentages. Baseline demographic and clinical parameters were compared using the chi-square test or Fisher's exact test, as appropriate. Outcome variables between the two groups were analyzed using an unpaired t-test for normally distributed continuous data. A p-value of <0.05 was considered statistically significant.

Results

Table 1: Distribution of Cases in Each Group

Group	Number of Cases
Femoral Block	35
Fascia Iliaca Block	35

Table 1 observes the equal distribution of patients across both study groups (35 each).

Table 2: Demographic and Anthropometric Characteristics of Study Groups

Variable	Group	N	Mean ± SD	P-Value
Age (in years)	Femoral	35	59.11 ± 15.55	0.396
	FICB	35	55.54 ± 19.20	
Weight (kg)	Femoral	35	60.09 ± 7.95	0.903
	FICB	35	59.86 ± 7.67	
Height (cm)	Femoral	35	159.97 ± 6.59	0.708
	FICB	35	159.42 ± 5.42	
BMI (kg/m²)	Femoral	35	23.43 ± 2.55	0.915
	FICB	35	23.50 ± 2.67	

Table 2 shows comparable baseline age, weight, height, and BMI between the two groups ($p>0.05$).

Table 3: Sex and ASA Grade Distribution

Variable	Femoral	FICB	Total	P-Value
Sex				
Male	21	19	40 (57.1%)	
Female	14	16	30 (42.9%)	
ASA Grade				
ASA I	13	18	31	0.229
ASA II	22	17	39	

Table 3 illustrates the distribution of sex and ASA grades, showing no significant differences between groups.

Table 4: Ease of Palpating Spine

Ease of Palpation	Femoral	FICB	Total	P-Value
Easily palpable	26	26	52	0.819
Palpable	8	7	15	
Difficult	1	2	3	

Table 4 observes that ease of palpation was similar between groups, with most spines being easily palpable.

Table 5: VAS Score Distribution Over Time

Time Interval	Femoral (Mean ± SD)	FICB (Mean ± SD)	P-Value
Before block	7.82 ± 0.75	7.91 ± 0.95	0.676
5 min	6.86 ± 0.81	6.74 ± 0.82	0.559
10 min	5.80 ± 0.87	5.31 ± 0.86	0.022*
15 min	4.20 ± 1.11	3.63 ± 1.00	0.027*
20 min	2.94 ± 0.64	2.34 ± 0.68	0.000*
During positioning	1.65 ± 0.64	1.23 ± 0.73	0.011*
* Significant ($p<0.05$)			

Table 5 shows that VAS scores reduced significantly faster in the FICB group after 10 minutes.

Table 6: Hemodynamic and Respiratory Parameters during Study

Parameter	Time	Femoral (Mean ± SD)	FICB (Mean ± SD)	P-Value
Heart Rate	Before block	86.31 ± 9.22	81.86 ± 7.30	0.028*
HR during positioning	79.05 ± 5.93	78.60 ± 5.87	0.747	
MAP before block	89.77 ± 8.72	92.71 ± 10.59	0.209	
MAP during positioning	86.31 ± 6.30	88.54 ± 10.52	0.286	
RR before block	15.23 ± 1.66	15.26 ± 1.40	0.938	
RR during positioning	12.94 ± 1.23	13.09 ± 0.98	0.594	
* Significant ($p<0.05$)				

Table 6 demonstrates that hemodynamic and respiratory parameters were mostly similar, except for a slightly lower baseline heart rate in the FICB group.

Table 7: Clinical Outcomes – Spinal Attempts and Patient Satisfaction

Outcome	Femoral	FICB	P-Value
No. of spinal attempts (Mean ± SD)	1.8 ± 0.86	1.3 ± 0.53	0.01*
Patient satisfaction (Satisfied/Not Satisfied)	27 / 7	34 / 1	0.02*

Table 7 shows significantly better outcomes with FICB, including fewer spinal attempts and higher patient satisfaction.

Discussion

Pain during positioning for SAB is a significant concern in patients with femur fractures, even in those with a normal spine. Inadequate analgesia leads to multiple attempts, prolonged painful positioning, and sometimes failure to accomplish SAB. Therefore, ensuring proper pain relief before surgical preparation or immobilization is crucial both for patient comfort and for the anaesthesiologist to achieve an effective block. [8-11]

Traditionally, opioids have been administered for positioning analgesia. However, opioids carry adverse effects such as nausea, vomiting, respiratory depression, cognitive impairment, and urinary retention, particularly in elderly patients. [12,13] PNBs have thus emerged as safer alternatives. Among them, FNB, three-in-one block, and FICB are commonly employed. Studies suggest that compared with FNB, both three-in-one block and FICB provide superior analgesia. [11,14] Hence, this study compared FICB and FNB in patients undergoing femur fracture surgery.

FNB and FICB are well-recognized for acute pain relief in lower extremity trauma. [15,16] While FICB blocks the femoral, obturator, and lateral femoral cutaneous nerves, providing broad sensory coverage of the hip joint, FNB mainly covers the anterior thigh and knee. Literature indicates that ultrasound-guided PNBs significantly reduce pain scores, opioid use, and opioid-related complications, while improving patient satisfaction. [17,18] Reported complications are rare but may include nerve injury, hematoma, or local anaesthetic toxicity.

The comparative efficacy of FNB versus FICB remains debated. Some studies found no difference; others favored FNB for early analgesia, while FICB was found better for preoperative positioning.[19,20] The consensus is that FICB is simpler, quicker to perform, and particularly useful in improving patient positioning for SAB.[21] Our study aligns with these observations, as FICB provided significantly lower VAS scores at 10, 15, and 20 minutes and during positioning compared to FNB ($p<0.05$).

Choice of local anaesthetic is also important. Although lignocaine has a rapid onset, its short duration is a drawback. Bupivacaine, as used in our study, provides longer-lasting analgesia compared to ropivacaine. [22,23] Use of ultrasound further enhances block accuracy, reduces anaesthetic dose, and improves block quality compared to blind or nerve stimulator techniques. [24,25]

Patient positioning during SAB can be lateral or sitting. Lateral positioning is often more comfortable and associated with fewer post-dural puncture headaches compared to sitting. [26-28] In our study, lateral positioning was adopted, and analgesia with FICB facilitated better comfort.

Previous studies comparing FNB and FICB have shown mixed results. Jadon et al. found FNB superior to intravenous fentanyl for positioning during SAB. [29] Jain et al. reported lower VAS scores with FNB compared to FICB. In contrast, our findings demonstrated superior analgesia with FICB, consistent with its broader nerve coverage. Similarly, Newman et al. reported FNB superiority in their trial,[30] while our results favoured FICB. Ghimire et al. found comparable positioning quality with both blocks using landmark technique,[31] but in our study, FICB required significantly fewer spinal attempts and had higher patient satisfaction.

Importantly, no block-related complications were reported in our study, consistent with findings from Ghimire et al. and Bantie et al. Even hemodynamic and respiratory parameters were comparable between groups, supporting prior results by Meeta et al. [32] This suggests that both FNB and FICB are safe techniques, but FICB provides better patient comfort and facilitates smoother SAB.

In summary, although both blocks provided effective analgesia, the fascia iliaca block was associated with superior pain control, fewer spinal attempts, and higher patient satisfaction. It can thus be recommended as the preferred option for positioning femur fracture patients for subarachnoid block.

Limitations

This study has several limitations, including a small sample size, subjective pain assessment via the Visual Analogue Scale, and variability in anaesthesiologist technique. Additionally, lack of postoperative follow-up and non-standardized timing between trauma and surgery may have influenced pain perception and block effectiveness.

Conclusion

Based on the findings of this study, it can be concluded that while both FNB and FICB are effective in providing preoperative analgesia for

patients undergoing femur fracture surgery, FICB offers superior analgesic quality for facilitating spinal anaesthesia. This is evidenced by significantly lower VAS scores during positioning, fewer attempts required for successful dural puncture, and higher patient satisfaction in the FICB group. Additionally, the administration of FICB did not result in any significant hemodynamic or respiratory changes during positioning for spinal anaesthesia, confirming its safety and efficacy as a pre-procedural analgesic technique.

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BIOCHEMISTRY

Original Article

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Correlation between Dyslipidemia and Urine Albumin Excretion in Non Diabetic Obese Subjects: A Cross-sectional Study

Biochemistry Section

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ABSTRACT

Introduction: Obesity is a global health concern, and recent research has shown that it can cause kidney problems, especially in non diabetics. Obesity-related dyslipidemia, characterised by aberrant lipid profiles, may contribute to kidney damage.

Aim: The purpose of the present cross-sectional study was to shed light on the complex interaction between dyslipidemia and renal health by examining the relationship between dyslipidemia and urine albumin excretion in non diabetic obese adults.

Materials and Methods: The cross-sectional investigation was conducted in the Outpatient Obesity Clinic of the Endocrinology Department at a Tertiary Hospital in Kerala, India. A total of 144 non diabetic obese individuals between the ages of 18 and 65 years. All subjects provided informed consent, and ethical approval was obtained. The primary inclusion criteria were a Body Mass Index (BMI) of less than 25.0, the absence of Type 2 Diabetes Mellitus (T2DM), and the absence of proteinuria. Urine and blood samples were collected for laboratory testing, and statistical analysis was conducted using International Business Machines (IBM) Statistical Package for Social Sciences (SPSS) Statistics 20.0.

Results: Dyslipidemia was found to be common, with low High-Density Lipoproteins (HDL) levels in 41.4% of participants, high Low-Density Lipoproteins (LDL) levels in 49.6%, high Triglycerides (TG) levels in 29.7%, and high Total Cholesterol (TC) levels in 43%. The study revealed that obese individuals with dyslipidemia excrete albumin at a significantly higher rate than obese individuals without dyslipidemia. Furthermore, a weak correlation between TG levels and the Urine Albumin Creatinine Ratio (UACR) was discovered. However, UACR did not significantly correlate with metabolic risk markers such as Fasting Plasma Glucose (FPG), serum insulin, blood pressure, HDL, LDL, TC, and systolic/Diastolic Blood Pressure (DBP).

Conclusion: The results of the present study demonstrate that dyslipidemia significantly contributes to kidney damage in non diabetic obese individuals. The presence of dyslipidemia in obese then could serve as an early warning sign of potential renal problems. Further research is needed to fully understand the complex interactions between obesity, dyslipidemia, and renal health. These insights could be crucial for developing effective preventative and intervention methods in this context.

Keywords: Albuminuria, Cholesterol, Metabolic risk factors, Obesity-related nephropathy, Renal dysfunction

INTRODUCTION

Chronic Kidney Disease (CKD) is a growing concern, with emerging evidence suggesting that even modest weight gain, falling within the normal range of BMI, can elevate CKD risk [1]. Obesity is linked to several mechanisms that aggravate renal problems and make people more vulnerable to CKD. These causes include inflammation brought on by obesity, endothelial dysfunction, altered renal haemodynamics, hyperlipidaemia, oxidative stress, podocyte stress, and an imbalance in adipokines. Even in the absence of hypertension or hyperglycaemia, endothelial dysfunction- a crucial early event in obesity- is still present, highlighting the significance of obesity as a risk factor for endothelial dysfunction [2]. In obesity, adipose tissue secretes adipokines and inflammatory cytokines, accompanied by elevated levels of Free Fatty Acids (FFA), increased LDL, reduced HDL, activation of the Renin-Angiotensin System (RAS), and Sympathetic Nervous System (SNS) activation, all of which contribute to endothelial dysfunction through direct or indirect effects on vascular endothelium-derived Nitric Oxide (NO) [3,4].

The substantial link between obesity and microvascular dysfunction in numerous tissues is further shown by the relationship between weight loss and better endothelial function [5]. One specific complication of obesity is known as Obesity-related Glomerulopathy (ORG) [6]. Renal lipotoxicity is caused by lipid dysmetabolism and abnormalities in lipid profiles, which also promote glomerulosclerosis and directly affect ORG [7]. Renal hyperfiltration, alterations in renal haemodynamics brought on by obesity, and slow-onset proteinuria with microalbuminuria as the initial clinical manifestation are the hallmarks of ORG [8].

Maintaining insulin sensitivity, promoting fatty acid oxidation, lowering plasma Triglycerides (TG), and enhancing glucose metabolism are all made possible by the adipocyte hormone adiponectin, which is also implicated in lipid and glucose metabolism. Endothelial dysfunction and associated co-morbidities are caused by decreased adiponectin levels in obesity [9].

In obese people, lower adiponectin levels are linked to higher TG and fatty liver [10]. Obesity-induced dyslipidemia may independently cause renal damage through the increase of Sterol-regulatory Element-binding Proteins (SREBP-1 and 2) in glomerular cells, resulting in lipotoxicity [11]. Increased FFA intake also contributes to tubulointerstitial inflammation, fibrosis, and glomerular podocyte damage in proximal tubular epithelial cells due to glomerular lipid accumulation and the production of foam cells [12,13]. Studies have shown that glomerular lipid deposition and foam cell production in dyslipidemia are related to the onset of Focal Segmental Glomerulosclerosis (FSGS) [14]. Additionally, it has been demonstrated that lipid-lowering medications slow the onset of ORG and proteinuria [13]. Obesity-related development of CKD is a complex interplay of numerous factors affecting renal pathophysiology rather than a single isolated event. Obesity is a "multi-hit" condition that starts and/or hastens kidney damage [15].

Therefore, the goal of the present study was to shed light on the complex pathways relating obesity to renal problems by examining the relationship between dyslipidemia and urine albumin excretion in

non diabetic obese individuals. Understanding these mechanisms is essential for successful preventive and therapeutic measures for CKD in the obese population.

MATERIALS AND METHODS

The cross-sectional investigation was conducted in the Outpatient Obesity Clinic of the Endocrinology Department at a tertiary hospital in Kerala, India. All participants provided informed consent, and ethical clearance was granted by the Ethics Committee [IEC number:- Order No. B6-155/2019/MCTCR(28)].

Sample size calculation: The minimum sample size required, considering the variables of UACR and BMI, was calculated to be 140 based on a 95% confidence level and 80% power.

Inclusion criteria: Participants with a BMI of less than 25.0 were selected from both sexes within the age range of 18 to 65 years. The following criteria were used for inclusion:

- No presence of red blood cells, pus cells, or proteinuria detected during routine urine dipstick screening for Type 2 Diabetes Mellitus (T2DM).
- No recent history of vigorous exercise within 24 hours of the test.
- HbA1c (haemoglobin A1c) less than 6.5%.
- Serum creatinine level of 1.4 mg% or less.

Exclusion criteria: The following groups of subjects were not included in the study:

- Age less than 18 or greater than 65 years.
- HbA1c ≥6.5%.
- Clinical suspicion of urinary tract infection.
- History of hypertension, chronic liver disease, CKD, or known cardiovascular disease.
- Presence of fever or any other recent or ongoing illnesses.
- Taking medications for diabetes, obesity, or high blood pressure.
- Taking corticosteroids, Non Steroidal Anti-inflammatory Drug (NSAIDs), or other nephrotoxic medications.
- Pregnancy or use of contraceptives.
- Participants menstruating at the time of the study.
- Extended upright posture prior to testing.

Study Procedure

- Spot urine samples were collected in sterile containers for the purpose of determining the UACR, and the ratio of albumin to creatinine was calculated.
- Venous blood samples were aseptically taken while the subject was seated. FPG samples were obtained using fluoride-containing vacutainers. Plasma was then transferred to labelled vials after centrifugation at 3000 g for 15 minutes.
- Vacutainers with Ethylenediaminetetraacetic Acid (EDTA) were used to collect samples for HbA1c testing.
- Blood was drawn into vacutainers devoid of anticoagulant to obtain samples for additional biochemical markers.
- The Beckman Coulter Olympus AU2700 was used to measure serum creatinine and FPG, while the Bio-Rad D-10 was used to measure HbA1c.
- The UACR was expressed as mg/g.

UACR calculation:

- Urine albumin (mg/dL)=UACR in mg/g/Urine creatinine (g/dL) was used to calculate UACR.
- The Beckman Coulter Olympus AU2700 was used to calculate the value.

Urine sample considerations: Urine samples tainted with blood were declared unacceptable for UACR computation, as blood might artificially raise albumin levels. Patients were instructed to avoid strenuous exercise 24 hours prior to the test.

Laboratory analysis:

- Urine albumin was estimated using an immunoturbidimetric technique.
- Urine creatinine was estimated using Jaffe's kinetic technique.

STATISTICAL ANALYSIS

For statistical analysis in this study, IBM SPSS Statistics 20.0 for Windows was used. Continuous variables were presented as mean±standard deviation. The Mann-Whitney U test was used to compare parameters with non normal distribution, while the Pearson's correlation coefficient was calculated for variables with normal distribution. Multiple regression analysis was used to find determinants of UACR. Log transformation was used for UACR due to its non normal distribution and significant unpredictability. The study maintained an 80% statistical power, and p-values less than 0.05 were considered significant. These techniques allowed for a thorough examination of the data and informed judgements.

RESULTS

The initial characteristics of the study group are shown in [Table/Fig-1]. The average BMI of the individuals was 36.78 kg/m^2, with an average age of 31.94 years. The average waist circumference (112.61 cm), Systolic Blood Pressure (SBP) (125.35 mmHg), and DBP (78.15 mmHg) were recorded. HbA1c averaged 5.64%, and the FPG level was 98.80 mg/dL. The mean lipid profile values were as follows: TC 195.92 mg/dL, LDL 129.68 mg/dL, HDL 44.38 mg/dL, and TG 134.03 mg/dL. The serum creatinine level was 0.8982 mg/dL, and the UACR had a mean value of 8.49. Pearson's correlations between several variables and UACR are shown in [Table/Fig-2]. It shows a positive association between BMI and UACR (r=0.23, p=0.006), indicating that a higher BMI is linked to a higher UACR. There was also a strong positive connection between TG and UACR (r=0.258, p=0.003). A larger waist circumference was associated with a greater UACR, as indicated by a strong positive correlation between waist circumference and UACR (r=0.302, p<0.001). Other factors such as FPG, HDL, LDL, TC, HbA1c, SBP, and DBP showed weaker or no significant correlations with UACR.

Characteristics	n	Mean	SD
Age (years)	144	31.94	11.9
BMI (kg/m^2)	144	36.78	5.15
WC (cm)	144	112.61	10.89
SBP (mmHg)	144	125.35	12.35
DBP (mmHg)	144	78.15	6.64
FPG (mg/dL)	131	98.80	14.75
HBA1c (%)	144	5.64	0.4476
Total Cholesterol (TC) (mg/dL)	129	195.92	41.6
LDL (mg/dL)	129	129.68	31.99
HDL (mg/dL)	128	44.38	14.85
TG (mmol/L)	128	134.03	62.11
UACR (mg/g)	144	8.49	9.42
Serum creatinine (mg/dL)	143	.8982	0.1187

[Table/Fig-1]: Baseline characteristics of study groups.
**BMI: Body mass index; WC: Waist circumference; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose; HbA1c: Haemoglobin A1c (Glycated Haemoglobin); TC: Total cholesterol; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglycerides; UACR: Urine albumin creatinine ratio

Factors	n	UACR	
		Pearson correlation	p-value
BMI (kg/m^2)	144	0.23	0.006
FPG (mg/dL)	131	0.155	0.073

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Insulin	111	0.105*	0.274
HDL (mg/dL)	128	0.014*	0.871
TG (mg/dL)	128	0.258*	0.003
LDL (mg/dL)	129	0.123	0.165
TC	129	0.106	0.231
WC (cm)	144	0.302	<0.001
HBA1c (%)	144	0.159	0.056
SBP (mmHg)	144	0.067	0.426
DBP (mmHg)	144	0.090	0.286

[Table/Fig-2]: Correlation of UACR with key factors in the study population.

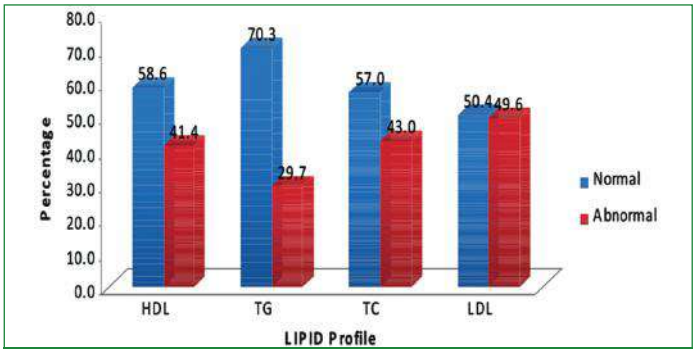
In [Table/Fig-3], the UACR between individuals with normal and disturbed lipid profiles was compared. The Mann-Whitney U test revealed that individuals with abnormal lipid profiles had significantly higher UACR (mean=9.70, SD=10.64) compared to those with normal lipid profiles (mean=5.97, SD=6.55) (p=0.011). In [Table/Fig-4], the Mann-Whitney U test indicated no statistically significant difference in UACR between people with normal TG levels (mean=8.08, SD=8.74) and those with aberrant TG levels (mean=9.92, SD=11.771) (p=0.388). [Table/Fig-5] presents a graph depicting the percentage distribution of lipid profile parameters in the research population. [Table/Fig-6] shows a scatterplot graph illustrating the association between UACR and TG levels.

Groups	Classification	n	UACR		p-value
			Mean	SD	
Dyslipidemia	Normal	38	5.97	6.55	0.011
	Abnormal	90	9.70	10.64	

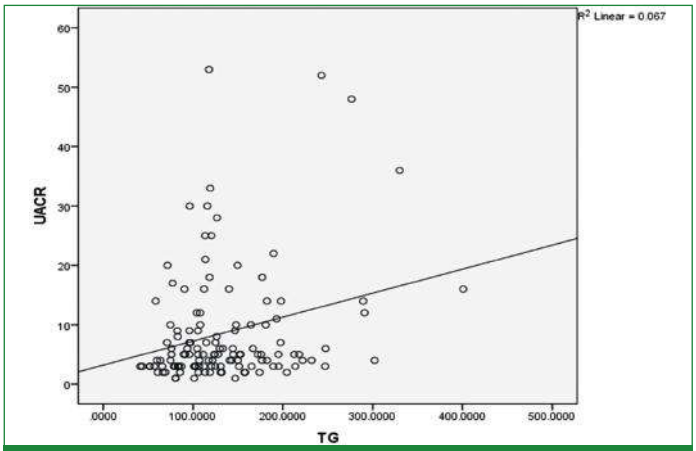
[Table/Fig-3]: Comparison of UACR in dyslipidemia (Mann Whitney U Test).

Factor	Classification	n	UACR		p-value
			Mean	SD	
TG	Normal <150 mgm/dL	90	8.08	8.74	0.388
	Abnormal >150 mgm/dL	38	9.92	11.771	

[Table/Fig-4]: Comparison of UACR with TG (Mann Whitney U Test).



[Table/Fig-5]: Graph showing the percentage distribution of lipid profile.



[Table/Fig-6]: Scatter diagram showing the correlation between TG and UACR.

Therefore, the findings suggest that higher UACR is associated with higher BMI, waist circumference, and dyslipidemia, particularly elevated TG levels. These results highlight the importance of controlling obesity and dyslipidemia in non diabetic obese individuals to reduce the risk of renal impairment. However, further research is needed to examine the underlying causes and potential therapies.

DISCUSSION

The present cross-sectional study examined 144 non diabetic obese individuals between the ages of 18 and 65 years who were enrolled in an obesity clinic at a tertiary hospital in Kerala. The aim was to better understand the complex association between UACR and dyslipidemia and determine whether dyslipidemia significantly affects kidney health. The results confirm the growing concern about the harmful effects of obesity on renal health, which is supported by previous research [1,16,17]. Obesity has been associated with an increased risk of CKD globally. Understanding the complex relationship between obesity and renal problems, including dyslipidemia, is crucial [1]. Dyslipidemia, characterised by abnormal lipid profiles, has been linked to kidney injury, particularly in the context of obesity [6,7]. Previous studies have demonstrated the relationship between obesity and hepatic triglyceride synthesis, leading to adverse changes in lipid profiles and hyperlipidemia [18]. These findings are consistent with the present investigation, which showed a significant proportion of participants with high TC, high TG, high LDL, low HDL, and high triglyceride levels [Table/Fig-1].

Furthermore, the present study reveals that obese individuals with dyslipidemia had significantly higher albumin excretion compared to those without dyslipidemia [Table/Fig-3]. However, it is noteworthy that the mean albumin excretion remained within the reference range for normalcy. Among the lipid profile characteristics examined, the TG profile showed a notable but weak association with UACR [Table/Fig-2]. Interestingly, these findings align with a study suggesting that visceral fat, plasma insulin, triglyceride, and low HDL cholesterol concentrations in obese individuals may not be closely correlated with urine albumin excretion, indicating a later onset of abnormal albuminuria during insulin resistance syndrome [19]. These results are consistent with other research highlighting the role of lipids in the development of kidney disease, suggesting that dyslipidemia contributes to renal damage, including glomerulosclerosis [6,7]. Dyslipidemia-induced glomerular lipid deposition and foam cell production have been linked to FSGS [7]. Moreover, there is clinical evidence indicating that controlling dyslipidemia can reduce kidney risks. For instance, LDL-apheresis has been shown to improve steroid-resistant FSGS by reducing proteinuria and increasing serum albumin levels [20]. This underscores the therapeutic potential of addressing lipid abnormalities in obese individuals to preserve renal function. The present study supports previous research by demonstrating that dyslipidemia is a contributing factor to renal damage and that dyslipidemic obese individuals have significantly higher albumin excretion compared to those without dyslipidemia [21]. However, it is important to note that the mean albumin excretion remained within the reference range for normality. Interestingly, among the evaluated lipid profile markers, only TG showed a significant albeit weak association with UACR [Table/Fig-2] [21].

These results align with a study suggesting that visceral fat, plasma insulin, triglyceride, and low HDL cholesterol concentrations in obese individuals may not be closely correlated with urine albumin excretion, indicating a later onset of abnormal albuminuria during insulin resistance syndrome [19]. Apart from Waist

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Circumference (WC), Chandie Shaw PK et al., (2007) found that markers for metabolic syndrome, such as insulin resistance, C-reactive protein, lipids, and high blood pressure, could not independently predict higher urine albumin excretion [22]. This is consistent with the findings of the present study, which also showed no conclusive links between metabolic risk markers such as FPG, serum insulin, blood pressure, and UACR. [Table/Fig-2] only demonstrates a very weak correlation between TG and UACR. However, the value of our study lies in elucidating the nuanced interaction between dyslipidemia and UACR in non diabetic obesity, paving the way for further research and new therapeutic approaches. The study emphasises the need of comprehensive strategies to address dyslipidemia in the context of obesity and its potential impact on renal health. Therefore, this study contributes to the existing body of research that demonstrates a connection between obesity, dyslipidemia, and kidney health. In non diabetic obese individuals, dyslipidemia emerges as a significant contributor to kidney injury. Our findings underscore the importance of managing lipid abnormalities as a potential treatment avenue to protect renal function in this vulnerable population, although further study is needed to elucidate the exact mechanisms involved.

It is crucial to understand the broader implications of the present study findings. Obesity is a global epidemic with significant health consequences, including kidney problems [16]. The present study sheds light on the complex interactions between obesity, dyslipidemia, and renal health. The intricate nature of these connections is highlighted by the limited association between UACR and specific markers, particularly BMI and TG [Table/Fig-2]. Additionally, these findings underscore the importance of targeting dyslipidemia as a treatment approach to reduce renal risks in obese individuals [20]. Managing lipid abnormalities may help protect renal function, especially in those at a higher risk of ORG [6].

Limitation(s)

It is important to acknowledge some limitations of the study. Firstly, the cross-sectional design prevents drawing conclusions about cause and effect, and the relatively small sample size may limit the applicability of the present study findings. Secondly, the study's focus on non diabetic obese individuals means that the results may not necessarily apply to other demographics or those with diabetes. Furthermore, factors such as dietary practices, genetic predispositions, and lifestyle choices were not thoroughly examined.

CONCLUSION(S)

The present study clarifies the intricate connections between dyslipidemia and kidney health in non diabetic obese individuals. The present study findings demonstrate the significance of dyslipidemia as a major risk factor for renal damage in this susceptible population. Dyslipidemia, characterised by abnormal lipid profiles, has been linked to ORG and FSGS, two renal problems. The relationship between obesity and kidney injury supports the "multi-hit hypothesis" of CKD, which suggests that CKD development is not a single isolated event but rather the result of multiple factors influencing renal pathophysiology. While shedding light on these intricate relationships, the present study also underscores the need for further investigation to fully understand how non diabetic obesity impacts renal function. A comprehensive strategy is necessary to address the various health effects, including kidney health, of the worldwide obesity epidemic. Recent advancements in obesity research are gradually uncovering the complex web of connections between obesity, dyslipidemia, and kidney health. Future studies should continue to explore these relationships to discover new therapeutic approaches for preserving renal function in obese individuals. By drawing this conclusion, the present study emphasises the significance of recognising dyslipidemia as a major contributor to kidney injury in non diabetic obesity.

These results highlight the importance of incorporating routine microalbuminuria testing into the clinical assessment and management of obesity. Identifying individuals at risk of renal problems is crucial. Therefore, conducting adequate research to study the complex relationships between obesity, dyslipidemia, and renal health is advised. By overcoming the challenges posed by the worldwide obesity epidemic, clinicians can develop effective preventive and intervention plans.

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STUDY ON VITAMIN D AND ALCOHOL RELATED PSYCHIATRIC DISORDERS.

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Abstract

Background

Deficiencies in vitamin D, which is linked to increased bone mineral density, are a worldwide epidemic. Psychiatrists have shown that low vitamin D levels are linked to psychotic symptoms, depression, schizophrenia, and, more recently, alcohol-related mental disorders. Among the most common mental illnesses globally, alcohol-related disorders rank high. That is why we decided to check for a link between low vitamin D blood levels and mental health issues after drinking. The reason for this examination was to look at vitamin D levels in two gatherings: one consisting of fifty patients with alcohol-related mental disorders and another consisting of fifty healthy controls.

Materials and methods: Taking place over the course of two years, from 2012 to 2014, this case control research was carried out at a tertiary care teaching hospital in Kochi, Kerala. Fifty individuals were evaluated for vitamin D levels; fifty were considered controls and fifty were classified with alcohol-related mental disorders as indicated by the Worldwide Arrangement of Illnesses, tenth rendition, Analytic Standards for Exploration. From the venous blood tests, the vitamin D levels were surveyed using Abbot Architect.

Results: itamin D insufficiency was found in 60% of the cases (30 people) and 26% of the controls (13 people). A p-value less than 0.001 indicates a statistically significant difference.

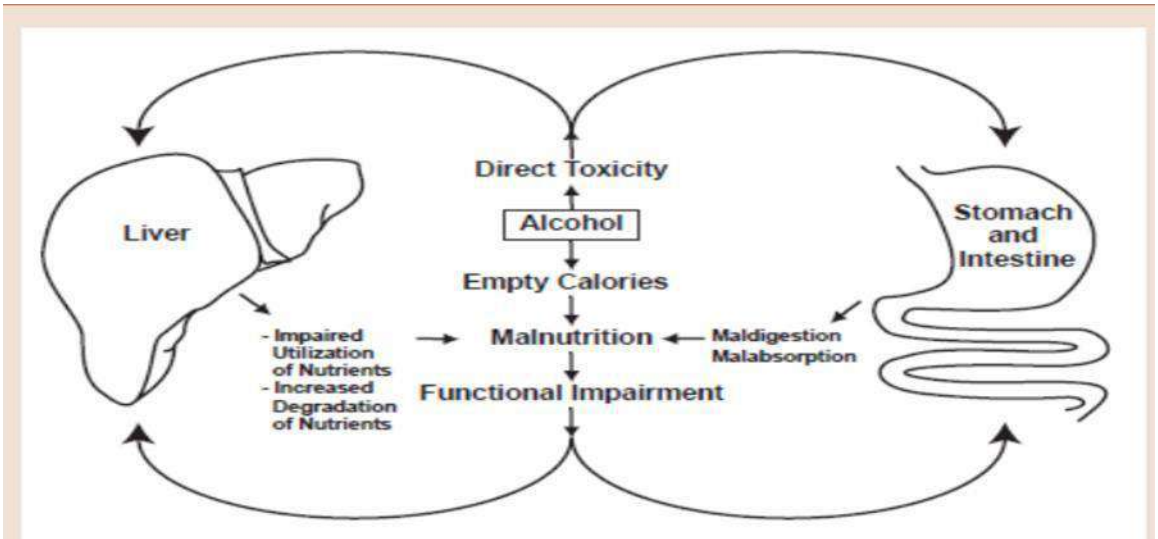
Conclusion: Compared to the control group, the patients in this research had substantially decreased blood vitamin D levels. A lack of sunlight, an unhealthy food, malabsorption, ethanol-induced liver damage, and an unhealthy lifestyle are all factors that contribute to low 25(OH)D levels in those who drink too much. Please validate the relationship between vitamin D deficiency and alcohol-related mental problems by conducting further case-control studies using bigger random samples.

Keywords: Alcohol; Alcohol use disorder; Vitamin D

Introduction

India traverses the entire tropical side of the equator, from 8.4° N to 37.6° N. The widespread assumption that Vitamin D (Vit D) insufficiency is rare in India stems from the fact that the vast majority of its inhabitants reside in regions that get abundant sunshine throughout the year.1 The published statistics, however, show that vitamin D insufficiency is widespread throughout India and affects people of all ages and both sexes.2-4. Somewhere about one billion individuals on our planet aren't getting enough vitamin D.5 According to previous research, a large percentage of the Indian population suffers from vitamin D insufficiency and has inadequate calcium consumption (ranging from 50 to 90%).2 Not only can a poor diet contribute to vitamin D deficiency, but so do alcoholics, inflammatory rheumatological illnesses, skin problems, kidney disease, and liver disease.

Common alcohol related psychiatric problems are alcohol dependence syndrome, alcohol induced mood disorders, alcohol induced psychosis. People who drink alcohol regularly often have low vitamin D levels, even if their livers aren't severely damaged. Despite these findings, very little is had some significant awareness of the vitamin D status of the individuals who experience the ill effects of both liquor use confusion and major depressive disorder (AUD/MD) simultaneously.



Reduced 25(OH)D levels in alcoholics are thought to be caused by a lack of sun exposure, an unhealthy diet, ethanol-actuated liver harm, and malabsorption.6 Vitamin D inadequacy was viewed as in 64 percent of alcohol use disorder patients treated by Sudan Prasad Neupane (2013) 72.Similar to other research on alcohol-abusing groups, our findings show that there is a high pervasiveness of vitamin D inadequacy (Lee, 20128; Naude et al., 2012 9).Vitamin D inadequacy is normal in alcohol treatment samples, and research by Sudan Prasad Neupane (2013) 7 demonstrates a correlation between this condition and the severity of alcohol use disorders. Possible reasons for low vitamin D status incorporate restricted sun openness, malabsorption, diminished adipose tissue, and inefficient hepatic hydroxylation 10, according to one research. Despite this, many people who regularly use alcohol suffer from inadequate intakes of certain micronutrients.

Materials and Methods: Patients using the inpatient and outpatient services of a tertiary care teaching hospital's psychiatric department in Kochi, Kerala, were the subjects of this case control research. Following the criteria and agreement of the Institutional Moral Panel and with the members' educated composed assent, the exploration was completed north of a two-year time span from October 2012 to October 2014. An example size of 40 cases and 40 controls was resolved utilizing information from the writing on vitamin D and significant burdensome issue. The confidence level was set at 95% and the power at 80%. Half of the participants were cases and half were controls. The patients ranged in age from fifteen to eighty years old, and they were all diagnosed with an alcohol-related mental disease according to the International Classification of Diseases, Tenth Revision, Diagnostic Criteria for Research (ICD- 10-DCR). The research did not include patients who were on vitamin D medication, had kidney illness, liver disease, or thyroid problems. Fifty healthy people who were similarly aged were used as a control group.

Procedure Methodology

The criteria included in this investigation were 25(OH) D levels, which were evaluated using Abbot Architect 1.

Sample Collection

A strict protocol for aseptic collection of venous blood samples was followed. The participants in this research were patients whose blood samples were requested for vitamin D assessment within the specified time period by the biochemistry laboratory and who met the criteria described above. For the duration of the vitamin D test, the blood samples were kept at -20oC.

Test Method

Chemiluminescence Immunoassay

Principle In order to quantify vitamin D in human blood and plasma, the engineer 25-Goodness nutrient D test use CMIA Technology, which is a chemiluminescence immunoassay. This deferred one-step immunoassay incorporates an example pre-treatment. The measure diluent, paramagnetic antivitamin D-covered microparticles, and pre-treatment reagent are blended in with the example.Once the microparticles coated with antivitamin D have been incubated, a conjugate complex of biotin and biotin acridinium is introduced to the reaction mixture. This combination attaches to the unoccupied restricting locales of the microparticles. Washing is trailed by the expansion of pretrigger and trigger answers for the response combination.

Relative light units are used to quantify the chemiluminescent response that follows. The ARCHITECT I system optics' relative light unit detection is indirectly related to the sample's vitamin D content.

Reference Range[11,12]

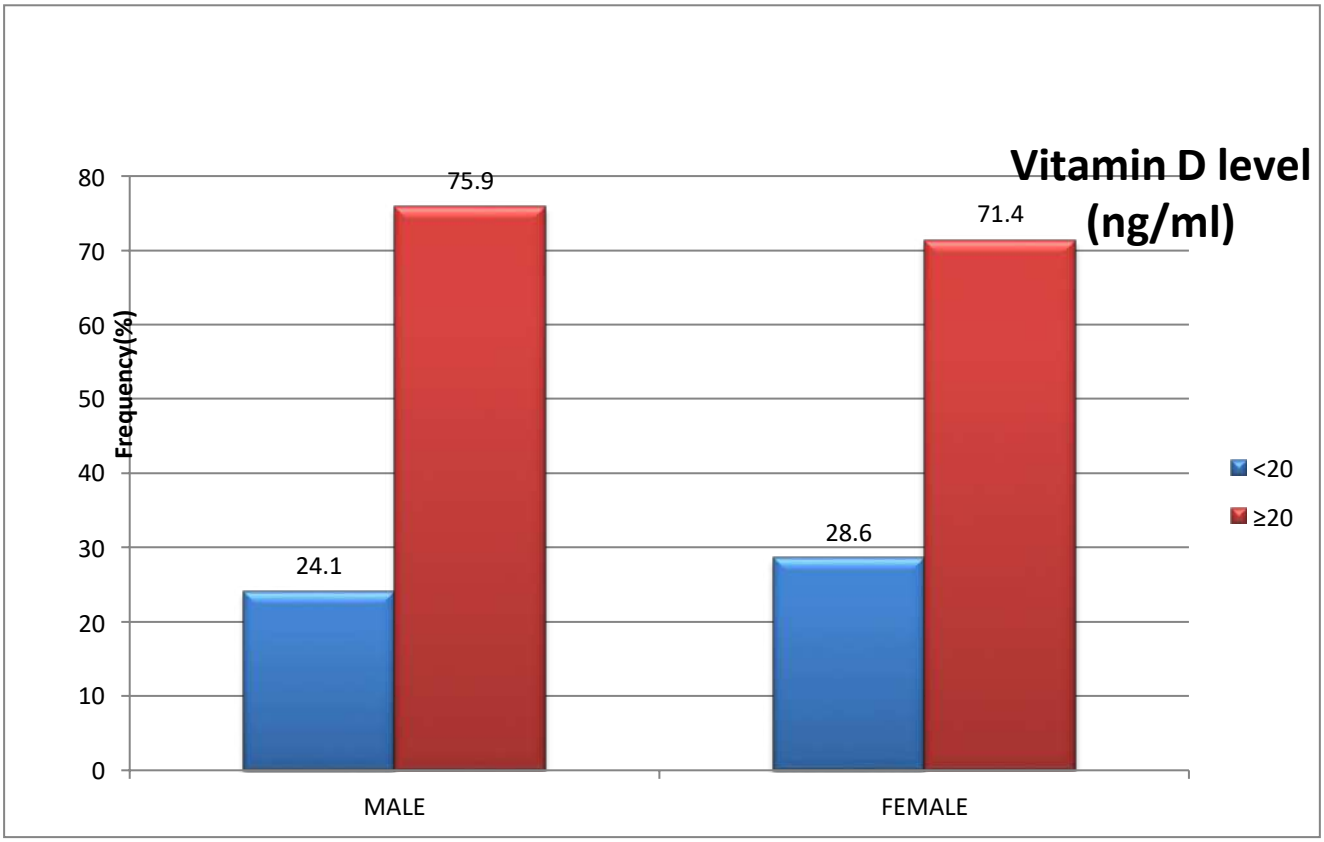
Vitamin D Deficiency = <20 ng/mNormal = >30 ng/ml

Data Analysis by Statistic Data was analysed using IBM SPSS Statistics 20 Windows, which is developed by SPSS Inc. and located in Chicago, USA. Data are presented as percentages or frequencies for all categorical categories. To determine whether two category variables were associated, chi-square analysis was used. The risk's odds ratio was calculated. The age method for the two gatherings were looked at utilizing a free two-example t-test. At the point when the p-esteem was lower than 0.05, factual importance was established.

Results

DEFICIENCY OF VITAMIN D AND GENDER IN CONTROL

	GROUP	NO	VITAMIN D				P VAUE
			<20		≥20		
			NO	%	NO	%	
GENDER	M	29	7	24.1%	22	75.9%	0.979
	F	21	6	28.6%	15	71.4%	

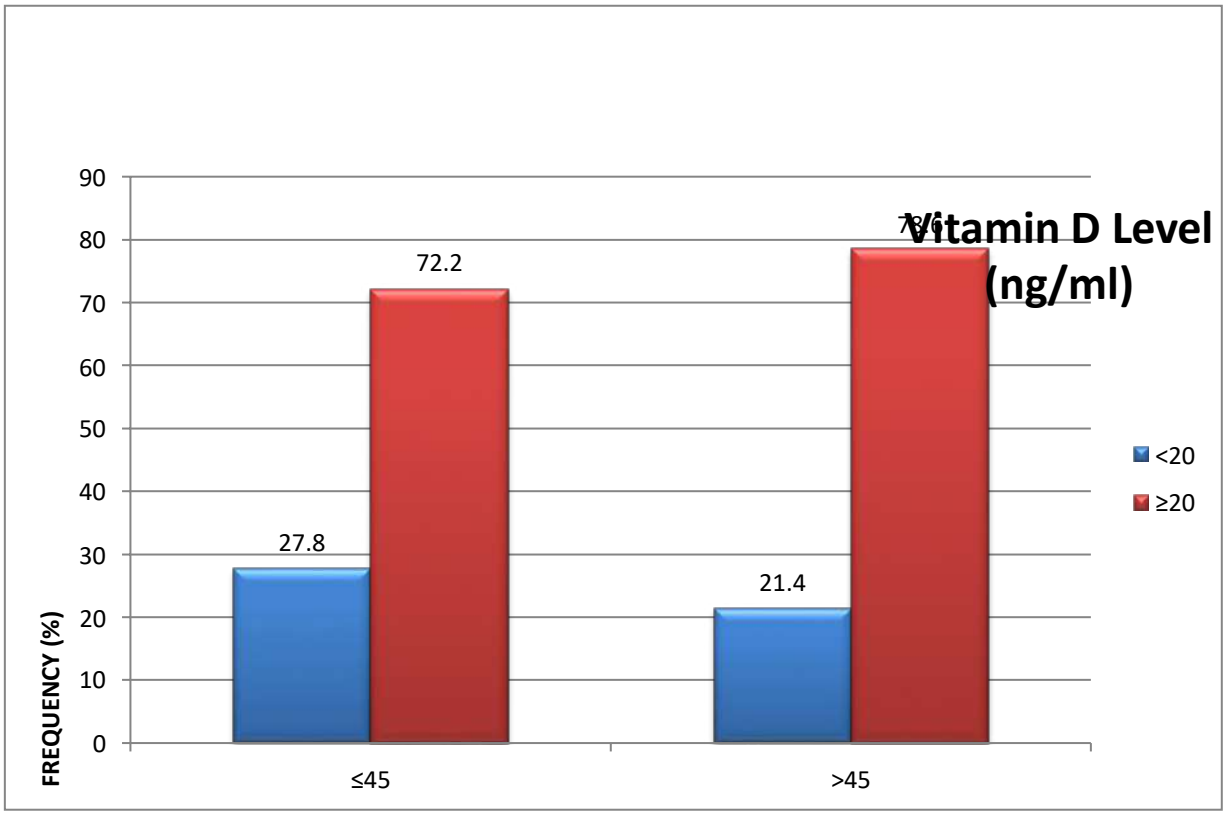


Gender:

As per the study, among the controls with Vitamin D deficiency24.1%(7)were Males and 28.6%(6)Females. The discrepancy did not reach statistical significance.

ASSOCIATION BETWEEN VITAMIN D DEFICIENCY & AGE AMONG CONTROL

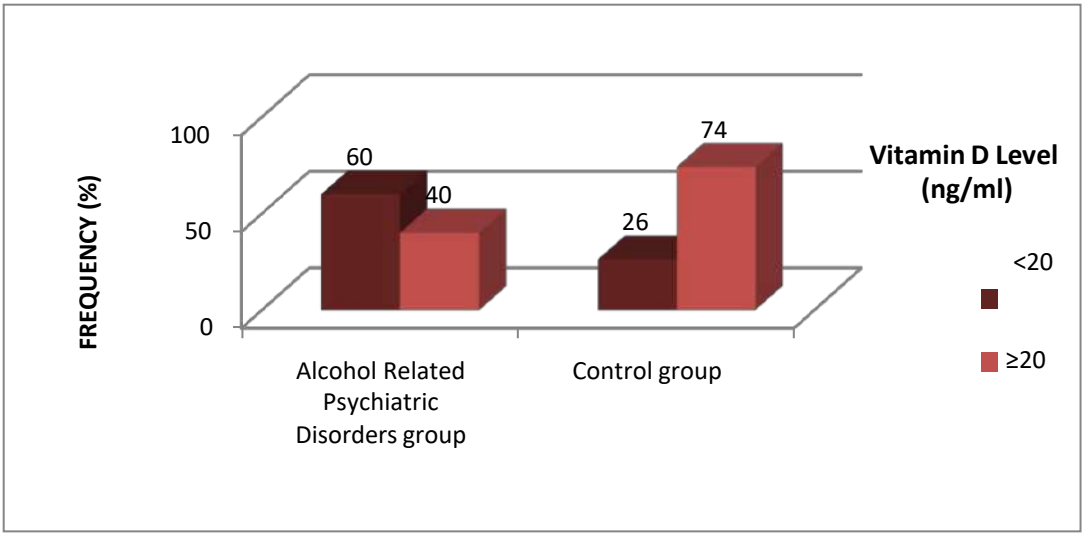
	GROUP	NO	VITAMIN D				P VAUE
			<20		≥20		
			NO	%	NO	%	
AGE	≤45	36	10	27.8%	26	72.2%	0.734
	>45	14	3	21.4%	11	78.6%	



Age Group
The age range of the controls with vitamin D insufficiency was 25–45 for 27.8% (10 individuals) and 21.4% (3 individuals) for another group. But the difference was not statistically significant.

Vitamin D deficiency and alcohol-related psychotic disorders–a correlation.

GROUP	NO	VIT D DEFI		OR	P VALUE
		<20			
		NO	%		
CONTROLS	50	13	26%		<0.001
ALCOHOL RELATED	50	30	60%	4.26	



Alcohol related psychiatric disorders and Vitamin D deficiency.
Vitamin D deficiency was found in 60% (30 patients) in the alcohol-related mental disorders group, compared to 26% (13 patients) in the benchmark group. There was a genuinely tremendous contrast. It also demonstrates that compared to controls, people with alcohol-related mental illnesses are 4.26 times bound to foster vitamin D insufficiency.

Discussion

Common alcohol related psychiatric problems are alcohol dependence syndrome,alcohol induced mood disorders ,alcohol induced psychosis. Reduced 25(OH)D levels in alcoholics are thought to be caused by a lack of sun exposure, an unhealthy diet, ethanol-induced liver damage, and malabsorption.[6] Indeed, even without any significant liver impedance, vitamin D levels tend to be lower in persistent alcohol drinkers. [13] In spite of these anecdotal findings, very little is known about the vitamin D status of individuals who experience the ill effects of both liquor use turmoil and major depressive disorder (AUD/MD) simultaneously. Vitamin D insufficiency was found in as much as 64 percent of alcohol use disorder patients treated by Sudan Prasad Neupane in 2013.Our findings on vitamin D insufficiency rates are consistent with those of previous research that have looked at people who abuse alcohol. (Lee,2012[8]; Naude et al., 2012 [9].

Sudan Prasad Neupane 2013 [7] provides more evidence that vitamin D insufficiency is prevalent in alcohol treatment samples and that there is a correlation between the seriousness of liquor use issues and vitamin D deficiency. This research found that factors such as less sun exposure, malabsorption, decreased fat tissue, and impaired hepatic hydroxylation [10] might be the reasons why your vitamin D levels are too low.Despite this, many people who drink alcohol do not get enough of certain micronutrients.[14] Patients with alcohol use disorder are more likely to seek medical attention when they also suffer from co-occurring mood problems.15 This suggests that patients admitted to hospitals for alcohol use disorder may not have more serious alcohol misuse issues, but that they may need treatment for extra depressive symptoms and illicit drug usage. Sudan Prasad Neupane2013 [7] reported before that major depressive disorder was present in more than a third of the sample of those receiving alcohol therapy. Without comorbidities that further lower vitamin D levels, those with liquor use problems sufficiently extreme to require systematization are probably going to have the most un-ideal vitamin D profile.

In our case control study we included the subjects having alcohol related psychiatric problems (alcohol dependene syndrome,alcohol induced mood disorders ,alcohol induced psychosis)as cases.While only 26% of the control group suffered from vitamin D deficiency, 60% of the patients with alcohol-related mental problems did.for the data in table 2 c A statistically significant difference was observed (p Value<0.001). Additionally, the results demonstrate that the risk of developing vitamin D insufficiency is 4.26 times higher in individuals with alcohol-related mental illnesses compared to controls (0.26 odds ratio). The findings are consistent with those of earlier research.

We need further studies in both the general public and clinical samples to determine if vitamin D interacts negatively with alcohol-use disorder and other co-occurring mental disorders.

Summary

- The study was conducted as a prospective case control study among 50known alcohol related psychiatric patients attending the outpatient wings of psychiatry department, AIMS. 50Agematched healthy subjects are taken as controls. The primary objectives were to concentrate on the predominance of lack of vitamin D in, Alcohol related psychiatric disorders. Secondary objective was to generate a hypothesis related to Lack of vitamin D liquor related mental problems and controlsVitamin D levels were measured by Chemiluminescence immunoassay using ABBOT ARCHITECT PLUS
- Vitamin D insufficiency was found in 28.6% of females and 24.1% of men in the study's controls. Statistical analysis failed to reveal a meaningful difference.The age range of the controls with vitamin D insufficiency was 27.8% (ten) for those aged 45 and under, and 21.4% (three) for those aged 45 and above. Nevertheless, there was no statistically significant change.
- Vitamin D deficiency was found in 60% (30 patients) in the alcohol-related mental disorders group, compared to 26% (13 patients) in the benchmark group. It was a measurably tremendous distinction. Vitamin D insufficiency is 4.26 times more likely to occur in people with alcohol-related mental problems compared to controls.Thus, vitamin D insufficiency is a distinct risk factor for mental health issues associated with alcohol use.

Conclusion

- Vitamin D insufficiency is prevalent yet sometimes overlooked; nonetheless, it may play a significant role in mental health issues; hence, it is imperative that this pressing matter be addressed.
- Possibly this might provide a solution to some lingering mysteries in the field of psychiatry about the origins of significant mental illnesses.
- The management of several treatment-resistant mental diseases may be aided by being knowledgeable about vitamin D insufficiency and various neuropsychiatric disorders.
- Vitamin D insufficiency or alcoholism may be the underlying cause of alcohol-related mental illnesses; nevertheless, further research is required to draw any firm conclusions.
- One possible approach is to perform case-control studies in this particular group to investigate any potential links to serious mental diseases.
- Vitamin D insufficiency and mental diseases may be causally related, but only after a randomised placebo controlled experiment.

  “Prevention is better than cure,” the old adage goes. For the readily avoidable vitamin D shortage, this is the case.

  Therefore, in order to prevent vitamin D insufficiency in the Indian population, it is recommended that they stick to the current dietary calcium guidelines of 1 to 1.5 gm and 2000 IU of vitamin D per day.

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Section: Psychiatry

Original Research Article

EXPLORING BIOLOGICAL CONTRIBUTORS TO DEPRESSION IN POSTMENOPAUSAL WOMEN IN CENTRAL KERALA

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Abstract

Background: Postmenopausal women are susceptible to depression due to various factors. Identifying these risk factors is crucial for recognizing individuals at a higher risk of developing depression during this life stage. Therefore, this study aimed to explore the biological contributors to depression in postmenopausal women. **Materials and Methods:** The study involved 50 cases and 50 age-matched controls. The diagnosis of depression in postmenopausal women was based on the International Classification of Diseases-10 Diagnostic Criteria for Research (ICD 10 DCR). Sociodemographic, medical, and gynecological data were collected using a specialized proforma. Menopausal symptoms were assessed with the Menopausal Rating Scale. Statistical analysis, including chi-square tests and odds ratios, compared data between cases and controls. **Result:** The study found significant associations between postmenopausal depression and the severity of menopausal symptoms, history of premenstrual symptoms, past depression, and medical disorders. **Conclusion:** This study brought out that several biological factors make postmenopausal women vulnerable to depression. These factors can serve as markers for identifying individuals at higher risk. Early recognition of these risk factors enables timely intervention and support, ultimately leading to improved outcomes for affected individuals.

INTRODUCTION

Menopause is a biological transition from reproductive to non-reproductive life, characterized by the cessation of menstruation for 12 consecutive months.[1] While the majority of women transition through menopause without experiencing psychiatric issues, approximately 20% may experience depression at some point. This phase brings about various physiological changes resulting from the decline in ovarian function and the natural aging process. Menopausal symptoms, including vasomotor, somatic, psychological, and sexual disturbances, can significantly impact the quality of life for postmenopausal women.[2] Depression, anger, anxiety, and mood swings are commonly observed psychological symptoms in postmenopausal women. In addition to this, menopause often coincides with important life events, such as changes in the family structure, such as children leaving home, and changes in women's roles, responsibilities, and relationships further adding to the distress.[3] Depression can have detrimental effects on both mental and physical health, leading to functional impairments and a decline in social functioning.[4] Unfortunately, many cases of postmenopausal depression go undiagnosed due to various factors. Therefore, it is crucial to identify the contributors associated with depression in postmenopausal women to recognize those who are vulnerable and enable early diagnosis and treatment. However, in India, research is scarce on this subject, and specifically, no case-control studies have been conducted.

Addressing this research gap is essential for a better understanding of the factors contributing to depression in postmenopausal women. This will ultimately improve the overall well-being and mental health outcomes of postmenopausal women.

MATERIALS AND METHODS

The study was initiated in a tertiary care hospital in central Kerala from February 2021 to 2022 August

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after approval from the Institutional Ethics Committee. The study sample included 50 postmenopausal women with depression and 50 normal postmenopausal women in the control group. The purposive sampling method was used in this study. Postmenopausal women who met the International Classification of Diseases 10 Diagnostic Criteria for Research (ICD-10 DCR) for depressive episode, under the age of 65 were included as cases with their consent. The cases were taken from the psychiatric outpatient department. After the exclusion of psychiatric disorders by using the MINI plus questionnaire, 50 age-matched postmenopausal women were included in the control group from the general population. A semi-structured proforma was prepared for this study, which included socio-demographic details, and medical and gynecological history. Each subject was assessed for menopausal symptoms using the Menopause Rating Scale. Data were entered into Microsoft Excel and analyzed using the Statistical Package for the Social Sciences (IBM SPSS), version 25. Sociodemographic variables, menopausal symptom scores, and other variables were analyzed as proportions or percentages for categorical variables and as either mean ± SD or median (IQR) for numerical variables. The chi-square test was used to analyze associations between study variables and groups. Differences in mean variables between groups were analyzed using the unpaired t-test for parametric variables and the Mann-Whitney U test for nonparametric variables. p-value <0.05 was considered statistically significant.

RESULTS

Sociodemographic details among groups are described in [Table 1]. The mean age of cases was 53.58 ± 4.58 and 54.56 ± 3.82 years in the control group. There was no statistical difference between the two groups in educational status, occupational status, marital status, religion, and socioeconomic status. No statistical significance was obtained for the presence of family history of depression (P=0.010) [Table 4] and duration of the reproductive period (P = 0.682) [Table 2]. Most of the cases had comorbid medical disorders (P = 0.015, Odds ratio=2.73) [Table 3]. History of premenstrual symptoms was present in 30% of cases and 6% of controls (P = 0.002, Odds ratio = 6.714). The mean score of MRS [Table 2] of cases was 27.12 ± 5.374 and of controls was 7.90 ± 3.72(P= <0.001).

Table 1: Comparison of the sociodemographic variables

Variables	Cases (n=50) Mean ± SD	Controls (n=50) Mean ± SD	t/ χ2	P value
Age (years)	53.58±4.58	54.56±3.82	1.161	0.248
Education				
Primary High school Above 10th	6(12%) 25(50%) 19 (38%)	4 (8%) 27(54%) 19 (38%)	0.477	0.788
Occupational status				
Employed Unemployed	13(26%) 37 (74%)	12 (24%) 38 (76%)	0.053	0.817
Marital status				
Married Unmarried Widowed	44 (88%) 1 (2%) 5 (10%)	43 (86%) 2 (4%) 5 (10%)	0.345	0.842
Socioeconomic status				
Upper middle class Lower middle class Lower class	11 (22%) 37(74%) 2(4%)	15 (30%) 35(70%) 0	2.671	0.263

Table 2: Association with menstruation-related factors

Variables		Cases (n=50) Mean ± SD	Controls (n=50) Mean ± SD	χ2 Value	P Value
Premenstrual symptoms	Present Absent	15 (30%) 35(70%)	3 (6%) 47 (94%)	9.756	0.002
MRS score		27.12 ± 5.37	7.90±3.72	20.801	0.000
Duration of the reproductive period		35.44± 3.61	35.72±3.201	0.410	0.682

Table 3: Association with medical disorders

Medical disorders	Groups				χ2 Value	p Value
	Case		Control			
	n=50	%	n=50	%		
Present Absent	35 15	70.0 30.0	23 27	46.0 54.0	5.911	0.015

Table 4: Association with the past history of depression and family history of depression

Variables		Cases (n=50) Mean ± SD	Controls (n=50) Mean ± SD	χ2 Value	P Value
Past history of depression	Present Absent	4 (8%) 46(92%)	0.00 50 (100%)	4.167	0.041

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Family history of depression	Present Absent	8(16%) 42 (84%)	3 (6%) 47 (94%)	2.554	0.110

DISCUSSION

The present case-control study aimed to explore the biological contributors to depression in postmenopausal women. The study included a sample of 50 postmenopausal women with depression (cases) and 50 postmenopausal women without depression (controls), matched for age.

The postmenopausal period has been recognized as a critical period associated with an increased vulnerability to depression and psychiatric disorders.[5] Findings from the Study of Women's Health across the Nation Mental Health Study (SWAN MHS) reveal a substantial three-fold higher risk of developing major depression during the late perimenopausal or postmenopausal phase compared to the pre- or early perimenopausal phase.[6] Hormonal changes during the menopausal transition, including decreased estrogen levels, have been implicated as risk factors for the development of depressive symptoms.[7]

Multiple studies have demonstrated the impact of hormonal changes during menopause on the development of various physical, sexual, vasomotor, and psychological symptoms.[8] Hot flashes have been associated with fluctuations in estradiol and follicle-stimulating hormone (FSH) levels, and the reduction of estrogen levels can lead to decreased serotonin levels and an upregulation of the 5-HT2A receptor in the hypothalamus, resulting in hot flashes.[9] The relationship between menopausal symptoms and depressive symptoms has been consistently reported in previous research.[10] These symptoms can be highly bothersome and represent a major risk factor for sleep disturbances, anxiety, and depressive symptoms.[11] In the current study, the severity of menopausal symptoms was assessed using the Menopausal Rating Scale (MRS). The findings revealed a significantly higher mean MRS score among women with depression (cases: 27.2 ± 5.37) compared to those without depression (controls: 7.90 ± 3.71). These results are in line with previous research that has consistently linked menopausal symptoms to depression in postmenopausal women.[10,12,13] This study also revealed a significant association between a history of premenstrual symptoms and postmenopausal depression, with a higher prevalence of premenstrual symptoms observed among women with depression (cases) compared to those without depression (controls) which is consistent with a previous study conducted by Ahuja et al.[14] This association underscores the importance of understanding reproductive hormone sensitivity as a potential contributor to depression.[15]

A longer reproductive period, characterized by a later age at menopause and extended exposure to endogenous estrogen, was seen to be associated with a decreased risk of depression in later life as per previous studies.[16,17] However, in the present study, the duration of the reproductive period did not significantly differ between cases and controls, hence could not establish any significant effect. It is important to acknowledge limitations such as sample size, recall bias, and the inclusion of women who underwent surgical menopause, which could have influenced our results. In the present study, hormone replacement therapy (HRT) was not used by any of the participants, which limited the examination of its relationship with postmenopausal depression.

The present study revealed a significant association between prior depression and postmenopausal depression, as cases had a higher prevalence of past depression compared to controls (P=0.041, Odds ratio=2.087). This finding is consistent with earlier research that has consistently established a link between a past history of depression and the increased risk of depression during the postmenopausal period.[15,18,19] In contrast, while some studies have suggested that a family history of depression may be a predictor of major depression in the postmenopausal period, the present study did not find a significant association in this regard. It is important to note that the methodology used in the present study only accounted for diagnosed relatives, potentially underestimating the true prevalence of family history.[20]

This study also revealed a significant association between the presence of chronic medical diseases and postmenopausal depression. Among the cases, there was a higher prevalence of medical disorders compared to the controls. This finding adds to the existing body of research that those with chronic medical conditions are at higher risk for depression.[21,22] Chronic illnesses not only impact physical health but also have a profound effect on individuals' psychosocial well-being.

This case-control study provides valuable insights into the biological contributors to depression in postmenopausal women. The findings highlight the importance of considering menopausal symptoms, premenstrual symptoms, past history of depression, the presence of medical disorders as potential indicators for identifying women at risk of postmenopausal depression.

However, several limitations need to be considered. The smaller sample size and lack of representation from the broader community may limit the generalizability of the findings, highlighting the need for larger-scale studies to confirm these results. Recall bias is also a potential limitation, as participants may face challenges accurately recalling past experiences or symptoms. Therefore, future research utilizing larger sample sizes and more diverse populations, along with a prospective study design, is warranted to further investigate these risk factors and enhance our understanding of postmenopausal depression.

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CONCLUSION

This case-control study investigated the biological contributors to depression in postmenopausal women. The study brought out that several biological factors make postmenopausal women vulnerable to depression. Specifically, the severity of menopausal symptoms, history of premenstrual symptoms, past history of depression, and presence of medical disorders were identified as significant risk factors for postmenopausal depression.

These findings are consistent with previous research, supporting the validity and generalizability of the study's results. The identified risk factors can serve as valuable indicators for identifying postmenopausal women who are at a higher risk of developing depression.

Further research is warranted to delve deeper into the factors that did not show significant associations in this study and to explore additional variables that may contribute to the development of postmenopausal depression.

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Section: Biochemistry

Original Research Article

PREVALENCE OF OVERWEIGHT AND OBESITY AMONG MEDICAL STUDENTS AT A TERTIARY CARE HOSPITAL IN KERALA

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Abstract

Background: The prevalence of overweight and obesity has increased to about three times since 1975. The worldwide prevalence of obesity has been reaching pandemic proportions. The WHO had estimated that in 2016, more than 1.9 billion adults worldwide (39%) were overweight, and approximately 650 million (13%) were obese. The medical students are future health-care providers who are more prone for obesity due to their sedentary lifestyle, stress, and disordered eating habits and spending more time with their books and gadgets. The objective is to assess the prevalence of overweight and obesity among medical students in Govt Medical College Thrissur. To study association between Obesity and factors like age, sex, year of MBBS, physical activity, type of diet , smoking, alcohol, sleep, screen time, frequency of consumption of non-vegetarian food, junk food, co-morbidities, frequency of skipping meals.
Materials and Methods: After obtaining the informed consent, the pre-designed questionnaire with 11 questions (mcqs) was sent to first, second and third year MBBS students in the age group 17-24 yrs Government Medical College, Thrissur (N=300) BMI was calculated with QUETELTS index(Body Mass Index: weight in kilo gram divided by height in meter square) and the participants were categorized on the basis of Asia-Pacific BMI CLASSIFICATION. Categorical data is presented as percentage. Tests of significance were performedusing Chi-square test and fischers exact test. **Result:** 13.3% of MBBS students were found to have Grade 1 obesity and 20.7% were overweight according to Asian BMI classification. Among the variables analyzed for association with Obesity, Sex, type of accommodation and frequency of consumption of junk food were found to be statistically significant. **Conclusion:** Since, obesity is a prominent risk factor for several comorbidities it is necessary to take precautions to prevent and control it.

INTRODUCTION

The prevalence of overweight and obesity has increased to about three times since 1975 worldwide.[1] Noncommunicable diseases (NCDs) are one of the leading causes of death and disability in developed and developing countries and include conditions such as cardiovascular diseases, cancer, chronic respiratory diseases, diabetes, obesity, and cognitive impairment [2]While genetic and environmental risk factors for non-communicable diseases are well known, there is a strong emphasis on the modifiable elements related to lifestyle at the individual level.[2-4] The worldwide prevalence of obesity has been reaching pandemic proportions. The WHO had estimated that in 2016, more than 1.9 billion adults worldwide (39%) were overweight, and approximately 650 million (13%) were obese.[5] The current trajectory of this prevalence acceleration would result in almost half of the world's population being overweight or obese by 2030.[6] The main cause for obesity in Indians is a nutritional shift from the typical carbohydrate diet to high calorie fast food which is more common among college students.[7]
The medical students are future health-care providers. They are themselves more prone for obesity due to their sedentary lifestyle, stress, and disordered eating habits and spending more time with their books and gadgets. Hence this study aims to assess the prevalence of overweight and obesity among medical students at a tertiary care hospital in Kerala.

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Objectives

- To assess the prevalence of overweight and obesity among first, second and third year MBBS students in Government Medical College, Thrissur in the age group 17-24 yrs
- To study association between Obesity and factors like age, gender, year of MBBS, physical activity, diet, smoking, alcohol, sleep, screen time, frequency of consumption of non-vegetarian food, junk food, co-morbidities, frequency of skipping meals among first, second and third year MBBS students in Government Medical College, Thrissur in the age group 17-24 yrs.

MATERIALS AND METHODS

A descriptive study was done among first, second and third year MBBS students in Government Medical College, Thrissur in the age group 17-24 yrs

Inclusion criteria:

MBBS students studying in first, second and third year at Govt medical college Thrissur who are willing to take part in the study.

Exclusion Criteria

1. Students on chronic medications.
2. Students with history of past or present pregnancy
3. Students not willing to participate in the study
4. Physically challenged students.

Sample Size- n =300(100 students each from first ,second and third year MBBS)sample size calculated by the formula n=4pq/d2, p=25.7% as calculated from least response rate obtained from the study conducted by Manojan KK etal in 2019 (Prevalence of Obesity and Overweight among Medical Students based on New Asia-Pacific BMI Guideline) q=1-p , d=14% precision ;Adjusted sample size N = 375 by using the formula N = (n /(1-d) where n is sample size and d is the anticipated dropout rate of 20%).Sampling technique used was Census sampling and the study period was 1 month after approval from IRC/IEC Study procedure: Questionnaire validation was done by senting the mcqs randomly to 10 mbbs students in the study population. Students who participated in the study received verbal and written explanation of the procedure involved and the expected benefits from the study. After obtaining the informed consent, the pre-designed questionnaire was sent to subjects and explained that results would only be expressed as a group data and confidentiality would be maintained throughout and after the study.

Questionnaire:It contains participant's demographic and socioeconomic characteristics such as age, sex, income, smoking, alcohol, family history, diet pattern, and physical activity, comorbidities of obesity such as GERD, arthritis and OSAS, history of being bullied for obesity, and history of any efforts taken for weight reduction. The participants were categorized on the basis of BMI, according to Asia-Pacific BMI CLASSIFICATION (under weight (BMI < 18.5), normal (BMI = 18.5 to 22.9), over weight (BMI= 23 to 24.9), obese grade 1 (BMI=25 to 29.9) and obesity grade 2 (BMI >30)).To measure weight, standardized weighing scales used. To measure height, portable anthropometry rod was used. Participants were asked to stand with back against rod, look straight, and heels touching the rod without any footwear. Sliding horizontal bar gently touches head compressing hair. BMI is calculated with QUETELTS index (weight in kilograms/height in square metre). The data will be entered in Microsoft excel and further analysis will be done using SPSS 16.0 version software.

RESULTS

A descriptive study was done among 300 students of first, second and third year MBBS students at Government Medical College, Thrissur in the age group 17-24 yrs. Categorical data is presented as percentage. Tests of significance were performed using Chi-square test and fischers exact test with statistical significance level set at $P < 0.05$.

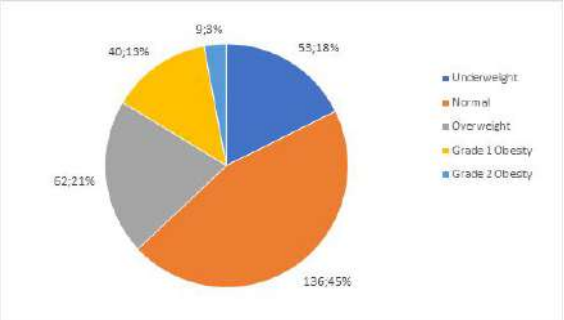


Figure 1: Distribution of study participants based on Asia Pacific BMI Classification

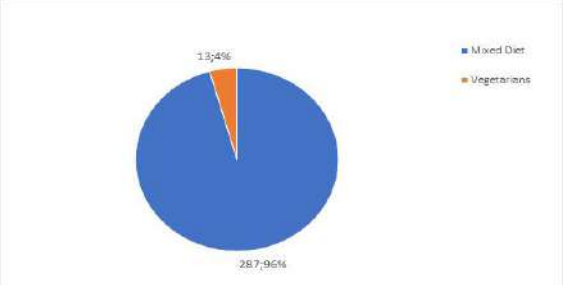


Figure 2: Distribution of study subjects based on diet

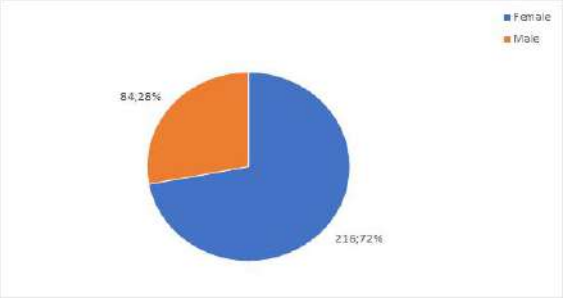


Figure 3: Distribution of study subjects based on gender

Highest proportion of the study participants (45.3%) had normal BMI. 37% of the study participants had high BMI, while 17.7% of the study subjects were underweight. [Figure 1]

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Majority of the study participants (95.7%) were consuming a mixed diet, while only 4.3% were pure vegetarians. [Figure 2]

Majority of the study subjects (72%) were females. [Figure 3]

Table 1: Frequency table of MBBS Students according to year of study.

Year of MBBS	Frequency	Percentage
1	129	43 %
2	115	38.3 %
3	56	18.7 %

Among the study subjects, 43% were from 1st year, while 38% were from 2nd year and the least number of participants were from 3rd year.

Table 2: Descriptive statistics of Height, Weight and BMI of MBBS students

	Height in m	Weight in kg	BMI
Mean	1.62	57.7	21.9
Median	1.61	55.3	21.7
Standard deviation	0.101	12	3.37
Minimum	1.4	37	15.2
Maximum	1.93	99	31.9

The mean height of the study subjects was 1.62m. The median height was 1.61m (+/- 0.101m).
The mean weight of the study subjects was 57.7kg. The median weight was 55.3kg (+/- 12kg).
The average BMI of the study subjects was 21.9. The median BMI was 21.7 (+/- 3.37).

Table 3: Frequency of consumption of non-vegetarian food

How often do you consume non-vegetarian food?	Frequency	Percentage
Daily	171	59.2 %
Weekly	106	36.7 %
Monthly	12	4.2 %

Nearly 60% of the study participants consumed non-vegetarian food daily.

Table 4: Frequency of consumption of junk/fast food

How often do you eat junk food / fast food?	Frequency	Percentage
Never	3	1.0 %
Daily	30	10.0 %
Weekly	193	64.3 %
Monthly	74	24.7 %

Junk food was consumed daily by 10% of the study subjects, whereas majority of the study population reported only weekly consumption of junk food.

Table 5: Association between Obesity and various factors

Sl. No	Variable	Groups	Not Overweight/ Obese	Overweight/ Obese	P value (Chi-square Test)
1	Gender	Female	145(48.3%)	71(23.7%)	0.018#
		Male	44(14.7%)	40(13.3%)	
2	Year of MBBS	1st year	89 (29.7%)	40(13.3%)	0.174#
		2nd year	67(22.3%)	48(16%)	
		3rd year	33(11%)	23(7.7%)	
3	Accommodation	Day scholar	13(4.3%)	16(5.3%)	0.042#
		Hosteler	176(58.7%)	95(31.7%)	
4	Diet	Vegetarian	11(3.7%)	2(0.7%)	0.142*
		Non-Vegetarian	178(59.3%)	109(36.3%)	
5	Smoking	No	189(63%)	109(36.3%)	0.136*
		Yes	0(0%)	2(0.7%)	
6	Alcohol	No	189(63.0%)	110(36.7%)	0.370*
		Yes	0(0%)	1(0.3%)	
7	Sleep	<6hrs	3(1%)	1(0.3%)	0.216*
		6-8hrs	131(43.7%)	87(29%)	
		>8hrs	55(18.3%)	23(7.7%)	
8	Physical Activity	Never	28(9.3%)	17(5.7%)	0.703#
		Occasionally	80(26.7%)	47(15.7%)	
		Weekly	15(5%)	5(1.7%)	
		Daily	66(22%)	42(14%)	
9	Screen time	<2hrs	14(4.7%)	6(2%)	0.795#
		2-4hrs	86(28.7%)	51(17%)	
		>4hrs	89(29.7%)	54(18%)	
10		Daily	101(34.9%)	70(24.2%)	0.197*
		Weekly	69(23.9%)	37(12.8%)	

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	Frequency of consumption of non-vegetarian food	Monthly	10(3.5%)	2(0.7%)	
11	Junk food	Never	3(1%)	0(0%)	0.012*
		Daily	12(4%)	18(6%)	
		Weekly	121(40.3%)	72(24%)	
		Monthly	53(17.7%)	21(7%)	
12	Co-morbidities (GERD	Nil	183(61%)	111(37%)	0.088*
		Yes	6(2%)	0(0%)	
13	Frequency of skipping of meals	Never	67(22.3%)	26(8.7%)	0.177*
		Sometimes	93(31%)	64(21.3%)	
		Weekly	5(1.7%)	3(1%)	
		Daily	24(8%)	18(6%)	
14	Age	</= 20yrs	98(32.7%)	46(15.3%)	0.081#
		>20years	91(30.3%)	65(21.7%)	

*Fisher's-Exact Test #Chi-square Test

Among the variables analyzed for association with Obesity; Sex, Type of accommodation and Frequency of consumption of junk food were found to have association with statistical significance. (p value <0.05).

DISCUSSION

From this study, highest proportion of the study participants (45.3%) had normal BMI, 37% of the study participants had high BMI, while 17.7% of the study subjects were underweight. Among the variables analyzed for association with obesity: females (23.7%) were affected than males (13.3%), hostelers (31.7%) were found to be more obese than day scholars (5.3%) and those consuming junk food daily (6%) were mostly included in the obese category compared to others.

Obesity is a condition which is characterized by an increase in the size and amount of fat cells in the body. It is a chronic disorder that is officially classified as a disease by the World Health Organization (WHO), and also by several other national and international organizations.[8] The definition of the term given by the Obesity Medicine Association captures both its complex etiology and diverse consequences: "a chronic, relapsing, multi-factorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical and psychosocial health consequences.[9] The body mass index (weight/height^2) is widely used in the adult populations, and a cutoff point of 30 kg/ m^2 is recognised internationally as a definition of adult obesity. The Western Pacific Regional Office of the World Health Organization (WHO) has recommended lowering the BMI cutoff levels for Asian people to 23.0 for overweight and 25.0 for obesity.[10] The obesity related disorders occur at a much lower body mass index (BMI) in ethnic Asian populations than in ethnic Caucasian. Elevated body fat percentage and cardiovascular risks at low body mass index levels among Asian people, including Indians were well documented.[11] According to studies conducted by Defronzo et al, an impaired appetite regulation in obese individuals is because of cerebral insulin resistance, leading to both an increased hepatic glucose production and a reduced muscle glucose intake, thus implicating the brain directly in the pathogenesis of the metabolic syndrome.[12] New evidence is emerging which indicates that obesity without type 2 diabetes results in a three-fold increase in the risk of developing Alzheimer's disease (AD).[13] Furthermore, because of the strong correlation between Alzheimer's disease and impairments in insulin and insulin-like growth factor gene expression and its signaling in the brain, AD may represent a brain-specific form of diabetes, sometimes referred to as "type 3 diabetes."[14]

Medical students are usually more prone to obesity due to their lifestyle with less physical activity and disordered eating habits. According to studies conducted by Parajuli K et al among medical allied science students in Karnataka, 28.7% were overweight among male students and 18.6% among female students.[15] In another study conducted by Rekha et al in Chennai among medical students, the overall prevalence of overweight and obesity was 53.2% among which 30.3% were obese exclusively and also that 63% of obese individuals consume fast food once or more in a week whereas only 22.8 % of non-obese fall under the same category.[16] The prevalence of Obesity in India has reached epidemic proportions in the 21st century, with morbid obesity affecting atleast 5 % of the country's population.[17] According to studies conducted by Gajewska et al in Poland, excessive body weight is perceived as one of the most grave public health problems. The university years also had a high influence on shaping adult habits, concerning everyday diet, physical activity, tobacco smoking, and alcohol consumption. Acquiring unhealthy lifestyle behaviours at very early stage of life may also result in a distorted body view.[18] According to studies conducted by Moldakozhayev et al, ageing of the body is associated with a physiological slowdown of metabolism and, consequently, an increase in abdominal obesity.[19] Both, early mitochondrial dysfunction and adipocyte hyperplasia, which also leads to metabolic dysregulation may be caused by an unhealthy lifestyle in students, support the physiological process of slowing down the metabolism. This may clarify higher BMI values in students in the second year of our study in comparison to the first year.

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According to studies done by Alhashemi et al, long college days, combined with daily fatigue, can lead to fast food being a popular choice for medical students which also supports findings in our study.[20]

CONCLUSION

Since, obesity is a prominent risk factor for several comorbidities it is necessary to take precautions to prevent and control it. This study can also create awareness among medical students to adopt a healthy lifestyle. There is also an increased psychosocial impact on these students due to obesity which can be looked upon.

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Section: Biochemistry

Original Research Article

CLINICAL AND LABORATORY SPECTRUM OF MULTIPLE MYELOMA: A TERTIARY CARE EXPERIENCE FROM CENTRAL KERALA

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ABSTRACT

Background: Multiple myeloma (MM) is a malignant plasma cell disorder with varied clinical presentations and significant morbidity. While global data on MM are well-documented, regional insights—especially from government tertiary care centres in India—remain limited. This study aimed to evaluate the trend of M-band detection through serum protein electrophoresis (SPEP) and describe the clinical and laboratory profile of MM patients in central Kerala.

Materials and Methods: A retrospective, hospital-based cross-sectional study was conducted at Government Medical College, Thrissur, including 82 MM patients diagnosed between January 2022 and March 2024. Data on clinical presentation, laboratory parameters, radiological findings, and treatment details were extracted from medical records. Additionally, 7451 SPEP reports from January 2018 to March 2024 were reviewed to determine the prevalence of M-band positivity.

Results: The mean age at diagnosis was 61.5 years, with equal male and female representation. Among those screened via SPEP, 4.8% were M-band positive, and 98.78% of confirmed MM cases exhibited M-band positivity. Lower back pain (43.90%) and fractures (17.07%) were the most common presenting complaints. Anaemia was present in 65.85% of patients, while hypercalcemia and renal dysfunction were seen in only 4.87% and 24.39%, respectively. Vertebral lytic lesions were most frequent (43.90%), though 39.02% showed no skeletal abnormalities. IgGκ was the predominant paraprotein subtype. ISS Stage 1 was most common, with a third of patients undergoing diagnostic workup. Bortezomib-based regimens were the most frequently used treatments.

Conclusion: This study reveals a shifting clinical landscape of MM in Kerala, marked by earlier detection, diverse presentations, and reduced frequency of advanced disease features. SPEP remains a highly sensitive diagnostic tool. These findings underscore the importance of routine screening, early diagnosis, and improved access to diagnostic and treatment facilities to optimize MM outcomes in regional healthcare settings.

Keywords: Multiple Myeloma, Serum Protein Electrophoresis, M-band, Clinical Profile, Kerala.

INTRODUCTION

Multiple myeloma (MM) is a malignant clonal disorder of plasma cells characterized by the presence of a monoclonal (M) protein in serum and/or urine, bone marrow plasmacytosis, and evidence of end-organ damage such as anaemia, hypercalcemia, renal dysfunction, or lytic bone lesions. Globally, MM accounts for approximately 1% of all cancers and over 10% of hematologic malignancies.[1-3] The disease predominantly affects individuals over the age of 60, and its incidence

continues to rise with increasing life expectancy and improved diagnostic capabilities.[3] While comprehensive national registries are still developing in India, smaller regional studies suggest rising detection rates, likely due to heightened clinical suspicion and better access to laboratory diagnostics, including serum protein electrophoresis (SPEP).[4]

The clinical presentation of MM has been undergoing a shift over recent decades. Earlier studies reported classic symptoms like bone pain and renal failure at the time of diagnosis in the majority of patients.[5] However, more recent findings reveal a growing number of asymptomatic or minimally symptomatic cases, often diagnosed incidentally through routine blood tests or evaluations for unrelated complaints.[5] In the Indian context, this trend is compounded by the heterogeneity of healthcare access and health-seeking behaviour. Despite a growing number of MM cases being diagnosed in Kerala, published data is scarce describing the clinical and laboratory profile of affected patients, especially from government-run tertiary centres where a diverse patient demographic is served.

Given the central role of M-band detection in SPEP as a diagnostic and screening tool for monoclonal gammopathies and the evolving clinical profile of MM, it is imperative to understand regional patterns in both laboratory and clinical parameters.[1,2] This is especially relevant for Kerala, where robust public health systems coexist with significant non-communicable disease burden. This study was therefore undertaken with two objectives: (1) to determine the pattern and prevalence of M bands in serum protein electrophoresis specimens at a tertiary care centre from January 2018 to March 15, 2024, and (2) to describe the clinical profile of patients diagnosed and treated for multiple myeloma at Government Medical College, Thrissur, from January 2022 to March 15, 2024.

MATERIALS AND METHODS

This hospital record-based cross-sectional study was conducted at Government Medical College, Thrissur, between 16th April 2024 and 30th April 2024. The study population included all patients diagnosed with multiple myeloma who sought treatment at the institution between January 1, 2022, and March 31, 2024. A total of 82 patients were included using convenience sampling. The objective was to assess clinical and laboratory profiles using a semi-structured questionnaire that captured demographic details (age, sex), department of presentation, presenting complaints, and key laboratory parameters such as ESR, serum calcium, creatinine, subtype of immunoglobulin, plasma cell percentage, beta-2 microglobulin levels, serum protein electrophoresis (SPEP) results, radiological findings, and treatment details.

Data were obtained retrospectively from hospital records, including case files and department registers. Information on serum protein electrophoresis tests and M band positive cases from January 1, 2018, to March 15, 2024, was collected from the Special Investigation Laboratory of the Department of Biochemistry. M band positive cases from January 1, 2022, to March 15, 2024, were traced using their UHID and inpatient numbers, and corresponding case files were retrieved from the Medical Records Library. The hospital-based cancer registry was also used to identify CR numbers of patients treated in the Department of Oncology and Radiotherapy, and their records were obtained from the Medical College Chest Hospital. All data were compiled using the study questionnaire.

Data were entered and analyzed using Microsoft Excel. Descriptive statistics were used to summarize demographic details, clinical presentation, and laboratory findings. The study obtained ethical approval from the Institutional Ethics Committee (IEC) and Institutional Research Committee (IRC) of Government Medical College, Thrissur.

RESULTS

The study included 82 patients diagnosed with multiple myeloma. The mean age at diagnosis was 61.5 years, ranging from 35 to 87 years. The majority (36.58%) were between 60 and 70 years old, and both sexes were equally represented (M: F = 1:1). Most patients (78%) were residents of the Thrissur district, reflecting the regional patient distribution.

Screening and Diagnosis: Out of 7451 patients screened, 358 (4.8%) tested positive for M-band on serum protein electrophoresis (SPEP), highlighting the diagnostic yield in the regional healthcare setting. Among the study population, 81 patients (98.78%) had M-band positivity, confirming the high sensitivity of SPEP in diagnosing multiple myeloma.

Clinical Presentation: The most common presenting complaint was lower back ache (43.90%), followed by fractures (17.07%), pedal oedema (17.07%), and infections (9.75%). Multiple other symptoms were reported, reflecting the heterogeneous clinical spectrum of the disease, including bone pain (7.32%), fatigue (7.32%), and fever (7.32%)—a subset presented with atypical or incidental findings such as amyloidosis-related features, ataxia, and urine abnormalities.

Laboratory Parameters: Anaemia was prevalent in 65.85% of patients, with 24.39% having mild anaemia, 40.24% moderate, and 18.28% severe to very severe. ESR values were elevated (>20 mm/hr) in 33 patients (40.23%), though nearly half the data (48.78%) was unavailable. Hypercalcemia was observed in 4.87%, while hypocalcemia occurred in 18.29%. Only 26.82% had normal serum calcium levels, with data missing for half the cohort.β2-

microglobulin levels were raised in 40.24%, suggesting significant tumour burden, though data was unavailable for 54.87% of cases. Plasma cell percentage in bone marrow ranged widely: 8.53% had <10% involvement, while 13.8% had >50%. The majority (30.5%) had 10–40% plasma cell infiltration.

Immunoglobulin Typing: Among patients with data available (n=36), the most common paraprotein subtype was IgGκ (21.95%), followed by IgGλ (17.07%). A smaller fraction had IgA variants (each 2.43%).

Radiological Findings: Radiographic evidence of lytic lesions was most frequently found in the vertebrae (43.90%), followed by the skull (14.63%), pelvis (8.53%), and ribs (6.09%). Notably, 32 patients (39.02%) had no detectable skeletal lesions at presentation.

Renal Function and Staging: Renal dysfunction was identified in 24.39% of patients with serum creatinine >2 mg/dL. Using the International Staging System (ISS), Stage 1 was most common (17.07%), with Stage 2 and 3 equally represented (15.85% each).

Treatment: At the time of data collection, 36.58% were still under diagnostic workup. The most common treatment regimen was bortezomib-lenalidomide-dexamethasone (BLD), administered to 23.17%. Other regimens included bortezomib + dexamethasone (B+D) in 14.63% and CY-BD in 3.65%. A total of 7.32% were referred out for further management.



Figure 1: Screening and Diagnosis for M-band on serum protein electrophoresis

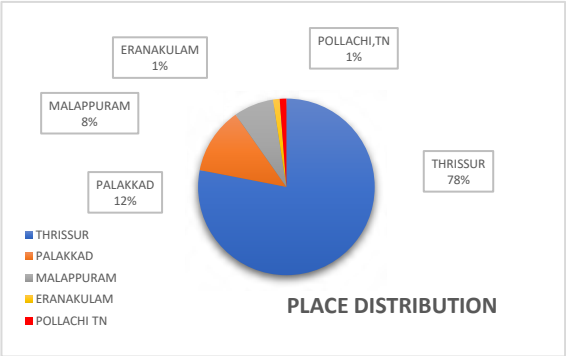


Figure 2: Distribution of patients according to their place

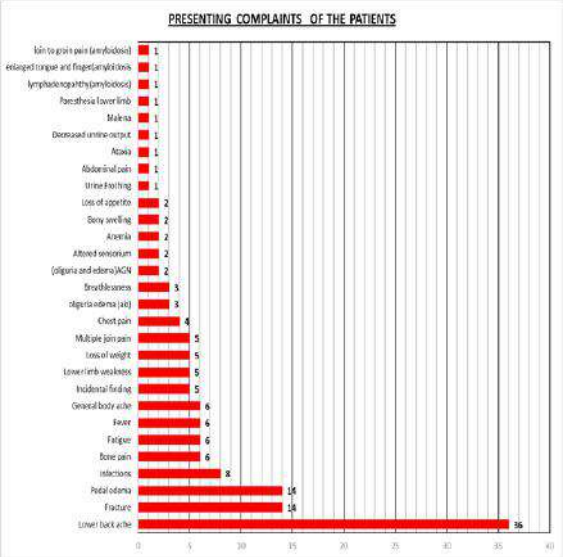


Figure 3: Presenting complaints of patients

Table 1: The Demographic and Clinical Characteristics

Variables:	N	%
Age in Years		
35-40	3	3.65
41-45	7	8.53
46-50	5	6.09
51-55	7	8.53
56-60	9	10.97
61-65	14	17.07
66-70	16	19.51
71-75	10	12.19
76-80	7	8.53
81-85	3	3.65
86-90	1	1.21
Sex		
Males	41	50
Females	41	50
District		
Thrissur	64	78.05

Palakkad	10	12.2
Malappuram	6	7.31
Ernakulam	1	1.22
Pollachi	1	1.22
Presenting Symptoms		
Lower back ache	36	43.90
Fracture	14	17.07
Pedal oedema	14	17.07
Infections	8	9.75
Bone pain	6	7.32
Fatigue	6	7.32
Fever	6	7.32
General body ache	6	7.32
Incidental finding	5	6.09
Lower limb weakness	5	6.09
Loss of weight	5	6.09
Multiple join pain	5	6.09
Chest pain	4	4.87
oliguria oedema (Aki)	3	3.65
Breathlessness	3	3.65
(oliguria and oedema) AGN	2	2.43
Altered sensorium	2	2.43
Anaemia	2	2.43
Bony swelling	2	2.43
Loss of appetite	2	2.43
Urine Frothing	1	1.21
Abdominal pain	1	1.21
Ataxia	1	1.21
Decreased urine output	1	1.21
Melena	1	1.21
Paraesthesia of lower limb	1	1.21
lymphadenopathy (amyloidosis)	1	1.21
enlarged tongue and finger (amyloidosis)	1	1.21
loin to groin pain (amyloidosis)	1	1.21
Anemia		
Mild <10	20	24.39
Moderate (8 – 10)	33	40.24
Severe (6.5 – 7.9)	8	9.75
Very severe (<6.5)	7	8.53
Normal	14	17.07
ESR		
Normal	5	6.09
20–100 mm at the end of 1 hour	11	13.41
100–200 mm at the end of 1 hour	22	26.82
Data Not Available	40	48.78
Serum Calcium		
Hypercalcemia	4	4.87
7–8.8 mg/dl (Hypocalcemia)	15	18.29
8.8–10.5 mg/dl (Normal)	22	26.82
Data Not Available	41	50
Type of Immunoglobulin		
IgGκ	18	21.95
IgGλ	14	17.07
IgAλ	2	2.43
IgAκ	2	2.43
Data Not Available	46	56.09
Plasma Cell Percentage		
<10	7	8.53
10–20	13	15.85
20–30	3	3.65
30–40	5	6.09
40–50	1	1.21
50–60	7	8.53
60–70	3	3.65
70–80	0	0
80–90	2	2.43
90–100	1	1.21
β2 Microglobulin Level		
Raised more than 2454 ng/ml	33	40.24
Normal	4	4.87
Data not available	45	54.87
Serum Protein Electrophoresis (SPEP)		
M BAND Positive	81	98.78

No Abnormal BANDS	1	1.22
Radiological Lesions		
Skull	12	14.63
Vertebrae	36	43.90
Pelvis	7	8.53
Rib	5	6.09
Sternum	3	3.65
Clavicle	3	3.65
Humerus	4	4.87
Femur	4	4.87
Sacrum	2	2.43
Mandible	1	1.22
No lesions	32	39.02
ISS Staging		
STAGE 3	13	15.85
STAGE 2	13	15.85
STAGE 1	14	17.07
Serum Creatinine		
> 2 mg/dl	20	24.39
< 2 mg/dl	62	75.60
Drug Therapy		
BLD	19	23.17
UNDER WORKUP	30	36.58
B+D	12	14.63
CY BD	3	3.65
CY B	1	1.22
REFERRED	6	7.32
B TH	3	3.65
C L D	1	1.22
C T D	2	2.43
B	2	2.43

DISCUSSION

The present study offers a comprehensive overview of the clinical and laboratory profile of multiple myeloma (MM) in a cohort of 82 patients from central Kerala. The mean age at diagnosis was 61.5 years, consistent with findings from large-scale studies such as the Mayo Clinic series, which reported a median age of 62.[5] Our cohort showed an equal sex distribution (M: F = 1:1), differing from the mild male predominance noted in earlier studies (e.g., M: F ratio of 1.56 in the 1960–1971 Mayo series and 1.27 in the 1972–1986 Italian series).[6] This variation may reflect regional demographic patterns or improved health-seeking behaviour among women in Kerala.

The diagnostic yield of serum protein electrophoresis (SPEP) in this study was notable, with 4.8% of 7,451 screened patients testing positive for M-band. Among confirmed MM cases, 98.78% exhibited M-band positivity, reaffirming SPEP's high sensitivity in diagnosing MM. This aligns with Kyle et al.'s findings, where a monoclonal spike was seen in over 76% of patients on serum electrophoresis and 75% on urine electrophoresis.[5] Our findings also emphasize the importance of routine screening, as many M-band-positive cases were likely identified during evaluations for non-specific symptoms or unrelated conditions.[3]

Musculoskeletal complaints dominated the clinical presentation in our cohort, with lower back pain (43.90%) and fractures (17.07%) being the most common. These findings are comparable to historical data, where bone pain was reported in 68% of cases in Kyle's series.[5] However, some patients presented with atypical or systemic symptoms such as pedal oedema, fatigue, and features suggestive of amyloidosis or ataxia. These observations are consistent with trends noted by Riccardi et al., who reported a shift toward more varied and less classic presentations of MM in recent decades.[6]

Laboratory analysis revealed that anaemia remains a prevalent feature (65.85%), similar to global data indicating anaemia in 60–70% of patients at diagnosis.[5,7] Elevated ESR was observed in 40.23% of patients, likely influenced by missing data (48.78%) or earlier disease detection. Interestingly, hypercalcemia—a hallmark of MM—was present in only 4.87% of our cohort, significantly lower than the ~30% reported in earlier studies.[5,6] This may again reflect earlier diagnosis before the onset of end-organ damage.

Renal impairment was noted in 24.39% of patients, considerably lower than the 55% reported in Kyle's cohort, possibly due to increased awareness and earlier referral.[5,8] Lytic lesions were found in 60.98% of patients, primarily affecting the vertebrae—consistent with prior studies where vertebral involvement predominated. However, nearly 40% of patients had no radiographic evidence of skeletal disease at diagnosis, which may indicate early-stage disease or the limited sensitivity of plain radiographs. Advanced imaging modalities such as PET-CT or MRI, which were not uniformly available during the study period, could have improved lesion detection.[1,9,10]

Section: Biochemistry

Original Research Article

SERUM MAGNESIUM AND TROPONIN T IN ACUTE CORONARY SYNDROME: INSIGHTS FROM A TERTIARY CARE TEACHING INSTITUTE

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Abstract

Background: Acute coronary syndrome (ACS) includes a spectrum of clinical conditions such as STEMI, NSTEMI, and unstable angina, all resulting from myocardial ischemia. Cardiac troponin T is a sensitive and specific biomarker of myocardial injury, while magnesium plays a critical role in cardiovascular stability. Emerging evidence suggests a possible inverse relationship between serum magnesium levels and myocardial damage severity. **Materials and Methods:** A comparative cross-sectional study was conducted over one year at Government Medical College, Kozhikode, involving 60 participants—30 ACS patients and 30 age- and sex-matched healthy controls. Serum magnesium was measured using a colorimetric method, and troponin T was assessed via chemiluminescent immunoassay. Statistical analyses included independent t-tests, Chi-square tests, and Pearson correlation. **Result:** The mean serum magnesium level in ACS patients was slightly lower than in controls (2.16 ± 0.37 vs 2.22 ± 0.298 mg/dL), while troponin T levels were significantly higher in cases (1.28 ± 1.96 vs. 0.0092 ± 0.004 ng/mL; $p < 0.001$). A significant negative correlation was found between magnesium and troponin T levels in the case group ($r = -0.644$, $p < 0.01$), indicating greater myocardial injury with lower magnesium levels. **Conclusion:** This study suggests reduced serum magnesium levels may be associated with increased myocardial damage in ACS. Routine magnesium assessment could be a valuable adjunct to troponin T in identifying high-risk patients and guiding management strategies in acute coronary settings.

INTRODUCTION

Acute coronary syndrome (ACS) encompasses a spectrum of clinical conditions, including ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina, all resulting from acute myocardial ischemia.[1] Diagnosis is based on a triad of clinical presentation, ECG changes, and elevated cardiac biomarkers, particularly troponin T, which is highly specific for myocardial injury. Troponin T, a subunit of the cardiac troponin complex, is released into the circulation during infarction and correlates with the extent of myocardial necrosis.[2,3]

Magnesium, an essential intracellular cation and cofactor in over 300 enzymatic reactions, plays a key role in cardiovascular physiology by modulating myocardial excitability, vascular tone, and arrhythmia risk.[4,5] Several studies have reported lower magnesium levels in patients with acute myocardial infarction and suggested a negative correlation with troponin levels, indicating its potential role in infarct progression.[1,6] In this context, the present study aimed to estimate and compare serum magnesium and troponin T levels in patients with ACS and healthy individuals and to evaluate the correlation between these two parameters.

MATERIALSANDMETHODS

This comparative cross-sectional study was conducted over one year, from 1 January 2015 to 31 December 2015, at Government Medical College, Kozhikode, to evaluate serum magnesium and serum troponin T levels in patients with acute coronary syndrome (ACS) compared to healthy controls. The Institutional Ethics Committee of Government Medical College, Kozhikode, approved the study.

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Thirty cases were recruited—hospitalized patients aged 30–70 years presenting with their first episode of ACS, including ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina, diagnosed based on clinical features and cardiac biomarkers. Controls were 30 healthy individuals within the same age range, with no evidence of ACS and normal ECG findings. Participants with severe skeletal muscle damage, infections, or inflammatory diseases were excluded. Informed written consent was obtained from all participants, and detailed clinical history, blood pressure, and body mass index were recorded.

Venous blood samples were collected under aseptic conditions. Serum magnesium was estimated using a colorimetric method with chlorophosphonazo III on the COBAS c-311 analyzer. Serum troponin T was measured using a high-sensitivity chemiluminescent immunoassay (Elecsys Troponin T hs STAT) on the COBAS e-411 analyzer.

All data analysis was performed using Microsoft Excel and the Statistical Package for the Social Sciences (SPSS, Version 16.0) software for Windows. Continuous variables were expressed as mean ± standard deviation. The Independent‘t’ test and Chi-square test were used to determine statistical significance between cases and controls. Pearson’s correlation coefficient (‘r’ test) was used to assess the relationship between serum magnesium and troponin T levels. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 60 participants were included in this comparative cross-sectional study, comprising 34 males (56.7%) and 26 females (43.3%) aged 30 to 70 years. The study population was divided into two groups: 30 patients diagnosed with acute coronary syndrome (cases) and 30 age- and sex-matched healthy individuals (controls). The mean age of the cases was 59.10 ± 7.59 years, while that of the control group was 62.40 ± 4.28 years. In the case group, males accounted for 60% and females 40%. Most cardiac events were observed in individuals above the age of 40 years, with nearly all female patients (n=12) experiencing their first cardiac event after the age of 45. Hypertension was prevalent in 73.3% of the case group. The mean body mass index (BMI) in the case group was 24.75 ± 2.46 kg/m².

Biochemical analysis revealed that the mean serum magnesium level in the case group was 2.16 ± 0.37 mg/dL, while the mean troponin T level was 1.28 ± 1.96 ng/mL. In comparison, the control group showed a slightly higher mean serum magnesium level of 2.22 ± 0.298 mg/dL and a significantly lower mean troponin T level of 0.0092 ± 0.004 ng/mL. Although the difference in mean magnesium levels between the groups was small, the difference in troponin T levels was markedly higher in the case group. Statistical analysis using the Independent 't' test confirmed that the difference in troponin T levels between cases and controls was highly significant ($p<0.001$).

Correlation analysis using Pearson’s correlation coefficient demonstrated a significant negative correlation between serum magnesium and troponin T levels in the case group ($r = -0.644$, $p < 0.01$), indicating that lower magnesium levels were associated with higher troponin T levels. In contrast, no significant correlation was observed between these variables in the control group ($r = -0.177$, $p = 0.35$). Neither group had a statistically significant correlation between magnesium or troponin T levels and age or BMI.

Table 1: Characteristics of the study population.

Variables	Cases	Controls
Quantitative		
Age in years (Mean±SD)	59.1±7.59	62.4±4.28
BMI(Mean±SD)	24.75±2.46	23.32±1.95
Serum Magnesium (Mean±SD)	2.16±0.37	2.227±0.29
Serum Troponin T (Mean±SD)	1.28±1.96	0.009±0.004
Qualitative		
Sex		
Male N(%)	18(52.9)	16(47.1)
Female N(%)	12(46.1)	14(53.9)
Hypertension		
Yes N(%)	22(53.6)	19(46.4)
No N(%)	8(42.1)	11(57.9)
Diabetes Mellitus		
Yes N(%)	21(65.6)	11(34.4)
No N(%)	9(32.1)	19(67.9)
Addictions		
Yes N(%)	13(61.9)	8(38.1)
No N(%)	17(43.5)	22(56.5)

Table 2: Correlation between Serum Magnesium(Mg),Troponin T(Trop t),Age and BMI

P/C			Trop t	age	BMI
P	Mg	Pearson Correlation Sig. (2-tailed)	**-.644	.229	.178
			.000	.224	.347
	Trop t	Pearson Correlation Sig. (2-tailed)		.112	*-.401

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				.556	.028
	age	Pearson Correlation Sig. (2-tailed)			.118
					.536
C	Mg	Pearson Correlation Sig. (2-tailed)	-.177	.019	-.196
			.350	.921	.298
	Trop t	Pearson Correlation Sig. (2-tailed)		-.135	.087
				.476	.649
	age	Pearson Correlation Sig. (2-tailed)			-.401
					.028

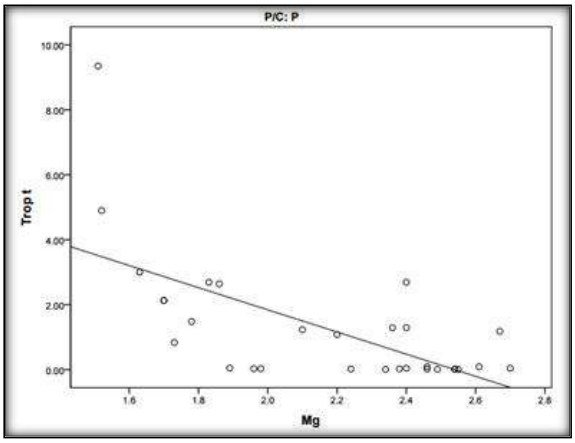


Figure 1: Correlation between magnesium and troponin T in cases

Pearson correlation r-value: -0.644 (p-value: 0.00)

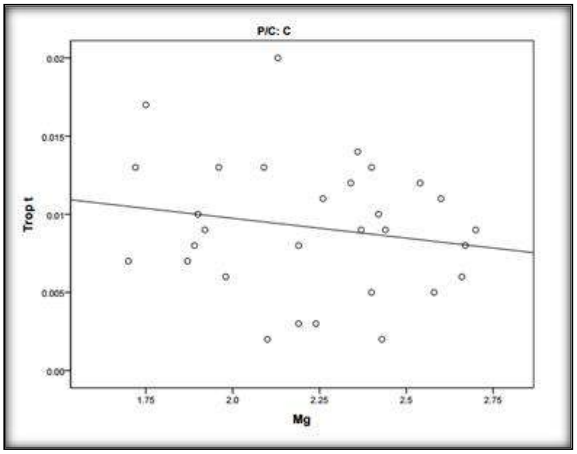


Figure 2: Correlation between magnesium and troponin T in controls

Pearson correlation r-value: -0.177 (p-value: 0.350)

DISCUSSION

In the present study, patients with acute coronary syndrome (ACS) exhibited significantly elevated serum troponin T levels and slightly lower serum magnesium levels than healthy controls. Although the difference in mean magnesium levels between cases (2.16 ± 0.37 mg/dL) and controls (2.22 ± 0.298 mg/dL) was modest, the difference in troponin T levels was pronounced and statistically significant ($p < 0.001$). A significant negative correlation was observed between serum magnesium and troponin T levels among ACS patients ($r = -0.644$, $p < 0.01$), indicating a potential relationship between lower magnesium levels and more significant myocardial injury. This correlation was not evident in the control group.

These findings agree with several previous studies that have demonstrated an inverse association between serum magnesium and the severity of myocardial infarction.[2,4,6-10] In a study by Quader et al., ACS patients had significantly lower mean serum magnesium levels (1.63 ± 0.27 mg/dL) compared to controls (2.35 ± 0.28 mg/dL), with hypomagnesaemia considered a contributing factor to myocardial damage.[2] Similarly, Singh et al. found that patients with lower serum magnesium levels were more prone to post-infarction complications such as arrhythmias and death.[4] Baset et al. also observed that serum magnesium was significantly lower in AMI patients with arrhythmias compared to those without, further supporting its prognostic value.[6] In contrast, a study by Annadatha et al. reported no statistically significant difference in magnesium levels between ACS patients and controls. However, a negative correlation with the Coronary Prognostic Index was noted.[5]

Additional studies further support the cardioprotective role of magnesium. Ajay Kumar and Shaveta Sagar found a weak negative correlation between serum magnesium and troponin T in ACS patients, suggesting lower magnesium may be linked to larger infarct areas.[11] Ramasamy et al. demonstrated that magnesium and related electrolyte ratios could be adjunctive markers for AMI diagnosis.[12] Guipeng An et al. found that low magnesium levels predicted a higher risk of major adverse cardiac events after stenting.[13] Long-term studies by Reffelmann and Wen Zhang et al. linked low serum or dietary magnesium to increased cardiovascular and all-cause mortality.[7,10] Furthermore, magnesium has shown benefits in improving heart rate variability in heart failure (Almoznino-Sarafian et al.),[14] and reducing left ventricular mass (Reffelmann et al.).[10] A meta-analysis by Xinhua Qu confirmed inverse associations between magnesium and total CVD events.[15] These studies emphasize the prognostic and potentially therapeutic significance of monitoring and managing magnesium levels in cardiovascular disease.

Our study supports the hypothesis that even marginal reductions in serum magnesium within the normal reference range may have clinical significance in the context of ACS. The lack of correlation between magnesium or troponin levels

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with age or BMI suggests that the observed relationships are independent of these variables. These findings highlight the potential utility of routine magnesium monitoring in ACS patients as a complementary biomarker alongside troponin T, especially in resource-limited settings.

CONCLUSION

This study identified a significant inverse correlation between serum magnesium and troponin T levels in patients with acute coronary syndrome, indicating that lower magnesium levels may be associated with greater myocardial injury. These findings, consistent with existing evidence, underscore the potential utility of serum magnesium as an adjunctive biomarker in the evaluation and risk stratification of ACS. Incorporating routine magnesium level assessment may enhance early detection of high-risk patients and inform targeted management strategies.

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The distribution of immunoglobulin subtypes in our study, with IgGκ being the most common, aligns with global trends. IgG accounts for approximately 60% of cases, followed by IgA and light chain-only variants.[2,5] Regarding disease staging, ISS Stage 1 was the most common (17.07%), with Stages 2 and 3 each accounting for 15.85%. This contrasts with historical cohorts, in which most patients presented with advanced disease, further highlighting the benefits of earlier detection.[11] Treatment regimens in our cohort were heterogeneous, reflecting ongoing diagnostic evaluations and evolving therapeutic approaches. Bortezomib-based combinations such as BLD and B+D were the most frequently administered, consistent with current practice favouring proteasome inhibitor-based induction therapies.[1-3] The fact that over a third of patients were still under evaluation or had been referred out underscores systemic delays and referral practices typical of tertiary care settings.

Overall, this study reflects an evolving clinical landscape of multiple myeloma in central Kerala, characterized by earlier diagnosis, a reduced incidence of severe biochemical abnormalities at presentation, and a more diverse clinical profile. These findings highlight the need for heightened clinical vigilance, the routine use of SPEP in evaluating unexplained anaemia or bone pain, and better access to diagnostic tools. Future studies incorporating long-term outcomes and advanced imaging are warranted to characterize MM in this regional context further.

CONCLUSION

This study demonstrates how the clinical picture of multiple myeloma in central Kerala is changing, with early detection, a variety of presentations, and a lower prevalence of severe disease characteristics such as renal failure and hypercalcemia. Serum protein electrophoresis showed high diagnostic sensitivity, confirming its use in regular screening. The results highlight the need for early diagnosis, heightened clinical vigilance, and prompt management to enhance patient outcomes in regional healthcare settings.

Limitations and Future Perspectives

The study's retrospective, single-centre design and incomplete records limited data accuracy for some parameters. Advanced imaging was not uniformly used, potentially underestimating disease extent. Future multicentric, prospective studies with standardized diagnostics and long-term follow-up are needed to better understand disease patterns and outcomes.

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Original Article

Genetics Section

Analysing the Functional and Structural Impact of Single Nucleotide Polymorphisms in Matrix Metalloproteinase 3 Gene: An In-silico Approach

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BY-NC-ND

ABSTRACT

Introduction: Matrix Metalloproteinase 3 (MMP3) is a vital member of the MMP family, known for its wide range of substrate specificity and proteolytic activity against Extracellular Matrix (ECM) components. The role of functional polymorphisms in the MMP genes has been previously investigated in relation to cancer susceptibility, particularly breast cancer. Several Single-Nucleotide Polymorphisms (SNPs) in the MMP3 gene have been linked to a number of clinical illnesses, such as Coronary Artery Disease (CAD); however, the results were not entirely conclusive.

Aim: To identify pathogenic missense SNPs in the human MMP3 gene and analyse their effects on structure and function.

Materials and Methods: This was a record-based cross-sectional study performed using data retrieved from online resources. The analysis was conducted using a series of different bioinformatic tools, for which ethical clearance was obtained from the institution. The online tools used included Sorting Intolerant from Tolerant (SIFT), PolyPhen-2, PhD-SNP, PANTHER, PROVEAN, and SNPs and GO to predict harmful non synonymous SNPs (nsSNPs). Further analysis was performed using I-Mutant 2.0, MutPred2, Consurf, and HOPE software. These tools were able to filter out damaging SNPs and predict the impact of deleterious SNPs on the structure and function of the MMP3 protein.

Results: This study predicted two potentially pathogenic SNPs (D175Y and Y116C) out of 443 missense SNPs from dbSNP, which is a database of SNPs available on the National Centre for Biotechnology Information website. Further analysis revealed that these SNPs were located in highly conserved regions and were predicted to decrease protein stability.

Conclusion: In this study, two potentially pathogenic SNPs (D175Y and Y116C) were identified. Characterisation of these SNPs can help us gain a better understanding of the molecular basis of clinical conditions. The results of this study can be further validated by designing population-based studies and wet lab experiments. This will help in augmenting research and personalised medicine.

Keywords: Computational molecular biology, Gene polymorphism, Human genome, Precision medicine

INTRODUCTION

The human genome is relatively large, comprising approximately six billion nucleotides. About 99.9% of the DNA sequences in the human genome are the same across individuals, with individual variations accounting for the remaining 0.1% [1]. Single Nucleotide Polymorphisms (SNPs), which refer to the substitution of a single nucleotide, are the most prevalent type of genetic variation. SNPs occur throughout the genome at a rate of one in every 1,000 base pairs. SNPs are broadly categorised into two types: synonymous and non synonymous (nsSNP). Non synonymous SNPs are responsible for protein variations and amino acid substitutions in humans, while synonymous SNPs do not change the amino acid sequences [2]. With the development of practical and readily accessible DNA sequencing tools, SNPs have gained substantial clinical significance over the past two decades. Regardless of their effects on the biological function of gene products, SNPs are increasingly recognised as valuable markers in mapping complex human diseases, population genetics, and evolutionary studies [3]. Efficient identification of important SNPs and understanding their impact on protein function will be beneficial for genetic studies aimed at elucidating the molecular basis of various diseases. Furthermore, targeted in-vitro and in-vivo experiments can be designed to predict the effects of specific SNPs [4]. In light of this, multiple studies are being conducted to predict the functional consequences of nsSNPs, particularly based on sequence information and structural attributes [5-10].

Matrix Metalloproteinases (MMPs) are a family of more than 25 zinc-containing enzymes that break down various proteoglycans, fibronectin, interstitial collagen, and basement membrane collagen during normal physiological remodelling and repair processes in development and inflammation [11]. MMP-3, also known as Stromelysin-1, is a crucial member of the MMP family that exhibits a wide range of substrate specificity. Additionally, MMP-3 plays a critical role in the remodelling of connective tissue by activating other MMPs, such as collagenase, matrilysin, and gelatinase B [12,13]. The role of MMP gene functional polymorphisms in cancer susceptibility, especially breast cancer, has been previously investigated. The 5A/6A polymorphism has been linked to patient survival, oestrogen receptor status, breast cancer risk, and tumour size based on multiple genome-wide association analyses [14]. However, the association between SNPs and breast cancer risk remains inconclusive and controversial, as it is largely influenced by the ethnicity of the population and sample size [14-16]. Apart from breast cancer, a meta-analysis indicates a significant correlation between gastrointestinal, colorectal, and oesophageal malignancies and the MMP-3-1171 5A/6A variation [17].

In addition to malignancies, MMP3 gene polymorphisms have been found to be associated with atherosclerosis. This is due to the critical role of MMP3 in the degradation of the Extracellular Matrix (ECM) of blood vessels. Several studies evaluating the influence of promoter polymorphism and MMP-3 (-1612 5A/6A) on CAD risk have produced contradictory results, including gender differences as well [18-20]. Two MMP3 polymorphisms, rs520540 A/G and rs679620 C/T, were associated with cerebral stroke risk; however, contrary results were obtained in a different population, probably due to racial differences [21].

Among these reported SNPs, distinguishing functional SNPs from neutral SNPs is a major challenge. Experimental wet lab studies aimed at identifying the effects of multiple SNPs are time-consuming, challenging, and costly. Applying computational approaches to filter out possibly detrimental SNPs is emerging as a novel strategy for understanding the molecular mechanisms of diseases [22].

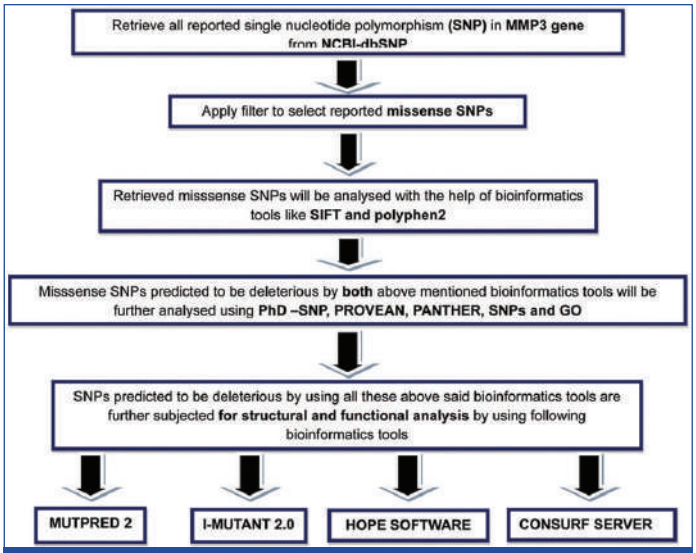
This was an in-silico study utilising bioinformatics computational tools with good predictive capabilities to identify the possible deleterious SNPs in the MMP-3 gene. Several studies have been conducted to find the association between specific SNPs in the MMP3 gene and diseases [14-21]. However, according to the literature search, there have been no comparable in-silico studies that examined every SNP in MMP-3 from the NCBI database. This study is expected to unravel the potential impact of polymorphisms on MMP3 structure and function. In addition, it can help in designing further specific experiments to confirm the importance of these SNPs in various clinical conditions. Combined with experimental data, it can aid in the development of personalised medicine.

MATERIALS AND METHODS

This online records-based cross-sectional study was conducted at Government Medical College, Manjeri, Kerala, India over a period from May to July 2024 (three months), which included data collection as well as analysis using online computational tools. IEC approval for this study was obtained from the institution (Ref. No: IEC/GMCM/133, date: 18/05/2024).

Methodology

The operational flow chart of this study is presented in [Table/Fig-1].



[Table/Fig-1]: Operational flow chart for in-silico analysis of missense SNPs in MMP3 gene.

The detailed methodology is as follows:

1. **Retrieval of SNPs in the MMP3 gene:** The ncbi SNPs database (dbSNP) (https://www.ncbi.nlm.nih.gov/snp/) was used to retrieve all known SNPs for MMP-3 in humans [23]. Non synonymous (missense) mutations were selected from the dataset for further analysis. The UniProt database was utilised to obtain the protein's sequence and other pertinent information.
2. **Prediction of the most deleterious missense SNPs:** The retrieved missense SNPs were analysed using bioinformatics-based web tools for identification of high-risk nsSNPs. Details of the tools used are provided in [Table/Fig-2]. Polymorphism phenotyping v2 (PolyPhen-2) and SIFT were the initial web-based tools employed. A SIFT score value between 0 and 1 indicates a potentially harmful effect, with scores below 0.05 being particularly concerning [24]. A PolyPhen score ranging from 0.85 to 1 is considered probably damaging [25,26]. SNPs identified as potentially harmful by the aforementioned tools were further subjected to additional bioinformatics tools for confirmation and further refinement [27]. The tools used included Predictions from Predictor of Human Deleterious Single Nucleotide Polymorphisms (PhD-SNP) [28], PANTHER-position-specific evolutionary preservation [29], PROVEAN [30], and SNPs and GO [31]. SNPs projected by every tool to be harmful were selected for further examination.
3. **Structural and functional analysis of SNPs with predicted damaging consequences:**
    a. **Identification of impact on the structural and functional properties of MMP3:** MutPred2 is a web application that integrates genetic and molecular data. It provides a ranked list of specific molecular changes with potential impacts on phenotype, along with a general pathogenicity prediction [32].
    b. **Prediction of change in stability of the MMP3 protein using I-Mutant 2.0 Suite:** The influence of nsSNPs on protein stability was assessed using the I-Mutant 2.0, which utilises the free energy change value (Delta Delta G: DDG). The DDG represents the difference between the free energy of the folded wild-type and mutant structures. DDG values fall into three categories: neutral (–0.5≤DDG≤0.5 kcal/mol), mostly stable (DDG >0.5 kcal/mol), or highly unstable (DDG <–0.5 kcal/mol) [33].
    c. **Prediction of evolutionary conservation of MMP3 using the ConSurf server:** The ConSurf web server was used to examine the evolutionary rate of conservation of amino acids in MMP3. ConSurf determines the conservation scores of the protein's amino acid positions by analysing the evolutionary relationships among similar

S. No.	Tool	Website	Based on	Input	Output
1	SIFT	https://sift.bii.a-star.edu.sg/	Sequence homology and the physical properties of amino acids	rsID	Score and prediction
2	Polyphen2	http://genetics.bwh.harvard.edu/pph2/	Structural and comparative evolutionary considerations	unitprotID or fasta protein sequence, amino acid change	Score and prediction
3	Phd-SNP	http://snps.biofold.org/phd-snp/phd-snp.html	Supervised learning based	FASTA sequence, swiss-prot code, amino acid change	RI value and prediction
4	PANTHER	https://www.pantherdb.org/	Sequence homology	FASTA sequence and substitutions	PSEP score and message
5	PROVEAN	http://provean.jcvi.org/index.php	Sequence homology	rsID	Score and prediction
6	SNPs&GO	https://snps.biofold.org/snps-and-go/snps-and-go.html	Supervised learning based	FASTA sequence, swiss-prot code, amino acid change	RI value and prediction
7	MUTPRED2	http://mutpred.mutdb.org	Machine learning-based method	Fasta sequence and amino acid change	Pathogenicity prediction, and a ranked list of specific molecular alterations
8	I-MUTANT	https://folding.biofold.org/i-mutant/	Support vector machine -based web server	Protein sequence and amino acid change	DDG value and reliability index

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9	CONSURF	https://consurf.tau.ac.il	Reconstruction of phylogenetic tree reflecting evolutionary relations	Uniprot ID	Amino acid sequence conservation scores
10	HOPE	https://www3.cmbi.umcn.nl/hope	BLAST, Homology modelling, information from Uniprot and Reprof	Unitprot ID, Fasta sequence and amino acid change	Effect of SNP on protein structure
11.	MUTATION3D	http://www.mutation3d.org/	Complete-linkage clustering	unitprotID, amino acid change	3D structure and linear protein models

[Table/Fig-2]: Details of the study's bioinformatics tools.

sequences. The highest conserved location is graded as 9, while conservation values range from 1 to 9 [34].

d. **Protein structure prediction and mutant analysis using HOPE software:** The web-based application Have (y) Our Protein Explained (HOPE) is used to analyse how SNPs affect the structural conformation and functionality of proteins. HOPE uses data from multiple web services and databases to generate reports regarding the impact of SNPs, which include text, graphs, and animations [35].

RESULTS

1. **Data on SNPs retrieved:** In the MMP3 gene, the dbSNP yielded a total of 4,120 SNPs. Among these SNPs, 443 were missense, 196 were synonymous, and 2,720 were located in the intronic region. For further in-silico research, only the missense or nsSNPs were selected. The remaining 761 SNPs belonged to other functional classes, for which authors were unable to retrieve information from dbSNP. The functional classes in dbSNP delineate the position of a polymorphism in relation to identifiable features of a specific gene transcript. Most functional classes are determined by the location of the variation in relation to the exon boundaries of the transcript [23]. Since present study requires only missense SNPs, only those were retrieved and analysed. The remaining 3,677 SNPs were excluded from the manuscript due to our inability to obtain accurate information about their functional class.
2. **Identification of predicted deleterious SNPs:** The selected missense SNPs were subjected to SIFT and PolyPhen-2 to identify possible deleterious SNPs. Out of the 443 SNPs, 14 were predicted to be damaging by both SIFT and PolyPhen-2 [Table/Fig-3] [24-26]. All 14 shortlisted SNPs identified by these two web-based techniques were further analysed using other bioinformatics tools: PhD-SNP, PANTHER, PROVEAN, and SNPs and GO [Table/Fig-4] [28-31]. Among all the analysed SNPs, two nsSNPs, rs201427128 (D175Y) and rs373783506 (Y116C), were predicted to be damaging by all six bioinformatics tools, including SIFT and PolyPhen.
3. **Prediction by MutPred2 on structural and functional effects [32]:** The selected two detrimental SNPs were analysed using MutPred2, which suggested a significant impact on the 3D structure of the MMP3 protein [Table/Fig-5].
4. **Prediction of changes in protein stability by I-Mutant 2.0 [33]:** I-Mutant predicted the extent to which the damaging SNPs alter the stability of the MMP3 protein. Both SNPs were predicted to decrease the stability of the protein [Table/Fig-6].
5. **Consurf server results [34]:** An analysis of conservation using the ConSurf server revealed that both SNPs, D175Y and Y116C, were located in highly conserved areas and were found to be exposed residues [Table/Fig-7].
6. **Predicted changes in the 3D structure of the MMP3 protein due to nsSNPs [35]:** HOPE software was used to generate results for both nsSNPs, with structural information obtained from the Protein Data Bank (PDB) database. The PDB ID used was 1SLM. In the case of D175Y, the mutant residue is larger, impacting hydrogen bond formation and its interaction with the metal ion in the original wild-type residue. Additionally, there is a disturbance in the ionic interaction made by the wild-type residue. For Y116C, the smaller residue results in an empty space in the protein core, which disrupts proper folding by causing a loss of hydrogen bonds in the core [Table/Fig-8].

S. No.	SNP rsID	Amino acid change	SIFT score	Polyphen-2 score
1	rs185081958	A391V	0.012	0.999
2	rs373335227	Y401H	0.001	0.992
3	rs201409153	Y344C	0.008	0.959
4	rs375381761	L294W	0	0.997
5	rs147533686	R316C	0	1
6	rs145941285	I159T	0.001	0.976
7	rs150552863	I220T	0.004	0.938
8	rs201427128	D175Y	0.015	0.92
9	rs140794544	P187S	0	0.993
10	rs141650167	R91W	0	1
11	rs61753776	W109G	0	0.996
12	rs142984123	Y116C	0.01	1
13	rs373783506	V144M	0.001	0.994
14	rs374032529	L10P	0.003	0.919

[Table/Fig-3]: Results of SIFT and Polyphen2 bioinformatics tools.

DISCUSSION

The MMP-3 gene, which codes for the MMP-3 protein, is a component of the MMP gene cluster located on chromosome 11q22.3. The NCBI gene ID for MMP3 is 4314, and its UniProt ID is P08254 [36,37]. The expression of the MMP3 gene may be regulated by DNA polymorphisms, which can exert allele-specific effects, resulting in fundamental variations in each person's susceptibility to diseases and other traits [11].

The goal of the current study was to use several computational techniques to discover SNPs that could be harmful and alter the structure or function of the MMP3 gene. A significant number of researchers have utilised in-silico tools to predict the structural and functional impact of SNPs on proteins, such as the human CTLA4 gene [38], IL-33 gene [39], and the androgen receptor gene [27]. This work represents the first comprehensive and systematic in-silico study of functional SNPs in the MMP3 gene.

Combining multiple computational methods can enhance the validity of predictions regarding damaging SNPs and improve efficiency. By employing six prediction methods (SIFT, PolyPhen-2, PROVEAN, PANTHER, PhD-SNP, and SNPs and GO), authors were able to obtain an integrated view of harmful SNPs in the MMP3 gene. Since

	Phd-SNP		PROVEAN		PANTHER			SNPs and GO	
Amino acid change	Prediction	RI	Score	Prediction	Preservation time	Message	Pdel	Prediction	RI
A391V	Neutral	7	-3.661	Deleterious	911	Probably damaging	0.85	Neutral	6
Y401H	Disease	4	-4.248	Deleterious	361	Possibly damaging	0.5	Neutral	6
Y344C	Disease	5	-7.689	Deleterious	455	Probably damaging	0.57	Neutral	6

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L294W	Neutral	7	-5.189	Deleterious	456	Probably damaging	0.57	Neutral	5
R316C	Neutral	1	-7.293	Deleterious	797	Probably damaging	0.74	Neutral	1
I159T	Disease	1	-4.934	Deleterious	911	Probably damaging	0.85	Neutral	4
I220T	Disease	5	-2.424	Neutral	176	Probably benign	0.27	Neutral	8
D175Y	Disease	5	-8.686	Deleterious	911	Probably damaging	0.85	Disease	3
P187S	Disease	2	-7.858	Deleterious	911	Probably damaging	0.85	Neutral	2
R91W	Neutral	1	-7.527	Deleterious	911	Probably damaging	0.85	Disease	3
W109G	Neutral	1	-12.841	Deleterious	911	Probably damaging	0.85	Disease	3
Y116C	Disease	3	-8.879	Deleterious	911	Probably damaging	0.85	Disease	2
V144M	Disease	2	-2.593	Deleterious	797	Probably damaging	0.74	Neutral	5
L10P	Disease	3	-4.604	Deleterious	176	Probably benign	0.27	Neutral	3

[Table/Fig-4]: Results of SNPs chosen to be damaging by SIFT and Polyphen when subjected to other bioinformatics tools.

SNP	Molecular changes (p-values <=0.05)	MutPred score
D175Y	Altered metal binding, ordered interface and Transmembrane protein Loss of Catalytic site at D175 Loss of Relative solvent accessibility Loss of Allosteric site at F174 Loss of Sulfation at Y172	0.921
Y116C	Alteration in ordered interface, Metal binding, DNA binding, Transmembrane protein Loss of Allosteric site at Y121 Altered stability	0.849

[Table/Fig-5]: Results from MutPred analysis.

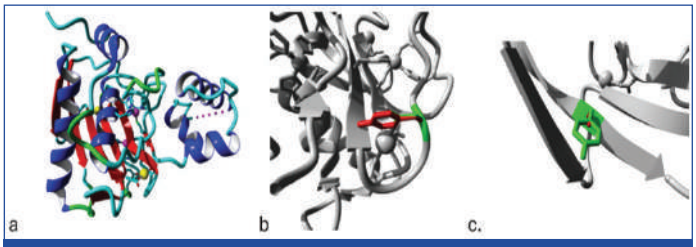
S. No.	SNP	DDG (Kcal/mol)	RI
1	rs201427128 (D175Y)	-1.40	3
2	rs373783506 (Y116C)	-0.03	2

[Table/Fig-6]: Results of I-mutant 2.0 analysis of nsSNPs.



[Table/Fig-7]: ConSurf results for MMP3 protein.

each method relies on a different set of parameters, two ns SNPs (D175Y and Y116C) were identified as high-risk in present study, which were predicted to be harmful by every algorithm. Additional research revealed that these two ns SNPs might be dangerous because they are located in a highly conserved region and have the potential to affect protein stability [6-9,22,27,38,39].



[Table/Fig-8]: a) An overview of the protein is presented in a ribbon format, with colours indicating different structural elements: α-helix in blue, β-strand in red, turn in green, 3/10 helix in yellow, and random coil in cyan; b) A close-up view of the D175Y mutation; c) A close-up view of the Y116C mutation. The protein is rendered in grey, while the side chains of both the wild-type and mutant residues are highlighted in green and red, respectively.

As an important member of the MMP3 family, several experimental studies have been conducted on genetic variation in MMP3, especially in malignancies [11,13-18,21]. Wang L et al., conducted an observational study and meta-analysis of MMP3 gene polymorphism in the Chinese population. The researchers concluded that while MMP-3 gene polymorphism raises the risk of ovarian cancer in the southern Chinese population, their meta-analysis showed that it had no effect on risk in other populations [40]. Durmanova V et al., demonstrated that the MMP3 SNP rs3025058 influences the age of onset of Alzheimer's disease [41].

The predicted ns SNPs from present study have not been linked to any clinical disease in published studies. Therefore, to support this finding, it is necessary to validate these ns SNPs through larger population-based studies and specifically designed wet lab experiments.

Limitation(s)

The present study utilised the limited dataset from the NCBI dbSNP database. More ns SNPs could have been analysed if other databases had been included.

CONCLUSION(S)

Using a variety of bioinformatics techniques, this study has identified two significant nsSNPs, D175Y and Y116C, from the extensive SNP dataset of MMP3. Based on these findings, it can be concluded that these SNPs should be regarded as significant candidates for planning functional experiments involving the MMP3 gene. This presents an opportunity to investigate the molecular basis of any associated clinical problems and may aid in the discovery of potential drugs or pharmacological targets. Although computational biology is powerful, it has its limitations; therefore, population-based research is necessary to provide definitive validation.

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Study on Vitamin D Levels in 30 to 40-Year-Old Females With Low Back Pain

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Abstract

Background: Vitamin D is associated with many skeletal-related processes in the body. A major health problem concerning decreased quality of life is chronic low back pain (LBP). Many studies have proved that chronic pain improves with Vitamin D supplementation. This study aimed to explore the correlation between vitamin D levels and the occurrence of LBP in women aged 30 to 40.

Materials and methods: A case-control study was taken up at PK Das Institute of Medical Sciences wherein 50 cases (women aged 30-34 years who had chronic LBP >3 months) and 50 age-matched controls were included. Frequencies of Vitamin D deficiency, inadequacy, and sufficiency were studied. The t-test for examining statistical significance was employed to compare means. Keeping a 95% confidence interval ($p<0.05$), the odds ratio was calculated.

Results: Vitamin D deficiency diagnosed when Vitamin D level is <20ng/mL was found in 74% of cases and 48% of controls. Vitamin D levels were not found to be statistically different between cases and controls. The odds ratio was found to be 3.083 ($p=0.009$), showing that participants with LBP are more expected to be deficient in Vitamin D compared to those without LBP.

Conclusions: Although a higher frequency of Vitamin D deficiency was found in cases compared to controls, the mean value of Vitamin D levels was not found to be statistically different amongst cases and controls. A significant Odds ratio establishes a positive association between LBP and Vitamin D deficiency. The reason could be due to most people being restricted indoors due to COVID-19 restrictions. It is essential to standardize the biochemical analysis of Vitamin D and establish appropriate Vitamin D level ranges specifically tailored for the Indian population.

Categories: Family/General Practice, Preventive Medicine, Epidemiology/Public Health
Keywords: vitamin d levels, 30-40 years females, females, chronic low back pain, vitamin d deficiency

Introduction

A vitamin that is known to play a very important part in maintaining good health is Vitamin D which is fat soluble. Various names like sunshine vitamin and antirachitic factor have been given to this vitamin. Vitamin D's distinctiveness lies in the fact that it is synthesized in our skin when we are exposed to sunlight [1]. Ample sunlight exposure and food items like oily fish (Salmon) are the main sources of vitamin D. Other than problems with the skeletal system, other health issues like increased risk of diabetes mellitus type 2, cancer, and cardiovascular diseases are associated with Vitamin D deficiency [2].

Vitamin D is linked to musculoskeletal function. Low back pain (LBP) is a significant health issue associated with reduced quality of life and elevated expenses for diagnosis and treatment. Disability and absence from work are mainly caused by chronic LBP (pain for more than three months). Three diagnostic categories are used for LBP - radiculopathy, specific LBP, and non-specific LBP. When no specific cause like malignancies, infections, etc., can be pinned to the LBP, it comes under the criteria of non-specific LBP. Non-specific LBP affects over 90% of patients with LBP, and extensive research has indicated a connection between chronic pain and inadequate levels of Vitamin D. Vitamin D plays an indispensable part in controlling inflammatory cytokines, which tend to be elevated in chronic pain conditions [3]. Additionally, some studies have shown that Vitamin D supplementation can improve chronic pain [4]. It has also been claimed that any pain continuing for more than six months also called chronic pain from any site will respond to pain therapy only when there is adequate Vitamin D in the body [5].

Vitamin D helps in maintaining serum calcium levels and in specialized muscle protein production. Serum Calcium which is important for muscle contraction and protein synthesis is increased by Vitamin D. The Vitamin D receptor (VDR) in the nucleus has a regulatory role in several Vitamin D actions. These VDRs are

found in all tissues of the body [2,6]. A direct effect of Vitamin D on muscles helps in improving musculoskeletal function. Out of the slow and fast types of muscle fibers, it is the Type II fast twitch muscle fibers that are the first to come into action to avert a fall [7].

The interesting point is that Vitamin D inadequacy has been found to cause type II muscle atrophy. A study done in 1979 clearly states that Vitamin D deficiency causes atrophic changes like increased interfibrillar space, necrosis, etc. [8]. It has been found that as a person grows old the risk for deficiency in Vitamin D levels increases significantly. This is evident from the fact that in the United States, around 20%-100% of older people are suffering from Vitamin D deficiency [9].

As the women between the age group 30 and 40 years are bound to home, they have minimal exposure to sunlight. We know that sunlight is a major factor contributing to the production of vitamin D in our body. Hence, factors like decreased skin synthesis of Vitamin D, more time spent indoors than outdoors, and decreased intake of Vitamin D-rich food contribute to Vitamin D deficiency. The fact worth noting is that tissues like fat and muscle cannot store cholecalciferol till its level in the blood is above 20-50ng/mL. Only when it crosses this level, Vitamin D can work without being affected by amounts coming from diet and exposure to sun [10]. Various inflammatory pathways related to chronic pain are known to be affected by Vitamin D. This could be a reason why Vitamin D supplementation helps in improving muscle strength. The discovery of VDRs all through the human body has brought more importance to the study of health conditions related to Vitamin D. Many health problems like hypertension, diabetes, cancer, etc., are now linked with Vitamin D deficiency [6,11]. In India, an average prevalence of 70%-100% has been found in the general population [12]. In a study, the prevalence of Vitamin D deficiency among rural women was found to be 69.94% [13]. As a result, it is the need of the hour to examine the role of Vitamin D in warding off various health issues as well as to study the part played by Vitamin D supplementation in treating those conditions in women. This study was done to study the prevalence of Vitamin D deficiency among women aged 30-40 years who have chronic LBP compared to those who do not complain of the same. This will help in analyzing the association between Vitamin D and chronic LBP.

Materials And Methods

This was a case-control study done at PK Das Institute of Medical Sciences, Vaniyamkulam, Kerala, India, from September 2021 to October 2021 and was started after getting approval from the Institutional Ethics Committee) (IEC Number: IEC/04/35/21). This study was supported and funded by ICMR. According to the study done by Garg et al., Vitamin D deficiency prevalence among rural women was found to be 69.94% [13]. Our study area is Vaniyamkulam which is a village in Palakkad district in Kerala. Test size was calculated utilizing the technique $4pq/L^2$ (where p refers to the prevalence of Vitamin deficiency, q is 100-p, and L is the total permissible error which was taken as 20%) (95% confidence interval) and a value of 43 was arrived at. To this non-response rate of 10% was added to arrive at 47.3. This was rounded off to 50. Due to the case-control nature of this investigation, a 1:1 ratio was taken and 50 age-matched women who came to the Biochemistry lab for a general body check-up and did not have LBP were taken as controls.

Exclusion criteria

Those who had specific LBP, radiculopathy, heavy occupational physical activity, lumbar surgery, kidney diseases, diseases of the liver, and thyroid, and those taking Vitamin D supplementation were excluded from the study.

Inclusion criteria

Women between the ages of 30 and 40 who had been experiencing chronic LBP for at least three months were included in the analysis. Fifty healthy women of similar age were used as controls. An informed consent for the study was collected from the participants.

Sample collection

The venous blood sample was taken under aseptic precautions. Blood samples of selected participants were collected in the Biochemistry laboratory. The parameter used for this study was the level of 25(OH) Vitamin D and it was estimated by using the Beckman Coulter Access 2 Machine (Beckman Coulter Inc., Brea California). The test method used is Chemiluminescence Immunoassay (CLIA). This assay determines a total of 25 hydroxyvitamin D levels in the sample using paramagnetic particle, chemiluminescent immunoassay, and shows a linearity and measuring range of 7.0ng/mL to 120ng/mL [14].

Internal quality was maintained by running the Internal Quality Assurance Program by RANDOX (Randox Laboratories Ltd., UK) at two levels every 24 hours. The values were checked for being within the 2 Standard deviation range, presence of positive or negative bias, errors according to Westgard rules of quality control, and if there was a need for calibration. External quality control was maintained using the External Quality Assurance Program by BIORAD (Bio-Rad Laboratories, Inc. USA). Calibration for this test was done every 28 days using Access 25(OH) Vitamin D Total Calibrators. The limit of the blank, the limit of detection, and the limit of quantitation were 1.5ng/mL, 2.0ng/mL, and 7.0ng/mL, respectively [15].

Statistical analysis

After entering and cleaning the data, an Excel sheet was created from the results. It was then exported for statistical analysis in SPSS version 21 (IBM Corp., Armonk, NY). Descriptive statistics were used to study the mean and standard deviation. The study examined the prevalence of vitamin D deficiency, inadequacy, and adequacy in both cases and controls. Vitamin D mean concentrations were compared between cases and controls using an independent t-test to identify any notable distinctions. This was assessed with a 95% confidence interval, and the p-value of <0.05 indicated statistical significance. To study the association between Vitamin D levels and chronic LBP, odds ratio was calculated to get the risk estimate with a 95% Confidence Interval, and a p-value of <0.05 was taken as statistically significant.

Results

This study was done among 50 cases who were females with low back pain within 30-40 years of age and 50 healthy controls who were women without low back pain within 30-40 years of age. The cases had a mean age of 36 years, while the controls had a mean age of 33. In the case group, the mean Vitamin D level was determined to be 19ng/mL, in contrast to the control group where it measured at 21.9ng/mL.

A categorization of 30ng/mL as an acceptable level, 20-29ng/mL as a suboptimal/inadequate level, and below 20ng/mL as a deficient level was employed to assess the prevalence of vitamin D deficiency, insufficiency, and sufficiency. In this study, vitamin D deficiency was observed in 74% of the 50 patients and 48% of the controls. Vitamin D inadequacy was noted in 16% of the cases and 32% of the controls. Adequate vitamin D levels were detected in 10% of the cases and 20% of the controls (Table *1*).

	Cases (%)	Control (%)
Deficiency (<20ng/mL)	74.0	48.0
Inadequate (20-29ng/mL)	16.0	32.0
Sufficient (>30ng/mL)	10.0	20.0

TABLE 1: Comparison of cases and controls with regards to frequencies of Vitamin D level categories among controls.

On using an independent t-test to know the statistical significance of the difference between the mean values of Vitamin D levels among cases and controls, it was found that the p-value was 0.132. Hence, Vitamin D levels in cases and controls were not found to be statistically different (Table *2*).

Independent sample t-test	Group	N	Mean	Std. deviation	t-value	P-value
Vit D levels	case	50	19.000	8.3005	1.518	0.132**
	control	50	21.920	10.7700		

TABLE 2: Independent t-test to know the statistical significance of the difference between the mean values of Vitamin D levels among cases and controls.

**p-value - Not statistically significant as p > 0.05

The odds ratio was calculated to get the risk estimate and it was found to be 3.083 with a 95% confidence interval and p-value of 0.009. Hence, the association between low back pain and Vitamin D Deficiency was found to be statistically significant (Table *3*).

Vitamin D levels	Case (with low back pain)	Control (without low back pain)	OR (95% CI)	B	P-value
1 (Vitamin D Deficient)	37	24	3.083 (1.33 – 7.149)	1.126	0.009*
2 (Vitamin D not Deficient)	13	26		2.172	

TABLE 3: Odds ratio calculation to get the risk estimate.

*p value < 0.05, hence statistically significant

Discussion

Vitamin D levels were not observed to be significantly different in the current investigation among cases were women aged 30-40 years who had LBP and controls who were women aged 30-40 years who did not have back pain (p-value 0.132(>0.05), using independent t-test). On the other hand, a noteworthy odds ratio of 3.083 (p-value 0.009, 95% Confidence Interval) was attained, signifying that individuals afflicted by LBP had vitamin D deficiency in comparison to those without LBP. As a result, a positive association between these two conditions is confirmed. Hence Vitamin D supplementation can be considered in women aged 30-40 years who come with complaints of chronic LBP. Also, Vitamin D levels should be measured in patients who come with such complaints, so that follow-up can be done regarding the same. Similarly, an extensive meta-analysis conducted by Zadro et al. concentrating on the relationship between Vitamin D and LBP, likewise uncovered a positive connection between LBP and lack of Vitamin D. The amalgamated results from 19 studies indicated that lack of Vitamin D was more prevalent among people with LBP than in those who did not experience any back pain. The association between LBP and Vitamin D deficiency was found to be statistically significant among women compared to men where it was not found to be statistically significant [16]. In a review observational examination done by Gokcek and Kaydu, it was found that decreased degrees of Vitamin D were related to increased severity of LBP [17]. In this study, there was no notable distinction observed in terms of Vitamin D levels between the case and the control group. This seems to have opened a Pandora's box in front of us. In the cases, the mean value was found to be 19ng/mL compared to controls where it was found to be 21.9ng/mL, both these values coming under deficient and inadequate levels. In the Indian population, it is noted that the average prevalence of Vitamin D deficiency is 70%-90% [12]. In that case, this study could not mark a difference between cases and controls when the prevalence is so high. Added to this is that this study was done from September 2021 to October 2021, when the country was still limping back to normalcy from COVID-19. For almost two years people have been indoors which might have affected the outcome of this study. Without sufficient sunlight exposure in these years, it will not be a surprise that Vitamin D deficiency might have established itself as a pandemic, the silent presence of which will be evident in the years to come due to the long-term effects that Vitamin D Deficiency has on the human body. Large-scale population studies that analyze the levels of Vitamin D in different population subsets based on age and gender are required to bring the black cat out of the darkroom so that actions can be taken at the state and national levels to address the issue of Vitamin D deficiency.

Some questions that arose when studying the consequences of this study are: 1. Is the scope of Vitamin D levels appropriate for the Indian population as a major chunk of the population was found to be deficient in Vitamin D levels? 2. Is the assay technique accurate and precise? In the review article by Selvarajan et al., 2,998 articles were reviewed, and it was found that the Lack of vitamin D is far-reaching among the sound Indian populace regardless of how much time was spent outside in daylight. The typical Vitamin D level among the Indian population is found to be below 20ng/mL. Although the classification given by endocrine society as sufficient, inadequate, and deficient is being widely accepted, as most of the world population is found to be in the deficiency range the basis of this classification is being scrutinized. It is suggested in their article that studies need to be done to establish a classification of Vitamin D levels for the Indian population [12].

A study done to gauge the link between bone mineral density, parathyroid hormone, and Vitamin D, found that bone health is dependent on PTH levels and not on Vitamin D levels alone [18]. Even in our study, including PTH levels might have given a better picture regarding LBP among cases. The classification of Vitamin D status as deficient, insufficient, and adequate is based on skeletal effects with the consistent increase in PTH and decrease in calcium absorption from the intestine. It is found that when serum levels reach 30ng/mL, intestinal calcium absorption is at its highest, and PTH levels start decreasing. A safe level of Vitamin D is considered 30-100ng/mL [19].

It is known that Vitamin D undergoes two hydroxylation processes in the body, first to form 5 hydroxyvitamin D in the liver and second to frame 1,25 dihydroxy Vitamin D in the kidney. Of these two metabolites, 25(OH)D is the principal metabolite to know Vitamin D status as 1,25 (OH)2D is viewed as either in the ordinary range or increased due to a secondary increase in serum PTH due to Vitamin D deficiency. Also, the half-life of 25(OH)D is two to three weeks compared to 1,25 dihydroxy vitamin D which is only two to three hours [20]. A very important point by Spedding et al. is that the optimal cut-off for

Vitamin D might be dependent on the disease in question [21]. There are various methods routinely used for Vitamin D quantification like liquid chromatography-mass spectrometry (LC-MS) or tandem mass spectrometry, chemiluminescence immunoassays (CLIA) radioimmunoassays (RIA), and (LC-MS/MS), LC with UV detection, most widely being utilized are RIA, and CLIA. The gold standard method for the estimation of Vitamin D is LC-MS/MS. The review article by Stokes on Analytical Methods for Quantification of Vitamin D discusses various factors responsible for discrepancies noted in Vitamin D measurement. It is stated that there are many sources of variation in Vitamin D analysis like tight binding of Vitamin D binding protein, matrix effects, and co-elution of interfering substances. It has been stated that the chance of an assay giving a lower than actual reading is much more than that assay giving a higher than actual reading. This was found because most of the commercial assays gave results lower compared to the gold standard test that is LC-MS. This has resulted in overtreatment with Vitamin D supplements in the world [22].

An upward trend is being noted amongst increasing awareness regarding Vitamin D deficiency in India. This goes without saying that, the 25(OH)D test is still unaffordable for most Indians. Here many questions arise like if it is necessary to get everybody's Vitamin D status checked. Is it necessary to treat subclinical cases? These do not seem to be economical. As suggested by the authors of the review article, food fortification seems to be one of the solutions for this. A minimum of 45 minutes of direct sun exposure to the bare face, legs, and arms is suggested for adequate vitamin D. The problem with this statement lies in the fact that those who must work outdoors seem to be the only people who can get this type of exposure. The rest of us must hide behind the veil of social and religious norms which makes most of us dress from neck to toe [19]. Added to this was the long indoor stay during the COVID-19 pandemic. Low levels of Vitamin D lead to an increase in serum PTH which in turn leads to bone resorption. Hence for good skeletal health, we need to keep our Vitamin D at optimum levels.

In our research, we identified a favorable connection between vitamin D and lower back pain. Nevertheless, the absence of a noteworthy distinction in vitamin D levels between the case and control groups implies that this merely scratches the surface regarding the widespread occurrence of vitamin D insufficiency. A bigger issue lies behind this veil of the term "Vitamin D deficiency," which includes not only the superficial causes of inadequate sun exposure and diet but also deeper issues like non-standardized lab techniques, complicated assays, and inappropriate population ranges. We have a long way to go before we say that the Vitamin D level and range are accurate and precise for a given individual in the given population.

The limitation of this study was that this was a cross-sectional study with a limited sample size and population. In our study a population subset of women aged 30-40 years was taken, hence findings of the same cannot be projected to the whole population. This study adds to the evidence that Vitamin D deficiency is associated with chronic LBP and hence provides more insight into its causation. A longitudinal study where, in different population subsets, cases are studied after giving Vitamin D supplementation would have converted the limitation of this study to the strength of this study. As was mentioned before serum PTH has a direct relationship to bone density, in our study too including PTH levels might have done justice in understanding the occurrence of LBP among Vitamin D deficient cases. To bring the Vitamin D deficiency pandemic out in the public eye, large population studies must be done across states and countries to know the levels of Vitamin D using standardized methods in the respective populations. These Vitamin D levels need to be categorized based on different population subsets. Doing so will give an exact picture of Vitamin D deficiency in a particular population subset.

Conclusions

This study was done to study the association between LBP and Vitamin D levels among cases and controls who were 30 to 40-year-old females with and without LBP, respectively. Among 50 cases, Vitamin D deficiency was found in 74% of cases compared to 48% of controls. No statistically significant difference was found in levels of Vitamin D among cases and controls. A statistically noteworthy positive association (OR-3.083, 95% confidence Interval, p=0.009) was established between Vitamin D deficiency and LBP. Hence Vitamin D levels can be estimated in women aged 30 to 40 years who come with complaints of non-specific chronic LBP. Also, Vitamin D supplementation might help in treating cases of non-specific LBP. Adding serum PTH levels and newer follow-up studies that study cases before and after Vitamin D supplementation are required to give a better answer. This study's findings might have been influenced by the fact that most participants spent the previous two years inside because of COVID-19 regulations. We also need to work on a new normal range for the Indian population as most of the population is coming under the category of Vitamin D deficiency. Analytical standardization is also required to reduce variability and reporting of lower than true values. The results of the study seem to have uncovered a bigger problem which might be staring at the face of humanity, that is explosive number of Vitamin D deficient people due to COVID-19 restrictions. Standardizing both the biochemical assessment of Vitamin D and the suggested Vitamin D level ranges is of utmost importance.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Angel Abraham, Gautham G. Nair, Nimisha V, Biju C. Jose

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Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Institutional Ethics Committee, PK Das Institute of Medical Sciences issued approval IEC/04/35/21. This study is approved by Institutional Ethics Committee, PK Das Institute of Medical Sciences, the date of review being 12/08/2021. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** This study was supported and funded by Indian Council of Medical Research (ICMR). This study was done as a part of student project under STS ICMR project (2020)- Student Reference ID 2020-08810. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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COMMUNITY MEDICINE

Breastfeeding Practices among Urban Mothers of Central Kerala, India: A Cross-Sectional Study

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ABSTRACT

Background: The practice of breastfeeding is vital in child nutrition and morbidity. The authors aimed to determine breastfeeding practices and factors related to Exclusive Breastfeeding (EBF) among mothers with children aged six months to 2 years in an urban area of Thrissur district, Kerala, India.

Methods: This was a community-based and cross-sectional study conducted on 339 mothers using cluster sampling in 2016 for one year in the urban area of Thrissur district, Kerala. Details regarding sociodemographic factors, obstetric history, child-related data and breastfeeding practices were collected from mothers using a pretested and semi-structured questionnaire. Analyses were done using SPSS16 and Epi Info 7.

Results: The mean age of study population was 27.21 ± 4.27. 223 mothers (65.78 %, 95% CI = 60.43-70.77) initiated breastfeeding within 1 hour, and prelacteal feeding was observed in 25 cases (7.37%, 95% CI = 4.92-10.83). 99.71% practiced feeding on demand, and 30.97% (95% CI = 26.15- 36.24) of children were exclusively breastfed up to 6 months with mean duration of 3.95± 1.79 months. The mean age at which complementary feeding started was 4.83 ± 1.32 months. Cultural beliefs, mothers' employment, and problems during breastfeeding were significant predictors of EBF for up to 6months.

Conclusion: Despite high educational status and good antenatal care among the study population, breastfeeding practices were not carried out at the recommended level. Breastfeeding was initiated within 1 hour of delivery by $2/3^{rd}$,and $1/3^{rd}$ of the children were exclusively breastfed up to 6 months. Cultural beliefs and mothers' employment were factors associated with EBF.

Keywords: Breastfeeding Practices, Exclusive Breastfeeding, Breastfed, Prelacteal Feeding, Central Kerala.

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Introduction

Breast milk is the best source of nutrition for an infant and plays a vital role in child survival. Even though breastfeeding is a common practice in India, the appropriate breastfeeding practices are not satisfactory, resulting in malnutrition among children. In 2020, it was estimated that 38.9 million children were overweight or obese, 45 million were wasted, and 149 million children under the age of five were stunted (i.e., too short for their age) (1). Breastfeeding practices are practices followed while breastfeeding a baby, and include prelacteal feeding, breastfeeding initiation, exclusive breastfeeding (EBF) for 6 months (EBF), predominant breastfeeding, bottle feeding, and timely initiation of complementary feeding (2). The World Health Organization (WHO) recommends that infants be exclusively breastfed for the first six months, followed by complementary foods until the age of 2 or above (3). The beneficial effects of breastfeeding depend on its initiation as early as possible (avoiding delay beyond an hour), duration and the age at which breastfed children are weaned (4). Several other factors like the community's educational, social, cultural, and economic factors also significantly affect the different breastfeeding practices (4). UNICEF and WHO launched Baby-Friendly Hospital Initiative in 1992 to protect, promote, and support breastfeeding (5).

The practice of prelacteal feeding, whereby infants receive food or liquid before initiating breastfeeding for the first time (2), is widespread in many Indian societies (6,7). This practice could introduce infection, sensitize the gut to foreign proteins, or delay the onset of lactation (8), resulting in harmful effects on the newborn. According to the National Family Health Survey, 46.3% of children in India are exclusively breastfed for six months of age (9). The low prevalence and duration of exclusive breastfeeding increase the risk of infant and childhood morbidity in both developed and developing countries (10). Predominant breastfeeding practices, including giving other fluids like tea, water, and sugar water in limited quantities, along with breastmilk (11), are also seen in many parts of India due to the lack of awareness. The practice of bottle feeding and feeding with infant formula is also widespread in many parts of India (12, 13). Data from various sources showed that a breastfed child has a greater chance of survival than an artificially fed child (3, 14). Continuing breastfeeding for 2 years along with EBF helps to prevent early malnutrition and is very important to achieve optimal growth and development (3).

There are a few studies conducted in Kerala regarding breastfeeding practices. Compared to other states in India, the literacy rate of Kerala is much higher, and the literacy rate in the urban areas is higher than rural area (15). Despite high literacy rate, breastfeeding practices are not improved substantially. The prevalence of EBF among infants under 6 is 55.5% (16), despite Kerala's high literacy rate of 94% (15). Moreover, most of the mothers in urban areas of Kerala are employed, and breastfeeding practices may be different. Hence, this study helps to promote appropriate breastfeeding activities in the community by assessing the different breastfeeding practices and factors associated with EBF up to six months among mothers with children of six months to 2 years in the urban area of Thrissur district, Central Kerala, India.

Methods

A community-based and cross-sectional study was conducted for one year during the year 2016, in the corporation area of Thrissur district, Kerala. Mothers with children aged 6 months to 2, residing in the area for a minimum period of 6 months, were included in the study. After obtaining written informed consent to participate in the study, an interview was conducted among mothers using the pretested semi-structured questionnaire. The authors interviewed the mothers individually, after explaining the purpose of the study and ensuring the subject's confidentiality. The study protocol was approved by the Institutional Research and Ethics Committees of Govt. Medical College, Thrissur. Consent for the

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study was also taken from the Mayor of the Thrissur Corporation.

Thrissur district is situated in central Kerala. Thrissur Municipal Corporation is the civic body which governs Thrissur city in Kerala. It has a population of 325474, spread over 101.42 sq. km and divided into five divisions such as Ayyanthole, Vilvattom, Ollukkara, Ollur and Koorkanchery, which was again divided into 55 wards (17). Cluster sampling technique was used in, and each ward in this corporation was considered a cluster. There were 55 wards in the corporation area of Thrissur district. Therefore, 55 wards were considered 55 clusters. 20 clusters were selected by simple random method using the lottery method. In order to achieve a required sample size of 352, 18 subjects were included from each cluster. The first subject was chosen from the first household on a randomly chosen lane at the site of arrival in the cluster, usually the main bus stop. The survey, then, proceeded to consecutive houses on either side of the road until 18 mothers were chosen. If more than one mother was present in the same household, all of them were included in the study. Houses, where the subject was absent during the visit, were revisited two more times in the subsequent days to increase the response rate.

The study was conducted for a period of one year, and data collection was completed in four months. Data included sociodemographic profile, obstetric history, infant details, and breastfeeding practices. Details of antenatal checkups, childbirth and postnatal checkups were cross-checked with their MCP card or hospital records wherever possible. The socioeconomic status of the concerned family was assessed using the modified Kuppuswamy's scale (18) for the urban population and classified accordingly.

The sample size was calculated as 352 by considering a prevalence rate of 38%, for the youngest surviving child exclusively breastfed for the first six months (19), α error of 5%, design effect as 2 ,and a 10% non-response rate. Data collected from each individual was entered into a Microsoft Excel sheet after coding and rechecking of variables. General characteristics of the sample population were described in terms of proportions. The pattern of different breastfeeding practices among the study population was measured using proportions and a confidence interval of 95%. Quantitative variables were summarized using mean duration and standard deviation. According to the nature of the covariates, factors associated with different breastfeeding practices were assessed by bivariate analyses through chi-square test or t-test. The odds ratios and their 95% confidence intervals were computed to measure the strength of the association. Regression analysis was carried out to discover determinant factors of various breastfeeding practices. The significance level was estimated with a 95% confidence interval, and analyses were done with the help of SPSS and Epi Info 7.

Results

Out of the 352 subjects eligible for the study, 339 mothers participated in the study. The overall response rate was 96.3%, and the mean age of the subjects was 27.21 ± 4.27. Among them, 78.48% of the mothers had an education above senior high school education level, and only 19.17% of the mothers were employed. The sociodemographic characteristics of the study participants are given in Table. 1

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Table 1. Sociodemographic characteristics of the participants

Variable	Category	Frequency	Percentage
Age group (years)	11- 20	8	2.36
	21- 30	262	77.29
	31- 40	67	19.76
	41- 50	2	0.59
Religion	Hindu	184	54.28
	Christian	122	35.99
	Muslim	33	9.73
Education	Primary	1	0.29
	Secondary	1	0.29
	Senior secondary education(Grades 10-12)	71	20.94
	Graduated and above	266	78.48
Occupation	Housewife	274	80.83
	Professional	11	3.25
	Semiprofessionals	21	6.19
	Others	33	9.73
Socio-economic status	Lower	0	0
	Upper lower	24	7.08
	Middle/lower middle	183	53.98
	Upper middle	115	33.93
	Upper	17	5.01
Type of family	Nuclear	62	18.29
	Joint	277	81.71

Breastfeeding practices of the participants

The distribution of different breastfeeding practices is described in Table 2.25 (7.37%) mothers gave prelacteal feeds to newborns. The common prelacteal feeds were giving Zam-zam water to (holy water from Mecca), 13 (52%) babies, 6 (24%) babies, Infant formula–lactogen, and 3 (12%) babies were fed with honey. The proportion of EBF was 30.97% (95%CI= 26.15-36.24). The mean duration of EBF was 3.95 ± 1.79 months, ranging from post-neonatal day 1 to 7 months, and the median duration was 4 months. The mean age at which complementary feeding started was 4.83±1.32 months, with a minimum of 1 month to a maximum of 6.5 months. Most mothers used banana powder (42.48%) followed by ragi (36.28%). About one-fourth of the mothers had one of the following problems during breastfeeding; the majority suffered from cracked nipples (63.16%), some insufficient milk (27.63%), and some other suffered from breast engorgement (3.95%). Reasons for early introduction (< 6 months) of feeds other than breast milk are presented in Figure 1.

Table 2. Summary of various breastfeeding practices (n = 339)

Variable	Frequency	Percentage	95% CI
Pre-lacteal feeding	25	7.37	4.92 - 10.83
Early initiation of breastfeeding (< 1 hour)	223	65.78	60.43 - 70.77
Colostrum feeding	339	100	100 – 100
EBF up to 6 months	105	30.97	26.15 - 36.24
Predominant breastfeeding before 6 months	115	33.92	28.95 – 39.27
Complementary feeding at 6 months	163	48.08	42.67 - 53.54
Bottle feeding	164	48.38	42.96– 53.83

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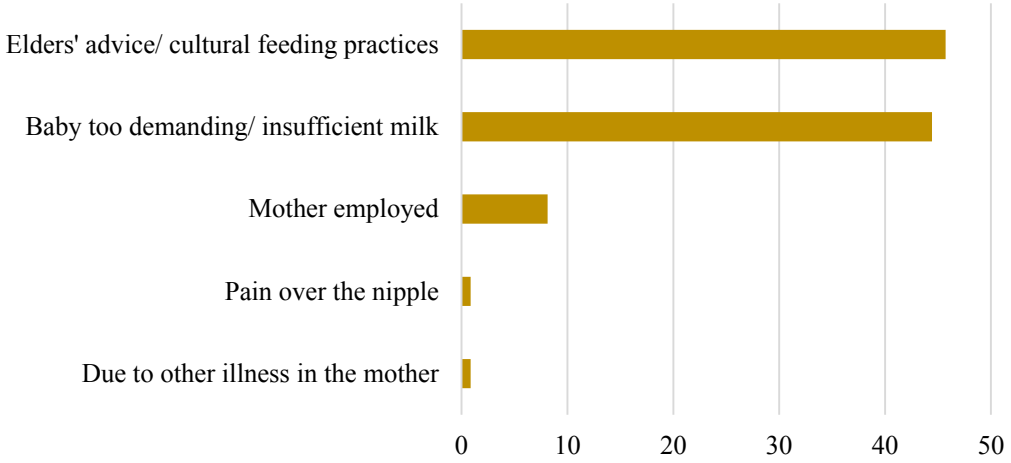


Figure 1. Reasons for early cessation of EBF (n = 234)

Benefits of EBF for 6 months

The benefits of exclusive breastfeeding in this study were assessed based on the occurrence of illness among the children during EBF period and the duration of lactational amenorrhoea (Tables 3 and 4). The odds of developing illness among those who were not exclusively breastfed until 6 months was 3.2 times higher as compared to those who were exclusively breastfed up to 6 months (OR = 3.20, 95% CI = 1.31- 7.82). The delayed return of menstrual period was observed in those mothers who practiced EBF, even though it was not significant.

Table 3. Association between illness in the child and EBF until 6 months of age

EBF up to 6months	Illness present (%)	Illness absent (%)	OR (95% CI)	χ^2	*P-value*
Not practiced (n = 234)	38 (16.24%)	196 (83.76%)			
Practiced (n = 105)	6 (5.71%)	99 (94.29%)	3.20 (1.31- 7.82)	7.108	0.007
Total (339)	44 (12.98%)	295 (87.02%)			

Table 4. Exclusive breastfeeding duration versus lactational amenorrhoea duration

EBF duration	Lactational Amenorrhoea	T value	P-value
< 6 months (n = 234)	4.25 ± 2.93months	1.687	0.09
≥ 6 months (n = 105)	4.83 ± 2.92 months		

Obstetric and child details of the study participants

240 (70.80%) mothers received breastfeeding advice at antenatal checkups, and health workers conducted home visits regarding 291 (85.84%) mothers. All the deliveries were institutional, 56 of which (16.52%) occurred in government hospitals. Among the 339 mothers, 210 (61.95%) were had vaginal delivery, and the rest, 129 mothers (38.05%) underwent Caesarian sections. The mean age of children in the study was 14 ± 5.6 months and ranged from 6 months to 24 months. The majority of the children, 173 (51%), belonged to the age group 6- 12 months, 109 (32.2%) were

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between 12 months to 18 months, and 57 (16.8%) children were between 19 months to 24 months. Most of the children, 183 (53.98%), were females. The mean birth weight was 2.99 ± 0.48 Kg, with a minimum birth weight of 950 gm to a maximum of 4.5 kg.

Factors associated with EBF until 6 months

Cultural beliefs, mothers' employment, and problems during breastfeeding (such as insufficient milk and cracked/retracted nipple) were significant predictors of EBF until 6 months of age (Tables 5 and 6). Being above 30, religion, joint family system, educational level of senior high school and below and breastfeeding advice given by public health staff during house visits also affected EBF in the study area, even though it was not significant.

Table 5. Sociodemographic factors associated with EBF

Variable	Category	EBF up to 6 months		Odds ratio (95% confidence interval)	
		No (%)	Yes (%)	COR* (95% CI)	AOR**(95% CI)
Age	Age ≤ 30yrs	188 (69.6)	82 (30.4)	1.146	1.07
	Age > 30 yrs	46 (66.7)	23 (33.3)	(0.65-2.01)	(0.58-1.99)
Religion	Hindu	134 (72.8)	50 (27.2)	1.74	1.19
				(0.79-3.75)	(0.52-2.78)
	Christian	80 (65.6)	42 (34.4)	1.23	1.23
				(0.55-2.73)	(0.54-2.86)
	Muslim	20 (60.6)	13 (39.4)	1	1
Type of Family	Joint	196 (70.8)	81 (29.2)	1.53	1.26
	Nuclear	38 (61.3)	24 (38.7)	(0.86-2.71)	(0.68-2.34)
Mothers' education	Senior secondary education and below	122 (71.3)	49 (28.7)	1.245	1.29
				(0.78-1.97)	(0.79-2.12)
	Graduated and above	112 (66.7)	56 (33.3)		
Mothers' occupation	Employed	50 (76.9)	15 (23.1)	1.63	2.01
	Unemployed	184 (67.2)	90 (32.8)	(0.87-3.06)	(1.02-3.94)

*Crude OR, **Adjusted OR

Table 6. Cultural and maternal factors associated with EBF

Variable	Category	EBF up to 6 months		Odds ratio (95% confidence interval)	
		No (%)	Yes (%)	COR* (95% CI)	AOR** (95% CI)
Cultural feeding practices	Yes	61 (85.9)	10 (14.1)	3.35	3.37
	No	173 (64.6)	95 (35.4)	(1.64- 6.84)	(1.53-7.43)
Breastfeeding advice by public health staff during house visit	Yes	37 (77.1)	11 (22.9)	1.605	1.01
	No	197 (67.7)	94 (32.3)	(0.79-3.29)	(0.539-1.73)
Problems during breastfeeding	Yes	65 (85.5)	11 (14.5)	3.29	3.38
	No	169 (65.43)	94 (35.7)	(1.65-6.53)	(1.67-6.83)

*Crude OR, **Adjusted OR

Discussion

Appropriate breastfeeding practices are necessary to achieve the fourth goal of MDG (Millennium Development Goals), which is reducing child mortality. Kerala is well known for its health indicators comparable with developed countries and its high female literacy rate (15). Despite high educational status and good antenatal care among the study population, breastfeeding practices were not up to the desired level in the

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study area. Every child should start being breastfed at the earliest. Breastfeeding was initiated within 1 hour of delivery by 2/3rd of the study population. In this study, 223 (65.78%) mothers began breastfeeding within one hour, which was comparable with other studies conducted in India (8, 9, 20, 21, 22) and was consistent with the NFHS-5 data of Kerala(16), which was 66.7 %. This percentage was lower, compared to the District Level Household and Facility Survey, in which 78.8% of the mothers initiated breastfeeding within one hour (23). and a study conducted in Africa, in which 72.9% initiated breastfeeding within an hour (24). This was while Patel A et al. (13) in their observed a 23.5%. rate of timely initiation, which was very low. All the children were fed with colostrum in the study area.

The problem of prelacteal feeding was observed in the study population, in line with other studies (7, 12, 25, 26), with the highest proportion belonging to Muslims. This practice is harmful to the newborn as they could introduce infection, sensitizes the gut to foreign proteins, and may delay the onset of lactation (8). The present study showed the prevalence of prelacteal feeding at 7.37%. The prevalence of prelacteal feeding in the present study was very low as compared to other studies conducted in different parts of India, which was from19% (27) to 91.25% (28). This lower prevalence of prelacteal feeding may be due to higher educational status of the mothers in the study population. The most common prelacteal fluid given in the present study was Zam-zam water (holy water from Mecca) among Muslims (52%), followed by lactogen (24%), Honey (12%), water (8%) and cow's milk (4%). Ghutti and honey were the most common prelacteal feeds in the study by Manish Chadurvedi et al. (7) in New Delhi. According to Vashney A M et al. (12), in Gujarat, animal milk and sugar water were the most common prelacteal fluids.

In the present study, all mothers (100%) have given breast milk to their babies, which was higher than the National Family Health Survey, in which 95.7% of the children in India were ever breastfed and 97.4% in Kerala (9). A study in Uttarakhand by Vyas Shili et al. (29) found the proportion of children ever breastfed to be 93.6%. According to a study in Villages of Karnataka by Banapurmath C R et al., (30) 97% of the children were ever received breast milk.

EBF is recommended because it contains all essential nutrients for the first six months of life. 1/3rd of mothers in the study area did EBF until baby was six months.. Although female literacy rate was higher in Kerala compared with other states, a lower prevalence of EBF was observed in the present study (30.97%), lower as compared to the National level, 46.4% (9), and other studies conducted in different parts of India (26, 29, 31, 32). This percentage was higher than Kerala, which was 22.3% (23). In a population where the mother's educational status is high, and most of them are currently unemployed, EBF can easily be practiced. In addition, this percentage is relevant considering that all the deliveries were institutional and received postnatal feeding advice. In the present study, common reasons for discontinuation of EBF were elders' advice with regard to cultural feeding practices (45.73%), followed by insufficient milk (44.44%) and maternal employment (8.12%). In a study by Nishimura H et al. (33) conducted at rural South India, it found that insufficient milk was the most common factor for early discontinuation of EBF, which was consistent with the findings of the present study. Other studies carried out in India demonstrated that Insufficient milk (42%) and (28.5%), mother's employment (20%), and weight gain of the baby (15%) were the reasons for early discontinuation (8, 34, 22, 29). Diseases like respiratory infections and diarrhoea were significantly higher among infants with EBF for less than six months, similar to other studies (35, 36, 37).

The present study revealed a critical barrier, i.e., elders' advice regarding prevalent cultural feeding practices. Similar findings were observed in a study conducted by Avneet Randhawa et al. (32) at Punjab where it was found that that nuclear families were more likely to exclusively breastfed their babies more than those staying in joint or extended nuclear families. This finding may be due

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to the cultural practices followed by the elders in the family. Hence, to improve EBF in a state with good health indices and a high literacy rate, focus group discussions may be conducted by involving elders of the house, religious leaders, local leaders, healthcare providers and mothers to address prevailing practices which hamper EBF. EBF is a simple and cost-effective method to reduce common morbidities like acute diarrheal diseases and acute respiratory infections among under-five children. Due to short maternity leave time, the return to work may hamper employed mothers from breastfeeding their infants exclusively for the recommended six months duration. Therefore, adequate support for breastfeeding mothers in the workplace should be ensured.

Since the data collected was pertaining to the previous two years, recall bias may have occurred. As mothers with children of over 2 were included in the study, it is impossible to assess the continuation of breastfeeding for up to 2 years.

Conclusions:

Breastfeeding practices among the women in the study area are not up to the recommended level, even though there is a high level of academic education in the study group. The prevalence of EBF up to 6 months is 30.9%, which is extremely low, compared to the WHO recommendations (100%) and the national average (55.5%) according to NFHS-5 data. This study also highlights certain crucial areas of concern, such as the cultural barriers imposed by the elders in the family, mother's employment, and problems faced by mothers during breastfeeding (insufficient breast milk, cracked nipple, retracted nipple). These factors were statistically consistent with other studies conducted in different parts of India.

Therefore, it is imperative to carry out in-depth studies to identify the gaps in breastfeeding practices and offer tailored interventions such as counselling the mothers and elders in the family antenatally, providing postnatal lactation support and counselling, and considering adequate maternity leave for mothers based on the needs of the study population. This in turn may positively influence breast feeding practices, thereby, improving child health and lowering healthcare costs.

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All the ethical principles have been observed in the present study. The study protocol was approved by the Institutional Research and Ethics Committees of Govt. Medical College, Thrissur

Conflict of interest

Authors declared no conflict of interest.

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Ethical considerations

All the ethical principles have been observed in the present study. The study protocol was approved by the Institutional Research and Ethics Committees of Govt. Medical College, Thrissur

Code of Ethics

Maintained during the entire study period.

Authors' contributions

All authors contributed to conception, design, and definition of the intellectual content of the study; Data were collected by F. O and J. KS; all authors participated in data analysis, interpretation, and manuscript drafting, and F. O, P. C, S. MV, and R. R provided critical revisions. The final draft of the manuscript was reviewed and approved by all authors.

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List of abbreviations

Abbreviation	Definition
EBF	Exclusive breastfeeding up to 6 months
MDG	Millennium Development Goals
WHO	World Health Organization
UNICEF	United Nations Children's Fund

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Original Research Article

Metabolic syndrome in children with overweight and obesity: a hospital based cross sectional study

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ABSTRACT

Background: Objective of the research was to study metabolic syndrome (MS) in children with overweight and obesity.
Methods: A cross sectional descriptive study was carried out on 264 children aged 3-16 years with overweight and obesity attending the endocrinology clinic of a tertiary care hospital in South India from January 2016 to March 2018. Children with and without MS were compared.
Results: Out of 264 children with overweight or obesity, 80 had MS (30.3%). Among children with obesity, proportion of patients with MS (40.5% versus 24.2%, p=0.012), hypertriglyceridemia (54.8% versus 37.5%, p=0.013), low high density lipoprotein cholesterol (HDL-C) (42.9% versus 28.1%, p=0.027) and dyslipidemia (78.6% versus 59.4%, p=0.004) were higher among girls versus boys. Proportion of patients with elevated systolic blood pressure (BP) (18.8% versus 4.3%, p<0.0001), elevated diastolic BP (34.5% versus 5.4%, p<0.0001), impaired fasting glucose (16.2% versus 7.6%, p=0.033), hypertriglyceridemia (85% versus 26.6%, p<0.0001), low HDL-C (75% versus 15.2%, p<0.0001) and dyslipidemia (97.5% versus 57.1%, p<0.0001) were higher in those with MS versus those without.
Conclusions: MS noted in younger children with overweight and obesity in the current study is concerning as these children are at increased risk for hypertension, type 2 diabetes and cardiovascular disease in early adulthood leading to huge economic burden on the country. It is therefore of utmost importance to take necessary steps to identify these children, manage obesity effectively before MS sets in and initiate preventive measures thereby ensuring a healthy young generation in the coming years.

Keywords: Children, Adolescents, Obesity, Overweight, Metabolic syndrome

INTRODUCTION

Marked increase in the prevalence of obesity among all age groups including children have been observed over the last 3 decades.[1] The rising trend in childhood obesity has witnessed a parallel increase in hypertension, type 2 diabetes mellitus (T2D), and subclinical atherosclerosis among children with obesity, which were thought to occur only in adults.[2-7] Metabolic syndrome (MS) is characterized by clustering of cardiometabolic risk factors: abdominal obesity, dyslipidemia, elevated blood pressure and impaired fasting glucose.[1] Children with MS are at high risk of developing T2D, cardiovascular disease and nonalcoholic fatty liver disease (NAFLD) in later life.[8,9] Very few studies from South Asia have assessed MS among children with obesity and none from South India.[10,11] We aimed to determine the prevalence of MS among children with overweight and obesity attending endocrinology clinic in a South Indian State and to compare those with MS and without MS. We hypothesized that prevalence of MS will be higher in those with obesity vs. those with overweight and the metabolic abnormalities will be higher in those with MS compared to those without MS.

METHODS

A hospital based descriptive cross-sectional study was carried out in children of 3-16 years with overweight or obesity attending the endocrinology clinic of Institute of Maternal and Child Health, Government Medical College, Kozhikode, Kerala, India from January 2016 to March 2018. Study was approved by the institutional ethics committee.

Inclusion criteria was children of ages 3-16 years with overweight or obesity of exogenous causes attending the endocrinology clinic during the study period. Children with obesity due to diseases such as Cushing syndrome, hypothyroidism or hypothalamic disease, syndromic causes such as Prader Willi syndrome, Laurence Moon Bardet Biedel syndrome or medication such as steroids, antipsychotics or antidepressants were excluded from the study. Children were enrolled for the study after getting written informed consent from the guardians. A diagnosis of overweight and obesity were made based on the Indian Academy of Pediatrics (IAP) reference percentiles proposed for Asian Indian Children with a BMI >23 kg/m^2 and >27 kg/m^2 adult equivalent cut off for overweight and obesity respectively for children aged 5-16 years and World Health Organization (WHO) growth charts for children <5 years.[12,13]

Clinical and demographic data were collected using a preformed questionnaire. Anthropometric measurements were taken for each subject. Electronic weighing machine was used for measuring body weight to an accuracy of 0.1 kg with the participants wearing light clothes and no foot wears and stadiometer for measuring height to an accuracy of 0.1 cm. Waist circumference (WC) was measured midway between the lowest rib cage and the iliac crest with a non-stretchable tape (applying uniform pressure on the tape), to the nearest 0.1 cm, with the subject in a standing position and no clothes covering the measuring area.[14] WC cut-offs as proposed by Kuriyan et al (WC>75th centile) were used to identify children with abdominal obesity.[15] General and systemic examinations were done on all children. Blood pressure (BP) was taken in the right upper limb in the sitting position and was repeated 30 minutes later if found to be high. Repeatedly measured systolic or diastolic BP ≥90th percentile for the child's age, gender and height was considered as elevated BP and BP ≥95th percentile as hypertension.[16]

Blood sample was collected after an overnight fast of at least 8 hours for blood sugar and lipid panel. MS was defined as per the international diabetes federation with the following modifications: An individual aged 3–16 years has metabolic syndrome if he or she has central adiposity plus at least two of the following criteria: triglycerides levels ≥95th percentile (0-9 years ≥100 mg/dl; 10-19 years ≥130 mg/dl), HDL cholesterol level (HDL-C) <5th percentile (<40 mg/dl), systolic BP (SBP) or diastolic BP (DBP) ≥90th percentile for the age, gender and height, and fasting blood glucose ≥100 mg/dl (impaired fasting glucose-IFG).[15,17-19,24] Hypercholesterolemia (≥200 mg/dl), hypertriglyceridemia, high LDL cholesterol (LDL-C) or low HDL-C was accepted as dyslipidemia.[18]

Statistical analysis

Statistical analysis was performed by statistical package for the social sciences (SPSS) version 16.0. Qualitative data was presented as frequency and percentage and quantitative data as mean±standard deviation (SD). Chi square test or Fisher's exact test was used to compare qualitative data and quantitative data was compared using Student's t test and a p value <0.05 was considered statistically significant.

RESULTS

Clinical and demographic factors of the study population are given in Table 1. Study group included 264 children: 212 with obesity and 52 with overweight. Majority of the study participants were males (n=163, 61.7%), prepubertal (n=156, 59%) and aged 10-13 years (n=147, 55.7%). Mean age of the children with obesity was significantly lower than that of children with overweight (9.5±2.8 y versus 11.5±2.1, p<0.0001). Family history of obesity was noted in 178 children (67.4%). Family history of hypertension, dyslipidemia, T2D and heart attack were seen in 64%, 53.4%, 70.4% and 39.4% of study subjects, respectively. Among the study participants, 47 children had elevated SBP, DBP or both (17.8%) and 26 children had IFG (9.8%), one had FBS (0.4%) in the diabetes range (146 mg/dl). Proportion of children with central adiposity was significantly higher among children with obesity versus children with overweight (99.5% versus 84.6%, p<0.0001). Out of 264 children, 80 had MS (30.3%) and majority of them were prepubertal (n=49, 61.2%).

Boys versus girls

Boys predominated in both children with obesity (128 versus 84) and overweight (35 versus 17) (Table 2). Mean age was significantly lower for girls vs. boys in children with obesity (8.8±2.6 years versus 10±2.8 years, p=0.002) and overweight (10.6±2.6 years versus 12±1.6 years, p=0.022). Among children with obesity proportion of participants with MS was higher among girls versus boys (40.5% versus 24.2%, p=0.012). Patients with hypert-riglyceridemia (54.8% versus 37.5%, p=0.013), low HDL (42.9% versus 28.1%, p=0.027) and dyslipidemia (78.6% versus 59.4%, p=0.004) were also higher among girls versus boys among children with obesity.

Children with MS and without MS

Sixty-five children with obesity (30.7%) and 15 children with overweight (28.8%) had MS (n=80). Children with and without MS (n=184) were compared (Table 3). Proportion of patients with elevated SBP (18.8% versus 4.3%, p<0.0001), elevated DBP (34.5% versus 5.4%, p<0.0001), IFG (16.2% versus 7.6%, p=0.033), hypert-

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riglyceridemia (85% versus 26.6%, p<0.0001), low HDL-C (75% versus 15.2%, p<0.0001) and dyslipidemia (97.5% versus 57.1%, p<0.0001) were higher in those with MS compared to those without MS. High WC, hypertriglyceridemia and low HDL were the most frequent MS components present in children with MS or without MS.

Table 1: Clinical and demographic factors of the study population.

Variables	All, n (%)	Obese, n (%)	Overweight, n (%)	P value
Number	264	212	52	
Age, years	9.9±2.8	9.5±2.8	11.5±2.1	<0.0001†
BMI, kg/m²	24.1±3.2	24.8±3.1	21.4±1.8	<0.0001†
Sex				
Boys	163 (61.7)	128 (60.4)	35 (67.3)	0.357
Girls	101 (38.3)	84 (39.6)	17 (32.7)	
Age group (years)				
3-5*	26 (9.8)	24 (11.3)	2 (3.8)	
6-9	83 (31.4)	76 (35.8)	7 (13.5)	0.634
10-13	147 (55.7)	108 (50.9)	39 (75)	0.037#
14-16	8 (3)	4 (1.9)	4 (7.7)	0.018#
MS components				
WC above the cut-off	255 (96.6)	211 (99.5)	44 (84.6)	<0.0001†
SBP ≥90th percentile	23 (8.7)	22 (10.4)	1 (1.9)	0.056
DBP ≥90th percentile	36 (13.6)	31 (14.6)	5 (9.6)	0.346
IFG	27 (10.2)	19 (9)	8 (15.4)	0.171
Hypercholesterolemia	68 (25.8)	50 (23.6)	18 (34.6)	0.103
Hypertriglyceridemia	117 (44.3)	94 (44.3)	23 (44.2)	0.989
Elevated LDL-C	69 (26.1)	50 (23.6)	19 (36.5)	0.057
Low HDL-C	88 (33.3)	72 (34)	16 (30.8)	0.662
Dyslipidemia	183 (69.3)	142 (67)	41 (78.8)	0.096
MS	80 (30.3)	65 (30.7)	15 (28.8)	0.799

BMI – body mass index; DBP- diastolic blood pressure; IFG – impaired fasting glucose; HDL – high density lipoprotein; LDL – low density lipoprotein; MS – metabolic syndrome; WC – waist circumference, * reference category, † significant at 1% level, # significant at 5% level

Table 2: Demographic factors and MS components, boys versus girls.

Patient characteristics	Children with obesity, n (%)			Children with overweight, n (%)		
	Boys, n=128	Girls, n=84	P	Boys, n=35	Girls, n=17	P
Age, years	10±2.8	8.8±2.6	0.002#	12±1.6	10.6±2.6	0.022#
BMI, kg/m²	25.04±3.1	24.4±3.1	0.135	21.5±1.5	21.2±2.4	0.572
Age group						
3-5*	14 (10.9)	10 (11.9)		0	2 (11.8)	
6-9	33 (25.8)	43 (51.2)	0.202	4 (11.4)	3 (17.6)	0.278
10-13	78 (60.9)	30 (35.7)	0.181	27 (77.1)	12 (70.6)	0.111
14-16	3 (2.3)	1 (1.2)	0.481	4 (11.4)	0	0.067
MS components						
WC above the cutoff	127 (99.2)	84 (100)	0.604	28 (80)	16 (94.1)	0.248
SBP ≥90th percentile	12 (9.4)	10 (11.9)	0.555	1 (2.9)	0	0.673
DBP ≥90th percentile	16 (12.5)	15 (17.9)	0.28	4 (11.4)	1 (5.9)	0.467
IFG	14 (10.9)	5 (6)	0.214	4 (11.4)	4 (23.5)	0.413
Hypercholesterolemia	26 (20.3)	24 (28.6)	0.166	11 (31.4)	7 (41.2)	0.488
Hypertriglyceridemia	48 (37.5)	46 (54.8)	0.013#	16 (45.7)	7 (41.2)	0.757
High LDL-C	26 (20.3)	24 (28.6)	0.166	15 (42.9)	4 (23.5)	0.175
Low HDL-C	36 (28.1)	36 (42.9)	0.027#	12 (34.3)	4 (23.5)	0.43
Dyslipidemia	76 (59.4)	66 (78.6)	0.004#	27 (77.1)	14 (82.4)	0.483
MS	31 (24.2)	34 (40.5)	0.012#	12 (34.3)	3 (17.6)	0.33

BMI- body mass index; DBP-diastolic blood pressure; IFG- impaired fasting glucose; HDL-C high density lipoprotein cholesterol; LDL-C-low density lipoprotein cholesterol; MS–metabolic syndrome; WC–waist circumference, *reference category # significant at 5% level

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Table 3: Children with MS and without MS.

Patient characteristics	Those with MS, n=80 (%)	Those without MS, n=184 (%)	P
Age, years	9.5±2.8	10.1±2.8	0.101
BMI, kg/m^2	24.1±3.1	24.2±3.2	0.831
Sex			
Boys	43 (26.4)	120 (73.6)	0.078
Girls	37 (36.6)	64 (63.4)	
Age group			
3-5*	8 (10)	18 (9.8)	
6-9	31 (38.8)	52 (28.3)	0.541
10-13	40 (50)	107 (58.2)	0.708
14-16	1 (1.2)	7 (3.8)	0.403
MS components			
WC above the cutoff	77 (96.2)	178 (96.7)	0.547
SBP ≥90th percentile	15 (18.8)	8 (4.3)	<0.0001†
DBP ≥90th percentile	26 (32.5)	10 (5.4)	<0.0001†
IFG	13 (16.2)	14 (7.6)	0.033$^{\#}$
Hypercholesterolemia	24 (30)	44 (23.9)	0.299
Hypertriglyceridemia	68 (85)	49 (26.6)	<0.0001†
High LDL-C	23 (28.8)	46 (25)	0.524
Low HDL-C	60 (75)	28 (15.2)	<0.0001†
Dyslipidemia	78 (97.5)	105 (57.1)	<0.0001†

BMI- body mass index; DBP-diastolic blood pressure; IFG- impaired fasting glucose; HDL-C high density lipoprotein cholesterol; LDL-C-low density lipoprotein cholesterol; MS–metabolic syndrome; WC–waist circumference, *reference category # significant at 5% level

DISCUSSION

Current cross sectional study involving 264 children and adolescents aged 3-16 years attending Pediatric Endocrinology clinic of a tertiary care hospital, South India observed that about one third of patients with obesity and overweight had MS. Proportion of participants with MS, hypertriglyceridemia, low HDL-C and dyslipidemia were higher in girls versus boys among children with obesity. Those with elevated SBP and DBP, IFG, hypertriglyceridemia, low HDL-C and dyslipidemia were significantly higher in those with MS compared to those without MS.

Various studies reported a prevalence of MS ranging from 3% to 62% among children with overweight and obesity.[5,10,11,21-34] The wide range in the prevalence of MS reported by the prior studies might be due to the differences in definition of MS and cutoffs used by various studies as well as the differences in patient characteristics. Most of these studies were from Europe and North America and only 2 studies were from South Asia.[10,11] South Asians are thought to be at increased risk of developing MS owing to body fat patterning characterized by excess adiposity and truncal obesity seen in this population compared to Caucasians.[35] Even among South Asians, prevalence of MS may vary based on region, degree of urbanization, socioeconomic and cultural factors.[35] Both the studies from South Asia were from 2 North Indian cities.[10,11] MS was found in about 1/3rd of the children aged 8-18 years old with obesity from Sri Nagar, Kashmir while a community based cross sectional survey assessing MS on school going children aged 12-17 years from Chandigarh observed MS in more than 1/3 of those with BMI ≥95th percentile and in about 1/10th of those with BMI between 85th and 95th percentile.[10,11] Ours is the first study from South India assessing MS among children with obesity and overweight and we observed a higher prevalence of MS among children with overweight compared to the Chandigarh study (28% versus 11%).[11] Both the North Indian studies used the modified adult treatment panel III criteria while the current study used modified IDF criteria to define MS and our study population involved more younger patients which might explain the difference in the prevalence of MS among children with overweight between our study and Chandigarh study.[10,17]

Almost all the study subjects had central adiposity in the current study and those with central adiposity was higher among children with obesity vs. children with overweight. Similar observation was made by 2 different studies from Spain.[28,30] A systematic review and meta-analysis of observational studies on the prevalence of MS among children with overweight and obesity in affluent countries found that prevalence of abdominal obesity ranged between 42-100%.[33] High prevalence of truncal adiposity noted in the current study is not surprising as higher abdominal obesity have been observed among South Asians compared to Caucasians.[35]

Proportion of patients with MS, hypertriglyceridemia, low HDL-C and dyslipidemia were higher in girls versus boys among children with obesity in the current study. Higher prevalence of MS among girls versus boys was reported by

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a study from Lebanon similar to our study while studies from Poland, Spain and Turkey observed no significant difference in the prevalence of MS by sex.[24,25,30,31] Our observation was also in contrast to the finding by Juárez-López, et al that showed no difference in terms of prevalence of MS, hypertriglyceridemia and low HDL levels between boys and girls.[20] Higher prevalence of MS observed in girls vs boys among children with obesity in the current study might be related to the difference in fat distribution in both sexes. Compared to boys prevalence of truncal adiposity was more in girls with obesity (100% versus 99% boys) and overweight (94% versus 80% boys).

The most common MS defining components among those with MS were central adiposity, hypertriglyceridemia and low HDL levels in the current study, similar to the observations made by prior studies.[24,29,33] Chandigarh study reported low HDL as the most common constituent of MS in the study participants.[11] Central adiposity was the least common constituent in this study in contrast to our observation.[11] Hypertriglyceridemia, elevated blood pressure and IFG were reported as the most common MS components in Romanian children aged 7-18 years with obesity and MS.[21] Again, the differences noted between the studies might be related to the differences in the definitions used to define central adiposity and MS components as well as the racial and ethnic differences of the study population.

Though not statistically significant, prevalence of MS was more among children with obesity compared to children with overweight in the current study (30.75 versus 28.8%, p=0.8). Various studies have reported a direct relation of MS prevalence with the degree of obesity.[10,22,34] Andrabi et al in his study on children of Srinagar city of Kashmir noticed that prevalence of MS was higher among obese subjects compared to overweight and normal weight subjects (30.7% versus 2.5% and 0.5%, respectively).[10] Sangun et al reported more than 2 fold increase in the prevalence of MS among children with BMI >2.5 SDS compared to those with BMI <2.5 SDS.[22] Weiss et al observed that MS was present in 38.7% and 49.7% of adolescents with obesity and severe obesity respectively.[5]

Present study observed a significantly higher proportion of patients with elevated SBP and DBP, IFG, hypertriglyceridemia, low HDL levels and dyslipidemia in those with MS group compared to those without. Similar observations were made prior studies.[10,23,25] Andrabi et al reported higher prevalence of truncal adiposity, IFG, low HDL and hypertriglyceridemia among children from Srinagar, Kashmir with MS versus those without MS while a study from Egypt on children with obesity reported higher prevalence of hypertension and dyslipidemia in those with MS compared to those without MS.[10,23] A study from Poland on 591 obese children reported higher prevalence of hypertension, low HDL levels and hypercholesterolemia in children with MS compared to children without MS.[25]

Major limitation of the current study was the lack of a control group. This was a cross-sectional study and hence did not allow causal or temporal inferences. Another limitation was its being a single institution study. However, this is the first study on the prevalence of MS among children with overweight and obesity from South India and the first study from India that looked into the prevalence of MS among children aged 3-8 years. India is a very diverse country with 29 states, each with their own unique languages and culture. A recent population based study on the prevalence of MS among adolescents in India reported wide variability across states owing to differences in lifestyles, degree of urbanization and socioeconomic factors.[36] Very few studies from India had addressed the prevalence of MS among children with obesity and both were from North India.[10,11]

CONCLUSION

Current study from South India observed MS even in younger children with overweight and obesity which is really concerning as these children are at increased risk for hypertension, T2D, NAFLD and cardiovascular disease in early adulthood which in turn leads to huge economic burden on the country. It is therefore of utmost importance to take necessary steps to identify these children early, manage obesity effectively before MS sets in and initiate preventive measures thereby ensuring a healthy young generation in the coming years.

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Section: Community Medicine

Original Research Article

CLINICO-SOCIAL FACTORS ASSOCIATED WITH TUBERCULOSIS AND DIABETES MELLITUS COMORBIDITY IN SOUTH INDIA – A CASE- CONTROL STUDY

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ABSTRACT

Background: Despite control strategies, tuberculosis remains a significant public health problem in many countries. Along with effective control measures currently available, it is essential to identify and target the risk factors of developing active TB to tackle the heavy burden of the disease. This study aims to find out the association of clinical and social factors with Tuberculosis and Diabetes mellitus co-morbidity.

Materials and Methods: A case-control study was done to assess the association of clinical and social factors with Tuberculosis and Diabetes mellitus co-morbidity. The study was done from a parent study conducted in South India to study the prevalence of diabetes mellitus among registered tuberculosis patients. Those patients diagnosed with both tuberculosis and diabetes mellitus were taken as cases, and those patients with tuberculosis without diabetes mellitus were taken as controls. Cases and controls were above the age of 15 years. The calculated sample size was 115:345, as there were only 92 cases in the parent study. All were taken. Social factors like age, gender, occupation, and socio-economic status, as well as clinical factors like various symptoms, symptom score, type of tuberculosis, category, and treatment outcome, were studied in this study. Data was coded in Excel and analyzed using SPSS version 16. Chi-square analysis was done to find out the association and odd's ratio.

Results: There was a significant difference in age between cases and controls. All symptoms are significantly higher (Chi-square 27.6p-0.0001) among those who have tuberculosis and diabetes co-morbidity when considering each symptom separately. Extrapulmonary tuberculosis was found more among controls. In this study, it was found that relapse and treatment after default were significantly higher among cases(Chi square 23.4 p-0.000034).

Conclusion: A significant difference was found among TB patients with DM as co-morbidity when compared with patients without DM. Uncontrolled diabetes will be one challenge for TB elimination. Hence, periodic screening is necessary to find out DM and the proper measures to be followed to control.

Keywords: Diabetes co-morbidity, Symptom score, treatment outcome.

INTRODUCTION

Tuberculosis (TB) is the second leading cause of death from an infectious disease next to Human Immuno-deficiency Virus (HIV) infection.[1] Despite control strategies, tuberculosis remains a significant public health problem in many countries. Along with effective control measures currently available, it is essential to identify and target the risk factors of developing active TB to tackle the heavy burden of

the disease. Diabetes mellitus (DM) is a clinically and genetically heterogeneous group of disorders with one common feature, i.e., abnormally high levels of glucose in the blood either due to insulin deficiency or resistance of the body's cells to the action of insulin. DM reduces immunity and has long-term complications that affect all vital organs of the body. It was a well-known risk factor for TB in the past, but this was largely forgotten during the second half of the 20th century because of widely available treatments for both diseases.[2,3] According to a recent meta-analysis, people with diabetes have three times the risk of contracting TB as compared to non-diabetics,[7] and studies report the fraction of TB cases attributable to diabetes to be between 15% and 25%.[8] The biological basis for the association between both diseases is that diabetes decreases the immune response, which in turn facilitates TB infection and progression to symptomatic disease. Active detection of diabetes amongst TB patients may provide an opportunity to identify previously undiagnosed diabetes, offer optimum diabetic care and, improve the outcomes of TB treatment and prevent the relapse of TB. The studies in this area are limited. Hence, this study aims to find out the association of clinical and social factors with Tuberculosis and Diabetes mellitus co-morbidity.

MATERIAL AND METHODS

A case-control study was done to assess the association of clinical and social factors with Tuberculosis and Diabetes mellitus co-morbidity. The study was done from a parent study conducted in South India to study the prevalence of diabetes mellitus among registered tuberculosis patients. This was conducted in three primary health centres (PHC) - Handignoor, Vantamuri, Kinaye and three urban health centres (UHC)- Ram Nagar, Asok Nagar, Rukmini Nagar, which are the field practice areas of the Department of Community Medicine, Jawaharlal Nehru Medical College, Belgaum and in RNTCP unit, Government District Hospital Belgaum. RNTCP registers maintained at the Primary Health Centres, Urban Health Centres and Government District Hospital were used to identify tuberculosis patients. Those patients diagnosed with both tuberculosis and diabetes mellitus were taken as cases, and those patients with tuberculosis without diabetes mellitus were taken as controls. Cases and controls were above the age of 15 years. Since the association of social factors was studied, no matching was done in this study. Screening for diabetes was done by estimating the fasting blood glucose (FBS) using a capillary method and a glucometer and strips. Those showing an FBS value of ≥ 110 were subjected to an Oral Glucose Tolerance Test (OGTT). Diagnosis of diabetes was made based on WHO criteria 77 (2 hr plasma glucose ≥200 mg/dl after 75 grams of oral glucose load). Pregnant women to exclude possible gestational diabetes mellitus. The sample size was calculated using Open epi the difference in the proportion of diabetes and TB co-morbidity among normal and obese patients from the study by Rajaa, Yuvaraj Krishnamoorthy et al,[5]assuming 80% power and 95% Confidence Interval and case-control as 1:3. Calculated sample size was 115:345, as there were only 92 cases in the parent study all were taken.

Social factors like age, gender, occupation, and socio-economic status, as well as clinical factors like various symptoms, symptom score, type of tuberculosis, category, and treatment outcome, were studied in this study. Data was coded in Excel and analyzed using SPSS version 16. A chi-square analysis was done to find out the association and odd ratio.

RESULTS

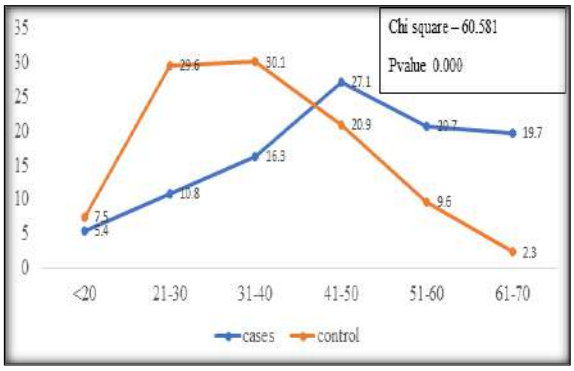


Figure 1: Comparison of different age groups in cases and controls

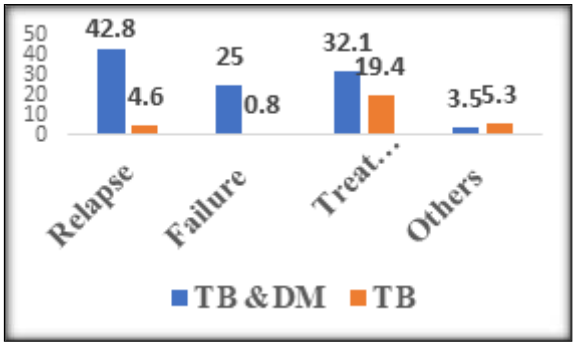


Figure 2: Type of category based on treatment in cases and control

A total of 92 cases and 345 controls were studied. There was a significant difference in age between cases and controls. The proportion of cases was above 30 years, and that of controls was below 30 years, which was statistically significant, as shown in Figure 1. Males were significantly higher among cases (chi-square 4.291; p-0.038). A significant difference was found in different occupations. Results are given in Table No. 1. There is a significantly higher proportion of semi-skilled and unskilled workers among patients with TB and DM co-morbidity (p-0.044).

Clinical symptomatology

All symptoms are significantly higher among those who have tuberculosis and diabetes co-morbidity when each symptom is considered separately. (Table no 2.) However, in tuberculosis, most of the persons present with more than one symptom. Hence, the symptom score was also considered in this study. It was found that cases had fewer symptoms when compared with controls. Patients with TB and DM co-morbidity had significantly less number of symptoms. Extra pulmonary tuberculosis was found more among controls. (Table no 3). In this study, it was found that relapse and treatment after default were significantly higher among cases.

Table 1: Difference in other social factors in cases and control

Variable	Tuberculosis with DM Number 92 (%)	Tuberculosis without DM Number 345 (%)	Chi square pvalue
Age			
<20	5(5.4)	26(7.5)	
21-30	10(10.8)	102(29.6)	
31-40	15(16.3)	104(30.1)	60.581
41-50	25(27.1)	72(20.9)	
51-60	19(20.7)	33(9.6)	p-0.000
61-70	18(19.7)	8(2.3)	
Gender			
Male	69(75)	219(63.4)	4.291
Female	23(25)	126(36.6)	p-0.038
Occupation			
Professional	2(2.1)	0	
Semi Professional	5(5.4)	8(2.3)	
Clerk	9(9.8)	26(7.5)	12.961
Skilled	12(13.1)	48(13.8)	
Semi-skilled	19(20.7)	82(23.7)	
Unskilled	25(27.2)	64(18.8)	p-0.044
Unemployed	2(2.1)	16(4.6)	
House wife	18(19.6)	101(29.3)	
Socioeconomic status			
I	1(1.1)	1(0.3)	
II	12(13)	20(5.8)	7.421
III	16(17.4)	82(23.7)	
IV	30(32.6)	112(32.5)	p-0.06
V	33(35.9)	130(37.7)	

Table 2: Clinical symptoms in both the cases and control

Symptom	Tuberculosis		Chi square value pvalue
	With DM No(%)	Without DM No(%)	
Cough			
Present	85(92.4)	288(83.5)	4.61
Absent	7(7.6)	57(16.5)	p-0.032
Fever			
Present	92(100)	301(87.2)	13.047
Absent	0	44(12.8)	p-0.001
Hemoptysis			
Present	73(79.4)	220(63.7)	7.98
Absent	19(20.6)	125(36.3)	p-0.005
Dyspnoea			
Present	47(51.1)	116(33.6)	9.47
Absent	45(48.9)	229(66.4)	p-0.002
Night sweats			
Present	83(90.2)	258(74.7)	10.09
Absent	9(9.8)	87(25.3)	p-0.01
Weight loss			
Present	65(70.6)	210(60.9)	2.98
Absent	27(29.4)	135(39.1)	p-0.084
Loss of appetite			
Present	50(50.3)	268(77.6)	23.672
Absent	42(45.7)	77(22.4)	p-0.001

Table 3: Other clinical profile among cases and control

Clinical variable	Tuberculosis		Chi square value pvalue
	With DM No (%) N-92	Without DM No (%) N 345	
Symptom score			
<4	152(44.05)	13(14.13)	27.68
≥4	193(65.90)	79(85.87)	p-0.0001

Type of TB			
Pulmonary	83(90.2)	285(82.6)	3.162
Extra pulmonary	9(9.8)	60(17.4)	p-0.025
Sputum result			
Negative	13(14.1)	82(23.4)	
1+	8(8.6)	50(14.6)	
2+	16(17.3)	92(26.8)	26.580
3+	53(57.6)	100(28.9)	p-0.001
Scanty	2(2.2)	21(6.3)	
Category			
New	64(69.6)	253(73.3)	0.518
Old	28(30.4)	92(26.7)	p-0.47

DISCUSSION

In this study, an advanced age group was found among cases compared with controls (p 0.00), similar to a study conducted in Kerala in 2011. It was found that among those patients with TB-DM co-morbidity, the majority were in the age group of ≥ 45 years (75%). In a study by Rajaa S et al.[5] also, there were more elderly among TB -DM co-morbidity. In this study, it was observed that the male-to-female ratio in the TB group was 1.74:1, whereas in the TB-DM group, it was 3:1; i.e., males were more affected in the TB-DM group. The findings were comparable with a study done in South India (Rajaa et al.), where the male-to-female ratio among TB-DM patients was 3.1:1 as compared to 1.53:1 among TB patients. Similarly, a study done in Bengaluru reported a higher proportion of males in the TB DM population.[6] A Higher proportion of low socio-economic status was found among cases in the present study. Men were more likely to develop TB-DM co-morbidity compared to women, according to a systematic review by Mahteme Haile Workneh et al,[7] according to which twenty-two studies reported that older age increased the risk of TB-DM co-morbidity. Urban residence and educational level beyond primary schooling were associated factors for TB-DM comorbid conditions.[2]All symptoms associated with tuberculosis were significantly higher among patients with TB-DM co-morbidity except in the case of weight loss. According to Xunliang Tong et al,[8] the TB-DM group had higher symptoms. Sputum smear positivity is lower among TB DM co-morbidity except in 3+ smears. Kelly E Dooley and Richard E Chaisson reported that active tuberculosis was found to be significantly higher in patients with diabetes mellitus.[9] In a study by Anthonia Okeoghene Ogbera et al,[10] published in 2015, showed a higher sputum positivity in Tb DM co-morbidity. Overall symptom scores were significantly high in patients with diabetes, which could be an indication of active tuberculosis among them. Kishore Shettihalli Gudegowda et al. reported a lower cure rate, and the incidence of death and failure was higher among patients with TB and DM.[6] Comparable results were found in this study. A significantly high level of treatment failure and default was found in the present study.

CONCLUSION

A significant difference was found in symptomatology, age of occurrence, gender and treatment outcome of Tuberculosis in patients who had diabetes mellitus as a co-morbidity. This will be a significant challenge in treating TB and, thus, elimination. This signifies the active control of diabetes and dietary management so that the immunity of the persons won't be compromised, which could be why TB control is affected. Regular screening should be done to detect diabetes early and manage it properly.

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Original Article

Prevalence and determinants of post-COVID-19 syndrome among patients 6 months post-discharge from a teaching hospital in South India

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Abstract

Background: The coronavirus disease 2019 (COVID-19) infection has affected millions of people worldwide in the last 4 years. Among those infected, the long-term COVID-19 syndrome, in which symptoms of COVID-19 persist for a variable period, is posing new challenges to the health system, but few studies are available in India that examine the post-COVID-19 syndrome, that is, 6 months and beyond COVID-19 infection. This study aimed to find the prevalence and determinants of post-COVID-19 syndrome among patients 6 months and beyond their infection. **Methodology:** This cross-sectional study was conducted among 300 patients who were admitted and discharged from Government Medical College, Thrissur, at least 6 months before with a diagnosis of COVID-19 infection. The data collection was performed using a semi-structured interview schedule through a telephonic interview. The analysis was performed using the Statistical Package for the Social Sciences (SPSS) software. **Results:** 21% of the patients studied had at least one persistent symptom at the end of 6 months, and 4.1% had more than one symptom. Among the symptoms persisting most commonly were fatigue (11%) and dyspnea (7.7%). Other than persisting symptoms, 21% of patients developed exertional dyspnea and 19% developed sleep disturbances during the 6 months after discharge. The factors that were associated with persistent symptoms in univariate analysis were increasing age, presence of chronic obstructive pulmonary disease (COPD), presence of chronic kidney disease (CKD), and admission to the intensive care unit (ICU). **Conclusion:** The study concludes that one-fifth of the patients still suffer from post-COVID-19 syndrome even 6 months after the COVID-19 infection. Our health systems should be prepared for the long-term management of COVID-19-infected people and prepare policies for the same.

Keywords: Kerala, long-term COVID-19 syndrome, persistent COVID-19, post-COVID-19 syndrome

Introduction

The coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has been more than 4 years since the first case of COVID-19 was reported, and still, this pandemic remains a challenge to our healthcare system and affects the well-being of the whole world. As of August 2023, over 769 million confirmed cases and over 6.9 million deaths have been reported globally due to COVID-19.[1] In the same period, India has reported a total of 44 million confirmed cases and about 5 lakh deaths.[2]

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Current knowledge on COVID-19 has shown that a majority had only mild disease, but a few could go from severe disease to even death. The infection-to-hospitalization ratio (IHR), defined as the percentage of infected individuals who are hospitalized, is approximately 2.1%.[3] In most of the cases, the patient experiences complete resolution of symptoms within 2–6 weeks.

A proportion of those infected with SARS-CoV-2 experience long-term symptoms. The World Health Organization (WHO) has developed a working clinical case definition for the post-COVID-19 condition. The post-COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis.[4] Patients usually present with persisting symptoms, such as fatigue and shortness of breath, or new-onset symptoms, such as cognitive dysfunction and sleep disturbances.[5] It has been found that post-COVID-19 effects can happen even in people who have only suffered mild COVID-19 infection.[6] The incidence of post-COVID-19 syndrome among patients who have received outpatient or home-based management has been found to be between 10% and 35%.[7,8] Evidence from an Indian setting has shown an incidence of post-COVID-19 symptoms in around 9.9% of patients beyond 12 weeks after recovery from acute infection.[9] The evidence regarding post-COVID-19 syndrome, its magnitude with time, determinants, and ways to manage it is going to evolve as time passes by. Thus, there is a need to better understand the clinical spectrum and long-term course of this clinical entity.

Prolonged health problems among those who have recovered from an acute infection, such as COVID-19, are posing a challenge to our health system, which has already been burdened by the pandemic. With millions of people being affected by COVID-19, even a small percentage of them developing post-COVID-19 conditions for a long time will have a serious effect on society and public health systems, with many people in need of long-term follow-up, management, and support, including rehabilitation. In Kerala, the government had to set up post-COVID-19 clinics in peripheral centers to address the long-term effects of COVID-19.[10] The need for such exclusive clinics to tackle these health problems largely points toward the importance of this entity of post-COVID-19 syndrome. Also, there is a lack of studies on long-term COVID-19 or post-COVID-19 syndrome, especially 6 months and beyond primary infection, from healthcare settings in South India. Thus, it is indeed an area to research and bring out a clearer picture of this syndrome so that we can have evidence-based planning and prioritization of our healthcare resources, besides contributing to a better understanding of the long-term natural history of COVID-19. This will also act as a guideline for primary healthcare physicians on what to expect among long-term post-COVID-19 patients.

Thus, the principal aim of this study was to determine the proportion of patients who have persistent symptoms or have developed new symptoms 6 months after COVID-19 infection and to determine the factors associated with it, among those who have been discharged from a tertiary care center in South India.

Materials and Methods

This cross-sectional study on long-term COVID-19 syndrome was conducted at Government Medical College, Thrissur, a tertiary care institution in the southern state of Kerala. The data collection was performed between October 2021 and January 2022 among those who were admitted and discharged from the hospital at least 6 months ago. The study was approved by the Institutional Ethics Committee as per the letter IEC/GMCTSR/189/2021 dated 6.10.2021.

Sample size

As per the study conducted by Dominik Menges *et al.*[11] in Switzerland, 26% of the patients had persistent symptoms or were unwell 6–8 months post-infection. Applying it to the formula 4 pq/d2, taking 26% as p Q = 1-p, an alpha error of 0.05, and an absolute precision of 5%, the sample size was calculated to be 296.

In the Government Medical College, Thrissur, the details of all COVID-19 patients admitted to the hospital, including their mobile number, were collected as a hospital policy. The study was conducted among patients who were discharged from the hospital at least 6 months before with a diagnosis of COVID-19 infection and were above the age of 18 years. The data collection was performed using a semi-structured interview schedule over the phone. In the first part of the interview, the investigator explains to the patient the objectives of the study and asks for telephonic consent, which is recorded. He was also given the assurance that the details he provided would not be used for any other purpose. The information that the call was being recorded was also intimated to the participants. Then, the interview moves to the second part only if the person gives consent. In other cases, the person is excluded and the next person on the list is called. The semi-structured interview consisted of questions regarding the sociodemographic details of the person, clinical details while in the hospital, and persistent or new symptoms as on the date of the interview. Thus, a total of 321 people were contacted over the phone, 21 did not give consent for the study and were excluded, and the final sample size was 300.

Once the data were collected, they were properly coded and entered in Microsoft Excel. Further analysis was performed using the software Statistical Package for Social Sciences (SPSS) version 16.0. The persistence of symptoms at 6 months was expressed as proportions and confidence intervals. For finding out the factors associated with the persistence of symptoms, the dependent variable taken was the persistence of at least one of the symptoms. The Chi-square test was used to find the association of the persistence of symptoms with other factors. The *P* value of less than 0.05 was taken as statistically significant. The factors that were found to be significant in univariate analysis

were also analyzed using binary logistic regression using the enter method.

Results

Among the 300 people included in the study, the mean age was 44.95 years, with a standard deviation of 15.5 years. There was almost an equal representation of males and females in the study sample (52.7% and 47.3%). The age group with the highest representation in the study sample was 45–60 years, followed by 30–45 years (30.3% and 30%) [Table 1]. 24.3% of the population had an educational qualification of graduate and above. The majority (72.3%) had studied up to high school or above. As far as the occupation of the study group is concerned, 35% were unemployed and 46.7% were skilled or unskilled laborers [Table 1].

74.7% of the total studied had no persistent symptoms at the end of 6 months of COVID-19 infection, but 21% had at least one persistent symptom and 4.4% had more than one symptom persisting [Figure 1].

Of the symptoms persisting, the most common ones were fatigue (11%) and dyspnea (7.7%). Apart from persistent symptoms, some patients developed new symptoms that were not present during the COVID-19 infection. Apart from the persistent symptoms, some patients developed some new symptoms, which were not present before the COVID-19 infection. Among them, the most common ones were exertional dyspnea (21%) and sleep disturbances (19%) [Table 2].

69.7% of patients perceived their current physical health as the same as pre-COVID-19, but 30.3% perceived their physical health to be slightly worse or definitely worse than pre-COVID-19 [Figure 2].

It was also found that the persistence of symptoms beyond 6 months of COVID-19 positivity was associated with increasing age, with 30.2% of those above 60 years having at least one symptom persisting compared with 5.4% among those below 30 years. It was also associated with comorbidities, such as chronic obstructive pulmonary disease (COPD), where 77.8% had persistence of symptoms compared with 23.7% among those without COPD. Persistence was also associated with chronic kidney disease (CKD), where 63.2% of those with CKD had persistence compared with 22.8% of those without. Among

Table 1: Basic demographic characteristics of the study population

Variable	Frequency	Percentage
Age group		
<30 years	56	18.7%
30–45 years	90	30%
45–60 years	91	30.3%
>60 years	63	21%
Gender		
Male	158	52.7%
Female	142	47.3%
Education		
Graduate/PG	73	24.3%
Higher secondary	60	20%
High school	84	28%
Primary/middle school	79	26.3%
Illiterate	4	1.4%
Occupational status		
Professional/semi-professional	21	7%
Clerk/shopkeeper/farmer	34	11.3%
Skilled/semi-skilled	62	20.7%
Unskilled	78	26%
Unemployed/retired	105	35%

Table 2: Symptoms persisting in post-COVID-19 patients

	Patients having persistent symptoms >6 months or new symptoms (*n* (%))
Fatigue	33 (11%)
Dyspnea	23 (7.7%)
Cough	12 (4%)
Myalgia	8 (2.7%)
Joint pain	8 (2.7%)
Pedal edema	7 (2.3%)
Others (decreased appetite, vertigo, headache, chest pain)	8 (2.7%)
New symptom (not present during hospital admission): exertional dyspnea	64 (21.3%)
Sleep disturbances (decreased, broken, delayed onset)	57 (19%)

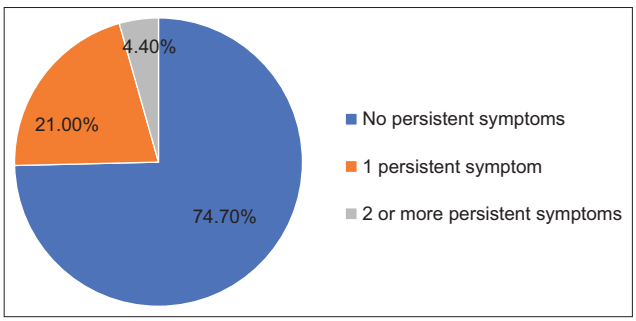


Figure 1: Persistence of symptoms in the study population

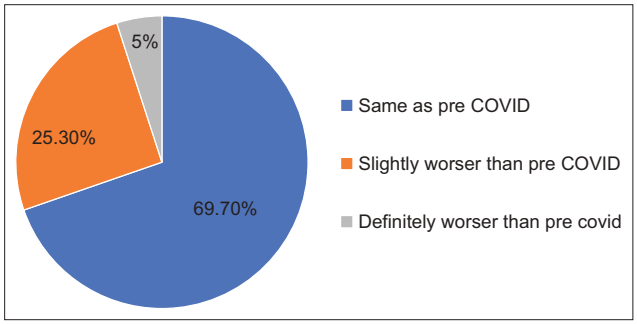


Figure 2: Patient's perception of current health by study population

those who were admitted to the intensive care unit (ICU), 64.3% had persistence compared with 23.4% among those who were in wards [Table 3].

Those factors that were found to be statistically significantly associated with the persistence of symptoms in the Chi-square test were also analyzed using binary logistic regression. In regression analysis, increasing age group (odds ratio: 2.33 (95% confidence interval (CI): 1.03–5.26)), presence of COPD in the patient (odds ratio: 9.64 (95% CI: 1.54–60.24)), presence of CKD (odds ratio: 4.5 (95% CI: 1.57–13.02)), and admission to an ICU (odds ratio: 5.03 (1.45–17.53)) were found to be significant predictors of the persistence of symptoms beyond 6 months post-COVID-19 infection.

Discussion

In the current study, the proportion of patients who had at least one persistent symptom at 6 months was 21% and 4.4% had more than one symptom. This is lower than what was reported in the study conducted by Max Augustin *et al.*[12] in Germany where the proportion of COVID-19 patients who had post-COVID-19 syndrome at 4 months and 7 months after symptom onset was 27.4% and 34.8%, respectively. In another study by Jennifer K. Logue *et al.*[13] in the United States, the proportion of patients with at least one symptom persisting at 6 months after discharge from the hospital was 32.8%, whereas 13.6% of people had more than three symptoms persisting. Yet, in another study from Italy by Maddalena Peghin *et al.*[14] the proportion of those with post-COVID-19 syndrome 187 days post-symptom onset was 40.2%. As per the study conducted by Deepa *et al.* in an urban area of north Kerala, the prevalence of post-COVID-19 syndrome was found to be 42.2%.[15] Compared to these studies, the present study had a slightly lower prevalence of post-COVID-19 syndrome. Still, it can be seen that even 6 months after the COVID-19 infection, approximately one-fourth of the patients still had persistent symptoms, which could have long-term implications both with respect to the health resources required for post-COVID-19 management and current policies for the same.

As per the current study, the most common symptoms persisting at the end of 6 months were fatigue (11%), dyspnea (7.7%), and cough (4%). This is similar to the study conducted by Ahmet Naci Emecen in Turkey, where at the end of 6 months of follow-up

Table 3: Association of the persistence of symptoms with clinicodemographic factors

Exposure factors	Symptoms persisted *n* (%)	Symptoms not persisted *n* (%)	Chi-square	*P*
Age group				
<30	3 (5.4%)	53 (94.6%)	20.011	0.00
30–45	20 (22.2%)	70 (77.8%)		
45–60	34 (37.4%)	57 (62.6%)		
>60	19 (30.2%)	44 (69.8%)		
Any comorbidity				
Yes	58 (38.7%)	92 (61.3%)	28.195	0.00
No	18 (12%)	132 (88%)		
Diabetes mellitus				
Yes	32 (39%)	50 (61%)	11.182	0.001
No	44 (20.2%)	174 (79.8%)		
Hypertension				
Yes	34 (41.5%)	48 (58.5%)	15.521	0.00
No	42 (19.3)	176 (80.7%)		
CAD				
Yes	8 (47.1%)	9 (52.9%)	4.497	0.034
No	68 (24%)	215 (76%)		
CVA				
Yes	8 (47.1%)	9 (52.9%)	4.497	0.034
No	68 (24%)	215 (76%)		
COPD				
Yes	7 (77.8%)	2 (22.2%)	13.491	0.00
No	69 (23.7%)	222 (76.3%)		
CKD				
Yes	12 (63.2%)	7 (36.8%)	15.343	0.00
No	64 (22.8%)	217 (77.2%)		
Oxygen support in the hospital				
Yes	52 (34%)	101 (66%)	12.361	0.00
No	24 (16.3%)	123 (83.7%)		
ICU admission				
Yes	9 (64.3%)	5 (35.7%)	11.780	0.001
No	67 (23.4%)	219 (76.6%)		

the most common symptoms persisting were fatigue (9.03%), muscle and body ache (5.13%), and dyspnea (3.06%).[16] In yet another study conducted by Nalinakumari Kesavan Nair Anjana *et al.*[17] in Thiruvananthapuram, among 154 patients discharged from COVID First Line Treatment Centre (CFLTC) at the end of 3 months, 5.8% still had fatigue, 5.8% had headache, 3,2% had myalgia, and 2.5% had joint pain, but unlike these studies some studies have reported a high prevalence of fatigue among post-COVID-19 patients at 6 months of follow-up like J. González-Hermosillo *et al.*[18] in Mexico among 130 patients who reported a prevalence of fatigue of 46.9%.

It was interesting to note that during the 6 months of follow-up period in the current study 21.3% developed exertional dyspnea and sleep disturbances (19%), which were not present before or during the COVID-19 infection. Alberto Fortini *et al.*[19] in Italy also reported similar findings, with 37.3% having exertional dyspnea and 28.3% having insomnia 3–6 months after COVID-19 infection. Sleep disturbances in long-term COVID-19 syndrome have also been reported by Mario Mekhael *et al.* and Evgenia Kalamara, who both reported that both total sleep time and deep sleep time were decreased in patients with long-term COVID-19.[20,21] The study results show that even at the end of 6 months a significant number of the population have not completely recovered from the COVID-19 infection and many have a new onset of symptoms, which were not present before or during the COVID-19 infection. Considering the sheer number of people infected with COVID-19 around the world, the persistence of such symptoms or new symptoms, such as exertional dyspnea and sleep disturbances, for an extended period of time could substantially hamper work efficiency and impact the net productivity and well-being of a large population.

Among the 300 patients who were part of the study, 30.3% of people perceived their health to be slightly or definitely worse than pre-COVID-19 condition. In a study conducted by Vincent Tarazona in France, COVID-19 patients even 1 year post-discharge had a much lower health-related quality of life than control when assessed using the EuroQol-5 Dimension scale (EQ-5D-5L).[22] Similar findings showing lower health-related quality of life among long-term COVID-19 patients have been reported in multiple studies around the world.[23,24]

The current study shows that older age groups have a higher risk of developing long-term COVID-19 syndrome compared with younger ones. Imad M. Tleyjeh *et al.*[25] in Saudi Arabia reported age more than 50 as a significant predictor for lack of return to normal 4–6 months after COVID-19 infection with an adjusted odds ratio of 10.05 compared with younger age groups. The association between increasing age and long-term COVID-19 syndrome has also been shown in other studies conducted by Mark W Tenforde in the United States and Roy H. Perlis in Columbia.[8,26]

The current study found that the long-term COVID-19 syndrome is closely associated with the presence of comorbidities. This is similar to the study conducted by Imad M. Tleyjeh *et al.*[25] who found that the presence of diabetes mellitus, hypertension, or liver disease was an important predictor of long-term COVID-19 syndrome. The relationship between comorbidities and long-term COVID-19 syndrome has also been shown in the meta-analysis conducted by Kin Israel Notarte *et al.*[27] A similar association was also shown by M. C. Arjun *et al.*[28] in India, who showed that the presence of a preexisting medical condition was a risk factor for long-term COVID-19 syndrome with an adjusted odds ratio of 2.1. In a country like India, where the prevalence of comorbidities, such as hypertension and diabetes, is high, this could have far-reaching implications in the long run.

The results of the current study showed that ICU admission was a significant predictor of symptoms that persisted 6 months following the COVID-19 infection. The multivariate analysis of a study conducted among 449 patients in Italy by L Boglione *et al.*[29] revealed ICU admission to be one of the independent predictors of long-term COVID-19 syndrome. Research by Aliae AR Mohamed Hussein *et al.* in Egypt and Ali Akbar Asadi-Pooya *et al.* in Iran also revealed an association between long-term COVID-19 syndrome and ICU admission.[30,31]

Conclusions and Recommendations

The current study shows that the health effects of COVID-19 infection linger even after 6 months post-COVID-19 infection, either as persistent symptoms or as new symptoms, such as exertional dyspnea or sleep disturbances. The authors recommend a long-term comprehensive management strategy for post-COVID-19 health issues, especially among primary health physicians.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Temporal Trends in SARS-CoV-2 Antibody Levels Among COVID-19 Patients in Kerala During the First Wave and Pre-vaccination Period

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Abstract

Background: The SARS-CoV-2 virus interacts with host cells through the S1 domain of its spike protein. This study measures the IgG immune response to this domain in COVID-19 patients from Kerala, India, and explores its association with various health factors.

Methods: A cohort of 258 COVID-19 patients was analyzed for IgG antibodies targeting the S1 spike protein domain. The temporal pattern of the IgG response and its correlation with hospitalization needs, intensive care, and pre-existing conditions such as diabetes, hypertension, and coronary artery disease were assessed.

Results: A significant IgG response (76.4%) was detected, indicating robust immune activation post-infection. The IgG levels peaked between two to four and four to eight weeks post-infection, with a notable increase at 12 weeks, hinting at possible secondary exposure or an immune memory response. No correlation was found between IgG levels and the presence of diabetes mellitus, hypertension, or coronary artery disease. However, higher IgG responses correlated with the severity of the infection, as seen in patients requiring hospitalization or intensive care.

Conclusions: The IgG response to the S1 spike protein domain serves as a potential marker of immune activation in COVID-19. It reflects the body's defense mechanism against the virus and may predict disease severity and outcomes. The findings suggest that IgG levels could be indicative of the viral load, inflammatory response, and possibly the likelihood of protection against reinfection.

Categories: Epidemiology/Public Health, Internal Medicine, Infectious Disease
Keywords: sars-cov-2, comorbidities, covid-19 vaccination, sars-cov-2 spike protein, pre-vaccination, first wave, kerala, igg, covid-19, antibody response

Introduction

The coronavirus COVID-19 pandemic is a global crisis that evolved in 2020. The disease was first reported in Wuhan city of China in December 2019, and it rapidly spread to other parts of the world, including Antarctica, and posed a heavy impact on all aspects of the human race [1]. SARS-CoV-2 falls under the genus Betacoronavirus (β-CoV) (family Coronaviridae) virus with a positive-sense ribonucleic acid (RNA) that is packaged in an envelope. The envelope facilitates the virus entry and evasion of the host cell's defenses. Non-structural proteins of coronaviruses have been shown to impair the function of host innate immune cells and alter cytokine production. Humoral response against SARS-CoV-2 has been found to be similar to that against other coronavirus infections, involving the characteristic IgG and IgM production [2]. B cells respond to the N protein of SARS-CoV early in the infection, whereas S protein-specific antibodies appear after four to eight days of symptom onset. IgA, IgG, and IgM antibodies against SARS-CoV are detected at various time points after symptom onset in infected patients [3]. IgM and IgA antibodies were detected five days after the onset of initial symptoms, whereas IgG was detected after 14 days [4].

In Kerala, the first COVID-19 case emerged in January 2020. Subsequently, the state experienced several waves of infection, each characterized by distinct variants. In this study, we analyzed the IgG response to the S1 domain of the spike protein of SARS-CoV-2, spanning from October 2020 to September 2021, utilizing a commercially available enzyme-linked immunosorbent assay (ELISA) in subjects diagnosed with COVID-19. The study was specifically focused on individuals who had developed natural naive immunity to COVID-19, excluding those who had been vaccinated and those cases of reinfection. Apart from a few selected centers, comprehensive data on the antibody response against COVID-19 from Kerala during the pandemic period are sparse [5].

Materials And Methods

This is a hospital-based cross-sectional study from October 2020 to September 2021 assessed in the Departments of Medicine and Microbiology, Government Medical College, Kozhikode, to measure the IgG antibody response in patients diagnosed with SARS-CoV-2 infection. The objective of this study was to investigate the dynamics and determinants of the antibody response to SARS-CoV-2 infection in a cohort of patients with or without different comorbidities. Our centre was providing diagnostic and treatment services during the pandemic. The subjects were identified from the institutional records and approached for participation in the study. Patients with a confirmed diagnosis of SARS-CoV-2 infection between two weeks and 17 weeks from the day of onset of symptoms or the diagnosis (in asymptomatic cases) were identified. Patients who had received convalescent plasma therapy or received vaccination were excluded.

After obtaining the written informed consent, a structured questionnaire was used to collect demographic and clinical details from 258 laboratory-confirmed (by rapid antigen test, reverse transcription-polymerase chain reaction (RT-PCR), TrueNat, or cartridge-based nucleic acid amplification test (CBNAAT)) COVID-19 subjects.

The patient data were meticulously documented, including comorbidities, exhibited symptoms, the duration of the illness, and patient outcomes. The Clinical Severity Stage was categorized into four distinct levels: asymptomatic, mild, moderate, and severe. The ‘Mild’ category is defined by a respiratory rate lower than 24 breaths per minute and an oxygen saturation (SpO_2) greater than 94% in ambient air. The ‘Moderate’ category is specified by a respiratory rate between 24 and 29 breaths per minute and SpO_2 ranging from 91% to 94% in ambient air. The ‘Severe’ category is marked by a respiratory rate of 30 breaths per minute or higher and SpO_2 below 90% in ambient air. These classifications provide a structured approach to assessing the severity of clinical presentations [6].

From each study participant, 2 mL of plain blood was withdrawn. The sera were then isolated, adhering to established protocols. Upon separation, these sera samples were preserved in a deep freezer (-80°C), maintaining their condition until the ELISA testing phase commenced. ELISA was performed adhering to the kit manufacturer’s instructions. The IgG antibodies against SARS-CoV-2 in serum were measured by a commercially available ELISA kit (EUROIMMUN anti-SARS-CoV-2 ELISA). In brief, the ELISA reagent wells were coated with the S1 domain of the SARS-CoV-2 spike protein, expressed recombinantly in HEK 293 cells. Diluted samples (1:101) and controls were added to microplate wells and incubated. After washing thrice with the provided wash buffer, peroxidase-labeled anti-human IgG was added and incubated. Chromogen/substrate solution was added then and incubated at room temperature as per the suggested protocol. Colour intensity was measured in an ELISA reader (ALTA ELISA Plate Reader; Swastika Ventures, West Bengal, India) at 450 nm, followed by adding a Stop solution. The results were analyzed and interpreted in accordance with the recommendations provided by the kit manufacturers.

The optical density (OD) of each sample was divided by the OD of the calibrator to obtain a ratio. This ratio was then used to categorize the results: values below 0.8 indicated a negative result, values between 0.8 and 1.1 were considered borderline, and values of 1.1 or above signified a positive result. Statistical analysis was performed using Statistical Product and Service Solutions (SPSS, version 16.0; IBM SPSS Statistics for Windows, Chicago, IL). Continuous data were reported as mean ± SD for symmetric data and as median with interquartile range (IQR) for skewed data. Categorical data were reported as frequency and percentages. Since for both positive and negative response groups the data on time after the onset of infection did not meet the normality assumption, the average time after the onset of infection between positive and negative response groups was compared by the Mann-Whitney U test. To test the association between antibody response and co-morbidities and other known factors, the chi-square test was used when all cells had expected frequency > 5. For data not satisfying this condition, Fisher’s exact test was used for testing the association. The correlation between time from the onset of infection and antibody response as titre was assessed by Pearson’s correlation. Two-sided tests were used, and the significance level was set at $p<0.05$.

Results

There were 258 patients in our study sample. The time after the onset of infection was between 15 and 119 days with a mean time of 53.8 ± 27.1 days. The median age of the patients was 32 (25-45) years (between two and 93 years). The antibody response (expressed as a ratio) was between 0.003 and 9.07, with a mean of 2.94 ± 2.13. Antibody response was positive in 197 (76.4%) and negative in 44 (17.1%). A total of 13 (5%) had a borderline response, while in four (1.6%) samples, the antibody response was indeterminate. Borderline and indeterminable responses were excluded from the analysis. A total of 68 patients received treatment in the intensive care unit (ICU). Oxygen therapy was administered to 160 individuals. The rate of IgG-positive response showed an increasing trend with the severity of the disease (Table *1*). Furthermore, the study found no significant association between comorbid conditions and antibody response (Table *2*).

Sl No.	Severity of illness (n)	Antibody response in number of subjects, n (%)	
		Positive	Negative
1	Asymptomatic (n=45)	28 (62.2)	17 (37.8)
2	Mild (n=140)	116 (82.9)	24 (17.1)
3	Moderate (n=29)	26 (89.7)	3 (10.3)
4	Severe (n=27)	27 (100)	0

TABLE 1: Relation between antibody response and severity of illness

n= number of subjects. Positive, Negative: Samples were compared to the calibrator using optical density ratios; below 0.8 was negative, 0.8-1.1 borderline, and above 1.1 positive.

Presence of comorbidities		Antibody response in number of subjects, n (%)		p value*
		Positive	Negative	
DM	Yes	26 (86.7)	4 (13.3)	0.456
	No	171 (81.0)	40 (19.0)	
HTN	Yes	23 (88.5)	3 (11.5)	0.432
	No	174 (80.9)	41 (19.1)	
CAD	Yes	11 (91.7)	1 (8.3)	0.7
	No	186 (81.2)	43 (18.8)	

TABLE 2: Relation between antibody response and the presence of comorbidities

DM: diabetes mellitus, HTN: hypertension, CAD: coronary artery disease.

*Significant at 5% level

The positive response was significantly higher among patients who required oxygen therapy (Table *3*). There was a significant negative correlation between time after the onset of infection and antibody response (r=-0.278, p<0.001). The median time from the onset of infection to antibody estimation was longer in patients with a negative response than with a positive response though could not attain statistical significance (57.5 (42-78) days vs 47 (26-73) days, p=0.061) (Table *4*). At 8-12 weeks, the positive response rate was significantly less compared to the positive response rate at two to four weeks, but the same increased from 12 weeks (Figure *1*).

Presence of known factors		Antibody response, n (%)		p value *
		Positive	Negative	
Hospitalized (n= 241)	Yes	107 (78.7)	29 (21.3)	0.145
	No	90 (85.7)	15 (14.3)	
ARDS (n = 196)	Yes	25 (96.2	1 (3.8)	0.137
	No	144 (84.7)	26 (15.3)	
ICU (n = 68)	Yes	19 (95.0)	1 (5.0)	0.664
	No	42 (87.5)	6 (12.5)	
Oxygen (n = 160)	Yes	33 (97.1)	1 (2.9)	0.022*
	No	102 (81.0)	24 (19.0)	

TABLE 3: Relation between antibody response in the number of subjects and other known factors

ICU: treatment in the intensive care unit, ARDS: acute respiratory distress syndrome, Oxygen: required oxygen therapy in a number of subjects.

*Significant at 5% level

Time after the onset of infection (weeks)	Antibody response, n (%)		p value*
	Positive	Negative	
2-4	51 (89.5)	6 (10.5)	Reference
4-8	68 (85.0)	12 (15.0)	0.445
8-12	43 (69.4)	19 (30.6)	0.007*
12-17	35 (83.3)	7 (16.7)	0.371

TABLE 4: Relation between antibody response and time after the onset of infection in weeks

n=number of subjects. *Significant at 1% level

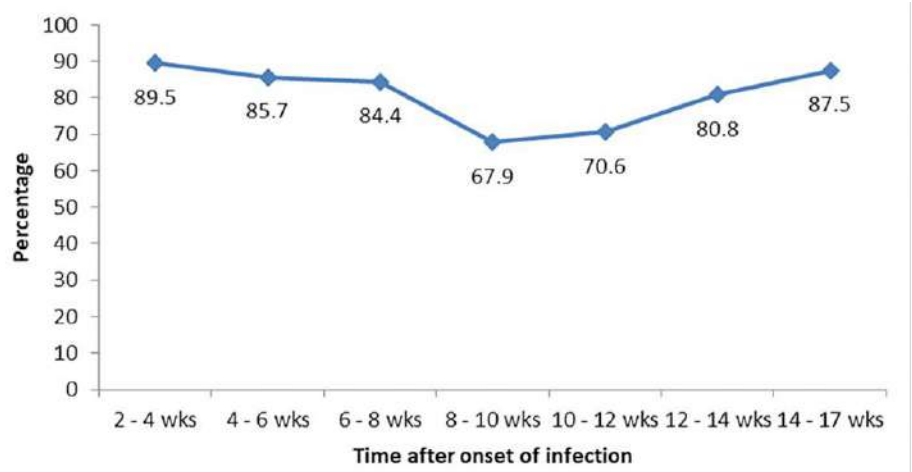


FIGURE 1: Trend in the positive response rates with reference to time after the onset of infection

wks: weeks. Percentage: positive antibody response in subjects

Discussion

The first confirmed case of COVID-19 in Kerala was reported on January 30, 2020, marking the commencement of the pandemic in the state. Despite effective initial containment, a surge in cases by March 2020 indicated the start of the first wave, initially driven by residents returning from abroad and other Indian states. The pandemic's progression in Kerala was characterized by several waves, each with distinct peaks in case numbers [6].

From October 2020 to September 2021, Kerala faced multiple COVID-19 waves and the emergence of various virus variants, including Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2), known for their increased transmissibility and potential impact on vaccine efficacy [7]. The state's vaccination campaign began on January 16, 2021, initially targeting healthcare and frontline workers, then expanding to older adults and those with comorbidities, and eventually the wider population [8]. By October 20, 2021, over 30 million vaccine doses had been administered, with 94% of the eligible population having received at least one dose and 47% fully vaccinated. Kerala's seroprevalence was reported at 44.4% in May 2021 by the Indian Council of Medical Research (ICMR) in the community, which was lower than the national average of 67.6%, reflecting the serological profile of the state during the pandemic [9,10].

In this study, we characterized the IgG response to the S1 subunit of the SARS-CoV-2 spike protein in patients from Kerala, India, during the initial wave of the COVID-19 pandemic and before the free availability of vaccines (from October 2020 to September 2021). The research was conducted at Government Medical College, Kozhikode, a tertiary care center, involved measuring IgG levels in serum samples from 258 patients at various time points following symptom onset. The analysis focused on understanding the dynamics of the IgG response over time and its association with comorbidities. Subsequently, the correlation between IgG responses and clinical parameters was examined providing insights into the immune response elicited by the virus in a diverse patient population.

The results indicate an increased positivity rate of IgG antibody response (76.4%) among the study participants, suggesting a robust immune reaction to SARS-CoV-2 infection in this population to the initial infection from a new viral outbreak. The antibody response varied over the severity of illness, with higher rates observed in patients with more severe manifestations of COVID-19. This observation aligns with previous studies indicating a correlation between disease severity and antibody response [11,12].

The S1 domain of the spike protein contains the receptor-binding domain (RBD) that mediates the interaction of the virus to the host cell receptor, angiotensin-converting enzyme 2 (ACE2) [13]. The RBD is a major target of neutralizing antibodies that can block the virus' attachment to the host cell and prevent infection, resulting in a better clinical outcome [14,15]. Using an ELISA kit that recognizes IgG antibodies to the entire S1 domain, encompassing the RBD and other epitopes, we measured the IgG response in patients with different disease severity. We found that patients with severe disease had higher IgG levels than those with mild or asymptomatic disease, consistent with prior reports [16]. This suggests that the IgG response reflects the viral load and the inflammatory response associated with COVID-19 infection in patients.

We also found that the IgG response was varying after the first infection period. The IgG response peaked at

two to four weeks and four to eight weeks after the onset of infection. However, the IgG response showed an increasing trend again at >= 12 weeks, which may indicate a secondary exposure or a memory response in the population, associated with another wave of COVID-19, such as Delta [17]. Previous studies have shown that the IgG response against SARS-CoV-2 can persist for several months after infection but may vary depending on the assay and the antigen used [18]. We measured IgG antibodies to the S1 domain of the virus using an ELISA kit, which might not reflect the complete antibody response to the virus [19]. Assessing IgG response to other viral antigens could provide additional insights. In a parallel study conducted concurrently, genomic surveillance revealed significant alterations in the virus over the final seven months of the study period. Notably, variants such as Delta were observed to be the predominant strain during this period [20,21]. This may also induce an increasing trend of IgG at >= 12 weeks.

We also examined the effect of comorbidities on the IgG response. We found that the IgG response was not significantly different between patients with or without diabetes mellitus (DM), hypertension (HTN), or coronary artery disease (CAD). The association between the above comorbidities and IgG response is unclear, as some studies report lower IgG levels in patients with DM or HTN, while others find no correlation [22-24].

Finally, we analyzed the clinical outcomes of the IgG response among patients. We found that the IgG response was higher in patients who required hospitalization, oxygen therapy, ICU admission, or developed acute respiratory distress syndrome (ARDS) than in those who did not. This is in line with previous studies that showed that the IgG response was associated with the disease severity and the need for intensive care [25]. It is possible that the IgG response is a marker of the immune activation, rather than a causal factor of the disease outcome. Depending on the viral load, host factors, IgG response, and disease severity may vary. Early and high IgG response may confer protection by neutralizing the virus and preventing infection, while late high or low IgG response may enhance the infection by causing inflammation or severity of infection [26]. Therefore, to determine the role of IgG in COVID-19 disease progression or suppression requires additional studies. It should also be mentioned that this study was done on data collected from direct interviews with recovered patients, as well as hospital discharge summaries and follow-up records, which included information on ICU stay and oxygen use.

This study substantiates the humoral immunity and possible protection against SARS-CoV-2 infection, but further studies are required to confirm our results and investigate the IgG response to other viral antigens and assays, as well as its function and mechanism in COVID-19.

This study has some drawbacks that should be acknowledged. The sample size in the study is small and may not reflect all COVID-19 patients during the period of study. The study was cross-sectional, and patients were not tracked over a period of time to test antibody response for a longer time. The study used only one ELISA kit that specifically binds to a region of the SARS-CoV-2 virus, which may not be the same by other methods of assay. The study did not examine other immune responses that could prevent reinfection or measure other factors such as viral load, variants, vaccination, previous coronavirus exposure, etc., which may affect the antibody response in the subjects studied.

This type of study may facilitate the development of enhanced immunization protocols and contribute to the optimization of vaccine strategies through detailed analysis of immune responses [27]. Hence, the present study may offer a foundation for future investigations into vaccine-induced immunity. The observations derived from this study may be of use to understand the immune response to a new unknown infection of the pandemic potential, and the disease spectrum could behave differently in patients infected when a similar pandemic strikes in the future.

Conclusions

The study conducted in Kerala has demonstrated a robust IgG seropositivity rate of 76.4% in response to SARS-CoV-2, indicating a strong humoral immune response. Notably, IgG titres were observed to correlate with the severity of the disease, exhibiting peak levels at intervals of two to four weeks, four to eight weeks, and ≥12 weeks post-infection. This temporal pattern suggests that IgG titres could serve as potential biomarkers for immune activation and prognostication of the disease trajectory. Interestingly, the presence of comorbid conditions did not significantly alter IgG levels, underscoring the uniformity of the immune response across diverse patient profiles. These initial findings provide a compelling basis for further research to elucidate the implications of IgG dynamics in COVID-19 disease management and outcome prediction.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Institutional Ethics Committee of Government Medical College, Kozhikode, issued approval GMCKKD/RP 2020/IEC/536 dated 18/NOV/2020. The study received ethical clearance from the Institutional Ethics Committee of Government Medical College, Kozhikode (Ref No. GMCKKD/RP 2020/IEC/536 dated 18/NOV/2020). **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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Original Research Article

Prevalence of hypertension and associated anthropometric indices among the non-medical employees working in medical college Thiruvananthapuram: a cross-sectional study

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ABSTRACT

Background: Hypertension is a major public health problem. Globally 1.28 billion adults aged 30-79 years have hypertension and among this 46% were undiagnosed. Kerala is one state undergoing epidemiological transition and having high prevalence of hypertension. So, we did this study to estimate the proportion of hypertension among non-medical employees of Medical College Thiruvananthapuram.
Methods: A cross-sectional study was conducted among 202 non-medical employees of medical college Thiruvananthapuram. Data was collected using an investigator administered questionnaire. Anthropometric indices were measured and recorded. Blood pressure (BP) was recorded twice in a gap of 15 min for each participant in sitting position using mercury sphygmomanometer. Mean systolic BP (SBP) and diastolic BP (DBP) was calculated to confirm hypertension. Participants those who were already detected as hypertensive and on treatment were also noted. Data was analysed using SPSS software version 27.
Results: Prevalence of hypertension in the study population was 61/202 (30.19%). Among the hypertensive 39 (63.9%) were already detected and on treatment and 22 (36.1%) were undiagnosed. Among already detected hypertensive 13 (33.3%) were found to be inadequately treated. Hypertension was found to be associated with waist circumference and BMI.
Conclusions: The study population was found to have high prevalence of hypertension and having association with waist circumference and BMI. The rule of halves for depicting the trend of hypertension in study population can be used as a tool to deduce various interventions in the community.

Keywords: Hypertension, Anthropometric indices, Rule of halves, Gender distribution of hypertension, Hypertension

INTRODUCTION

Hypertension is a major public health problem and acting like a hidden sword killing many even in their young age.[1] Hypertension (HTN) is one of the most prevalent non communicable diseases in the world. According to WHO 1.28 billion adults aged 30-79 years have hypertension globally and about 46% were undiagnosed.[2] The prevalence of hypertension has increased, in low and middle-income countries, owing to ageing of the population and increased exposure to lifestyle risk factors like unhealthy diets, lack of physical activity and habits. In India more than 1 in 4 people are hypertensive and more than 90% of adults who are hypertensive are either undiagnosed, untreated or inadequately treated.[3]

According to NFHS-5 data Kerala has comparable distribution of hypertension among males (32.8%) and females (30.9%).[4] Kerala is in advanced stage of epidemiological transition and account for higher prevalence of hypertension.[5] In Kerala also the important risk factors associated with hypertension are physical inactivity, diet containing high saturated fatty acids, high salt intake and habits like smoking and alcoholism.

Anthropometric indices like waist circumference, hip circumference, waist hip ratio and body mass index which are non-invasive quantitative measurements of the body are associated with increase in prevalence of life style diseases especially hypertension.[6] The present study focuses on the prevalence of hypertension in non-medical permanent employees of Medical College Trivandrum and association of hypertension with anthropometric measures

The non-medical employees in medical college, the majority are doing sedentary works like office work, lab work and assisting the teaching and training activities and they have good access to health services. The work place forms a setting for health interventions promoting the health of employees and thereby preventing NCDs.[7] So we did a study to estimate the proportion of hypertension in this particular occupational group and hence this study.

METHODS

A cross-sectional study was done among the 202 non-medical permanent employees of age between 20-60 years working in medical college Thiruvananthapuram. The primary objective was to estimate the proportion of hypertension in the study population based on JNC 8 criteria and secondary objective to describe the associated anthropometric indices in the study population and to depict the existence of rule of halves in the study population. Study period was from October 2023 to December 2023. According to NFHS -5 mean prevalence of hypertension among adults aged 15 years and above was 23% in India. Using this prevalence with 95%confidence interval and 6% allowable error the minimum sample size was calculated as 196. Attendance register of all departments, administrative office and security wing was considered as sampling frame. A total of 225 employees were there in the attendance roll. Those with loco motor disability, pregnant women and those who were on leave were excluded from enrolling into the study and finally 202 were included in the study with a participation rate of 89.7%.

After getting consent from the participants a predesigned structured questionnaire was used to collect basic information and history regarding previous diagnosis and treatment of hypertension followed by measurement of anthropometric measures and measurement of blood pressure by mercury sphygmomanometer. All measurements were taken after ensuring adequate privacy to the study participants. Height was measured using stadiometer and weight by standardized weighing machine. Using the height and weight measured, BMI was calculated and classified according to WHO Asian criteria.[8] Waist circumference was classified according to NFHS-5, below 94 cm for men and 80 cm for women were considered normal.[4] Hip circumference was measured using measuring tape at the largest width around hip by the investigator in sitting position at the level of hip. Waist hip ratio was calculated and classified according to NFHS-5, a ratio above 0.9 for men and above 0.858 for women were considered as high values.[4] Blood pressure (BP) was recorded twice in a gap of 15 min for each participant in sitting position using mercury sphygmomanometer. The patient was given rest for 5 minutes before recording blood pressure by making them sit in a chair with back supported and arm placed on the table with palm facing upwards and supported at heart level while measuring blood pressure.[1] Mean systolic BP (SBP) and diastolic BP (DBP) was calculated to confirm hypertension. Further BP was classified according to JNC 8 classification.[9] In whom BP was found to be elevated this was confirmed by a second examiner after 5 minutes and was referred for further evaluation. Self-reported hypertension was also noted. Among self-reported hypertensive taking anti-hypertensive medication those with blood pressure below 140/90 mmHg was considered as having controlled hypertension.

Statistical Analysis

The data was collected using investigator administered questionnaire, entered and analyzed using SPSS software version 27. Quantitative variables were expressed in mean and standard deviation and the qualitative variables were expressed in proportion. t test was used to find out the statistical significance between two means and the significance level was fixed as p below 0.05.

RESULTS

We recruited total of 202 study participants.

Table 1: Demographic characteristics of study participants.

Demographic characters	Frequency	Percentage
Age group (years)		
20-29	15	7.4
30-39	44	21.8
40-49	82	40.6
50-60	61	30.2
Gender		
Male	69	34.2
Female	133	65.8
Education		
SSLC and below	25	12.4
Diploma/pre-degree	47	23.3
Degree	89	44.1
Post graduation	41	20.3

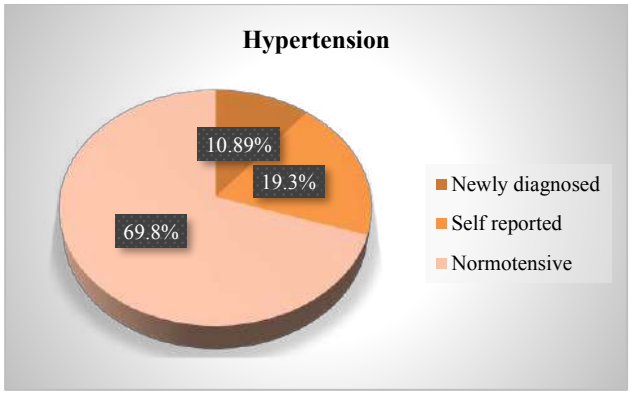


Figure 1: Proportion of hypertension in the study population.

Mean age of the study participants was 44.6±8.39. Majority of the participants were females (65.8%) and were educated up to Degree and above (64.4%).

In the study population the overall prevalence of hypertension was 30.19%. Among this 19.3% were diagnosed and on treatment and 10.89% were newly detected hypertensives. 69.8% were having normal blood pressure recordings.

Stage 2 hypertension in males and females was 2.8% and 3.75% respectively. Stage 1 hypertension was found to be 17.3% and 12.03% among males and females respectively. 14.49% males and 12.03% females were already diagnosed hypertensive but having controlled blood pressure. Pre-hypertension was found to be 31.88% among males and 15.78% among females. 33.33% males and 56.39% females had normal blood pressure. This shows that males had high stage 1 hypertension, diagnosed but controlled blood pressure and pre hypertension whereas females had high stage 2 hypertension and normal blood pressure values.

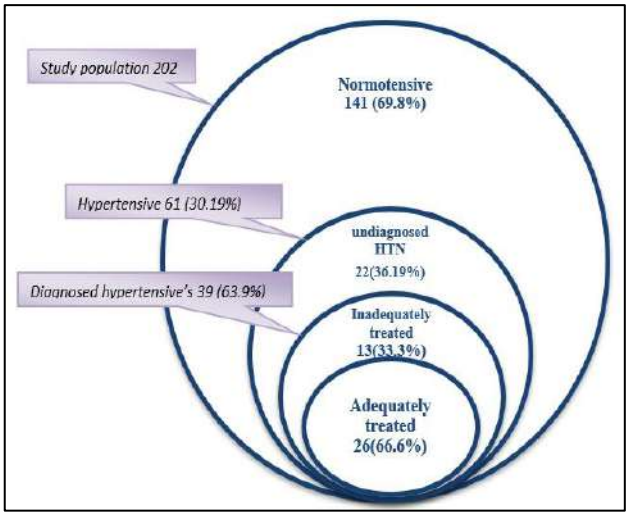


Figure 2: Depiction of rule of halves for hypertension in study population.

The overall prevalence of hypertension in the study population was 30.19% (61/202), among the hypertensive, 22 (36.19%) didn't know their hypertensive status. Among the 39 (63.9%) known hypertensive all were under antihypertensive therapy, but 13 (33.3%) did not have controlled blood pressure even after antihypertensive therapy and 26 (66.6%) had controlled blood pressure. The association between anthropometric measurements and hypertension was tested using t test, and analysis showed significance association between waist circumference and BMI ($p<0.05$).

Table 2: Distribution of measured blood pressure status in study participants based on gender.

Blood pressure status	Male (n=69)		Female (n=133)		Total (n=202)	
	N	%	N	%	N	%
Stage 2 hypertension	2	2.8	5	3.75	7	3.46
Stage 1 hypertension	12	17.3	16	12.03	28	13.86
Diagnosed but controlled hypertension	10	14.49	16	12.03	26	12.87
Pre-hypertension	22	31.88	21	15.78	43	21.28
Normal	23	33.33	75	56.39	98	48.51

Table 3: Association between anthropometric indices and hypertension.

Anthropometric indices	Difference in mean	S.E of mean	t test value	df	95% confidence interval	P value
Waist circumference	6.66	1.18	4.19	200	3.53-9.8	0.0001
Waist hip ratio	0.02	0.0084	1.76	200	-0.0028-0.049	0.08
BMI	2.04	0.55	2.94	200	0.67-3.41	0.004

Table 4: Application of rule of halves for hypertension and its interpretation.

	Undiagnosed (%)	Not treated (%)	Not controlled (%)
Rule of halves	50	50	50
Study population	36.1	0	66.6

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DISCUSSION

This study was conducted among permanent non-medical employees of Government Medical College Thiruvananthapuram to assess the proportion of hypertension and its association with anthropometric measurements and depicting the results according to of rule of halves in hypertension. We recruited 202 study subjects from various departments the mean age of study participants was 44.6±8.39 years, 65.8% were females and 34.2 % were males. About 64.4% have educational status Degree and above.

The overall prevalence of hypertension in the study population was 30.19% including the diagnosed and newly detected. According to NFHS-5, the prevalence of hypertension is 24% among men and 21% among women which is less compared to our study.[4] But in a study conducted by Venkatachalam Jayaseelan et al among sanitary workers in Puducherry the prevalence of hypertension was 36.6%.[10] In another study done by Chaithanya et al. in young adults (18-40 years) attending tertiary care institute of Nagpur, prevalence of hypertension was found to be 23.24%.[11] So the overall prevalence of hypertension is showing some difference according to the population studied and across different occupational groups.

The proportion of severe hypertension (stage 1 and 2) was 17.3% and 2.8% among males respectively and 12.03% and 3.75% among females respectively. Comparing with the data of NFHS-5 of Kerala, the proportion of population with stage 1 and stage 2 hypertension was 19.2 and 6.7% among men respectively and 15.5 and 6.6% among women respectively, which is higher than our study.[4] In a study done by Chaitanya R et al among younger adults attending a tertiary care centre in Nagpur, the proportion of stage 1 and stage 2 hypertension was 15.91 and 9.09% among males respectively and 16.39 and 5.88% among females respectively, which is quite higher compared to our study.[11] The difference may be due to high educational status and access to proper health care.

In our study the overall prevalence of hypertension including diagnosed and newly diagnosed was 61/202 (30.19%) and among hypertensive's 22/61 (36.1%) were undiagnosed and were detected by our survey. Among detected (39) all are under treatment but 26/39 (66.6%) were adequately treated. In another study done by Jayaseelan V et al among sanitary workers in Puducherry the prevalence of hypertension was 36.67% (114/311). Among this 80/114 (70.17%) patients were undiagnosed. Among detected (34) all were under treatment and 12/34 (35.3%) were adequately treated.[10] In a study done by Rao V et al among urban slums at Davangere the overall prevalence of hypertension was 367/1000 (36.7%). Of these 367 hypertensives' 340/367 (92.6%) were undiagnosed. Among this 87/127 (68.5%) were under antihypertensive therapy and 21/87 (24.1%) were adequately treated.[12] In the above two studies the proportion of undiagnosed hypertensive's is higher than our study but the proportion of adequately treated is less compared to our study.

According to the global hypertension status report by WHO 16 March 2023 46% of hypertensive's was undiagnosed, 42% were diagnosed and treated and among this only 21% were having adequate blood pressure control.[2] As our study population was tertiary care employees, we got a low proportion of undiagnosed (36.1%) and higher proportion of controlled hypertension (66.6%).

Applying the rule of halves for depicting the trend of hypertension in the study population, it can use as a tool to deduce the prevention strategies. According to the rule of halves in hypertension 50% of the people in a community will be undiagnosed and 50% will be under treatment and 50% will have controlled hypertension. But in our study, this is 36.1 were undiagnosed hypertensive's, among diagnosed 100% were on treatment but 66.6% were adequately treated.

The variation may be due to the higher educational status and access to the health care facility. Even though the hypertension is a silent invisible killer that rarely causes symptoms 66.6% is having adequate controlled blood pressure. This is pointing towards different occupational group-based screening and improving awareness which is essential for adequate control of hypertension. As per the strategies of NCD control program for the prevention and control of non-communicable diseases work place-based intervention and stress management is an important intervention. The anthropometric measurements are always associated with non-communicable diseases especially hypertension .In our study also waist circumference and BMI was significantly associated with hypertension In study done by Chaitanya .R et al among younger adults attending a tertiary care centre in Nagpur, the they also got significant association between hypertension and BMI and waist circumference.[11] In another study done by Oumer F et al to determine association of blood pressure and anthropometric indices among hypertensive at health care centre in Addis Ababa Ethiopia, they got significant association for waist circumference, waist hip ratio and BMI.[1]

CONCLUSION

We found slightly high prevalence of hypertension among the permanent non-medical employees of medical college Thiruvananthapuram of 20-60 years. Among this 10.89% were undiagnosed and 66.6% of diagnosed had adequate blood pressure control. There was significant association of hypertension with waist circumference and BMI.

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A Study to Assess Women's Autonomy in Household Decision Making Under Field Areas of Medical College Health Unit, Pangappara

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ABSTRACT

Background: Women play a central role as the primary caregivers for both children and the elderly, globally. Indian culture attaches great importance to women, who comprise the half of world's population. In sustainable development, goal 5 advocates gender equality and women empowerment. When women empowerment is hindered, they lack the ability to make choices regarding their own health care, education and career, they are restricted from moving freely without family permission, leading to a state of neglect and dependency.

Aim: The aim of this study was to assess Women's autonomy in household decision making under field areas of Medical College Health Unit, Pangappara, Thiruvananthapuram and the secondary objective was to find out the factors associated with women's autonomy in household decision making.

Methodology: The design adopted for the study was cross sectional survey. The study was conducted in a community setting. The data was collected from 330 women who met the eligibility criteria and they were selected by cluster sampling method. Data collected includes socio demographic data of women and women's autonomy was assessed using Women's autonomy Measurement scale.

Results: The result showed that 31.8% of women had poor autonomy, 6.1% of women had average autonomy and 62.1% of women had good autonomy in household decision making. The factors associated with women's autonomy were age, marital status, independence in handling financial matters, living pattern and involvement in monthly household expenditure preparation. This study concludes that women's autonomy in Kerala is better than other states of India.

Keywords: Women's autonomy, Household decision making, Married women

INTRODUCTION

Women are the pioneers of nation. Indian culture attaches great importance to women, who comprise the half of world's population. Women are the key to sustainable development and quality of life in the family. Various role women assume in the family are those of wife, leader, administrator, manager of family income, and last but not least the mother [1]. The family is the area in which the role of women is most prominent. Women's decision making power in the family is assumed to be reflective of their position in the household. Good decision making and autonomy helps women to empower themselves. Women empowerment helps them to live happy and lead a respectful life in society. It is the most important factor in

a country's overall growth. Poor autonomy in decision making will lead to loss of self-confidence, individuality, self-respect, personality and talent.

A demographic study conducted on women's autonomy in household decision making in Nepal revealed that almost half (47.1%) of married women took decisions on their own health care alone or jointly with their husband. 52.8% make major household purchases, 57.6% make daily household purchases, and 56.6% make visits to family/friends. Participation in own health care decision making gradually increased with age, from 17% among women aged 15-19 to 60.3% in middle-aged women (45 - 49)[2]. A study on women decision making for health care in South Asia in 2009 revealed that 13.4% of married women in the reproductive age group in Nepal, 17.6% in Bangladesh, and 28.1% in India had taken the decisions alone regarding care for their own health. The decision was made without women's participation in majority of women in Nepal (72.7%) and approximately half of the Bangladesh (54.3%) and Indian (48.5%) household [3]. A study on factors influencing women's decision-making authority and autonomy in rural Rajasthan showed that 34% of women take decisions with the permission of family elders and 21% of women take decisions along with their husband [4]. In NFHS-5 India, a total of 71% of currently married women participate in making decisions about their own health care, major household purchases (80%), and visits to their own family or relatives alone or jointly with their husband (81%). Women participation in decision making has increased since NFHS-4, from 73% in NFHS – 4 to 80% in NFHS – 5[5]. In NFHS – 5 Kerala shows, 83% of currently married women participate in decisions about their own health care, visit to their family and relatives 85%, and major household purchases 81%. Overall, 69% of currently married women participate in making all three of these decisions, and 6% do not participate in making any of the three decisions. Participation in all three decisions varies by age [6].

AIM: A study to assess Women's autonomy in household decision making under field areas of Medical College Health Unit, Pangappara, Thiruvananthapuram.

OBJECTIVE:

1. Estimate women's autonomy in household decision making under field areas of Medical College Health Unit, Pangappara.
2. Find out the factors associated with women's autonomy in household decision making

LITERATURE REVIEW

- Jejeebhoy et.al (2001) compares the lives of women and explores dimensions of their autonomy in different regions of south Asia like India and Pakistan. They selected Punjab in Pakistan, and Uttar Pradesh in north India and Tamil Nadu in south India for comparison. This study revealed that women who have freedom of mobility in Tamil Nadu, Uttar Pradesh and Punjab was 81.7%, 34.8% and 35.4% respectively. The woman who had freedom from threatening relations with husband, and access to and control over economic resources in Tamil Nadu is 15.7% and 88.9% respectively. So this study concludes that women's autonomy in terms of decision-making in mobility, freedom from threatening relations with husband, and access to and control over economic resources in Tamil Nadu is better than other women in Pakistan and Uttar Pradesh[7].
- A demographic study conducted by Bandari T R et. al(2016) on Women's autonomy and its correlates in western Nepal of Kapilvastu district reveals that mean score for women's autonomy was 23.34± 8.06. The education status of women is a key predictor of women's autonomy in Kapilvastu district and other important predictors are husband's

education and economic status of the household[8].

- A study of women autonomy and its correlates in India finding from national family health survey 4 reports that women's participation in decision making with her husband is high and women taking independent decision is very low. About 12.1% and 8.5% of women can take independent decision about their own health care and mobility respectively. Moreover 20% of women's partner alone control the above two decision[9].
- Goswami (2021) conducted a study in Assam state to examine the role of women in decision-making process in the family. This study reveals that family budget was prepared by both husband and wife is 53.7%, 55.3% of women purchase clothes and ornaments themselves, while 41.3% consulted with their husbands for this. Moreover 68.3% of women had control over their family expenditure[10].
- Tiwari et.al (2021) Study of autonomy of women's decision making at household level: an empirical study conducted in 950 non-working married women in the Ahmedabad city, to evaluate the women's autonomy in household decision making. This study explains how the freedom of decision making of females at household level is influenced by various other factors and their contribution in decision making freedom. This study shows that factors like freedom of social decision (r=0.954), freedom of personal decision(r=0.901) and freedom of buying decision (r=0.912) are mainly contributors which influence mostly the autonomy of decision Making[11].
- Patel et al.(2022) A study on women autonomy and its socio demographic correlates in high focus states of India like Bihar, Chhattisgarh, Jharkhand, Madhya Pradesh, Odessa, Rajasthan, Uttar Pradesh, and Uttarakhand and Assam based on NFHS 4. This study conducted in 381927 women of reproductive age group (15-49). This study revealed that 9.1% of women participate in own health care,4.8% of women involved in large household purchases, 6.6% of women visit to family or relatives alone and 8.3% of women decides contraceptive use. This study also shows that Jharkhand (8.6%) is the most autonomous state and Bihar (6.4%) is the least autonomous state [12].

MATERIALS & METHODS

Source of data: The data was collected from married women aged between 18- 49 years residing under field areas of Medical College Health Unit, Pangappara, Thiruvananthapuram.

Method of Data collection:

Tool 1

Socio demographic data including socio economic class assessed using Kuppuswamy socio economic status scale 2022.

Sampling Technique: Cluster sampling

Sample Size: 330

Age Criteria: 18 - 49years

Study Duration: 2 years

Study Sample: Married women (18- 49 years) living under field areas of Medical College Health Unit, Pangappara.

Study Setting: Field areas of Medical College Health Unit, Pangappara, Thiruvananthapuram

Type of Data: Quantitative

Study Design: Descriptive, Cross sectional study

Tool:

Tool 1: Socio demographic data

Socio demographic data including age, religion, education, occupation, monthly family income, type of family, number of children, age at marriage, type of house, duration of marriage, media exposure, education of husband, occupation of husband and habits of husband. Socioeconomic status of women was assessed using Kuppuswamy socio economic status scale 2022[13].

Tool 2: Women autonomy measurement scale[14].

Women's autonomy was measured using women's autonomy measurement scale which was developed by Tulsi Ram Bhandari. This scale consists of 23 items and covers major three dimensions of women's autonomy i.e. decision making autonomy, freedom for movement autonomy, financial autonomy with a total score range from 0 to 46. Decision making autonomy has 9 item with score range from 0 to 18 and score is categorised as independent (score 2), joint (score 1), and dependent (score 0). Freedom for movement autonomy and financial autonomy having 7 items in each with score ranges from 0 to 14 and score is categorised as never (score 2), sometimes (score 1) and always (score 0). The reliability coefficient of tool to assess Women's autonomy is 0.84. After pilot study score of women's autonomy was calculated (The calculated value more than 66.7 percentile, women is considered to have good autonomy. If calculated value less than 33.3 percentile considered poor autonomy. So scoring of women's autonomy is >36: Good autonomy, 29 - 36: Average autonomy, <29: Poor Autonomy)

Materials:

1. Informed consent form
2. Participation information sheet
3. Sociodemographic data sheet
4. Women autonomy measurement scale

Data collection process:

- The investigator explained the purpose of the study and informed consent obtained.
- Participant information sheet was given to each participant and confidentiality is ensured.
- Strict covid protocol is followed during data collection. It took around 30 minutes to collect data from each participant.

SELECTION CRITERIA

Inclusion criteria

Married women aged between 18- 49 years

- Living under field areas of Medical College Health Unit, Pangappara
- Who can read and understand Malayalam or English
- Who are willing to participate in the study

Exclusion criteria

- Married women who have major psychiatric illness

STATISTICAL ANALYSIS

Quantitative data was expressed as frequency and percentage. Factors associated with women's autonomy were evaluated by multivariate logistic regression analysis. Findings were communicated through tables, graphs and figure.

RESULT

Table 1 Distribution of Women based on Age (n = 330)

Age (in years)	f	%
18-21	1	0.3
22-25	13	3.9
26-29	32	9.7
≥ 30	284	86.1

Table 1 shows that 86.1% of women belonged to ≥ 30 years of age group and 0.3% of women belonged to 18-21 years of age group.

Table 2 Distribution of Women based on Marital status (n = 330)

Marital status	f	%
Living with spouse	314	95.2
Widow	14	4.2
Separated	2	0.6

Table 2 shows that majority 95.2% of women were living with spouse and 4.2% were widow and 0.6% of women were separated.

Table 3 Distribution of Women based on Kuppuswamy socio economic status (n = 330)

SES	f	%
Upper Middle	39	11.8
Lower Middle (III)	36	10.9
Upper Lower (IV)	255	77.3

Table 3 shows 77.3% belonged to upper lower class and 11.8 % of women belonged to upper middle class.

Table 4 Distribution of Women based on Independence in handling financial matters (n = 330)

Independence in handling financial matters	f	%
Self	45	13.6
Husband	140	42.4
Both	145	43.9

Table 4 depicts that 13.6% of women had independence in handling money themselves

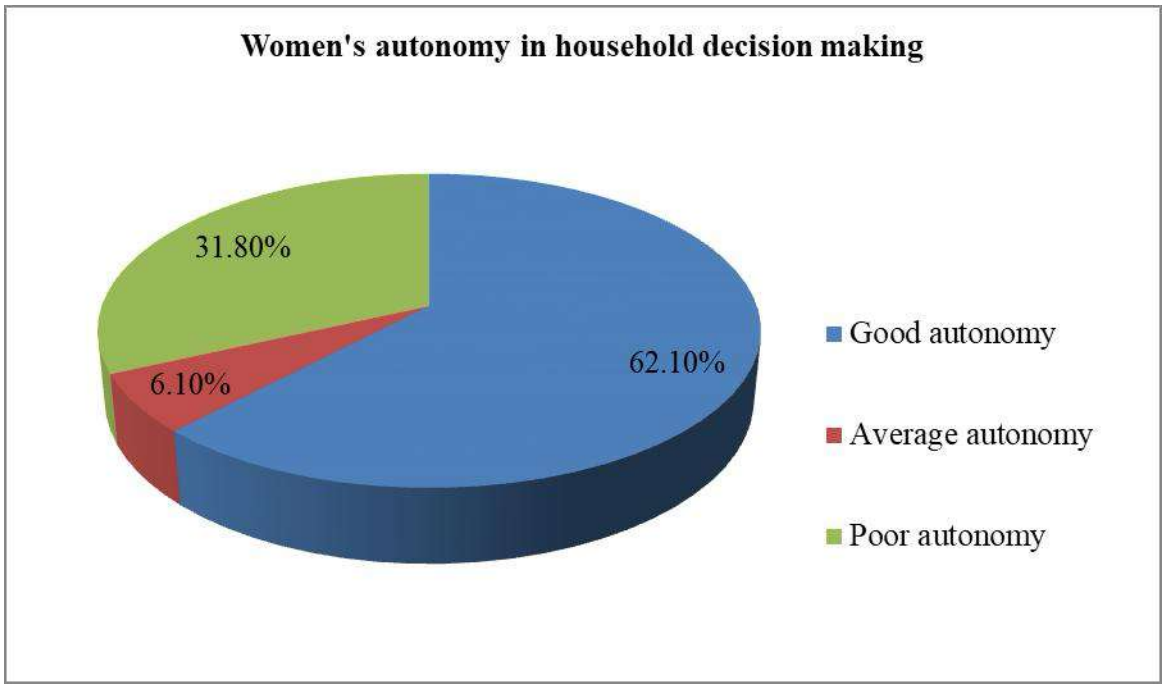


Figure 1 Distribution of Women based on Women's autonomy in household decision making

Figure 8 reveals that, 31.8% of women had poor autonomy, 6.10% of women had average autonomy and 62.1% of women had good autonomy.

Table 5 Distribution of women based on Decision making autonomy (n = 330)

Decision making autonomy	f	%
Good	65	19.7
Average	225	68.2
Poor	40	12.1

Table 5 highlights that 19.7% of women had good decision making autonomy, 68.2% had average decision making autonomy and 12.1% had poor decision making autonomy.

Table 6 Distribution of women based on Freedom for movement autonomy (n = 330)

Freedom for movement autonomy	f	%
Good	219	66.4
Average	5	1.5
Poor	106	32.1

Table 6 shows that 66.4% of women had good freedom for movement autonomy, 1.5% had average freedom for movement autonomy, and 32.1% had poor freedom for movement autonomy

Table 7 Distribution of Women based on Financial autonomy (n = 330)

Financial autonomy	f	%
Good	216	65.5
Average	8	2.4
Poor	106	32.1

Table 7 reveals that 65.5% of women had good financial autonomy, 2.4% had average financial autonomy and 32.1% had poor financial autonomy

Table 8 Factors associated with Women's autonomy in household decision making after univariate analysis

Variables	Categories	Women's autonomy				χ^2	p	OR
		Good autonomy		Average/poor autonomy				
		f	%	f	%			
Age	<30	35	76.1%	11	23.9%	4.4	0.035	2.1
	>30	170	59.9%	114	40.1%			
Marital status	Married	190	60.5%	124	39.5%			
	Divorced/separated	15	93.8%	1	6.3%	7.1	0.008	9.8
Age at marriage	<30	195	61.1%	124	38.9%			
	>30	10	90.9%	1	9.1%	4.0	0.045	6.4
Independence in handling financial matters	Self	36	80%	9	20%			
	Husband/both	169	59.3%	116	40.7%	7.0	0.008	2.7
Living Pattern	Husband	88	53.3%	77	46.7%			
	Others	117	70.9%	48	29.1%	10.8	0.001	2.1
Involvement in monthly household expenditure preparation	Self	41	85.4%	7	14.6%			
	Others	164	58.2%	118	41.8%	12.9	0.001	4.2

Table 9 Multivariate logistic regression analysis of Women's autonomy in household decision making and significant factors

Variables	B	S.E.	Wald	df	p	OR	95% C I for OR	
							Lower	Upper
Age	0.784	0.377	4.332	1	0.037	2.191	1.047	4.587
Living pattern	0.627	0.243	6.630	1	0.010	1.872	1.162	3.017
Involvement in monthly household expenditure preparation	1.176	0.521	5.098	1	0.024	3.242	1.168	9.002

Table 9 depicts that age < 30 years, Women living with relatives, Women who have involved and preparing monthly household expenditure were found to be significant factors of Women's autonomy in household decision making.

Compared to women aged < 30 years the odds of having good autonomy was 2.19 times more among women aged > 30 years

Compared to women living with relatives other than their husband were 1.87 times more likely to have autonomy.

Women who were involved in preparing and executing the monthly household expenditure were 3.24 times more likely to possess autonomy compared to others who preparing monthly household expenditure

DISCUSSION

The purpose of the study was to assess the Women's autonomy in household decision making among married women residing under field areas of Medical College Health Unit, Pangappara.This was a cross sectional study conducted for a period of 2 years and

among 330 married women who met the eligibility criteria. Socioeconomic status of women was assessed using Kuppuswamy socio economic status scale 2022 and Women's autonomy was measured using women's autonomy measurement scale. The data analysed using descriptive and inferential statistics.

In the present study 86.1% of women participated were between the age group of > 30 years. In a similar study conducted in Punjab, 80.1% of women aged >35 years participated in economic decision matters (Kaur R et.al) [15]. In the present study, it is clear that 31.8% of women had poor autonomy, 6.1% of women had average autonomy and 62.1% of women had good autonomy. The finding is congruent with another study conducted in Rural Rajasthan, 27.5% had poor autonomy (Sadhu G et. al) [4].

In the present study it is found that age, marital status, independence in handling financial matters, living pattern, involvement in monthly household expenditure preparation was found to be factors of women's autonomy in household decision making. The finding is in congruent with another study conducted in rural Punjab, age has significant association with women's autonomy (Kaur et.al)[15]. The finding congruent with another study conducted in high focus state of India (Bihar, Chhattisgarh, Jharkhand, Madhya Pradesh, Odessa, Rajasthan, Uttar Pradesh, and Uttarakhand and Assam) found that age was significant factor influencing women's autonomy (Patel V S et.al)[12] .

CONCLUSION

The result of the study found that 31.8% of women had poor autonomy, 6.1% of women had average autonomy and 62.1% of women had good autonomy. In this study investigator found out major three dimensions of women's autonomy i.e. decision making autonomy, freedom for movement autonomy and financial autonomy. In this study19.7% of women had good decision making autonomy, 68.2% had average decision making autonomy and 12.1% had poor decision making autonomy. Moreover 66.4% of women had good freedom for movement autonomy, 1.5% had average freedom for movement autonomy, and 32.1% had poor freedom for movement autonomy. Regarding financial autonomy 65.5% of women had good financial autonomy, 2.4% had average financial autonomy and 32.1% had poor financial autonomy. Age, marital status, independence in handling financial matters, living pattern, involvement in monthly household expenditure preparation were found to be significant factors of women's autonomy in household decision making.

Declaration by Authors

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Original Research Article

Factors Affecting Utilization of Public Health Services for Noncommunicable Diseases in a Panchayath of Malappuram District, Kerala

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Conflict of interest: Nil

Abstract:

NCDs have a substantial impact on our community, and the government's health services are a cost-effective and efficient strategy to prevent and reduce the burden of NCDs. The identification of factors influencing the utilization of NCD clinics is critical for determining the gap between the goals of these programs and their implementation. It can be used to evaluate the efficacy of various strategies.

The aim of this study was to determine the percentage of people who prefer public sector NCD programmes along with the factors affecting the utilization of the same. in Malappuram, Kerala. Cross-sectional research of 100 people selected using multistage systematic random sampling was carried out in Kerala's Malappuram district. The obtained data were analysed using descriptive and analytical statistical approaches using Jamovi version 2.3.

NCDs are a major health burden in our society, and treating and preventing them is critical. Many factors influence the selection of health care facilities for chronic diseases, and the study found that education, occupation, awareness of government programs, distance to the health center, and insurance coverage all influenced these decisions. The cost of therapy also plays an important part in selecting a health care facility.

Keywords: Non-Communicable Diseases, Diabetes, Hypertension, Healthcare Utilisation, Healthcare Delivery.

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Introduction

Noncommunicable diseases (NCDs), also known as chronic diseases, tend to be of long duration and are the result of a combination of genetic, physiological, environmental and behavioral factors. The main types of NCD are cardiovascular diseases (such as heart attacks and stroke), cancers, chronic respiratory diseases (such as chronic obstructive pulmonary disease and asthma) and diabetes. NCDs disproportionately affect people in low- and middle-income countries, where more than three quarters of global NCD deaths (31.4 million) occur. [1]. NCDs have significant impact over the life expectancy and productivity of a community. Increased prevalence of NCD had caused financial burden to the community. It can be tackled effectively by utilization of NCD preventive clinics provided by government health services. Under the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) now known as NPNCD, (launched in 2010) as part of National Health Mission (NHM), The Department of Health & Family Welfare had launched several health programmes. The programme focuses on strengthening infrastructure, human resource development, health promotion & awareness generation for prevention, early diagnosis, management and referral to an appropriate level of healthcare facility for treatment of the Non-Communicable Diseases (NCDs). WHO under 2030 Agenda for Sustainable Development recognizes NCDs as a major challenge for sustainable development. As part of the agenda, heads of state and government committed to develop ambitious national responses, by 2030, to reduce by one third premature mortality from NCDs through prevention and treatment. [2]

Noncommunicable diseases (NCDs) kill 41 million people each year, equivalent to 74% of all deaths globally. Each year, 17 million people die from a NCD before age 70; 86% of these premature deaths occur in low- and middle-income countries. [1]. According to the study report “India: Health of the Nation's States”- The India State-Level Disease Burden Initiative in 2017 by Indian Council of Medical Research (ICMR), it is estimated that the proportion of deaths due to Non-Communicable Diseases (NCDs) in India have increased from 37.9% in 1990 to 61.8% in 2016 **[2]**. In low-

resource settings, health-care costs for NCDs quickly drain household resources. The exorbitant costs of NCDs, including treatment, which is often lengthy and expensive, combined with loss of income, force millions of people into poverty annually and stifle development. The diagnosis, screening, and treatment of NCDs are all part of the management process, as is giving those who require palliative care access to it. A primary health care approach can be used to deliver high impact key NCD therapies, strengthening early identification and prompt treatment. Based on available data, early implementation of these measures can significantly lower the need for more costly medical care, making them attractive financial investments. [1]

Determining the variables influencing the use of NCD clinics is essential to evaluating the discrepancy between the goals of these initiatives and their implementation. It can be applied to evaluate these schemes' efficacy. The percentage of people who preferpublic sector NCD programmes is to be estimated by this study along with the factors affecting the utilization of the same. This will support the creation of sufficient action plans for carrying out additional health programs. Since there isn't a comparable study being conducted among the study population right now, it will be helpful in determining the accessibility of health programs as well as the assessment of prevalent health conditions in the community.

Materials and Methods

Study Design: The current study was conducted as a cross-sectional study design so as to estimate the proportion/percentage of individuals utilizing NCD services (screening and treatment) in a selected geographical area (Puzhakattiri panchayath of Malappuram district)

Study setting and participants: The study was conducted in Puzhakattiri panchayath of Malppuram district which is the most populous district of Kerala state. The study participants were residents of Puzhakattiri panchayath who were above the age of 30 years.

Inclusion Criteria: participants aged 30 years and above residing at Puzhakattiri panchayath for atleast 6 months and who are willing to participate.

Exclusion Criteria: Those who had any cognitive impairment.

Sample Size: According to study conducted in Kasargod, Kerala by C.K Bhagyalakshmi, Prakash Babu Kodali on Utilization of Noncommunicable Disease Services Provided by Public Health Facilities showed that over 34.67% have used NCD clinics [3]

Using the equation: $((1.96)^2 \times (p \times q))/_{d \times d}$

p= 34.67

q= 100-p

= 65.33

d= absolute error 9.5% for confidence interval 95%

Sample size, n = Z 1-α/22 PQ /d2

for 95% Confidence interval,

Z=1.96

n = 100

So, sample size will be 100

Sampling Method

The participants for the study were selected using multistage systematic random sampling. The first stage of sampling employed was a simple random sampling to select wards from the panchayath. Puzhakattiri panchayath has 17 wards, among these 4 wards were randomly selected by lottery method. For selecting 100 participants from these 4 wards systematic random sampling technique was used. As all the wards of the panchayat had approximately equal population size 25 each participant was selected from each ward. Each ward had minimum of 600 houses, 25 houses were selected from each ward using systematic random sampling technique. 24 was taken as sampling interval to choose houses. First house was selected randomly by lottery method. Available member of the house satisfying the inclusion and exclusion criteria were interviewed for data collection.

Methods:

Study Procedure- The patients were chosen from the Puzhakattiri panchayath by multistage systemic random sampling.

NCDs chosen for the study were

i. Diabetes

ii. Hypertension

iii. Dyslipidemia

iv. Coronary vascular diseases

v. Cancer

vi. Thyroid disease

Patients were interviewed regarding their health conditions, whether they were suffering from any of the above-mentioned disease conditions. They were asked about their treatment, compliance to medication, satisfaction, knowledge about government organized health programmes

Data Analysis: Data were entered into Microsoft Excel and analyzed using Jamovi version 3.2 software. The quantitative variables are summarized as mean with standard deviation. The statistical significance of association is tested using Pearson Chi square test for dichotomous variables.

Results

The study has included 100 participants using a multistage random sampling technique.

Socio-demographic details: The mean age of the study participants was found to be as 52.14± 8.24 years with maximum number of participants from the age group 51-60 years (39%) followed by age group 41-50 (33%). The study had 79% of the participants identified as males and rest as females. 89% of the families were of nuclear type and rest were joint families.

The current study had majority of population with completed higher secondary education (77%) and nearly half of the study population were unskilled and semiskilled workers.

Table 1: Socio-demographic variables of the study population

	Age Group	Frequency (%)
Age Group	**36-40**	1 (1%)
	41-50	33 (33%)
	51-60	39 (39%)
	61-70	27 (27%)
Gender	**Female**	21 (21%)
	Male	79 (79%)

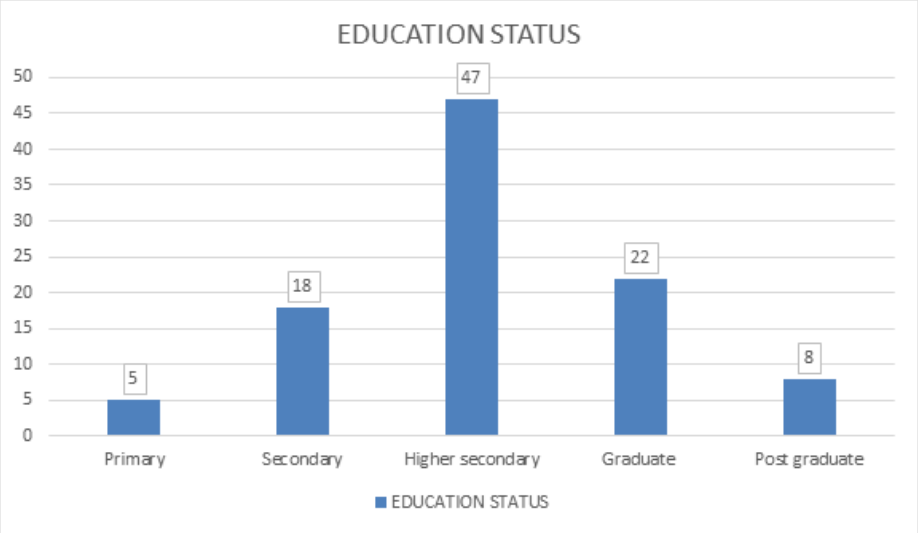


Figure 1: Education status of the study population (n=100)

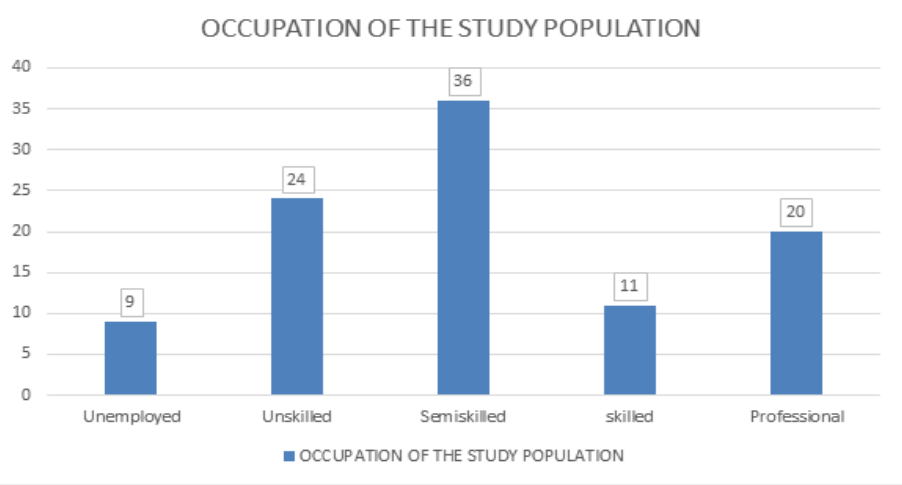


Figure 2: Occupation status of the study population (n=100)

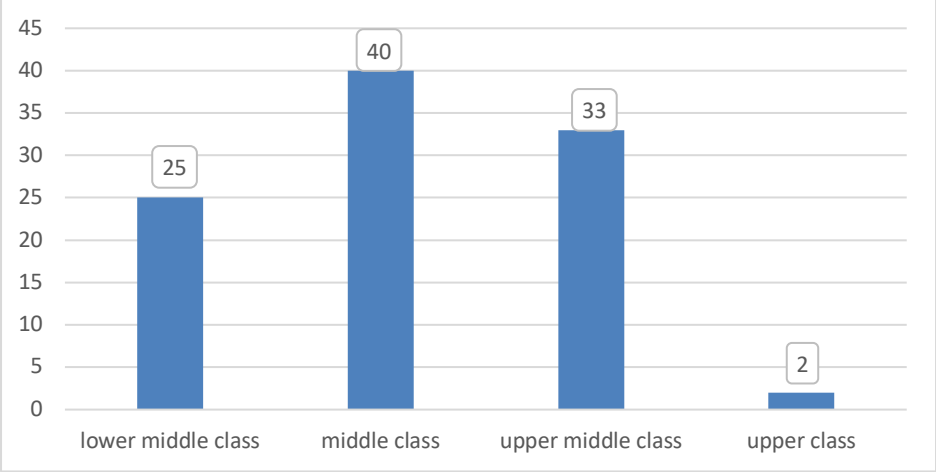


Figure 3: Socio-economic status of the study population (n=100)

Understanding Patient Behavior and Preferences in Managing Non-Communicable Diseases: Non-communicable diseases (NCDs) are a major health challenge worldwide, and understanding how individuals manage these conditions is crucial for improving public health strategies. This article examines various aspects of patient behavior and preferences related to the treatment and management of NCDs, based on recent survey data.

Medication Adherence and Healthcare Visits: One of the key findings from the study is the high rate of medication adherence among patients with NCDs. An overwhelming 98% of respondents reported that they are taking medication for their illness, while only 2% indicated that they are not on any medication. This suggests that most patients are actively managing their conditions with prescribed treatments.

Regular visits to healthcare centers are also common among the respondents, with 96% reporting that they visit a healthcare facility every month. Only 4% do not adhere to this routine, indicating a strong commitment to continuous care.

Engagement with Public NCD Clinics and Awareness Initiatives: The survey revealed that 88% of respondents have visited a public NCD clinic at least once, showing a high level of engagement with public health services. However, 12% have never visited these clinics, indicating a gap in outreach or accessibility.

Awareness about government-organized NCD screening and preventive camps is relatively high, with 85% of respondents being aware of such initiatives. Yet, 15% remain unaware, highlighting the need for improved communication and outreach efforts.

Participation in these preventive camps is more moderate, with 53% having attended at least one, while 47% have not. This suggests that while awareness is high, there may be barriers to participation that need to be addressed.

Community Support and Health Sector Preferences: The role of Accredited Social Health Activists (ASHAs) is pivotal in the management of NCDs at the community level. The survey indicates that 86% of respondents were visited by an ASHA worker in the past six months, reflecting active community engagement. However, 14% did not receive such visits, suggesting that some areas may require more attention.

When it comes to choosing a healthcare provider, 66% of respondents prefer government services for the treatment of NCDs, while 34% opt for private healthcare. However, when the cost of treatment is removed as a factor, the preference shifts significantly, with 65% favoring private healthcare services and 35% choosing government facilities. This indicates that cost is a significant factor in healthcare decision-making.

Accessibility and Satisfaction with Healthcare Services: Access to healthcare facilities is evenly distributed among the respondents, with 50% living within 5 kilometers of a healthcare center and the other 50% living 5 kilometers or more away. This balance suggests that while half of the population has convenient access to healthcare, the other half may face challenges in reaching services.

Regular access to medicines from public NCD clinics remains a concern, as only 53% of respondents report receiving their medications consistently. The remaining 47% face difficulties in obtaining their necessary medications, which could hinder effective disease management.

Insurance coverage is another important factor, with 65% of respondents having some form of insurance. This coverage likely eases the financial burden of treatment, while the 35% without

insurance may face financial barriers to accessing care.

Despite these challenges, a significant majority of respondents are satisfied with their current treatment services. 78% expressed satisfaction, while 22% are not satisfied. This high satisfaction rate suggests that the healthcare services, whether public or private, are generally meeting the needs of most patients.

Table 2: Understanding Patient Behavior and Preferences in Managing Non-Communicable Diseases

Variable	Category	Number	Percentage
Taking medication for their illness	**Yes**	**98**	**98%**
	No	**2**	**2%**
Visiting a health care center regularly(every 1 month)	**Yes**	**96**	**96%**
	No	**4**	**4%**
Visited a public NCD clinic at least once	**Yes**	**88**	**88%**
	No	**12**	**12%**
Awareness about NCD Screening and preventive camps organized by government	**Aware**	**85**	**85 %**
	Not aware	**15**	**15%**
Participated in government organized preventive camps	**Yes**	**53**	**53%**
	No	**47**	**47%**
Visited by an ASHA worker in past 6 months	**Yes**	**86**	**86%**
	No	**14**	**14%**
Preferred health service sector for treatment of NCD	**Government**	**66**	**66%**
	Private	**34**	**34%**
Preferred health service sector for treatment of NCD if cost of treatment is kept aside	**Government**	**35**	**35%**
	Private	**65**	**65%**
Distance from the nearest health care center	**<5km**	**50**	**50%**
	>/=5km	**50**	**50%**
Getting medicines regularly from public NCD clinics	**Yes**	**35**	**53%**
	No	**31**	**47%**
Having an insurance coverage	**Yes**	**65**	**65%**
	No	**35**	**35%**
Satisfied by current treatment service	**Yes**	**78**	**78%**
	No	**22**	**22%**

Key Factors Influencing Utilization of Government NCD Services: The current study identified that 66% preferred government health sector for treatment of NCDs.

The utilization of government services for managing non-communicable diseases (NCDs) is significantly influenced by various socio-demographic factors, as highlighted in this study. Education plays a crucial role, with individuals holding higher secondary education levels showing the highest utilization rate of government services at 37%. In contrast, those with only primary education have a much lower utilization rate of 2%. This difference, supported by a strong statistical significance (Chi-square = 35.87, p = 0.000), indicates that higher educational attainment may lead to better awareness and access to these services.

Occupation also significantly impacts the use of government NCD services. The study found that semiskilled workers have the highest utilization rate at 36%, while those who are unemployed or in skilled professions have much lower rates, at 7% and 1%, respectively. This relationship, with a Chi-square value of 40.406 and a p-value of 0.000, suggests that the nature of one's employment can influence their reliance on government healthcare services.

Interestingly, socioeconomic status did not show a significant impact on the utilization of these services. While the middle class had the highest usage at 25%, followed by the lower middle and upper middle classes at 19% and 21% respectively, the upper class had the lowest at 1%. However, the Chi-square value of 1.64 and a p-value of 0.650 indicate no statistically significant association between socioeconomic status and service utilization.

Proximity to healthcare centers was found to be a significant factor, with individuals living more than 5 kilometers away from a healthcare center utilizing government services more frequently (38%) than those living closer (28%). The statistical significance here (Chi-square = 16.501, p = 0.011) suggests that those in more remote areas may have fewer alternatives and therefore rely more on government services.

Visits from Accredited Social Health Activists (ASHA) also play a critical role, as individuals who were visited by an ASHA worker had a much higher utilization rate of government services (64%) compared to those who were not visited (2%). This strong association (Chi-square = 19.40, p = 0.000) underscores the importance of community health workers in connecting people to available healthcare services.

The study also examined whether the availability of medicines affects service utilization and found no significant association, as the utilization rates were similar between those who had access to medicines (35%) and those who did not (31%). The lack of statistical significance (Chi-square = 0.412, p = 0.520) suggests that other factors may be more influential in determining service utilization.

Finally, insurance coverage was identified as a significant factor, with individuals both with and without insurance showing equal utilization rates (33%). The strong association here (Chi-square = 19.198, p = 0.000) indicates that insurance status can influence the decision to use government services, possibly due to the perceived reliability or lower out-of-pocket costs.

In conclusion, this study highlights that education, occupation, proximity to healthcare centers, and ASHA worker visits are key determinants of government NCD service utilization. Although socioeconomic status and the availability of medicines did not show a significant impact, these findings emphasize the need for targeted interventions, such as community outreach and education, to enhance access to and the effectiveness of government healthcare services for managing NCDs.

Table 3: Factors affecting health care service utilization among study population (n=100)

		Percentage of study population utilizing government NCD services	**Pearson chi square value**	**Asymptotic significance (p) value**
Highest level of education	Primary	2	35.87	**0.0001**
	Secondary	8		
	Higher secondary	37		
	Graduate	9		
	Post graduate	0		
Occupation	Unemployed	7	40.406	**0.0001**
	Unskilled	13		
	Semiskilled	36		
	Skilled	1		
	Professional	9		
Socioeconomic status	Lower middle class	19	1.64	0.650
	Middle class	25		
	Upper middle class	21		
	Upper class	1		
Distance from the nearest health care center	<5km	28	16.501	**0.011**
	>5km	38		
Visited by ASHA worker	Yes	64	19.40	**0.000**
	No	2		
Availability of medicines	Yes	35	0.412	0.520
	No	31		
Insurance coverage	Yes	33	19.198	**0.000**
	No	33		

Discussion

The findings from the current survey provide a comprehensive view of the utilization of non-communicable disease (NCD) services across various settings, shedding light on the patterns and factors influencing healthcare access.

Utilization Rates and Preferences: The survey reveals that 66% of the study population prefers public NCD clinics, which is notably higher compared to the 34.67% utilization reported in Kasaragod, Kerala by C. K. Bhagyalakshmi and Prakash Babu Kodali [3]. However, the preference for private healthcare services rises to 65% when the cost is not considered, suggesting that affordability significantly influences healthcare choices. This contrasts with a higher overall utilization rate of 55.3% for NCD services from upgraded primary care centers in Kerala, as reported by Resmi Mathew and Jeby J. Olickal [4].

Factors Influencing Utilization: Several factors influencing NCD service utilization have been identified in different studies. Devarshi Bhattacharyya et al. found significant factors to include residence, health insurance, provider preference, income, education, waiting time, and distance to the health center, with an outpatient utilization rate of 74.1% [5]. Similarly, our study highlights the significant impact of educational status, occupation, distance to healthcare centers, visits by healthcare workers, and insurance coverage on the choice of healthcare facilities.

Sanghamitra Pati et al. reported a positive association between the number of NCDs and healthcare utilization for both outpatient and inpatient services [6], emphasizing that higher NCD burden may drive increased service use. This is consistent with our finding that individuals with greater healthcare needs may rely more on government services, particularly when facing financial constraints.

Awareness and Accessibility: Awareness and accessibility issues also play a crucial role. Dr. Oommen P. Mathew's study indicated that nearly 58% of individuals had never visited a facility for NCD screening or treatment, with higher awareness observed among younger patients, females, those with secondary or lower education, and individuals from below-poverty-line (BPL) families [7]. In contrast, our survey found that 85% of participants were aware of government-organized NCD screening and preventive camps, yet only 53% attended them. This suggests a gap between awareness and actual service utilization, possibly due to accessibility issues or perceived inadequacies of the services.

Government Facility Utilization: Devi Nair and Krishnanunni Raveendran's study showed that 60.5% of NCD respondents used government facilities regardless of socioeconomic status [8]. This is slightly lower than the 66% preference for public NCD clinics observed in our survey, highlighting a consistent trend of reliance on government services for NCD management across different studies.

In contrast, a study on the NPCDCS in Kerala found that only 40.9% of individuals diagnosed with NCDs utilized the program's services, suggesting that infrastructure and service availability may be inadequate [9]. This aligns with findings from a study in Dakshina Kannada district, Karnataka, which reported that while health promotion activities were well-prepared, there were deficiencies in resources and infrastructure for NCD management [10].

Care-Seeking Practices: Finally, Nilanjan Bhor's study on care-seeking practices in a low-income neighborhood highlighted issues such as delayed diagnosis and failure to meet treatment goals [11]. This underscores the importance of timely and effective screening and treatment, which may be compromised by barriers such as inadequate infrastructure and long wait times.

In summary, while the survey aligns with several findings from previous research regarding the utilization of public NCD services, it also highlights critical areas for improvement, such as accessibility, infrastructure, and the alignment between awareness and utilization. Addressing these factors through targeted interventions can enhance the effectiveness of NCD management programs and improve overall healthcare outcomes.

Conclusion

This study provides valuable insights into the factors influencing the utilization of government non-communicable disease (NCD) services. The findings highlight that while a significant portion of the population engages with public NCD clinics, preferences shift markedly towards private healthcare when the cost of treatment is not a consideration. Key determinants of healthcare service utilization include educational attainment, occupation, proximity to healthcare centers, visits by healthcare workers, and insurance coverage.

Individuals with higher education and those in skilled or professional jobs tend to favor private healthcare, while those living closer to public health centers, visited by ASHA workers, or without insurance are more likely to rely on government services. These results underscore the importance of addressing barriers to public healthcare access and improving the quality and availability of services to meet the needs of diverse populations.

The study also emphasizes the critical role of community health workers in increasing awareness and facilitating access to public health programs. Overall, these findings suggest that targeted interventions are necessary to enhance the effectiveness and reach of government NCD services, particularly in underserved communities. By addressing these factors, public health strategies can be better tailored to improve healthcare outcomes and equity in NCD management.

Ethics approval and consent to participate: Ethical approval for the study was obtained from the Institutional Research Committee of MES Medical College, Perinthalmanna. Written informed consent was obtained from all individual participants involved in the study.

List of abbreviations:

1. NCDs - non-communicable diseases
2. NCD - Non-communicable disease (used as both singular and plural)

3. Jamovi - Statistical software (version mentioned: 2.3)
4. p - Probability value (commonly used in statistical tests)
5. q - Complementary probability value (q = 100 - p)
6. d - Absolute error or precision in the sample size formula
7. Z - Z-score (related to confidence intervals in statistics)
8. ASHA - Accredited Social Health Activist
9. CHC - Community Health Center
10. PHC - Primary Health Center
11. THQH - Taluk Headquarters Hospital
12. DH - District Hospital
13. BPL - Below Poverty Line
14. HTN - Hypertension
15. DM - Diabetes Mellitus
16. CAD - Coronary Artery Disease
17. NPCDCS - National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke.

Conflicts of Interest: The authors declare that there is no conflict of interest regarding the publication of this paper.

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Authors' Contributions: AR analyzed the interpreted the patient data and done the statistical analysis and was major contributor in writing the manuscript. AP was involved in collecting the data and in conceiving the research. LKK and AS has helped in preparing the manuscript while MS was involved in conceptualization and protocol preparation of the study. All other authors were involved in data collection and data entry. All authors read and approved the final manuscript

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Original Article

EXPLORING THE INFLUENCE OF METEOROLOGICAL FACTORS ON SCRUB TYPHUS INCIDENCE: AN ECOLOGICAL TIME SERIES ANALYSIS IN KERALA, INDIA

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ABSTRACT

Background: Scrub typhus, a re-emerging neglected tropical disease, now poses public health concerns in tropical and subtropical countries. Kerala, situated in the southwestern part of India, has been showing an increasing incidence of scrub typhus over the last few years. The dynamic nature of meteorological parameters such as temperature and rainfall influence the survival and activity of chiggers as well as the abundance and distribution of their rodent hosts. Consequently, elucidating these associations can

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aid in the development of early warning systems, targeted interventions and resource allocation to mitigate the impact of scrub typhus outbreaks in Kerala. In this study we aimed to analyse the relationship between meteorological factors (maximum temperature, minimum temperature and rain fall) and scrub typhus incidence in Kerala from 2012-2020.

Methods: Number of monthly reported scrub typhus cases for the period of 2012-2020 was obtained from Integrated Disease Surveillance Project (IDSP) of Directorate of Health Services, Kerala. Monthly district wise weather parameters viz. rain fall, maximum and minimum temperatures were obtained from India Meteorological Department (IMD), Pune. IMD daily gridded data was converted to district level. Influence of meteorological parameters on occurrence of scrub typhus was studied through correlogram using time series analysis technique.

Results: The present study shows that the maximum and the minimum temperatures negatively correlate with the scrub typhus incidence in Kerala. Rainfall has no influence on the scrub typhus incidence in Kerala. Temperature plays a more crucial role in predicting scrub typhus occurrence than seasonality or trends.

Conclusion: The study suggests a model of predicting the possibility of a scrub typhus incidence some three months in advance by observing the temperature conditions prevailing in a given area and also found that the climatic factor like rainfall do not show any significant influence on the occurrence of scrub typhus incidence in Kerala.

Keywords: Scrub typhus, temperature, rainfall, correlation

INTRODUCTION

Scrub typhus, a re-emerging neglected tropical disease, now poses public health concerns in tropical and subtropical countries. This disease is caused by *Orientia tsutsugamushi*, a bacterium belonging to the family Rickettsiaceae. The pathogen is transmitted from man to man by the bite of larvae of infected trombiculid mites (chiggers), which are ectoparasites of rodents and shrews[1]. The pathogen is transmitted from one stage to another through trans stadial and trans

ovarian transmission[2,3] The term "scrub typhus" originates from the presence of chiggers and rodents in scrub vegetation (shrub vegetation)[3].

Kerala, situated in the southwestern part of India, has been showing an increasing incidence of scrub typhus over the last few years[4]. The dynamic nature of meteorological parameters such as temperature and rainfall influence the survival and activity of chiggers as well as the abundance and distribution of their rodent hosts[5–7] Consequently, elucidating these associations can aid in the development of early warning systems, targeted interventions and resource allocation to mitigate the impact of scrub typhus outbreaks in Kerala.

In this study we aimed to analyse the relationship between meteorological factors (maximum temperature, minimum temperature and rain fall) and scrub typhus incidence in Kerala from 2012-2020.

Incidence of scrub typhus is highly influenced by meteorological factors like temperature, humidity and rainfall[8]. A study from China described the temperature and the scrub typhus association as initial elevated – descendent pattern. They found that heavy rainfall was associated with a sharp increase in scrub typhus risk[9]. In Japan, during 1984-2014, the average temperature in July and August of the previous year, cumulative rainfall in the September of previous year, snowfall throughout the winter and maximum depth of snow cover in January and February were positively correlated with number of scrub typhus cases[5]. Scrub typhus outbreak was reported in cooler months in Southern India[10].

Only a few studies have explored the influence of meteorological factors on the incidence of scrub typhus in India[7,10,11]. Given the variation in climatic factors from place to place and the re-emergence of scrub typhus in Kerala, we conducted a study on the influence of weather conditions on scrub typhus incidence in Kerala.

MATERIAL AND METHODS

The month wise data of scrub typhus cases in Kerala from 2012 – 2020 was obtained from the Integrated Disease Surveillance Project (IDSP) of Directorate of Health Services (DHS), Kerala[4]. The daily gridded rainfall, maximum and minimum temperature data from 2012–2020 was obtained from India Meteorological Department (IMD), Pune. The daily gridded weather data was

converted into district level data using Thiessen polygon approach using an area weighted average approach[12,13]. Further the district level data was compiled to get the state level data and the study design is ecological time series analysis.

STATISTICAL ANALYSIS

Influence of weather variables namely maximum temperature, minimum temperature and rainfall on the occurrence of scrub typhus in Kerala was studied through correlogram using time series analysis in R Statistical Software.[14] Trend analysis using decomposition of additive time series method was done from 2012 to 2020. Mann Kendal test was performed to check the trend of the occurrence of scrub typhus. Cross correlation plots of total monthly rainfall, monthly average maximum and minimum temperatures with number of reported cases were prepared.

RESULTS

In this study, we conducted a statistical analysis to explore the correlation between monthly scrub typhus cases and meteorological factors, including total rainfall, average maximum temperature, and average minimum temperature from 2012 to 2020. The results are summarized below**.**

Total number of scrub typhus reported in Kerala from 2012 to 2020 was 4064 (Table 1). Maximum number of cases were reported in December and January (Fig.1).

Table 1. Year-wise Incidence of Scrub Typhus in Kerala from 2012 to 2020

Year	No. of scrub typhus cases
2012	39
2013	68
2014	433
2015	1149
2016	633
2017	340
2018	400
2019	579
2020	423
Total	**4064**

Source: Directorate of Health Services, Kerala[4]

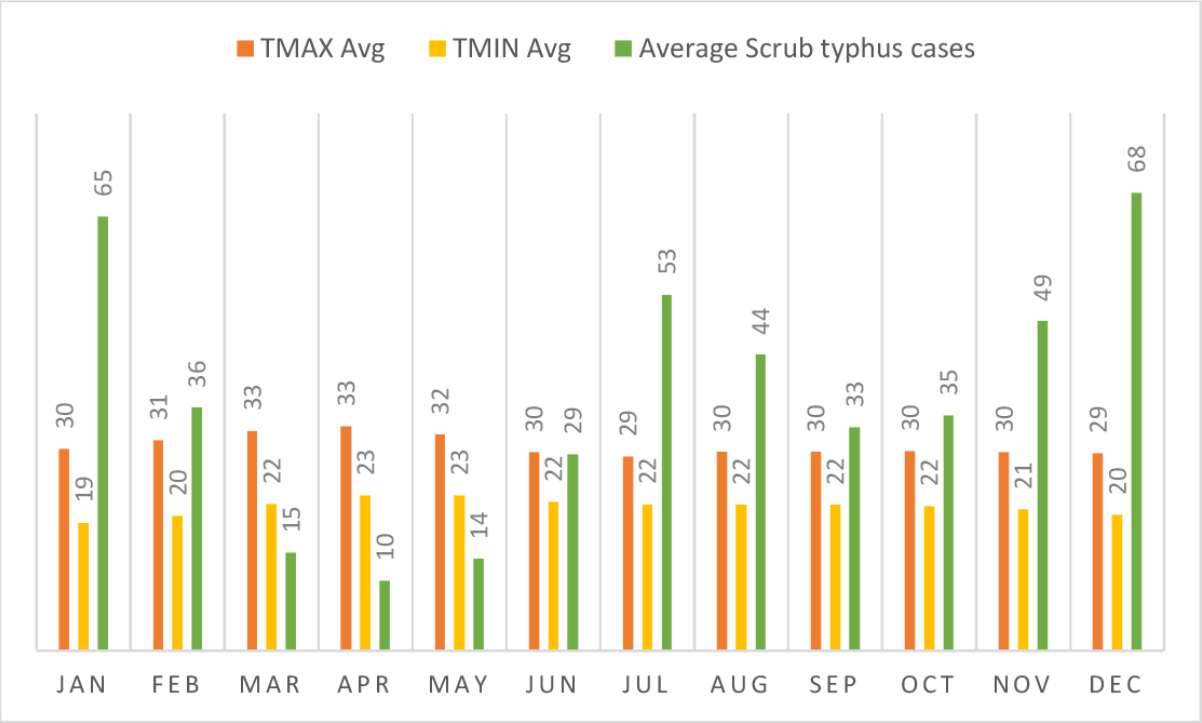


Fig. 1. Data on Maximum and Minimum Temperatures and scrub typhus incidence in Kerala from 2012 to 2020

CROSS-CORRELATION ANALYSIS OF AVERAGE MAXIMUM AND MINIMUM TEMPERATURES AND SCRUB TYPHUS INCIDENCE

Our analysis revealed a significant negative correlation between scrub typhus occurrence and the average maximum and minimum temperatures of the preceding three months. Specifically, an increase in both the average maximum and minimum temperatures during the previous three months was associated with a decrease in scrub typhus cases in the subsequent month. This relationship indicates a lag time of one month, meaning the effect of temperature changes manifests in scrub typhus incidence after a delay of approximately four weeks (Fig.1 and Fig.2).

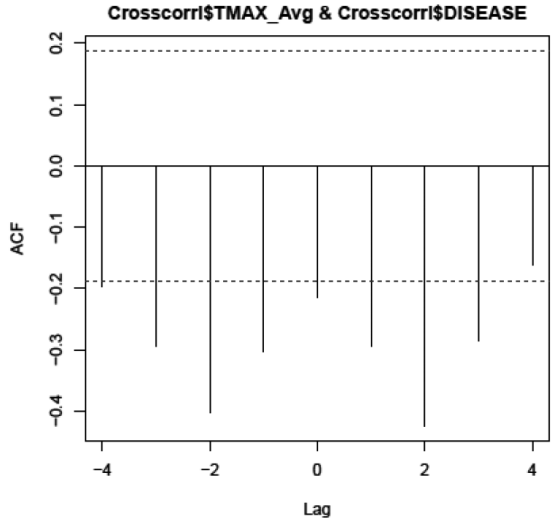


Fig. 2. Cross correlation plot of monthly average maximum temperature and average number of scrub typhus cases from 2012-2020

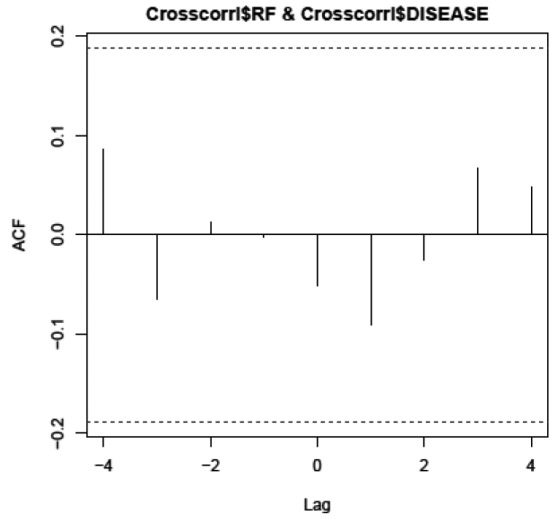


Fig. 3. Cross correlation plot of monthly total rainfall and average number of scrub typhus cases from 2012-2020

The analysis shows an evident trend and seasonality in scrub typhus occurrence in Kerala (Fig. 4). Further statistical testing using the Mann-Kendall test resulted in a tau value of 0.182, with a two-sided p-value of 0.0055516. This significant p-value indicates a statistically meaningful increasing trend in scrub typhus cases over time in the region (Fig.5)

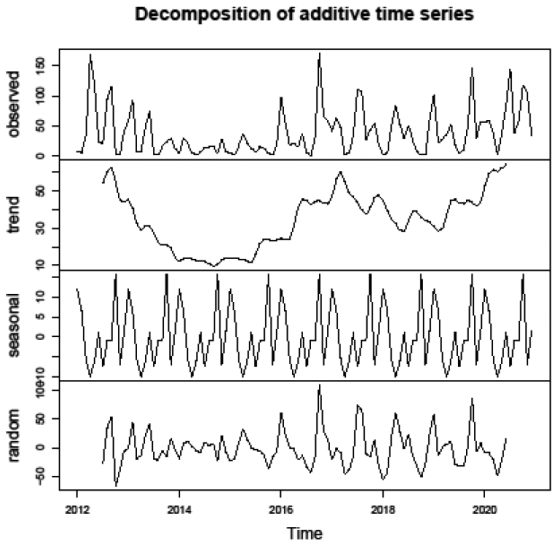


Fig. 4. Decomposition of Additive time series showing trend and seasonality of scrub typhus incidence in Kerala

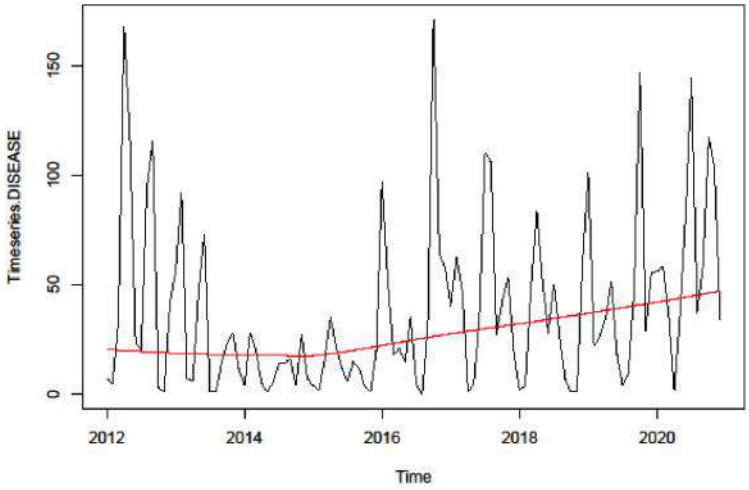


Fig. 5. Time Series Plot with trend showing increasing trend of scrub typhus incidence in Kerala

The results suggest that scrub typhus is becoming more prevalent in Kerala, with an upward trend. This trend should be closely monitored to assess the potential impact of climatic and environmental changes on disease transmission and to develop timely public health interventions.

Table 3. Impact of Relative Humidity on Disease Transmission across Regions

Region	Relative Humidity Range (%)	Scrub Typhus Incidence Rate (per 100,000)	Seasonal Trends	Reference
Global	60-90	5-20	Higher in monsoon season	CDC, WHO
Southeast Asia	70-85	15-30	Peaks in wet season	
India (Northeast)	75-95	25-40	Monsoon and post-monsoon	NCVBDC, India
India (North)	60-80	10-20	Monsoon and post-monsoon	Local epidemiology reports
China	65-85	8-15	Summer and monsoon	Local health reports, WHO
Japan	60-70	3-10	Early summer	Local epidemiology reports
Australia	50-70	2-5	Summer	WHO, Local government health reports
Indian Subcontinent	65-90	20-35	Monsoon	CDC, WHO

The table 3 indicate a strong correlation between higher relative humidity, typically above 60%, and increased scrub typhus incidence. Regions like Southeast Asia and Northeast India, where humidity levels often range between 75-95%, report incidence rates reaching 30-40 cases per 100,000 individuals, suggesting that high humidity may create favorable conditions for the vectors and hosts of *Orientia tsutsugamushi*, the bacterium responsible for scrub typhus. Seasonal patterns also influence incidence rates, with regions experiencing wet or monsoon seasons, such as India, Southeast Asia, and parts of China, seeing more cases during these periods. In India's Northeast and North regions, cases surge during the monsoon and post-monsoon months, likely due to the lifecycle of the mites that transmit scrub typhus, which thrive in warm, humid environments. Globally, there is significant variation in incidence rates, with Southeast Asia and parts of India exhibiting the highest rates, while Japan and Australia report lower rates, potentially due to differences in vector distribution, environmental conditions, and

public health measures. Notably, Japan's incidence peaks in early summer when humidity is moderate, underscoring regional variability in seasonal patterns. These findings highlight the importance of factoring in environmental aspects such as humidity and seasonal climate for public health strategies. Areas with high humidity and predictable monsoon seasons could benefit from targeted interventions, including awareness campaigns, surveillance, and preventive actions during peak transmission times, to help mitigate the spread of scrub typhus.

Table 4: Impact of Temperature on Disease Transmission across Regions

Region	**Optimal Temperature Range (°C)**	**Disease Incidence Rate (per 100,000)**	**Transmission Pattern**	**Source**
Tropical Regions	25-30	20-50	High year-round due to consistent warmth	WHO CDC Local health agencies
Southeast Asia	24-28	30-60	Peaks in summer and monsoon	
India (Northern)	20-35	10-40	Increases in summer and monsoon	National Centre for Vector Borne Diseases Control (NCVBDC)
Sub-Saharan Africa	22-32	15-45	High during warmer months	Local epidemiology reports
South America	23-29	10-30	Peaks during warmer, wetter months	WHO, Local health agencies
Temperate Regions	15-25	5-15	Peaks in summer	Local health agencies

The table 4 illustrates the impact of temperature on disease transmission across various global regions, highlighting optimal temperature ranges for vector activity and corresponding disease incidence rates. In tropical regions, where temperatures consistently range between 25-30°C, disease incidence remains high year-round, with rates from 20 to 50 cases per 100,000 as the warmth supports continuous vector breeding. Southeast Asia and Northern India show similar patterns, where temperatures between 24-35°C during summer and monsoon seasons result in heightened disease rates, peaking between 30-60 and 10-40 cases per 100,000 respectively. Sub-Saharan Africa, with an optimal range of 22-32°C, experiences higher transmission during warmer months, with incidence rates from 15 to 45 per

100,000 as noted in local reports. South America sees a spike in cases, 10-30 per 100,000 during warmer, wetter months, aligning with its 23-29°C range. In temperate regions, where ideal temperatures fall between 15-25°C, disease incidence peaks in summer but remains lower, between 5 and 15 per 100,000.

DISCUSSION

Scrub typhus is an emerging vector borne disease in Kerala[4]. Its incidence is influenced by many factors like vector population[15] and meteorological factors[9].

The present study provides valuable insights into how climatic factors impact the incidence of scrub typhus in Kerala. The findings have significant implications for public health planning and disease prevention in the region. In this study we assessed the impact of temperature and rain fall on the occurrence of scrub typhus in Kerala using data from 2012 to 2020 of the State. The study shows that the number of scrub typhus cases are showing increasing trend and seasonality in Kerala.

In our study average maximum temperature and average minimum temperature had a negative correlation with number of scrub typhus cases. The same trend was found in Vellore, Tamil Nadu[7]. A study from China shows scrub typhus incidence was positively correlated when mean temperature was at 19-20°C and in Japan, scrub typhus cases increased when average temperatures were at 22.5^{o}C and 24.1^{o}C.[5,16] The present study also shows that the maximum number of cases occurred when average maximum and minimum temperatures were at 29^{0}C and 20^{0}C respectively. The average minimum temperature at which maximum number of cases occurred in the present study is in agreement with the above reported studies. A multi-centric study in Taiwan reported a positive correlation between scrub typhus cases and temperature, with the highest number of cases occurring when the temperature ranged between 25°C and 30°C[17]. Similarly, in China, the association between temperature and scrub typhus followed an initial elevated–descendant pattern, with the highest number of cases occurring at 24.5°C [9]. The favourable temperature for scrub typhus occurrence in the present study is in conformity with the findings from the above referred studies conducted in various geographical locations. One reason for the impact of temperature on scrub typhus incidence is its influence on chigger activity. The favourable temperature for egg laying of mites was between 23°C and 25°C. There was no egg laying when

temperature was less than 20°C and more than 30 °C[18]. Frances *et al*. reported that scrub typhus infection increases when chigger population is high and more chiggers were attached to *Rattus rattus* during wetter months of the year[19]. This suggests that temperature plays a more crucial role in predicting scrub typhus occurrence than seasonality or trends.

Many studies have reported a positive correlation between rainfall and scrub typhus occurrence[7,9,16]. In Japan, cumulative rainfall in September of the previous year showed a positive correlation with scrub typhus incidence. But cumulative rainfall in July of the previous year showed a negative correlation with disease incidence. According to authors, too much rainfall in July might interfere with fertilization by washout of male mites or spermatophores around the females[5]. Studies from China reported that there was a sharp increase in scrub typhus incidence with a heavy rainfall[9,16]. The present study found no relationship between scrub typhus incidence and monthly average rainfall in Kerala. This could be due to the fact that averaging rainfall across all districts could potentially mask localized relationships. Rainfall can indeed vary significantly across Kerala due to its diverse topography, ranging from coastal to mountainous regions.

The results suggest that scrub typhus is becoming more prevalent in Kerala, with an upward trend. This trend should be closely monitored to assess the potential impact of climatic and environmental changes on disease transmission and to develop timely public health interventions. The data underscores the role of temperature in influencing vector-borne disease transmission, with warmer climates and seasons creating higher risk periods and highlighting the need for climate-sensitive public health responses.

Climatic and environmental changes play a crucial role in disease transmission by creating favorable conditions for vectors and pathogens. Warmer temperatures, increased humidity, and heavy rainfall can accelerate vector breeding and prolong pathogen survival, leading to higher incidences of diseases like malaria, dengue, and scrub typhus. Urbanization and deforestation further increase human exposure to wildlife reservoirs and vectors. Timely, adaptive public health interventions—such as vector surveillance, early-warning systems, and community-level measures like insecticide-treated nets and improved sanitation—are essential to mitigate these risks. Aligning public health strategies with environmental changes enables more effective disease prevention and protection for vulnerable populations.

While most studies have reported a positive correlation between rainfall and scrub typhus occurrence, our study did not find any significant association[7,9,16]. This discrepancy may be influenced by region-specific environmental factors, human outdoor activity and vector biology. In the future, incorporating vector biology alongside meteorological factors will be crucial for improving scrub typhus prediction models.

We could not analyse the correlation between district wise disease incidence and meteorological parameters. Bionomics of the vector also plays an important role in disease re-emergence. However, we observe that the incidence of scrub typhus occurrence is showing an increasing trend in the last few years in Kerala and the future research on the influence of weather parameters on vector bionomics could give more clear information on this increasing trend of scrub typhus incidence in Kerala.

CONCLUSION

The present study demonstrates an increasing trend in scrub typhus cases in Kerala over the period of study. Both maximum and minimum temperatures were found to be negatively correlated with scrub typhus occurrence. Our findings suggest that temperatures three months prior to disease incidence significantly influence the likelihood of scrub typhus outbreaks. Therefore, it may be possible to predict scrub typhus outbreaks up to three months in advance. However, no significant relationship was observed between cumulative rainfall and the occurrence of scrub typhus in Kerala. Understanding the influence of weather factors on disease dynamics can help to develop predictive models for forecasting outbreaks.

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Global Journal of Medicine & Public Health

Diabetes prevalence and associated risk factors in a Northern Kerala community: A Multistage Sampling Approach

Mubarack Sani T P[1], Narayanan Namboothiri G[2], Fathima Thasleema T E[3], Krishnaraj Rajeev[4], Sebastian N M[5], Ajith V[6]

ABSTRACT

Introduction

Diabetes is a significant metabolic disorder characterized by high blood glucose levels, leading to various complications if not properly managed. Understanding these factors is crucial for early identification, effective prevention, and management of diabetes within this community. Our study focused on the prevalence and risk factors of diabetes in Puzhakkatiri, a village in Malappuram district, Kerala, aiming to provide insights into local epidemiological patterns and targeted public health interventions.

Methodology

The community-based cross-sectional study included 582 participants (≥18 years) selected via multistage sampling from Puzhakkattiri Panchayath, Northern Kerala, India. Selected participants were invited to a camp that was held at the Government school in collaboration with the panchayath office, where participants had their BMI, waist-to-hip ratio, fasting blood sugar (FBS), and postprandial blood sugar (PPBS) levels measured. Sociodemographic data were collected through interviews, and the data were analyzed using SPSS software, with a p-value of 0.05 or lower indicating statistical significance.

Results

The study, with participants having a mean age of 39.13 ± 12.56 years, found a diabetes prevalence of 30% and an impaired glucose tolerance prevalence of 47.4%. Higher diabetes rates were observed among individuals over 40 years (37.2%), those divorced/widowed/separated (46.5%), those with lower education levels (40%), those in unskilled occupations (34.4%), and those with overweight BMI (33%) or high waist-to-hip ratios (34.5%). Significant associations (p-value<0.05) were found between diabetes prevalence and age (p=0.0001) , marital status (p=0.001), education level (p=0.001), occupation (p=0.0001), family type (p=0.0003), BMI (p=0.029), and waist-to-hip ratio (p=0.043).

Conclusion

Our study revealed a high prevalence of diabetes and IGT among participants, highlighting a significant burden of impaired glucose regulation within the population. Key risk factors identified include age over 40, certain marital statuses, lower education levels, unskilled occupations, specific family living arrangements, being overweight, and having a high waist-to-hip ratio.

Key Words: diabetes, Kerala, diabetes prevalence, diabetes complication, prediabetes, waist-hip ratio, body mass index, family adoption program, Malappuram

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INTRODUCTION

Diabetes encompasses various metabolic disorders marked by high blood glucose levels due to issues with insulin secretion, insulin action, or both. This persistent hyperglycemia is linked to long-term damage and failure in organs such as the eyes, kidneys, nerves, heart, and blood vessels. Common symptoms include excessive urination, thirst, weight loss, increased hunger, and blurred vision. Chronic hyperglycemia can also impair growth and increase infection risk. Severe uncontrolled diabetes can lead to life-threatening conditions like ketoacidosis or hyperosmolar syndrome. [1] Over time, diabetes can cause serious complications like vision loss from retinopathy, kidney failure from nephropathy, foot ulcers and amputations from peripheral neuropathy, and gastrointestinal, genitourinary, cardiovascular issues, and sexual dysfunction from autonomic neuropathy. Additionally, diabetic patients are more prone to atherosclerotic cardiovascular diseases, peripheral arterial disease, and cerebrovascular disease, often accompanied by hypertension and lipid metabolism disorders. [1,2]In India, an estimated 77 million adults over 18 years old suffer from type 2 diabetes, and nearly 25 million are prediabetic, indicating a high risk of developing diabetes soon. India has the second highest number of type 2 diabetes mellitus (T2DM) cases worldwide, following China, and this number is expected to nearly double by 2030. Over 50% of individuals are unaware of their diabetic status, leading to health complications if undiagnosed and untreated. The prevalence of diabetes in India among those aged 15-49 is 4.90% (4.80-5.00%), with 24.82% (24.07-25.59%) of cases undiagnosed, higher among males (28.82%) than females (24.22%). According to the ICMR-INDIAB study, Kerala has a diabetes prevalence of 23.6%, ranking third after Goa (26.4%) and Puducherry (26.3%). The pre-diabetes rate in Kerala is 18.1%, and with a weighted diabetes to pre-diabetes prevalence ratio of 1:1, the state faces significant challenges. The mean HbA1c value in Kerala is 8.3 mg/dl, indicating poor glycemic control. [3,4] Researchers attribute the poor achievement of glycemic targets, despite widespread use of NCD drugs, to inadequate treatment escalation, often due to insufficient monitoring and follow-up care. Diabetes mellitus is rapidly emerging as a global epidemic. As a metabolic disorder, improper management of diabetes can result in severe, life-threatening complications and premature death. Additionally, the financial burden of managing this disease and its associated complications is substantial. [3-5]

Diabetes mellitus is influenced by various modifiable and non-modifiable risk factors. Non-modifiable factors include race, family history, genetic predisposition, general immune status, and gender. Modifiable risk factors, which can be mitigated, include education level, occupation, BMI, and waist-to-hip ratio. Additional predictors of diabetes encompass family type, marital status, and age group. Comorbid conditions like hypertension and hyperlipidemia often coexist with diabetes. According to the NFHS-5, middle-aged individuals (45-49), those with a higher BMI, individuals in lower wealth index groups, and residents of southern India are at greater risk of having undiagnosed diabetes. [6-8] Untreated diabetes can lead to numerous complications. Acute issues include diabetic ketoacidosis (DKA) and non-ketotic hyperosmolar coma. Long-term complications can be severe, such as heart disease, stroke, kidney failure, foot ulcers, and eye damage. Insulin's crucial role as an anabolic hormone means that metabolic abnormalities in carbohydrates, lipids, and proteins arise when insulin levels are insufficient or when target tissues primarily skeletal muscles, adipose tissue, and to a lesser degree, the liver exhibit insulin resistance. This resistance can occur at the level of insulin receptors, the signal transduction system, or effector enzymes and genes. [9-11]

Early identification of risk factors for diabetes mellitus is crucial for effective prevention and management of the disease. Recognizing these factors such as genetic predisposition, obesity, sedentary lifestyle, poor diet, and comorbid conditions like hypertension and hyperlipidemia allows for timely intervention, which can delay or prevent the onset of diabetes. [10-12] Early detection enables healthcare providers to implement lifestyle modifications, medical treatments, and monitoring strategies to manage blood glucose levels and reduce the risk of severe complications. This proactive approach not only improves the quality of life for individuals but also reduces the economic burden on healthcare systems by preventing the progression of diabetes and its associated complications. [11-13]

Kerala is experiencing a significant epidemiologic transition, greatly impacting the state's morbidity and mortality rates. Rapid urbanization and modernization have permeated all levels of society, regardless of religion or economic status, altering lifestyles and creating a conducive environment for non-communicable diseases (NCDs) to thrive. The prevalent NCDs in Kerala include hypertension, diabetes mellitus, stroke, coronary artery disease, and cancer, with diabetes being the most common. Studying the prevalence and risk factors of diabetes in Malappuram district, Kerala, is crucial for developing targeted public health interventions to manage and prevent the disease in this specific region. Understanding local epidemiological data helps in identifying high-risk populations and tailoring prevention strategies to address specific lifestyle and genetic factors prevalent in Malappuram. Additionally, such studies contribute to the broader knowledge base necessary for formulating effective state-wide and national diabetes control programs. [12-14] Under the new curriculum by CBME, as proposed by NMC, the Family Adoption Programme has been initiated for medical students since 2021. This initiative mandates each MBBS student to adopt five families within their field practice area. In line with this, our medical college has undertaken the adoption of Puzhakkatiri, a village located in the Malappuram district in northern Kerala. Gathering data on the prevalence and risk factors of diabetes within this village will provide valuable insights for predicting similar patterns in neighboring villages across northern Kerala.Therefore, the main goal of our study is to determine the prevalence of diabetes among common people in a village in Kerala, India, as well as the determinants that are related to it.

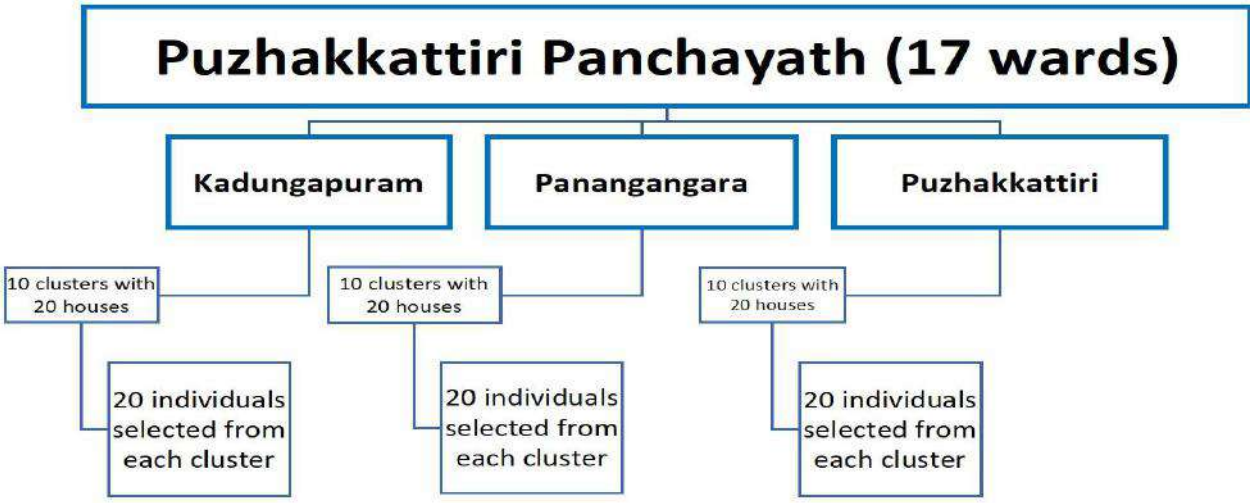
2. METHODOLOGY

2.1. Study Design, Setting,

The current community-based cross-sectional study was carried out in a Family adoption field practice area of a tertiary healthcare facility in Northern Kerala, India.

2.2. Study population and Sample size

The study enrolled participants aged 18 and above residing in the Puzhakkattiri Panchayath.Based on a study conducted in Kerala by Anjana et al., the sample size was estimated using the formula 4pq/d2, where p is prevalence and d is precision, the target confidence level was 95% and the relative precision was 5%. [5] In the suggested study, diabetes was 23.6% prevalent. The formula yielded a minimal sample size of 288.



600 Participants Selected

Figure 1: Flowchart illustrating the multi-stage sampling approach employed in our study.

The participant selection process involved three distinct stages employing multistage sampling.

Stage 1: Puzhakkattiri panchayath consisted of 17 wards divided into 3 zones, namely Kadungapuram, Panangangara, and Puzhakatiri, based on the distribution of houses.

Stage 2: Comprised of selecting 10 clusters from each of the 3 zones, each cluster consisting of 20 houses, employing convenient sampling methods.

Stage 3: Entailed constructing a sample frame comprising all individuals above 18 years from the 30 clusters. From this frame, 20 individuals were systematically selected from each cluster using a random method and invited to attend the camp. However, 18 individuals opted out due to various reasons such as inconvenience in attending the camp, illness, or infection. Thus finally, 582 participants were included in the study ie, twice the minimum sample size calculated.

2.3. Method of data collection

A camp was organized at the Government school, Puzhakkatiri in collaboration with the panchayath office to facilitate data collection. Participants were instructed to attend the camp between 6 am and 10 am. In addition to glucose testing, BMI and waist-to-hip ratio measurements were conducted during the camp. Following their consent, fasting blood sugar (FBS) and postprandial blood sugar (PPBS) levels were measured. Diabetic status was defined as FBS values exceeding 126mg/dl and PPBS values surpassing 200mg/dl. Individuals with FBS levels between 110-125mg/dl and PPBS levels between 140-200mg/dl were categorized as having impaired glucose tolerance. [9] Sociodemographic data was gathered through face-to-face interviews utilizing a pre-designed and pretested questionnaire.The gathered data underwent categorization into percentages and cross-tabulation across multiple variables. Analysis was conducted using Version 26 of the SPSS software. Bivariate analysis included the generation of chi-square values, with statistical significance set at a p-value of 0.05 or lower.

2.4. Ethical consideration

All study participants were assured of complete confidentiality and anonymity, and their involvement was entirely voluntary. Prior to participation, potential participants were provided with comprehensive information regarding the study's objectives and nature, and written informed consent was obtained from each individual. Ethics clearance with reference number No.IEC/MES/13/2023 was obtained before commencing the study from the Institutional Review Board.

3. RESULTS

3.1. Sociodemographic features (n=582)

Our study included participants ranging in age from 18 to 85 years, with a mean age of 39.13 +/- 12.56 years. The largest proportion fell within the age range of 40 to 49 years, comprising 23.4% of the sample. Gender distribution was diverse, with females constituting 62.5% of the participants. Occupation varied among participants, with 58.4% being unemployed, primarily homemakers, 15% working as unskilled laborers, and 3.6% holding semi-professional positions. Education levels varied, with 36% having completed high school and nearly 18% having attained a degree. The majority of participants came from nuclear families (44.8%), were married (80%), and identified as Muslim (75.4%). Under BMI, the majority fell within the pre-obese category at 30.5%, overweight and obese participants represent 19.3% and 11.3% of the sample, respectively. The majority of participants (91.7% males and 89.3% females) had a high waist-hip ratio (Table -1)

Table 1:Sociodemographic characteristics of the study population (n=582)

SOCIODEMOGRAPHY		Frequency (n)	Percentage (%)
GENDER	Male	218	37.5
	Female	364	62.5
RELIGION	Hindu	143	24.6
	Islam	439	75.4
MARITAL STATUS	Unmarried	43	07.4
	Married	466	80.1

	Legally divorced	2	0.30
	Separated	9	01.5
	Widow/widower	62	10.7
EDUCATION STATUS	Illiterate	49	08.4
	Primary school	94	16.2
	Middle school	113	19.4
	High school	210	36.1
	Degree	103	17.7
	Professional degree	13	02.2
OCCUPATION	Professional	21	03.6
	Clerical/shop/farm	30	05.2
	Skilled worker	27	04.6
	Semiskilled worker	40	06.9
	Unskilled worker	87	14.9
	Student	37	06.4
	Unemployed	340	58.4
TYPE OF FAMILY	Nuclear	261	44.8
	Joint	99	17.0
	Three generation	222	38.1
AGE GROUP	19-29	82	14.1
	30-39	116	19.9
	40-49	136	23.4
	50-59	103	17.7
	60-69	86	14.8
	>70	59	10.1
BMI	Underweight	52	09.5
	Normal	162	29.5
	Overweight	106	19.3
	Pre-obese	168	30.5
	Obese	62	11.3
WHR MALE	Normal	18	08.3
	High	200	91.7
WHR FEMALE	Normal	39	10.7
	High	325	89.3

3.2. Prevalence of diabetes (n=582)

The prevalence of diabetes among the study participants was 30% (95% CI: 26.28% - 33.72%), with 174 individuals identified as diabetic. Impaired glucose tolerance(IGT) was more common, accounting for 47.4% of the sample, with 276 participants falling into this category. Those classified as having normal glucose levels represent 22.7% of the total, comprising 132 individuals. These findings underscore the significant burden of impaired glucose regulation within the population, with nearly three-quarters of participants exhibiting abnormal glucose metabolism- either impaired glucose tolerance or diabetes.

3.3. Risk factors of diabetes (n=582)

Participants aged more than 40 years had the highest proportion of diabetes (37.2%), compared to those less than 40 years (15.7%). The p-value of 0.0001 and an odds ratio (OR) of 3.196 suggested a statistically significant and substantially increased risk of diabetes for individuals over 40 years old. Participants who were divorced/widowed or separated had the highest proportion of diabetes at 46.5%, compared to their counterparts, while 71% of married participants were

non-diabetic, showing a highly statistically significant association. Additionally, 40% proportion of participants with below higher secondary education had diabetes, in contrast to 22% among those with higher education, with a p-value of 0.001, indicating a significant relationship between education level and diabetes. Furthermore, 34.4% of participants in unskilled or lower occupations had diabetes, compared to 11.8% in skilled or higher occupations, also showing a highly significant association. Those living in nuclear and three-generation families had higher proportions of diabetes at 35% and 32%, respectively, compared to those in joint families, with a statistically significant relationship. In our study, a higher proportion of diabetes was found among those in the overweight and above BMI category (33%), compared to a lower proportion (24.3%) in the normal and below BMI category. The odds ratio was 1.537, with a statistically significant p-value of <0.0001. In the current study, 34.5% of male participants with a high waist-to-hip ratio were diabetic, compared to 11.0% of those with a normal waist-to-hip ratio. This demonstrates a higher prevalence of diabetes among males with a high waist-to-hip ratio. The association between the waist-to-hip ratio and diabetes was statistically significant, with a p-value of 0.043. (Table-2)

Table 2: Risk factors and its association with diabetes mellitus (n=582)

Risk Factors		DIABETIC STATUS		Total	P value and risk
		DIABETIC n(%)	NOT DIABETIC n(%)		
Age	>40	143 (37.2)	241 (62.8)	384	**0.0001** **(OR= 3.196)**
	<40	31 (15.7)	167 (84.3)	198	
Religion	Hindu	37 (25.9)	106 (74.1)	143	0.226
	Muslim	137 (31.2)	302 (68.8)	439	
Gender	Male	71 (32.6)	147 (67.4)	218	0.276
	Female	103 (28.3)	261 (71.7)	364	
Marital status	Unmarried	5 (11.6)	38 (88.4)	43	**0.001**
	Married	135 (29.0)	331 (71.0)	466	
	Others	34 (46.5)	39 (53.5)	73	
Education	Below high school	104 (40)	152 (60)	256	**0.001**
	Above high school	70 (22)	256 (78)	326	
Occupation	Skilled and above	14 (11.8)	104 (88.2)	118	**0.0001**
	Unskilled and below	160 (34.4)	304 (65.6)	464	
Type of family	Joint	11 (11.1)	88 (88.9)	99	**0.0003**
	Nuclear	92 (35.0)	169 (65.0)	261	

	Three generation	71 (32.0)	151 (68.0)	222	
BMI	Overweight and above	111 (33.0)	225 (67.0)	336	**0.029 (OR=1.537)**
	Normal and below	52 (24.3)	162 (75.7)	214	
WHR Male	Normal	2 (11.0)	16 (89.0)	18	**0.043 (OR= 0.237)**
	High	69 (34.5)	131 (65.5)	200	
WHR Female	Normal	10 (25.6)	29 (74.4)	39	0.697
	High	93 (28.6)	232 (71.4)	325	

4.DISCUSSION

Diabetes is a critical and multifaceted disease, gaining significance due to its iceberg phenomenon and the numerous complications it can cause. Despite extensive research on diabetes prevalence and contributing factors, awareness remains insufficient in many rural areas. Providing these communities with accurate research findings is essential for increasing awareness of their condition and encouraging proactive measures to prevent diabetes and its associated complications.

The prevalence of diabetes varies significantly across different studies conducted in various regions and populations. In our study, the prevalence of diabetes was found to be 30%, which falls within the range of the reported prevalence rates. In our study, more proportion of diabetes was found among the male population. According to NFHS-5, the prevalence of diabetes in India is 14.5%, with 15.6% in males and 13.5% in females. In rural areas, the prevalence rate is slightly lower at 13.4%. [15] In contrast, our study found a significantly higher prevalence of diabetes at 30%. This discrepancy may be due to differences in the age group selected, lifestyle factors, or healthcare access in the specific population we studied. According to recent statistics by ICMR, the prevalence of diabetes in Kerala is 23.6%. [5] The NFHS-5 district data sheet reported a diabetes prevalence of 22.7% among the population 15 years and above in Malappuram, closely aligning with the overall state prevalence. [16] Although our study found a higher prevalence rate of 30%, it remains relatively consistent with these reported figures, suggesting regional variations and similarities in diabetes prevalence.

Several studies have reported lower prevalence rates than ours, including Usha Menon et al in Central Kerala (19%), S Ashwathy et al in the coastal areas of southern Kerala (7.4%), V Ramankutty et al in Trivandrum (16.3%), C R Soman et al in Southern Kerala (6%), P S Sharma et al in Kerala (19.2%), Ramachandran et al in South India (12.1%), Mathur et al in India (9.3%), Gupta et al in North India (2.6%), Shora et al in Jammu (8.9%), and Kokiwar et al in North India (3.67%). [17-26] Similarly, international studies like those by Alireza et al in Iran (7.7%), Limin Wang et al in China (12.4%), Witcher et al in the United Kingdom (7.1%), and Reis et al in Brazil (7.6%) also reported lower prevalence rates compared to our study. [27-30] Conversely, studies by Sachin Athre et al in South Indian states (1.9% to 25.2%), Vijayakumar et al in Kerala (22%), V Mohan et al in Kerala (20.2%), Magliano et al in districts of Australia (35%), Yousef et al in Jordan (71%), Vasanthakumar et al in Belgavi, Karnataka (60%), B Zhou et al in American Samoa (>30%), and Sathyan M et al in Bangalore (33%) reported higher prevalence rates of diabetes. [31-37] These discrepancies are often attributed to behavioral traits linked to socioeconomic status, as well as regional, dietary, and cultural variations among different populations. In the present study, we observed a higher percentage of IGT at 47.4%. Various other studies reported lower prevalences, such as Usha Menon et al (4.1%), [17] Ramankutty et al (3%), [19] Ramachandran et al (4.6%), [22] Mathur et al (24.5%), [23] Kokiwar et al (13.6%), [26] Alireza et al (16.8%), [27] Wang et al (38.1%), [28] and Vijayakumar et al (45%). [32] The ICMR INDIAB study reported an IGT prevalence of around 15.3%. [5] The differences in results may stem from varying age group selections, as many studies, including NFHS-5, included

individuals aged 15 and above, along with cultural and geographic differences.

In our study, a higher proportion of diabetes was observed in individuals over the age of 40. This finding aligns with the WHO report, which predicts that India and other developing countries will see the most significant increase in diabetes cases among those aged 41-60 years and older. [38] Studies by Usha Menon et al, S. Ashwathy et al, Ramankutty et al, and Ramachandran et al also support this trend. This higher prevalence in older age groups is likely due to the cumulative effects of prolonged exposure to risk factors such as poor diet, sedentary lifestyle, and genetic predisposition. Our study found a higher proportion of diabetes among divorced or separated individuals. Research by Inas Pellon et al supports this, showing that divorced people have a higher incidence of chronic conditions like hypertension and diabetes compared to married individuals. [39] Concurrently, Oliveira et al found that those who remained married were less likely to develop diabetes, despite weight gain, than their divorced counterparts. [40] Further, Cornellis et al also found higher relative risks (RR) for developing T2D in divorced or separated individuals compared to those who are married. [41] This may be due to the increased stress and lifestyle changes associated with marital separation. Our study found that individuals with lower education and occupational levels tend to have a higher proportion of diabetes. This finding is supported by studies conducted by S Aswathy et al, [18] R Mehrotra et al and Yuwei Qui et al. [42, 43] This may be due to limited access to health information, lower health literacy, and fewer resources for maintaining a healthy lifestyle in these populations.

Contrary to our finding of a higher proportion of diabetes in nuclear families, Kittima et al found no statistical significance between family type and diabetes in their research. [44] However, Saranya Ravi et al reported that joint families with strong support networks tend to reduce the incidence of diabetes among members. [45] Similarly, a study by Suzanne et al found that larger families with good communication can help decrease diabetes and other disease conditions. [46] In our research, a BMI over 23.5 and a high waist-to-hip ratio in males were identified as risk factors for diabetes. This finding is consistent with several studies across India, which have also found that an above-normal BMI and abdominal obesity, including high WHR, are significant risk factors for diabetes. Research by Usha Menon et al, [17] Ramankutty et al, [19] Gupta et al, [24], and Ramachandran et al [22] supported this conclusion. The increased risk of diabetes associated with high BMI and WHR is likely due to the accumulation of visceral fat, which leads to insulin resistance and inflammation, thereby increasing the likelihood of developing diabetes.

Overall, the results of our study demonstrated a higher prevalence of diabetes which is influenced by factors such as age, education, occupation, marital status, type of family, BMI category, and WHR. These variables can be addressed through focused interventions, resulting in good clinical practices and better healthcare results in the rural village.

5. CONCLUSION

Our study revealed a high prevalence of diabetes among the participants, with 30% identified as diabetic. Impaired glucose tolerance was even more common, affecting 47.4% of the sample. These findings highlighted the significant burden of impaired glucose regulation within the population, indicating that nearly three-quarters of participants exhibited abnormal glucose metabolism, either in the form of impaired glucose tolerance or diabetes. Several risk factors for diabetes were identified in this study. Age over 40 years, marital status (divorced, widowed, or separated), lower education, unskilled occupations, living in nuclear or three-generation families, being overweight, and having a high waist-to-hip ratio were identified as significant risk factors for diabetes. These findings highlight the complex interplay of sociodemographic, educational, and lifestyle factors in diabetes risk. Targeted interventions are needed to promote responsible medication practices, and improve public awareness, healthcare provider education, and patient-centered care. Enhancing the availability and accessibility of professional healthcare services can reduce reliance on self-medication and improve healthcare outcomes.

6. LIMITATIONS

The study's limitations include its reliance on a single geographic location, which may not be representative of broader regional or national populations. Also, the study may not be generalizable to other cultural or regional contexts, which would reduce the external validity of the findings. Despite

these limitations, the study provides valuable insights into the prevalence and risk factors of diabetes, laying a strong foundation for future research in this critical area.

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Declarations

The authors of this article declare that they have no financial or personal relationships with other individuals or organizations that could inappropriately influence or bias their work. There are no employment affiliations, consultancies, stock ownership, honoraria, paid expert testimonies, patent applications/registrations, or any other financial or personal relationships that could be perceived as a conflict of interest in connection with this research.Furthermore, there are no non-financial relationships, such as partnerships, collaborations, or affiliations of any nature, that could potentially affect the objectivity, integrity, or impartiality of this study. The authors have not been involved in the development of any system or technology under evaluation in this study. This article is presented with full transparency and adherence to ethical standards, and the authors affirm that there are no conflicts of interest that could compromise the credibility or validity of the research presented herein.

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Proportional hazards regression for zero-inflated cure rate models - An application to cervical cancer data

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ABSTRACT

In lifetime studies, on many occasions, a proportion of individuals may experience the event of interest at the beginning of the study itself, while another group of individuals may not experience the event of interest, even after a long follow up period. We obtain zero inflated cure rate data in these situations. In this article, we study the regression analysis of zero inflated cure rate models. We propose a proportional hazards regression model to estimate the effect of covariates on lifetime. A simulation study is conducted to asses the finite sample behavior of the proposed estimator. The procedures are applied to a real data on cervical cancer, to demonstrate the practical utility.

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Cure rate model; EM algorithm; proportional hazards regression; zero-inflated data

1. Introduction

In survival studies, we generally assume that all study subjects will experience the event of interest, if they are followed sufficiently long. However, in many situations, a non-negligible proportion of individuals may not experience the event of interest even after a long period of observation. For example, in many clinical trials on cancer patients, a large proportion of individuals survive the disease completely. These patients can not be treated as censored, and should be considered as cured individuals (long term survivors). Accordingly, in cure rate models the entire population is considered as a mixture of two groups of individuals, susceptible (non-cured) and non-susceptible (cured). The traditional methods for analyzing survival data need modification when a proportion of individuals is cured.

Mixture and non-mixture cure rate models are proposed for the analysis of cure rate data in literature. However, mixture cure rate models are more popular in practice. The standard mixture cure rate model was first proposed by Berkson and Gage (1952). Standard mixture model has been studied by several authors, including Farewell (1986), Peng and Dear (2000), Sy and Taylor (2000), and Zhang and Peng (2007) among others. The books by Maller and Zhou

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(1996) and Yin and Ibrahim (2005) serve as excellent references on this topic. Recently, Asano and Hirakawa (2017) and Wu (2017) studied various aspects of modeling cure rate data among many others. Recently, machine learning-based mixture cure models gain attention over the logistic regression-based mixture cure model. The cure model has been used to analyze duration data from education sector by Kalamatianou and McClean (2003). Balakrishnan and Milienos (2020) proposed a generalization of the mixture cure rate model using a proper nonlinear transformation on the survival function of susceptible population to analyze a competing risks scenario where there exists a zero modified distribution on the initial number of causes. Machine learning based models possess the capability to capture nonlinear patterns in the data. Important literature in this direction include Li et al. (2020), Aselisewine and Pal (2023), Pal, Peng, and Aselisewine (2023a), and Pal et al. (2023b).

In some survival studies, a proportion of study subjects may experience the event of interest, even at the beginning of the study itself. These lifetimes should be considered as early failures and treated separately. If we consider early failures as normal lifetimes in the analysis, the survival probability will be overestimated. Early failures are recently referred to as zero-inflated lifetimes in survival studies. To handle zero-inflated lifetimes in survival data, one has to use zero-inflated lifetime models. Zero inflated model is first discussed in Lambert (1992), in the context of analyzing defects in manufacturing. Further this model is studied by Rodrigues (2003), Famoye and Singh (2006), Ospina and Ferrari (2012), Long et al. (2014), Hamada and Margevicius (2016), Sellers and Young (2019), Jiang et al. (2021) among others. Some recent research on zero inflated models arising from medical data include Preisser et al. (2012), Kurz, Lewitschnig, and Pilz (2014), Neelon, O'Malley, and Smith (2016), Molina et al. (2021), and Wen et al. (2024).

In certain situations, we come across zero-inflated lifetime data while some individuals are cured. For example, consider the data on cervical cancer patients from Brazil discussed in Brenna et al. (2004). In this data, some individuals experience the death due to cancer immediately after the treatment. The corresponding lifetimes should be treated as zero-inflated lifetimes. The data also contains observed lifetimes and censoring times. As well, the Kaplan Meier (KM) survival curve of the data with a long and stable plateau with heavy censoring at the tail, indicates the presence of cured individuals (Sy and Taylor 2000). Hence, this data should be analyzed using methods for zero inflated cure rate data. We discuss this data set in detail, in Sec. 5.

Zero inflated cure rate models become a topic of interest in recent years. The application of zero inflated promotion cure rate model to financial data has been studied by Ribeiro de Oliveira, Moreira, and Louzada (2017). Louzada, Moreira, and de Oliveira (2018) proposed a Weibull regression model for zero inflated cure data as an extension of the standard mixture model to analyze the fraud propensity in bank loan applications. A log normal zero inflated cure rate

regression model is developed by de Souza et al. (2022a) to analyze the labor time in an African obstetric population. Toledo et al. (2022) studied a Gompertz zero inflated cure rate regression model to study credit scoring data. A Bayesian approach for the analysis of zero inflated cure models is proposed by de Souza et al. (2022b).

All the above mentioned works, use parametric approach for the analysis of zero inflated cure rate data. In many practical situations, it is difficult to identify a parametric model for the given lifetime data. In such contexts, we employ semiparametric or nonparametric methods for the analysis. There exist only a sparse amount of literature on semiparametric or nonparametric analysis of zero inflated cure rate models. Motivated by this, in this paper, we present a proportional hazards regression model for zero inflated cure rate data.

The rest of the paper is organized as follows. In Sec. 2, we present a semiparametric regression model to assess the covariate effect on lifetime for zero inflated cure data. The estimation of the parameters using EM algorithm is discussed in detail. An extensive simulation study is carried out in Sec. 3 to assess the performance of the proposed estimators. In Sec. 4, we apply the proposed procedures to a real life data on cervical cancer patients, to illustrate the practical utility. Finally, we conclude the study with a brief discussion on future works in Sec. 5.

2. Model and inference procedures

We present a proportional hazards regression model for zero inflated cure rate data in this section. We also discuss the computational procedures for the estimation of regression coefficients using EM algorithm.

2.1. The model

Suppose that the population consist of two groups of subjects say, the susceptible group and the cured group. Let Y denote the indicator variable, which takes the value 1 for susceptible group of individuals and 0 for cured group. Let Z be the $d \times 1$ vector of explanatory variables. Without loss of generality, the same covariate vectors are considered for zero inflated and cured lifetimes. Now the proportion of cured individuals is given by $p_1(Z) = p(Y = 0|Z)$. Let T be a nonnegative random variable representing the time to occurrence of the event of interest, defined only when $Y = 1$. Further, assume that there exist a fraction of individuals who experienced the event of interest, in the beginning of the study itself (early failures) and let $p_0(Z)$ be the proportion of those individuals. We have $0 \leq p_0(Z), p_1(Z) \leq p(Z)$, where $p(Z) = 1 - \max(p_0(Z), p_1(Z))$. Let $S_0(t|Y = 1, Z) = P(T \geq t|Y = 1, Z)$ be the proper conditional survival function of the susceptible group of individuals, excluding those with zero-inflated lifetimes. Now, the survival function of the zero-inflated cure rate

regression model is

$$S(t|Z) = p_1(Z) + (1 - p_0(Z) - p_1(Z))S_0(t|Y = 1, Z). \quad (1)$$

In (1), if we take $p_0(Z) = 0$, it reduces to the survival function of standard mixture cure rate model given by

$$S(t|Z) = p_1(Z) + (1 - p_1(Z))S_0(t|Y = 1, Z).$$

If we set $p_1(Z) = 0$, (1) reduces to the survival function of zero inflated model given by

$$S(t|Z) = (1 - p_0(Z))S_0(t|Y = 1, Z).$$

The cumulative distribution function and the probability density function of survival time T are

$$F(t|Z) = p_0(Z) + (1 - p_0(Z) - p_1(Z))F_0(t|Y = 1, Z)$$

and

$$f(t, |Z) = \begin{cases} p_0(Z), & \text{if} \quad t = 0 \\ (1 - p_0(Z))f_0(t, |Y = 1, Z), & \text{if} \quad t > 0. \end{cases}$$

respectively. It can be noted that, when $t \to 0$, $F(t|Z) = p_0(Z)$ and $S(t|Z) = 1 - p_0(Z)$. Also, $\lim_{t\to\infty} F(t|Z) = 1 - p_1(Z)$. We model $p_0(Z)$ and $p_1(Z)$ using logistic distribution (Farewell 1982). Let the vector $b = (b_0, b_1, \ldots, b_d)'$ with intercept b_0 be the regression coefficient associated with the zero inflated lifetimes and $c = (c_0, c_1, \ldots, c_d)'$ with intercept c_0 be the regression coefficient associated with cured individuals. Under logistic regression assumption, the proportion of zero-inflated lifetimes $p_0(Z)$ and the proportion of cured individuals $p_1(Z)$ are defined as

$$p_0(Z) = \frac{\exp(b'Z)}{1 + \exp(b'Z) + \exp(c'Z)} \quad (2)$$

and

$$p_1(Z) = \frac{\exp(c'Z)}{1 + \exp(c'Z) + \exp(b'Z)}. \quad (3)$$

Now we specify Cox proportional hazards (PH) regression model to study the effect of covariate Z on lifetime T of nonzero inflated, non-cured individuals. Under Cox PH model, the zero-inflated survival function of the model is given by

$$S(t|Y = 1, Z) = (S_0(t|Y = 1))^{\exp(\beta'Z)} \quad (4)$$

and the probability density function

$$f(t|Y = 1, Z) = \lambda(t|Y = 1, Z)S_0(t|Y = 1, Z) \quad (5)$$

where $\lambda(t|Y = 1, Z)$ is the conditional hazard rate corresponding to nonzero inflated uncured individuals.

Suppose that we observe n independent and identically distributed observations of the form $(t_i, \delta_i, \delta_i^*, Z_i)$, where t_i is the observed time or censoring time and the indicator variables δ_i takes the value 1, when t_i is uncensored and 0 otherwise; δ_i^* equals to 1 when $t_i \geq 0$ and 0 if $t_i = 0$ and Z_i is the observed $d \times 1$ vector of covariates for $i = 1, 2, \ldots, n$.

Now the data consist of individuals whose lifetimes are zero inflated, individuals with observed or censored lifetimes and cured individuals. Then the likelihood of the observed data for the model (1) can be expresses as

$$\begin{aligned} L(\Theta) = \prod_{i=1}^{n} \Big\{ & p_0(Z_i)^{(1-\delta_i^*)} p_1(Z_i)^{(1-\delta_i)\delta_i^*} \\ & \times \left[(1 - p_1(Z_i) - p_0(Z_i)) f(t_i|Y = 1, Z_i)\right]^{\delta_i \delta_i^*} \\ & \times \left[(1 - p_1(Z_i) - p_0(Z_i)) S_0(t_i|Y = 1, Z_i)\right]^{(1-\delta_i)\delta_i^*} \Big\} \end{aligned} \tag{6}$$

where $\Theta = (b, c, \beta, \Lambda_0(t))$. Let y_i be the observed value of the random variable Y_i. We assume that, if $\delta_i = 1, y_i = 1$ and if $\delta_i = 0, y_i$ is unobserved (Sy and Taylor 2000). Then the complete data be $(t_i, \delta_i, \delta_i^*, Z_i, y_i)$ which includes the observed and unobserved y_i's, $i = 1, 2, \ldots, n$. Now the likelihood given in (6) can be written as

$$\begin{aligned} L_c(\Theta; y) = \prod_{i=1}^{n} \Big\{ & p_0(Z_i)^{(1-\delta_i^*)} (1 - p_1(Z_i) - p_0(Z_i))^{\delta_i^* y_i} p_1(Z_i)^{(1-\delta_i)\delta_i^*(1-y_i)} \\ & \times (f(t_i|Y = 1, Z_i))^{\delta_i \delta_i^* y_i} (S_0(t_i|Y = 1, Z_i))^{(1-\delta_i)\delta_i^* y_i} \Big\} \end{aligned} \tag{7}$$

Now (7) can be re written as

$$\begin{aligned} L_c(\Theta, y) = \prod_{i=1}^{n} \Big[& p_0(Z_i)^{1-\delta_i} (1 - p_1(Z_i) - p_0(Z_i))^{\delta_i^* y_i} p_1(Z_i)^{(1-\delta_i)\delta_i^*(1-y_i)} \\ & \times [\lambda_0(t_i|Y = 1) \exp(\beta' Z_i)]^{\delta_i \delta_i^* y_i} \\ & \times \exp(-\Lambda_0(t_i|Y = 1) \exp(\beta' Z_i))^{(1-\delta_i)\delta_i^* y_i} \Big] \end{aligned} \tag{8}$$

The likelihood function given in (8) is now factorized into logistic model and PH model as

$$L_c(\Theta; y) = L_1(b, c; y) L_2(\beta, \Lambda_0(t); y) \tag{9}$$

where

$$L_1(b, c; y) = \prod_{i=1}^{n} p_0(Z_i)^{(1-\delta_i^*)} (1 - p_1(Z_i) - p_0(Z_i))^{\delta_i^* y_i} (p_1(Z_i))^{(1-\delta_i)\delta_i^*(1-y_i)} \tag{10}$$

and

$$L_2(\beta, \Lambda_0(t); y) = \prod_{i=1}^{n} \left[\lambda_0(t_i|Y=1)\exp(\beta' Z_i)\right]^{\delta_i \delta_i^* y_i} \exp[-(\Lambda_0(t_i)\exp(\beta' Z_i))]^{(1-\delta_i)\delta_i^* y_i}. \quad (11)$$

The parameters of the model are estimated by maximum likelihood estimation method via EM algorithm (Dempster, Laird, and Rubin 1977) since partial information of random variable Y is missing. The estimation procedure using EM algorithm is explained below.

2.2. EM Algorithm

The E step takes the expectation of log likelihood function $l_c(\Theta; y)$ of full likelihood function given in (8) with respect to the distribution of the unobserved y_i's given the current parameter values and the observed data O, where $O = \{(\text{observed } y_i\text{'s}, t_i, \delta_i, \delta_i^*, Z_i), i = 1, 2, \ldots, n\}$. For the censored individuals, we estimate

$$\begin{aligned}
\pi_i^{(r)} &= E(Y_i|\Theta^{(r)}, O) \\
&= \Pr(Y_i = 1|T_i > t_i, \delta_i = 0, Z_i, \Theta^{(r)}) \\
&= \left[\frac{(1-\hat{p}_1(Z_i)-\hat{p}_0(Z_i))\hat{S}_0(t_i|Y=1)^{\exp(\hat{\beta}' Z_i)}}{\hat{p}_1(Z_i)+(1-\hat{p}_1(Z_i)-\hat{p}_0(Z_i))\hat{S}_0(t_i|Y=1)^{\exp(\hat{\beta}' Z_i)}}\right]_{|\Theta^{(r)}|}
\end{aligned}$$

where $\Theta^{(r)}$ denotes the values of parameters $\Theta = (b, c, \beta, \Lambda_0(t))$ at the rth iteration and $\hat{S}_0(t_i|Y=1) = \exp\left(-\hat{\Lambda}_0(t_i|Y=1)\right)$. For uncensored i, $E(Y_i|\Theta^{(r)}, O) = \hat{y}_i = 1$. At the rth iteration, the E step value of y_i is

$$w_i^{(r)} = \begin{cases} 1, & \text{if the } i\text{th individual is uncensored} \\ \pi_i^{(r)}, & \text{if censored.} \end{cases}$$

Thus the E step replaces the $y_i's$ in (8) with suitable value of $w_i^{(r)}$ according to the censoring status of ith individual. Then the expected log-likelihood function can be written as

$$\tilde{l}_c(\Theta; w^{(r)}) = \tilde{l}_1(b, c; w^{(r)}) + \tilde{l}_2(\beta, \Lambda_0(t); w^{(r)}) \quad (12)$$

where $\tilde{l}_1(b, c; w^{(r)})$ and $\tilde{l}_2(\beta, \Lambda_0(t); w^{(r)})$ are the expected log-likelihood functions corresponding to (10) and (9), respectively and $w^{(r)} = \{w_i^{(r)} : i = 1, \ldots, n\}$.

In the M Step, we maximize the conditional expectation of the complete-data log-likelihood given by $\tilde{l}_c(\Theta; w^{(r)})$ with respect to each parameter b, c, β and $\Lambda_0(t)$. The estimators $\hat{b}$ and $\hat{c}$ of b and c are obtained by maximizing the likelihood function $l_1(b, c; w^{(r)})$. To estimate β and $\Lambda_0(t)$, we adopt the profile

likelihood method (PFL approach) by Breslow (1972). Let $t_{(1)}, t_{(2)}, \ldots, t_{(k)}$ be the ordered distinct failure times, d_i be the number of events at time $t_(i)$ and R_i be the risk set at time $t_{(i)}^{-}$. Now, using $\tilde{l}_2(\beta, \Lambda_0(t); w^{(r)})$, it can be shown that the estimator of $\Lambda_0(t|Y=1)$,

$$\hat{\Lambda}_0(t_i|Y=1) = \sum_{i,t_{(i)}\le t} \left(\frac{d_i}{\sum_{l\in R_i} w_l^{(m)} \delta_i^* \exp(\hat{\beta}' Z_i)} \right). \tag{13}$$

Using the expression in (11), the partial likelihood equation of β obtained as

$$L_3(\beta, \varpi^{(r)}) = \prod_{i=1}^{n} \left(\frac{\exp(\beta' Z_i)}{\sum_{l\in R_i} w_l^{(r)} \delta_i^* \exp(\beta' Z_i)} \right)^{\delta_i \delta_i^*}. \tag{14}$$

Now maximizing $L_3(\beta, w^{(r)})$ with respect to β, given $w^{(r)}$, we get the estimator $\hat{\beta}$. This procedure is repeated until we meet the convergence criteria of parameters. The maximization can be done using numerical methods. We use "optim" function from R programming software to maximize the likelihood and estimate the parameters.

To study the asymptotic properties of the estimators, we obtain an approximation for the asymptotic variance of the estimators $(\hat{b}, \hat{c}, \hat{\beta})$, based on the inverse of the observed full information matrix $I(b, c, \beta, \lambda)$, where $\lambda(.) = \Lambda'(.)$. The observed full likelihood of the model is given as

$$\begin{aligned} L(b, c, \beta, \lambda) = \prod_{i=0}^{k} \Bigg[& \prod_{l\in D_i} \Big((1 - p_{0l} - p_{1l})(1 - \exp(-\lambda_l \exp(Z_l' \beta)) \Big) \\ & \times \exp\Big(- \sum_{j:t(j)\le t_{(i-1)}} \lambda_j \exp(Z_l' \beta) \Big) \Bigg] \\ & \times \prod_{l\in C_i} \Big(P_{1l} + (1 - p_{0l} - p_{1l}) \exp\Big(- \sum_{j:t(j)\le t_{(i-1)}} \lambda_j \exp(Z_l' \beta) \Big) \Big). \end{aligned}$$

2.3. The estimation of $I(b, c, \beta, \lambda)$

Suppose that there are k distinct event times, excluding zero-inflated lifetimes denoted by $t_{(1)}, t_{(2)}, \ldots, t_{(k)}$. Also denote D_i as the set of individuals experiencing the event at time $t_{(i)}$ and C_i as the set of individuals censored in the interval $[t_{(i)}, t_{(i+1)})$, $i = 0, 1, 2, \ldots, k$. We follow the method of Louis (1982) and use the complete data log-likelihood from the EM algorithm and then derive the score function. Following Sy and Taylor (2000), we use Z, Z_0 and Z_1 to separate the effect of covariates on individuals with individuals with actually observed or censored lifetimes, zero inflated lifetimes, cured individuals. In practice as

mentioned in Sec. 2, we observe the same covariate vector in all groups. Also in forthcoming expressions we write, p_0 for $p_0(Z)$ and p_1 for $p_1(Z)$ for avoiding lengthy equations. Following Sec. 2, we re-write the likelihood $L(b, c, \beta, \lambda)$ in (13), here.

$$L(b,c,\beta,\lambda) = \prod_{i=0}^{k}\Bigg[\prod_{l\in D_i}\Big((1-p_{0l}-p_{1l})(1-\exp(-\lambda_l\exp(Z_l'\beta))\Big) \times \exp\Big(-\sum_{j:t_{(j)}\le t_{(i-1)}}\lambda_j\exp(Z_l'\beta)\Big)\Bigg] \times \prod_{l\in C_i}\Big(P_{1l}+(1-p_{0l}-p_{1l})\exp\Big(-\sum_{j:t_{(j)}\le t_{(i-1)}}\lambda_j\exp(Z_l'\beta)\Big)\Big).$$

Let $l(\Theta) = \log L(b, c, \beta, \lambda)$ and $l(\Theta; y) = \log L(\Theta; y)$, where $L(\Theta; y)$ is the likelihood function defined in (8). Let

$$w_l = \frac{(1-p_{01}-p_{1l})\Big[\exp(-\Lambda_0(t_l|Y=1)\exp(Z_l'\beta)\Big]}{p_{1l}+(1-p_{01}-p_{1l})\Big[\exp(-\Lambda_0(t_l|Y=1)\exp(Z_l'\beta)\Big]}$$

when l is censored and $w_l = 1$ when l is uncensored with $\Lambda_0(t_l|Y = 1) = \sum_{t_{(j)}\le t_l}\lambda_j$. Now

$$\frac{\partial}{\partial b}l(\Theta;y)\Big|_{y_l=w_l\forall l} = \sum_{l=1}^{n}Z_{0l}(w_l-p_1l),$$

$$\frac{\partial}{\partial c}l(\Theta;y)\Big|_{y_l=w_l\forall l} = \sum_{l=1}^{n}Z_{1l}(w_l-p_2l),$$

$$\frac{\partial}{\partial \beta}l(\Theta;y)\Big|_{y_l=w_l\forall l} = \sum_{i=1}^{k}\Bigg[\sum_{l\in D_i}\frac{Z_l\lambda_i\exp(Z_l'\beta)}{1-e^{-\lambda_i\exp(Z_l'\beta)}} - \lambda_i\sum_{l\in R_i}w_lZ_l\exp(Z_l'\beta)\Bigg],$$

$$\frac{\partial}{\partial \lambda_i}l(\Theta;y)\Big|_{y_l=w_l\forall l} = \sum_{l\in D_i}\frac{\exp(Z_l'\beta)}{1-e^{-\lambda_i\exp(Z_l'\beta)}} - \sum_{l\in R_i}w_l\exp(Z_l'\beta),$$

for $i = 1, 2, \ldots, k$. We can see that $\frac{\partial}{\partial b}l(\Theta; y) = \frac{\partial}{\partial b}l(b, c, \beta, \lambda)$, $\frac{\partial}{\partial c}l(\Theta; y) = \frac{\partial}{\partial c}l(b, c, \beta, \lambda)$, $\frac{\partial}{\partial \beta}l(\Theta; y) = \frac{\partial}{\partial \beta}l(b, c, \beta, \lambda)$ and $\frac{\partial}{\partial \lambda_i}l(\Theta; y) = \frac{\partial}{\partial \lambda_i}l(b, c, \beta, \lambda)$ for $i = 1, 2, \ldots k$. Now we find the expression for the second order partial deviates, which are the components of the score function and obtain an approximation for the asymptotic variance of $(\hat{b}, \hat{c}, \hat{\beta}, \hat{\lambda})$. The components of $I(\hat{b}, \hat{c}, \hat{\beta}, \hat{\lambda})$ are

$$-\frac{\partial^2}{\partial b^2}l(\Theta) = \sum_{l=1}^{n}Z_{0l}Z_{0l}'(1-p_{01}-p_{1l})p_{1l} - \sum_{l=1}^{n}Z_{0l}Z_{0l}'w_l(1-w_l)$$

$$-\frac{\partial^2}{\partial c^2}l(\Theta) = \sum_{l=1}^{n} Z_{1l}Z_{1l}^{'}(1-p_{01}-p_{1l})p_{1l} - \sum_{l=1}^{n} Z_{1l}Z_{1l}^{'}w_l(1-w_l)$$

$$-\frac{\partial^2}{\partial \beta^2}l(\Theta) = \sum_{i=1}^{k}\lambda_i \sum_{l\in R_i} w_l Z_l Z_l^{'}\exp(Z_l^{'}\beta)$$

$$-\sum_{i=1}^{k}\lambda_i \sum_{l\in D_i}\frac{Z_l Z_l^{'}h_{il}(1-\exp(-h_{il})-h_{il}\exp(-h_{il}))}{(1-\exp(-h_{il}))^2}$$

$$-\sum_{l=1}^{n} w_l(1-w_l)Z_l Z_l^{'}(\exp(Z_l^{'}\beta)\Lambda_0(t_l|Y=1))^2$$

$$-\frac{\partial^2}{\partial \lambda_i^2}l(\Theta) = \sum_{l\in D_i}\frac{(\exp(Z_l^{'}\beta))^2\exp(-h_{il})}{(1-\exp(-h_{il}))^2}$$

$$-\sum_{l\in R_i} w_l(1-w_l)(\exp(Z_l^{'}\beta)^2 \quad i=1,2..,k$$

$$-\frac{\partial^2}{\partial \lambda_i\lambda_j}l(\Theta) = -\sum_{l=1}^{n} w_l(1-w_l)(\exp(Z_l^{'}\beta))^2 \times I(t_l \geq t_{(i)})I(t_l \geq t_{(j)}) \quad i\neq j$$

$$-\frac{\partial^2}{\partial b\beta}l(\Theta) = \sum_{l=1}^{n} w_l(1-w_l)Z_{0l}Z_l^{'}\exp(Z_l^{'}\beta)\Lambda_0(t_l|Y=1)$$

$$-\frac{\partial^2}{\partial c\beta}l(\Theta) = \sum_{l=1}^{n} w_l(1-w_l)Z_{1l}Z_l^{'}\exp(Z_l^{'}\beta)\Lambda_0(t_l|Y=1)$$

$$-\frac{\partial^2}{\partial b\lambda_i}l(\Theta) = \sum_{l\in R_i} w_l(1-w_l)Z_{0l}\exp(Z_l^{'}\beta) \quad i=1,2,\ldots,k$$

$$-\frac{\partial^2}{\partial c\lambda_i}l(\Theta) = \sum_{l\in R_i} w_l(1-w_l)Z_{1l}\exp(Z_l^{'}\beta) \quad i=1,2,\ldots,k$$

$$-\frac{\partial^2}{\partial \beta\lambda_i}l(\Theta) = \sum_{l\in R_i} w_l Z_l\exp(Z_l^{'}\beta)$$

$$-\sum_{l\in D_i}\frac{Z_l\exp(Z_l^{'}\beta)(1-\exp(-h_{il})-h_{il}\exp(-h_{il}))}{(1-\exp(-h_{il}))^2}$$

$$-\sum_{l\in R_i} w_l(1-w_l)Z_l(\exp(Z_l^{'}\beta))^2\Lambda_0(t_l|Y=1) \quad i=1,2,\ldots,k$$

where $-\frac{\partial^2}{\partial bc}l(\Theta)$ vanishes and $h_{il} = \lambda_i\exp(Z_l^{'}\beta)$. We can see that the method we follow here is able to handle tied lifetimes also.

Remark

We discuss the identifiability of the model specified in (1). Let $S(t|Z) = p_1(Z) + (1 - p_0(Z) - p_1(Z))S_0(t|Z, Y = 1)$ and $S^*(t|Z) = p_1^*(Z) + (1 - p_0^*(Z) - p_1^{'}(Z))S_0^*(t|Y = 1)$, be two different zero-inflated cure rate models. The model is identifiable if $S(t|Z) = S^*(t|Z)$ implies and implied by $p_1(Z) = p_1^*(Z), p_0(Z) = p_0^*(Z)$, and $S_0(t|Y = 1) = S_0^*(t|Z, Y = 1)$. If $p_0(Z) = 0$ the identifiability of the model follows directly from Li, Taylor, and Sy (2001) under the stated conditions. If $p_0(Z) = 0$, the model can be expressed in the form of Li, Taylor, and Sy (2001) by which the identifiability of the model is direct. Assume $p_1(Z) \neq 0$ and $p_0(Z) \neq 0$. We now consider, two different cases when the conditional survival function $S_0(t|Z, Y = 1)$ is independent of Z, as well as the scenario when conditional survival function depends on Z through a proportional hazards model.

For both Case I and Case II, $p_1(Z) = p_1^*(Z)$ and $p_0(Z) = p_0^*(Z)$ and $S_0(t|Z, Y = 1) = S_0^*(t|Z, Y = 1)$, implies that $S(t|Z) = S^*(t|Z)$. Now to prove the "only if" part we consider the two cases separately.

Case I : Assume that $S(t|Z) = S^*(t|Z)$ and we consider the situation where both $S_0(t|Z, Y = 1)$ and $S_0^*(t|Z, Y = 1)$ are independent of the covariate vector Z. Then

$$\begin{aligned} &p_1(Z) + (1 - p_0(Z) - p_1(Z))S_0(t|Y = 1) \\ &\quad = p_1^*(Z) + (1 - p_0^*(Z) - p_1^*(Z))S_0^*(t|Y = 1). \end{aligned}$$

Let $p_2(Z) = (1 - p_0(Z) - p_1(Z))$ and $p_2^*(Z) = (1 - p_0^*(Z) - p_1^*(Z))$. Now the above equation can be expressed as

$$\begin{aligned} &(1 - p_2(Z) - p_0(Z)) + p_2(Z)S_0(t|Y = 1) \\ &\quad = (1 - p_2^*(Z) - p_0^*(Z)) + p_2^*(Z)S_0^*(t|Y = 1), \end{aligned}$$

which follows

$$p_2(Z)S_0(t|Y = 1) - p_2^*(Z)S_0^*(t|Y = 1) = (p_2(Z) - p_2^*(Z) + p_0(Z) - p_0^*(Z)).$$

For a fixed Z, the right side of the above expression is a constant, while the left side is a function of t. The only possible trivial solution for this expression is

$$p_2(Z)S_0(t|Y = 1) - p_2^*(Z)S_0^*(t|Y = 1) = 0$$

which leads to

$$\frac{p_2(Z)}{p_2^*(Z)} = \frac{S_0^*(t|Y = 1)}{S_0(t|Y = 1)} = k(\text{say}).$$

Now using similar arguments from Li, Taylor, and Sy (2001), we have the only possible value for the ratio k is 1. This follows $p_2^*(Z) = p_2(Z)$, $S_0(t|Y = 1) = S_0^*(t|Y = 1)$. Since $p_2(Z)S_0(t|Y = 1) - p_2^*(Z)S_0^*(t|Y = 1) = (p_2(Z) - p_2^*(Z) + p_0(Z) - p_0^*(Z))$, it is direct that $p_0^*(Z) = p_0(Z)$. It follow, $p_1^*(Z) = p_1(Z), p_0^*(Z) = p_0(Z)$, and $S_0(t|Y = 1) = S_0^*(t|Y = 1)$ whenever $S(t|Z) = S^*(t|Z)$.

Case II: Let $S(t|Z, Y = 1) = p_1(Z) + (1 - p_0(Z) - p_1(Z))(S_0(t|Y = 1)^{r(Z)})$ and $S^*(t|Z, Y = 1) = p_1^*(Z) + (1 - p_0^*(Z) - p_1^*(Z))(S_0^*(t|Y = 1)^{r^*(Z)})$ where $r(Z)$ and $r^*(Z)$ are nonconstant functions defined on $\mathcal{R}$. Under the condition $p_0^*(Z) = p_0(Z)$, we show that, $S(t|Z) = S^*(t|Z)$, holds only when $p_1^*(Z) = p_1(Z)$, $S_0(t|Y = 1) = S_0^*(t|Y = 1)$ and $r(Z) = r^*(Z)$.

Now the condition, $S(t|Z) = S^*(t|Z)$ can be expressed as

$$(1 - p_2(Z) - p_0(Z)) + p_2(Z)(S_0(t|Y = 1)^{r(Z)}) = (1 - p_2^*(Z) - p_0^*(Z)) + p_2^*(Z)(S_0^*(t|Y = 1)^{r^*(Z)})$$

which is further reduced to

$$(p_0^*(Z) - p_0(Z)) = p_2(Z)(1 - (S_0(t|Y = 1)^{r(Z)})) - p_2^*(Z)(1 - (S_0^*(t|Y = 1)^{r^*(Z)})).$$

Under the condition $p_0(Z) = p_0^*(Z)$, we have

$$\frac{p_2(Z)}{p_2^*(Z)} = \frac{(1 - (S_0^*(t|Y = 1)^{r^*(Z)})}{(1 - (S_0(t|Y = 1)^{r(Z)})}.$$

Now in similar lines of Case I, we can prove $p_1^*(Z) = p_1(Z)$, $S_0(t|Y = 1) = S_0^*(t|Y = 1)$ and $r(Z) = r^*(Z)$.

3. Simulation study

In this section, we assess the finite sample behavior of the proposed estimators using simulation studies. We choose the baseline distribution as Weibull distribution with $F_0(t) = 1 - \exp(-(\frac{t}{\mu})^k)$, where

$$F(t|Z) = \left[1 - \exp(-(\frac{t}{\mu})^k)\right]^{\exp(\beta' Z)}$$

to generate lifetimes. Various choices of parameter μ and k is used in simulation, including $k = 1$, which corresponds to the exponential distribution. The censoring variable C is generated from a uniform distribution over the interval $(0, k')$, where k' is chosen in such a way that 20% of the observations or 40% of the observations are censored. The censoring percentage is denoted as Δ in tables presenting simulation results. This helps to study the effect of censoring in two scenarios, viz, mild censoring and heavy censoring. The data for each observation consist of (t, Z, δ, δ^*), where $t = \min(T, C)$, δ and δ^* are indicator variables as defined in the previous section. We consider two covariates Z_1 and Z_2, where Z_1 is generated from a Bernoulli distribution with probability of success 0.5 and Z_2 is generated from a standard normal distribution. The proportion of early failures and the probability of cure are estimated using the equations (2) and (3). The steps employed in the simulation study are summarized in the following algorithm.

Step 1: Choose the parameter values b_0, b_1, c_0, c_1, and β.

Step 2: Generate the covariate vector $Z_i = (Z_{i1}, Z_{i2})$, where Z_{i1} is generated from a Bernoulli distribution with probability of success = 0.5 and Z_{i2} from a standard normal distribution for $i = 1, 2, \ldots, n$.

Step 3: Generate a random variable u_i from Uniform $(0, 1)$, $i = 1, 2, \ldots, n$.

Step 4: Compute the proportion of cure rate p_1 and the proportion of early failures p_0 for every Z_i, $i = 1, 2, \ldots, n$ using the following equations;

$$p_1(Z_i) = \frac{\exp(c^{'} Z_i)}{1 + \exp(c^{'} Z_i) + \exp(b^{'} Z_i)}$$

and

$$p_0(Z_i) = \frac{\exp(b^{'} Z_i)}{1 + \exp(b^{'} Z_i) + \exp(c^{'} Z_i)} .$$

Step 5: If $u_i \leq p_0(Z_i)$, set $v_i = 0$.

Step 6: If $u_i > 1 - p_1(Z_i)$, set $v_i = \infty$.

Step 7: If $p_0(Z_i) < u_i \leq 1 - p_1(Z_i)$, generate $\pi_i \sim$ Uniform$(p_0(Z_i), 1 - p_1(Z_i))$ and generate the lifetimes v_i from the model as

$$v_i = \Lambda_0^{-1}(-\log(\pi_i) \exp(\beta^{'} Z_i)),$$

where $\Lambda_0(.)$ is the baseline cumulative hazard rate function of Weibull distribution, $i = 1, 2, \ldots, n$.

Step 8: Simulate $C_i \sim$ Uniform$(0, k')$ where k' is set to control the proportion of censored observations.

Step 9: Find $t_i = \min(v_i, C_i)$. If $t_i < C_i$, set $\delta_i = 1$, otherwise $\delta_i = 0$.

Step 10: If $t_i > 0$, set $\delta_i^* = 1$, otherwise $\delta_i^* = 0$.

Step 11: The data set for the ith subject is $(t_i, Z_i, \delta_i, \delta_i^*)$, $i = 1, \ldots, n$.

We generate random samples of sizes $n = 50$, 100, 200, and 500. The simulations are repeated 1,000 times. Maximum likelihood estimation of the parameters is carried out for the proposed model. The absolute bias, mean square error (MSE), standard error (SE) and 95% coverage probability (CP) of the estimators are computed. We consider different combinations of parameter realizations and observe that the results are similar. We present the values of the absolute bias, MSE, SE, and 95% CP for the estimator of β_1 and β_2 when $\mu = 1$ and $k = 1$ (standard exponential distribution) and when $\mu = 2$ and $k = 0.5$ in Table 1. For the same combinations of μ and k, the values of the absolute bias, MSE, SE and 95% CP of the estimators of $(b_0, b_1, b_2, c_0, c_1, c_2)$ are reported in Table 2.

From Tables 1 and 2, we can see that the estimates absolute bias and MSE of the estimates are negligible. Also we can note that, the absolute bias and MSE decrease as the sample size increases. However, both absolute bias and MSE increase when the censoring percentage increases. The values of SE are also admissible and they decrease with increase in sample size. Also, the coverage probability is approaching 95% as the sample size increases. We also estimate

Table 1. Absolute bias, MSE and coverage probability of the estimator $\hat{\beta}_1$ and $\hat{\beta}_2$.

Δ	n	Bias	MSE	SE	CP	Bias	MSE	SE	CP
			$\hat{\beta}_1$				$\hat{\beta}_2$		
					$\mu = 1, k = 1$				
20	50	0.0264	0.1088	0.3287	93.16	0.0192	0.1032	0.3206	93.88
	100	0.0182	0.0871	0.2945	93.87	0.0150	0.0923	0.3034	94.21
	200	0.0169	0.0432	0.2071	94.42	0.0113	0.0761	0.2756	94.87
	500	0.0115	0.0144	0.1194	95.12	0.0009	0.0242	0.1555	95.08
40	50	0.0311	0.1209	0.3463	93.03	0.0236	0.1287	0.3580	93.54
	100	0.0276	0.0911	0.3006	93.59	0.0182	0.1052	0.3238	93.89
	200	0.0218	0.0684	0.2606	93.96	0.0137	0.0788	0.2804	94.55
	500	0.0146	0.0256	0.1593	94.57	0.0102	0.0393	0.1980	94.86
					$\mu = 2, k = 0.5$				
20	50	0.0282	0.1095	0.3297	93.05	0.0203	0.1044	0.3225	93.27
	100	0.0191	0.3142	0.0991	93.65	0.0165	0.0992	0.3145	93.82
	200	0.0169	0.0517	0.2267	94.05	0.0128	0.0819	0.2859	94.19
	500	0.0118	0.0218	0.1472	94.55	0.0119	0.0422	0.2051	94.72
40	50	0.0341	0.1378	0.3696	93.00	0.0264	0.1281	0.3569	93.17
	100	0.0288	0.1005	0.3157	93.44	0.0216	0.1002	0.3158	93.61
	200	0.0259	0.0792	0.2802	93.72	0.0193	0.0927	0.3039	93.93
	500	0.0177	0.0377	0.1934	94.32	0.0139	0.0482	0.2191	94.54

the absolute bias, MSE, SE and CP of the estimator of baseline survivor function $S_0(t)$ at different time points and the results are presented in Table 3. The time points are chosen to be 0.2,0.4,0.6, and 0.8. We note that, the absolute bias, MSE, SE and CP of the estimators of $S_0(t)$ exhibit decreasing trend with increase in sample size, while they increase with censoring percentage. There is no pattern of bias, MSE, SE and CP is observed as time points change from 0.2 to 0.8.

4. Data analysis

We illustrate the applicability of the proposed model with a Brazilian invasive cervical cancer data set studied in Brenna et al. (2004) and de Souza et al. (2022b) in the context of zero inflated cure rate models. The data consist of information on 124 women diagnosed with invasive cervical cancer who have completed the standard treatment recommended by the International Federation of Gynecology and Obstetrics, which is collected between 1992 and 2002 in Brazil. The time between the date of surgery and date of death, and disease recurrence status, which is the covariate information are available for each patient. The recurrence status give the information about whether the disease has recurred for the same individual before one year or not. Six women died immediately after the surgery and the corresponding lifetimes are considered are zero-inflated lifetimes. Martinez and Achcar (2018) analyzed this data using defective Dagum distribution. We plot a Kaplan Meier curve, to get a basic information about the presence of long term survivors in the data (Maller and Zhou 1996). The KM curve for cervical cancer data set is given in Fig. 1.

Table 2. Absolute bias, MSE and coverage probability of the estimator $\hat{b}_0, \hat{b}_1, \hat{b}_2, \hat{c}_0, \hat{c}_1$, and $\hat{c}_2$.

Δ	n	Bias	MSE	SE	CP	Bias	MSE	SE	CP	Bias	MSE	SE	CP
							$\mu = 1, k = 1$						
			$\hat{b}_0$				$\hat{b}_1$				$\hat{b}_2$		
20	50	0.0351	0.0268	0.1599	93.29	0.0314	0.0261	0.1585	93.22	0.0298	0.0220	0.1453	93.18
	100	0.0298	0.0243	0.1530	94.14	0.0219	0.0221	0.1470	93.83	0.0201	0.0178	0.1319	93.64
	200	0.0281	0.0211	0.1425	94.84	0.0178	0.0198	0.1396	94.20	0.0162	0.0149	0.1210	94.12
	500	0.0256	0.0187	0.1343	95.15	0.0092	0.0152	0.1229	94.81	0.0101	0.0113	0.1058	94.75
40	50	0.0349	0.0286	0.1587	92.79	0.0325	0.0264	0.1592	92.34	0.0317	0.0289	0.1670	92.98
	100	0.0316	0.0245	0.1533	93.18	0.0247	0.0220	0.1463	93.10	0.0255	0.0219	0.1458	93.24
	200	0.0305	0.0232	0.1492	93.67	0.0174	0.0207	0.1428	94.18	0.0182	0.0162	0.1260	93.88
	500	0.0243	0.0197	0.1382	94.15	0.0109	0.0172	0.1307	95.15	0.0152	0.0144	0.1190	94.36
			$\hat{c}_0$				$\hat{c}_1$				$\hat{c}_2$		
20	50	0.0359	0.0284	0.1647	93.67	0.0309	0.0221	0.1454	94.29	0.0301	0.1256	0.3531	93.85
	100	0.0336	0.0275	0.1624	94.21	0.0235	0.0212	0.1437	94.87	0.0283	0.0982	0.3121	96.01
	200	0.0324	0.0266	0.1598	94.85	0.0206	0.0198	0.1392	95.17	0.0231	0.0686	0.2609	95.88
	500	0.0273	0.0209	0.1420	95.15	0.0109	0.0176	0.1322	95.12	0.0192	0.0298	0.1716	95.12
40	50	0.0406	0.0338	0.1793	95.15	0.0323	0.0222	0.1455	94.01	0.0376	0.1492	0.3844	93.25
	100	0.0338	0.0282	0.1645	93.56	0.0274	0.0213	0.1434	94.67	0.0343	0.1028	0.3188	93.88
	200	0.0315	0.0267	0.1603	94.12	0.0227	0.0204	0.1410	94.88	0.0287	0.0847	0.2896	94.10
	500	0.0309	0.0234	0.1498	94.76	0.0128	0.0189	0.1369	95.34	0.0201	0.0439	0.2086	94.67
							$\mu = 2, k = 0.5$						
			$\hat{b}_0$				$\hat{b}_1$				$\hat{b}_2$		
20	50	0.0346	0.0308	0.1721	94.13	0.0445	0.0280	0.1613	95.60	0.0312	0.1288	0.3575	93.22
	100	0.0334	0.0272	0.1615	94.89	0.0306	0.0238	0.1512	95.26	0.0287	0.1092	0.3292	94.12
	200	0.0297	0.0227	0.1477	95.25	0.0165	0.0201	0.1408	95.04	0.0236	0.0873	0.2945	95.36
	500	0.0236	0.0175	0.1302	95.34	0.0926	0.0174	0.0939	94.87	0.0189	0.0561	0.2361	95.10
40	50	0.0352	0.0301	0.1699	93.45	0.0462	0.0296	0.1657	93.34	0.0367	0.1494	0.3848	92.98
	100	0.0337	0.0277	0.1630	94.15	0.0321	0.0249	0.1545	93.88	0.0302	0.1266	0.3545	93.27
	200	0.0303	0.0238	0.1513	94.78	0.0173	0.0209	0.1435	94.56	0.0284	0.0981	0.3119	93.89
	500	0.0266	0.0199	0.1385	95.13	0.0976	0.0185	0.0953	95.21	0.0208	0.0878	0.2956	94.56
			$\hat{c}_0$				$\hat{c}_1$				$\hat{c}_2$		
20	50	0.0403	0.0337	0.1791	93.33	0.0359	0.0244	0.1520	93.19	0.0418	0.1332	0.3626	92.95
	100	0.0327	0.0238	0.1508	93.75	0.0305	0.0209	0.1413	93.89	0.0364	0.0957	0.3072	93.47
	200	0.0302	0.0235	0.1503	94.56	0.0277	0.0174	0.1290	94.11	0.0273	0.0602	0.2438	93.66
	500	0.0272	0.0205	0.1406	94.87	0.0126	0.0108	0.1032	94.63	0.0167	0.0398	0.1988	94.54
40	50	0.0447	0.0309	0.1700	92.19	0.0385	0.0229	0.1463	93.01	0.0434	0.1405	0.3723	92.78
	100	0.0358	0.0291	0.1668	93.12	0.0317	0.0219	0.1446	93.78	0.0382	0.1293	0.3575	93.09
	200	0.0316	0.0237	0.1507	93.78	0.0241	0.0250	0.1566	94.22	0.0310	0.1002	0.3150	93.49
	500	0.0281	0.0232	0.1497	94.56	0.0128	0.0198	0.1401	95.12	0.0189	0.0784	0.2794	94.44

From Fig. 1, it is evident that, a large fraction of individuals does not experience the event. The initial points in KM curve also depict the presence of zero-inflated lifetimes. Now we compute the estimates of the regression coefficient and the baseline cumulative hazard rate function of the cervical cancer data set using the proposed methods. The estimate of the regression coefficient is obtained as $\hat{\beta} = 2.388$ with a standard error of 0.0182. The positive value of the estimate gives evidence that the hazard of death is more for patients with disease recurrence compared to others. Figure 2 shows the plot of the hazard rate functions for patients belonging to recurrence group and non-recurrence

Table 3. Absolute bias, MSE and coverage probability of the estimator $\hat{S}_0(t)$ at different time points.

n	time	Bias	MSE	SE	CP	Bias	MSE	SE	CP
					$\mu = 1, k = 1$				
			$\Delta = 20$				$\Delta = 40$		
50	0.2	0.0257	0.1237	0.3508	93.01	0.0298	0.1392	0.3719	92.87
	0.4	0.0287	0.1255	0.3531	93.26	0.0303	0.1277	0.3561	92.99
	0.6	0.0178	0.1381	0.3712	93.19	0.0265	0.1406	0.3740	93.05
	0.8	0.0184	0.1132	0.3359	93.15	0.0219	0.1329	0.3639	92.94
100	0.2	0.0194	0.1024	0.3194	93.42	0.0262	0.1271	0.3555	93.13
	0.4	0.0211	0.1018	0.3184	93.47	0.0254	0.1103	0.3311	93.36
	0.6	0.0158	0.1192	0.3449	93.61	0.0199	0.1285	0.3579	93.28
	0.8	0.0165	0.1002	0.3161	93.45	0.0182	0.1292	0.3590	93.22
200	0.2	0.0159	0.0912	0.3016	93.89	0.0194	0.1062	0.3253	93.55
	0.4	0.0175	0.0882	0.2965	94.12	0.0209	0.1021	0.3188	95.74
	0.6	0.0113	0.0981	0.3130	93.98	0.0165	0.1034	0.3211	95.88
	0.8	0.0132	0.0827	0.2873	94.21	0.0168	0.0985	0.3134	93.82
500	0.2	0.0117	0.0585	0.2416	94.62	0.0137	0.0782	0.2793	94.56
	0.4	0.0134	0.0499	0.2230	94.82	0.0163	0.0691	0.2624	95.24
	0.6	0.0092	0.0582	0.2411	94.72	0.0117	0.0614	0.2475	95.35
	0.8	0.0095	0.0552	0.2348	94.65	0.0121	0.0683	0.2611	94.57
					$\mu = 2, k = 0.5$				
			$\Delta = 20$				$\Delta = 40$		
50	0.2	0.0292	0.1367	0.3686	93.18	0.0313	0.1498	0.3858	92.78
	0.4	0.0283	0.1288	0.3578	92.95	0.0309	0.1402	0.3732	92.80
	0.6	0.0266	0.1290	0.3582	93.07	0.0284	0.1383	0.3708	92.94
	0.8	0.0182	0.1183	0.3435	93.22	0.0255	0.1293	0.3587	93.03
100	0.2	0.0226	0.1192	0.3445	93.63	0.0286	0.1235	0.3503	93.16
	0.4	0.0218	0.1047	0.3228	93.23	0.0265	0.1268	0.3551	93.04
	0.6	0.0193	0.1076	0.3275	93.27	0.0218	0.1176	0.3422	93.34
	0.8	0.0166	0.1015	0.3182	93.59	0.0187	0.1087	0.3292	93.39
200	0.2	0.0189	0.0986	0.3134	94.09	0.0211	0.1044	0.3224	93.78
	0.4	0.0177	0.0964	0.3100	93.88	0.0196	0.1096	0.3305	93.73
	0.6	0.0154	0.1002	0.3162	93.92	0.0177	0.1145	0.3379	93.67
	0.8	0.0136	0.0934	0.3053	95.64	0.0164	0.0988	0.3139	93.97
500	0.2	0.0125	0.0724	0.2688	94.64	0.0148	0.0857	0.2924	94.45
	0.4	0.0116	0.0656	0.2559	94.57	0.0121	0.0833	0.2884	94.52
	0.6	0.0097	0.0873	0.2953	94.43	0.0103	0.0934	0.3054	94.31
	0.8	0.0089	0.0621	0.2490	95.19	0.0112	0.0856	0.2924	94.67

group separately. The curve in blue color denote the hazard rate function of non-recurrence group and red color curve denote the hazard rate function of recurrence group. From Fig. 2 also, it is evident that the hazard rate of patients belonging to recurrence group is higher compared to the hazard rate of patients in non-recurrence group.

As the proposed method assumes the proportional hazard (PH) assumption for the covariates, we also carry out a graphical diagnostic for PH models based on the scaled Schoenfeld residuals (Therneau and Grambsch 2000). The graph of scaled Schoenfeld residuals for the covariate recurrence status is presented in Fig. 3. The horizontal line ensures that the PH assumption holds good for the covariate, recurrence status.

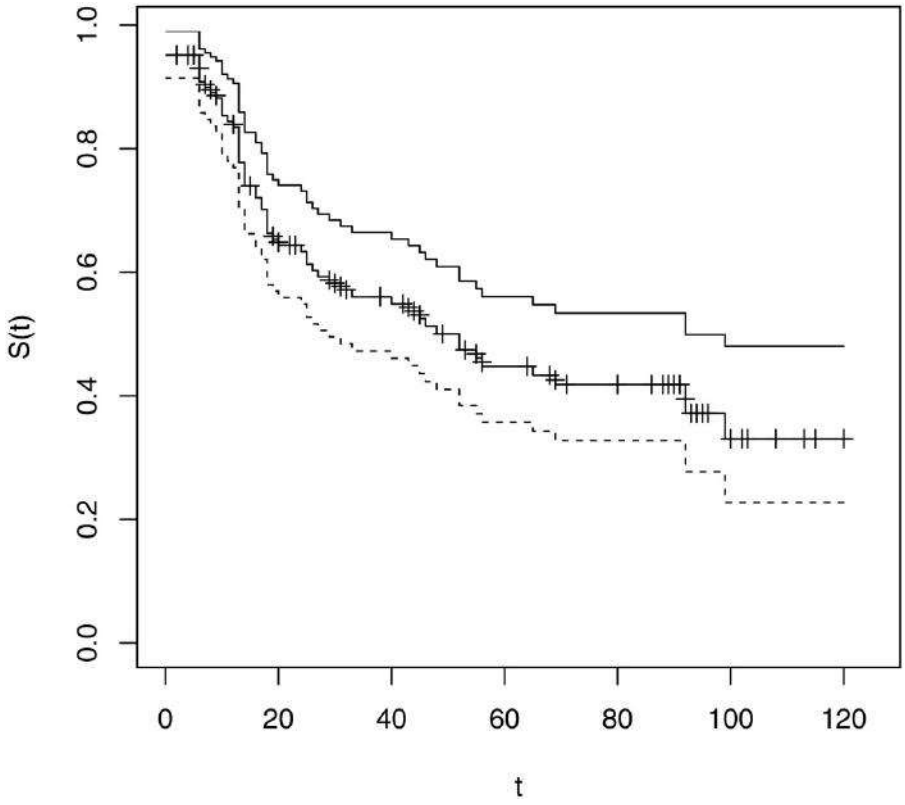


Figure 1. KM plot of the cervical cancer patients.

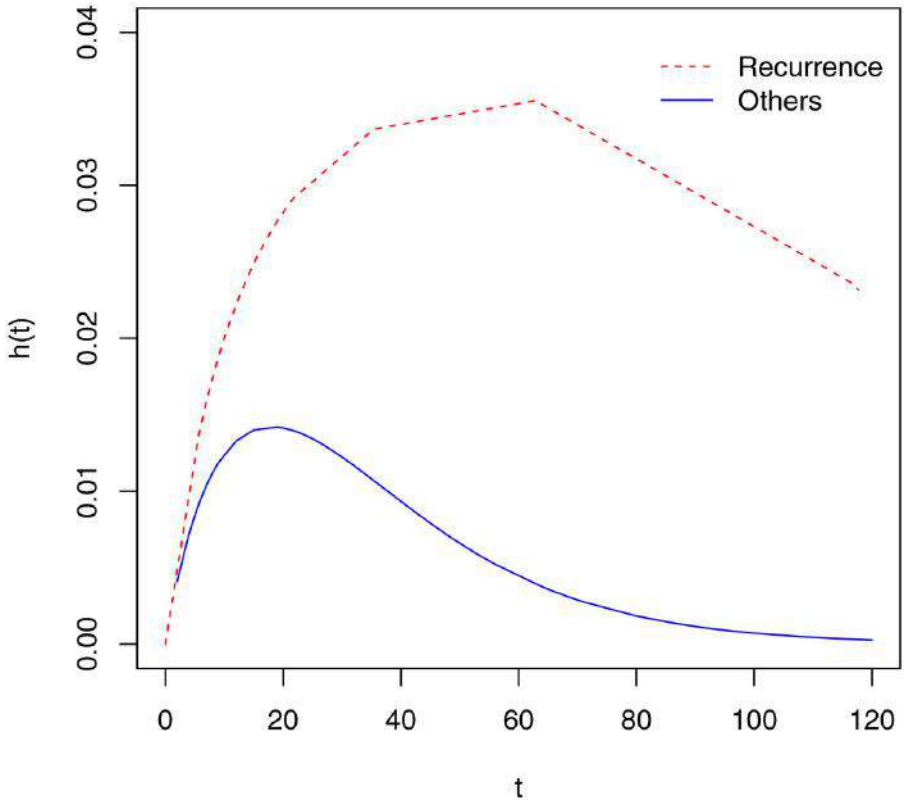


Figure 2. Plot of hazard rate functions of the patients belonging to recurrence and non-recurrence group.

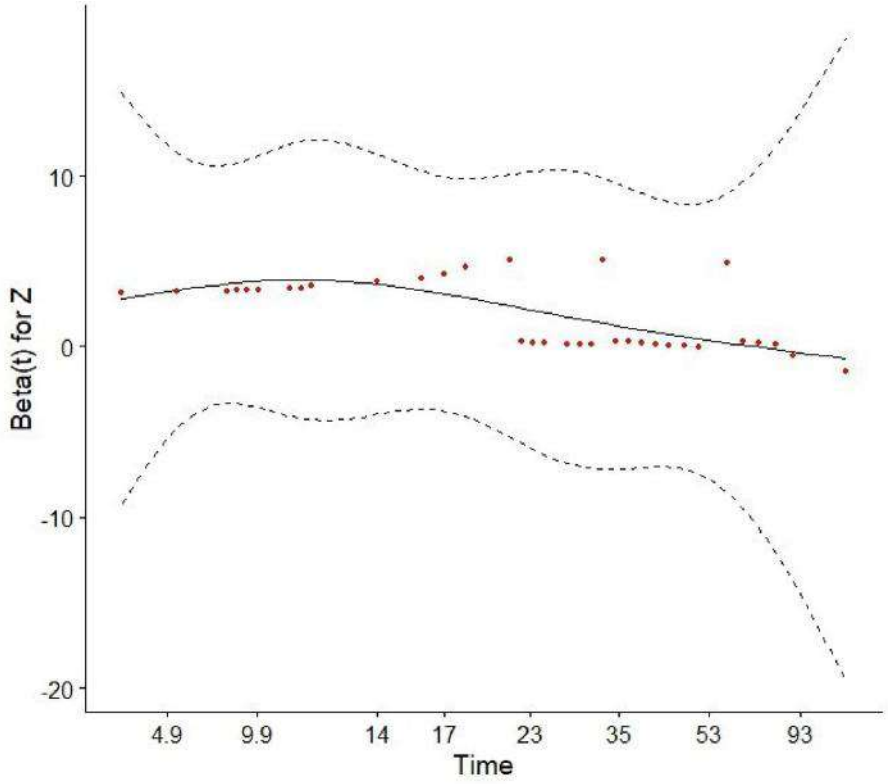


Figure 3. Scaled Schoenfeld residual plot.

The estimates of the model parameters with corresponding standard error, estimated using boot strap method and 95% confidence intervals are given in Table 4. In Table 4, p_{0r} and p_{1r} represent the proportion of individuals with zero inflated lifetimes and cured individuals in recurrence group, while p_{0nr} and p_{1nr} represent the same in non-recurrence group. From Table 4, we can see that estimated cure fraction of patients belong to recurrence group is 0.0988, while proportion of zero inflated lifetimes for the group is 0.1334. However, patients in non-recurrence group exhibit a higher probability of cure, estimated to be 0.5425, while the proportion of zero inflated lifetimes in the group yield a value of 0.0053. From the results it is clear that, the cure rate for patients who experience disease recurrence is small, while more than half of the patients, who did not experience disease recurrence are surviving. The same data set is analyzed by de Souza et al. (2022b) using a Bayesian approach. For the recurrence group, de Souza et al. (2022b) estimated the proportion of cured individuals and zero inflated lifetimes as 0.0372 and 0.1138, while for non-recurrence group the cure fraction is given to be 0.4952 and the proportion of zero inflated lifetimes as 0.0028. We can see that, their method underestimate the parameters comparing to the proposed model, however, the inferences are same.

Table 4. Estimates of the model parameters with corresponding standard error.

Parameter	Estimated		95% CP	
	Parameter	Standard error	Lower	Upper
b_0	−18.2812	0.0271	−26.7834	−8.4824
b_1	16.5319	0.0380	5.5681	26.8923
c_0	0.1701	0.0155	0.0082	0.0453
c_1	−2.2100	0.0567	−5.9823	1.6342
p_{0r}	0.1334	0.0176	0.0341	0.2327
p_{1r}	0.0988	0.0217	0.0122	0.1874
p_{0nr}	0.0053	0.0511	0	0.0213
p_{1nr}	0.5425	0.0189	0.4326	0.6254

5. Conclusion

In this paper, we proposed a proportional hazards cure rate regression model for zero-inflated survival data. We employed logistic distribution to model the proportion of cured individuals and zero inflated lifetimes in presence of covariates. The conditional survival function of the susceptible group of individuals, excluding those with zero-inflated lifetime given by $S(t|Y = 1, Z)$ is modeled using Cox PH model. The method of maximum likelihood estimation using EM algorithm was employed to estimate the parameters of the model. The performance of estimators was evaluated using simulation studies. The proposed model was applied to a real data set on invasive cervical cancer to illustrate the practical utility.

The methods proposed in this paper consider the right censored survival data only. It is of interest to develop semiparametric regression models for the analysis of zero inflated cure data when the lifetimes are subjected to other forms of censoring including interval censoring and double censoring. We can also employ accelerated failure time model for the regression analysis of zero inflated cure data.

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Disclosure statement

The authors declare, no conflict of financial or non-financial interests that are directly or indirectly related to this research work.

Data availability statement

The complete data set on cervical cancer, we used for illustration purpose is available in the Appendix A of de Souza et al. (2022b). The R codes for numerical studies are available in Github. It can be accessed through the link https://github.com/sreedeviep/ZICR-Code.

Ethical statement

The submitted work is original and has not been published elsewhere.

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Original Research Article

Knowledge, attitude and practice regarding menstrual cups in a veterinary college in central Kerala, India: a cross-sectional study

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ABSTRACT

Background: Menstrual cup is a novel, safe, sustainable, cost-effective menstrual product. Despite its advantages, it is not widely accepted in our country, probably due to varied reasons. Objective was to assess the knowledge, attitude and practice of menstrual cups among veterinary college students of central Kerala.
Methods: A cross-sectional study was conducted among 177 students at a government veterinary college in Kerala, India. Data was collected using a structured questionnaire to assess knowledge, attitude and practice of menstrual cup. Knowledge score was calculated for all respondents based on eight knowledge-related questions. Practice questions were asked to female students who had used menstrual cups at least once.
Results: Thirty of the 177 respondents were male. Majority (84.7%) had adequate knowledge; knowledge was significantly better in females. The most common concern raised by the respondents was the risk of leakage of menstrual blood (30.0%) and breakage of hymen (13.0%). Forty-five respondents had used a menstrual cup at least once, 37 were current users. Insertion, removal and usage were difficult in the initial cycles but later became easier. About one-fifth of the users faced problems like dryness, irritation, allergy or rashes.
Conclusions: The study concluded that despite having adequate knowledge regarding menstrual cups, the acceptance and usage is still not achieved.

Keywords: Cost effectiveness, Menstrual cup, Menstrual hygiene, Sustainability

INTRODUCTION

A woman's life passes through certain unique stages that have a bearing on her physical, mental and social life. Menstruation is one such physiological condition, often embedded in some harsh cultural realities. Many times, girls and women are unable to perform safe menstrual practices. For the attainment of a good menstrual health women need to have access to safe and hygienic menstrual products.[1] Women in India predominantly depend on clothes or sanitary napkins for their menstruation. Cloth, as a sanitary product, is difficult to manage due to the need for washing and drying in sunlight before the next use. Sanitary napkins, if not handled properly, can pose serious risk to the health of the women as well as the environment. There is a serious risk of genitourinary infection if proper management of these products are not performed.[2]

Into this backdrop came the eco-friendly menstrual cup, a device for menstrual flow management. These cups are made from higher level medical grade silicone, latex,

rubber, or elastomer and when inserted inside the vaginal canal are capable of collecting menstrual flow.[3] They can be emptied and reinserted and they are required to be boiled after each cycle. They can be used for 5-10 years. They reduce the waste generated during menstruation and hence are more eco-friendly and environmentally sound. Despite the many advantages of the menstrual cup, there is a lack of penetration of the practice of using the menstrual cup, especially in countries like India.

Studies about the knowledge on the use of menstrual cup conducted among the student population have thrown light on the major barriers that hinder their use among young women like lack of awareness about the use of menstrual cup.[4] Even the studies conducted among the college going youth in the urban cities demonstrated a surprisingly less level of awareness about menstrual cup.[5] Studies conducted among rural women in the reproductive age group in a tertiary care setting have shown that though most of the participants were aware of the usage of the menstrual cup the acceptance of the cup is still not achieved. Even the knowledge level is poor in most of the participants and more than half of them were not using menstrual cup due to the fear of leakage.[7]

Studies done previously have examined various aspects related to menstruation like menstrual hygiene, knowledge about menstruation and practices during menstruation, but very few have examined the knowledge, attitude and practices around the use of menstrual cups especially from central Kerala.[10-14] With growing concerns over sustainability and use of environmentally friendly products, identifying the gap in knowledge, attitude and practice in the use of menstrual cups will provide the right directions to encourage the use of menstrual cups. This is especially important in the young generation who are always welcoming to the newer technologies.

Thus, this study sought to evaluate the knowledge, attitude and practices (KAP) regarding menstrual cup among college students of central Kerala.

METHODS

A cross-sectional study was conducted among students at a veterinary college in Kerala, India in April 2022. Undergraduate veterinary students in different batches were approached and responses were collected from those who gave consent. These respondents included both males and females.

Data was collected using a structured self-administered questionnaire. The questionnaire consisted of sociodemographic details, and questions to assess knowledge, attitude and practice related to use of menstrual hygiene and specifically about menstrual cups. A scoring system was developed by the investigators to assess the level of knowledge based on the responses to the questionnaire.

Knowledge score was calculated based on eight knowledge-related questions; individuals who scored above 5 were considered to have good knowledge, while a score of 5 or less was classified as poor knowledge. All participants, irrespective of gender, were asked to respond to knowledge and attitude questions. Practice questions were directed towards female students who had used Menstrual cups at least once. Statistical analysis was performed using SPSS software (version 16.0).

RESULTS

A total of 177 respondents were included into the study. Their age ranged from 18 to 30 years, with a mean age of 21.16 (SD=1.598) years. Thirty (17.5%) were males. Ten of the respondents (5.6%) were married (Table 1).

Table 1: Socio demographic profile of participants.

Sociodemographic factors		Frequency	Percent
Age (years)	18-20	51	28.8
	21-23	119	67.2
	>23	5	4.0
Sex	Female	146	82.5
	Male	31	17.5
Religion	Hindu	99	55.9
	Muslim	41	23.2
	Christian	26	14.7
	No response	11	6.2
Marital status	Married	10	5.6
	Unmarried	167	94.4
Total		177	100.0

Knowledge

Majority of the respondents had good knowledge regarding menstrual hygiene in general, and also about menstrual cups. Overall, 84.7% got five or more of the eight questions correct, and thereby have adequate knowledge.

Sixty-nine (39.0%) got all the answers correct. The knowledge was significantly better among females, with 91.8% scoring 5 or above, as compared to 51.6% of the males. ($p<0.001$). Religion and marital status of the respondents did not have a significant association with the knowledge level (Table 2).

When asked how they would grade their own knowledge, nearly half the respondents (49.7%) rated their knowledge regarding menstrual cups as good, 67 (37.87%) felt it was average; 22 (12.4%) said their knowledge was poor. Only seven of the 31 males (22.6%) considered themselves to have good knowledge, as compared to 55.5% of the females ($p=0.002$).

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Table 2: Correct responses to knowledge questions.

Knowledge questions	Sex (%)		Total n=177 (%)
	Female n=146	Male n=31	
What is the average duration of menstruation in females?	134 (91.8)	26 (83.9)	160 (90.4)
Which of these menstrual products are you aware of? (list sanitary pads, menstrual cups, tampon)	99 (67.8)	15 (48.4)	114 (64.4)
Have you heard about menstrual cups?	145 (99.3)	29 (93.5)	174 (98.3)
What is a menstrual cup made of?	116 (79.5)	10 (32.3)	126 (71.2)
Are you aware that the menstrual cups are available in various sizes?	113 (77.4)	16 (51.6)	129 (72.9)
How frequently do you think a menstrual cup should be removed and cleaned during a day of menstruation?	142 (97.3)	26 (83.9)	168 (94.9)
Can the cup be used by a nulliparous woman?	142 (97.3)	27 (87.1)	169 (95.5)
Can the cup be used by a parous woman?	141 (96.6)	27 (87.1)	168 (94.9)
Total score (≥5)	134 (91.8)	16 (51.6)	150 (84.7)

Attitude

The most common concern raised by the respondents was the risk of leakage of menstrual blood (30.0%) and breakage of hymen (13.0%). Other concerns included loss of virginity, loss of fertility, difficulty or pain in insertion and infections. Two respondents mentioned the risk of the cup getting stuck as a concern. Eight respondents felt their religious beliefs restricted the use of menstrual cups; 22 (12.4%) said they experienced family restrictions. Majority of the respondents (84.75%) opined that menstrual cups can ease outdoor activities. When asked if Menstrual cups are safe to use, 49.7% agreed and 39.0% strongly agreed.

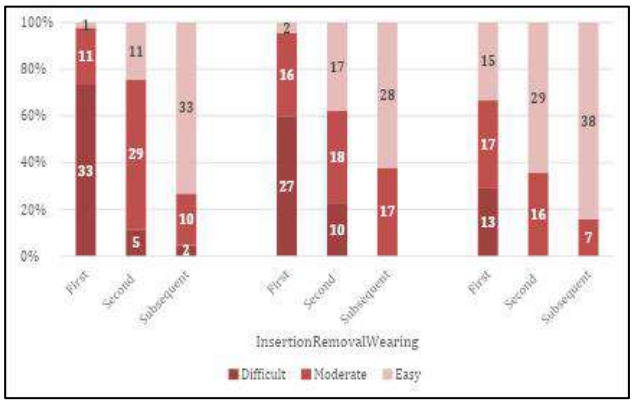


Figure 1: Difficulty in insertion, removal and wearing of menstrual cup over the period of use.

Practice

Out of the 177 participants, only 45 (25.4%) had used a menstrual cup at least once; of them, 37 were using it currently. Questions regarding practice were asked to these 45 respondents. Thirty-three of the 45 found it difficult to insert the menstrual cup the first time, five found it difficult the second time; in subsequent attempts, ten respondents had moderate difficulty while 33 found it easy. For removal, 27 found it difficult in the first attempt, none in the subsequent attempts. Overall, insertion, removal and usage were difficult in the initial cycles but later became easier. Ease during practice has a greater role when it comes to the menstrual cup being the menstrual product of choice (Figure 1). About three-quarters (77.7%) experienced leakage while using menstrual cups. Seven users said they always experienced leakage in the initial usage; the frequency came down in the subsequent cycles. However, over half the users (26/45) continued to have occasional leakage even in subsequent cycles. This was one of the cardinal factors that made them opt for other menstrual products; 60% of the participants depend on other additional products also during their cycle. Ten of the 45 users (22.2%) reported problems during the use of cups, which included dryness, local rashes and allergic reactions. Thirty-five of the users cleaned the cups with warm or boiling water; four used disinfectant solution to clean their menstrual cups. Among the 45 users, all except one agreed that they felt any economic advantage when switching to menstrual cups; 43 recommended it to others (Figure 2).

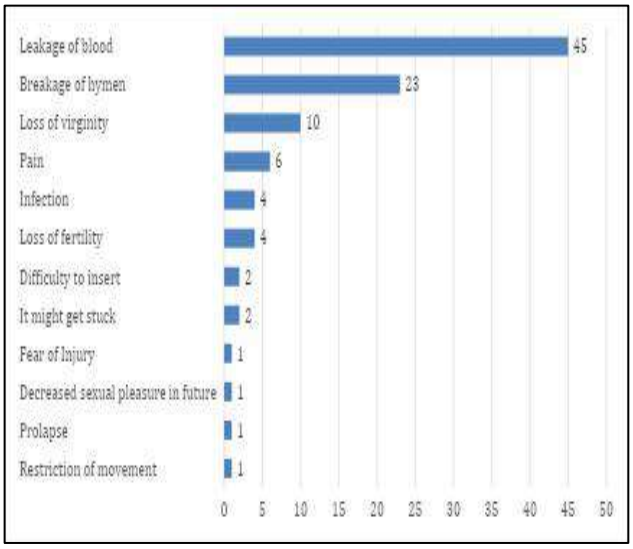


Figure 2: Concerns regarding use of menstrual cup.

DISCUSSION

This study assessed the knowledge, attitude and practice regarding menstrual cups among veterinary college students in central Kerala, India. Out of 177 study participants 84.7% demonstrated adequate knowledge regarding menstrual cups. Moreover, a significant proportion of respondents expressed positive attitudes towards the use of menstrual cups. However, concerns regarding leakage and injury to hymen were noted among some participants. Among the 45 students who used menstrual cups, initial challenges in insertion and removal were reported, but the ease of use improved over the subsequent cycles.

We compared our results with previous studies. A study by Ballal et al among women in the reproductive age group reported 82% of the participants had good knowledge about the menstrual cup; the respondents were predominantly from medical and paramedical backgrounds.[15] This aligns with our findings, where the academic setting may have contributed to higher awareness levels. In contrast, a similar study conducted among reproductive women in a rural tertiary care hospital reported a low percentage (5.8%) of the study population had good knowledge about the menstrual cup.[16] Similarly, Ali et al found that only 11.4% of the general population were aware of menstrual cups, highlighting the urban-rural divide in menstrual health awareness.[17]

Regarding safety perceptions, a study conducted among healthcare workers and students found that 62.5% thinks that menstrual cup as a safe device, whereas in our study, this was only 49.7%.[16] Interestingly, a study by Eti et al in Bangalore reported that 92.4% of the medical undergraduate students perceived menstrual cups to be safe.[18] This disparity may reflect variations in education levels, cultural perceptions, and exposure to menstrual health information. Leakage of menstrual blood is an important concern faced by most users. Bhat and Kakani reported leakage issues only in 6.6% of the participants, while the current study found significantly higher leakage concerns, with 42 out of 45 experiencing leakage in the initial use.[19]

Sociocultural factors also play an important role in adoption of menstrual cups. In a qualitative study among school-going adolescents in rural Nepal, possibility of ‘loss of virginity’ and fertility emerged as points of concern. About a third (37.3%) of the participants in our study expressed concerns about loss of virginity and breakage of hymen; religious and family restrictions were reported by 4.5% and 12.4% of participants, respectively. These findings underscore the need for targeted awareness programs addressing cultural taboos and misinformation surrounding menstrual cup use.

A few of our participants were males; the level of awareness was significantly lower when compared to females. Religion and marital status had no association with awareness. Other studies show similar results, with lower levels of awareness among males.[5,20] While menstrual hygiene primarily affects females, increasing awareness among young males is essential, given its relevance to half the population and its environmental impact.

This study highlighted the need for awareness programs within educational institutions to address misconceptions and to promote the use of menstrual cups as a sustainable menstrual hygiene product. Practical issues like leakage and difficulty in insertion and removal need to be addressed.

CONCLUSION

While the awareness levels are relatively high among our study population, significant challenges remain in terms of practical application and perception of safety. Addressing misconceptions through targeted educational interventions can enhance acceptance and usage of menstrual cups. Additionally, policy initiatives from the government to promote accessibility and affordability will further support sustainable menstrual health management.

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DERMATOLOGY

Brief Report

Quality of Life and Perceived Stress in Chronic Spontaneous Urticaria: Counting the Burden

Abstract

Background: Chronic spontaneous urticaria (CSU) is a dermatosis with a significant psychological component. Only a few studies have assessed the quality of life (QoL) and perceived stress in CSU patients. **Objectives:** To evaluate the QoL and perceived stress in patients with CSU. **Materials and Methods:** A cross-sectional study was done on 54 patients of CSU attending the Urticaria clinic of the Dermatology department in a tertiary care postgraduate teaching hospital in North Kerala. QoL in chronic urticaria was assessed using the Chronic Urticaria-Quality of Life (CU-QoL) questionnaire and perceived stress was assessed using the Perceived Stress Scale (PSS). **Results:** The mean scores of CU-QoL and PSS were 55.78 and 16.31, respectively. Out of 54 patients, 26 (48.1%) had mild impairment, 26 (48.1%) had moderate impairment, and 2 (3.7%) had severe impairment of QoL. Low stress was seen in 20 (37%) patients, moderate stress in 28 (51.9%), and six (11.1%) patients had high stress. **Conclusion:** This study shows that more than half of the patients with CSU had moderate to severe impairment of QoL and had moderate to severe stress.

Keywords: *Chronic spontaneous urticaria, chronic urticaria quality of life, perceived stress scale*

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Introduction

Quality of life (QoL) can be defined as an individual's satisfaction with life in domains that the subject considers to be important.[1] Chronic symptoms of urticaria have a detrimental effect on the daily activities and emotional wellbeing of the patient.[2] Stress plays a major role in the onset and exacerbation of chronic spontaneous urticaria (CSU). Moreover, the itch associated with chronic urticaria itself can be a source of distress to the patient and influence the QoL negatively.[3]

The studies on QoL in chronic urticaria in India have mostly used generic questionnaires like the Dermatology Life Quality Index (DLQI) which can be used for any skin disease. The Chronic Urticaria-Quality of Life (CU-QoL) questionnaire is a specific and valid tool that evaluates QoL in chronic urticaria patients. It is preferred over generic questionnaires as it picks up minor and clinically important disease-centric changes.[4]

Materials and Methods

A cross-sectional study was conducted on 54 CSU patients aged 15 years and above attending the Urticaria clinic of the Dermatology department in a tertiary care postgraduate teaching hospital in North Kerala from June 2018 to December 2020. Sample size (n) was calculated as 54 assuming mean CU- QoL to be 36 (standard deviation, SD = 22) from the previous study, allowable error (d) to be 6%, and alpha error (α) to be 5%.[1] Patients having other chronic diseases, mental illness, and patients who cannot read and comprehend the questionnaire were excluded from the study. Prior approval was obtained from the institutional ethics committee (Ref. No. GMCKKD/RP 2018/IEC/170). Written informed consent was taken from each patient. A specially designed proforma was used to collect data regarding patient demographics, history of disease, severity of disease, treatments taken, and clinical examination. The severity of the disease was estimated using Urticaria Activity Score (UAS-7) which involves daily assessment of wheals and pruritus

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over 1 week.[5] QoL in chronic urticaria was assessed using the CU-QoL questionnaire.[6] Perceived stress was assessed using the Perceived Stress Scale (PSS).[7] The questionnaires were translated into the regional language, and back translated to English, and appropriate modifications were made. The questionnaires were pilot-studied in 15 patients to ensure the reliability and validity.

Data collected from each patient was entered into a master chart. Coding of variables and analysis was done using IBM SPSS Statistics for Windows, Version 24.0. A categorical comparison was carried out using the Chi-square test and a *P* value below 0.05 was considered significant.

Results

The mean age of the study sample was 41.13 years. The demographic data of the study population is shown in Table 1. In the study, 19 (35.2%) patients had the disease for 5 years and more, 14 (25.9%) patients had the disease for 3 to 5 years, 13 (24.1%) patients had the disease for 1 to 3 years, and 8 (14.8%) patients had the disease for less than 1 year. Among the study participants, 23 (42.6%) patients had angioedema. Out of 54 respondents, 22 patients (40.7%) had severe disease, 22 (40.7%) had moderate disease, and 10 (18.5%) had mild disease.

Exacerbating factors were identified from the history in 39 (72.22%) patients. Twenty-seven patients (50%) had exacerbations following exposure to house dust and 22 (40.8%) had exacerbations with intake of food/food additives. The number of patients whose urticarial symptoms were exacerbated due to sweat, stress, drugs, sunlight, and pressure was 13 (24.1%), 10 (18.6%), 4 (7.5%), 3 (5.6%), and 1 (1.9%), respectively. More than one exacerbating factors were reported by 27 (50%) patients. Single exacerbating factor was reported by 12 (22.2%) patients. Systemic features were observed in 17 patients out of which 13 patients (24%) had headache, 4 (7.4%) had abdominal pain, 2 (3.7%) had syncope, 1 (1.9%) had fever, and 1 (1.9%) had wheeze associated with urticaria. All 54 patients had taken H1 antihistamines for treatment of chronic urticaria. Oral steroids were taken by 42 (77.8%) during flare-ups, autologous serum therapy by 12 (22.2%), H2 antihistamines by 6 (11.1%), and other treatment options like ayurveda and homeopathy by 1 (1.9%) patient.

Table 1: Demographic data of study population

Demographic variables	Categories	Number (percentage) of patients
Age (years)	15–25	6 (11.1%)
	26–35	12 (22.2%)
	36–45	17 (31.5%)
	46–55	11 (20.4%)
	56–65	8 (14.8%)
Gender	Male	21 (38.9%)
	Female	33 (61.1%)
Employment status	Employed	32 (59.3%)
	Unemployed	22 (40.7%)

The mean score of CU-QoL in the study was 55.78. Among the six domains, "impact on life activities" had the highest mean value of 15.78. Mean values for limits, sleep problems, looks, pruritus, and swelling were 9.94, 9.93, 9.59, 7.02, and 4.06, respectively. All patients enrolled in the study experienced impairment in QoL. CU-QoL was observed to have a statistically significant association with angioedema (P = 0.002), severity of illness (P = 0.002), and associated systemic features (P = 0.004).

The mean PSS score in the study was 16.31 with 20 (37%) patients having low stress, 28 (51.9%) having moderate stress, and 6 (11.1) having high stress. There was a statistically significant association between PSS and both angioedema (P = 0.031) and severity of illness (P = 0.010). The association between CU-QoL and PSS with angioedema and severity of urticaria is shown in Table 2.

Discussion

The mean age of patients in this study was 41.13 years which was comparable to previous studies.[1,2] Among this, 42.6% had angioedema, a pattern observed by other researchers as well.[8] Another study found a prevalence of 29% for urticaria with angioedema, 19% for urticaria without angioedema, and 8% for angioedema without urticaria.[9] The severity of disease as measured by UAS-7 score revealed that 40.7% of patients had severe and moderate disease consistent with the fact that studies in chronic urticaria have mostly included patients with moderate to severe disease.[3,10] The majority of the study sample (96.2%) had mild to moderate impairment of QoL with a mean CU-QoL score of 55.78. In the study by Choi *et al*.[8] using the CU-QoL questionnaire with 17 items grouped into four categories (urticarial symptoms, emotional stress, stigma, and food/environmental stress), the urticarial symptom domain had the lowest score and the stigma domain scored the highest. The mean CU-QoL score was 70.6 implying severe impairment of QoL. Another study using the Brazilian version of CU-QoL comprising 23 items that are divided into three dimensions (sleep/mental status/eating, pruritus/impact in daily activities, and limitations/appearance/edema) had a mean CU-QoL score of 36. Dimension 1 (sleep/mental status/eating) had the highest score. The mean score was highest for the item "nervousness" followed by " shame over lesions" and "pruritus" whereas in our study, " impact on life activities" was the domain with the highest mean value (15.78) followed by " limits" (9.94) and sleep problems (9.93).[1]

The present study revealed a statistically significant association between the presence of angioedema

Table 2: Association between CU-QoL and PSS with angioedema and severity of urticaria

Variables	Category	Number (percentage) of patients in each category	Angioedema	"*P*"	Severity of urticaria			"*P*"
					Mild	Moderate	Severe	
CU-QoL*	Mild	26 (48.1%)	5 (21.7%)	0.002	9 (90%)	14 (63.6%)	3 (13.6%)	0.002
	Moderate	26 (48.1%)	16 (69.6%)		1 (10%)	8 (36.4%)	17 (77.3%)	
	Severe	2 (3.7%)	2 (8.7%)		0	0	2 (9.1%)	
PSS†	Low stress	20 (37%)	4 (17.4%)	0.031	7 (70%)	10 (45.5%)	3 (13.6%)	0.010
	Moderate stress	28 (51.9%)	15 (65.2%)		3 (30%)	11 (50%)	14 (63.6%)	
	High stress	6 (11.1%)	4 (17.4%)		0	1 (4.5%)	5 (22.7%)	

*CU-QoL - Chronic urticaria-quality of life. †PSS - Perceived stress scale

and the worsening of the QoL in chronic urticaria patients ($P = 0.002$) consistent with previous researches.[8,11] Similarly, there was a significant association between the severity of disease and CU-QoL ($P = 0.002$) which could be possibly due to the fact that disease severity can have a direct effect on factors like sleep, concentration and performance at work, leisure time, and appearance; impacting the QoL of the patient. Such an association was documented by other researchers as well.[3,12] According to some studies, women tend to be more sensitive and aware of the symptoms of urticaria and are more severely influenced by changes in appearance compared to men.[1] However, our study did not reveal any significant difference of association of impact of gender on QoL. In the study by Dias GAC, a greater impact was observed in all dimensions of CU-QoL in women, though the association was not statistically significant.[1] In another study using DLQI, women with chronic urticaria were found to be more affected than men in domains like daily activities, vitality, emotional role, and mental health.[13] According to several other studies, middle-aged people suffered a worse impact on QoL, particularly in aspects of sleep, mental status, and eating. Since this age group comprises individuals at the peak of their professional lives, any disruption in sleep and mental state can profoundly limit their work efficiency.[1] Nevertheless, no significant association was observed between age and QoL in this study. Duration of illness did not seem to play a significant role in QoL in our study. The study using DLQI though, could identify a statistically significant difference with patients having a disease duration of up to one year having poorer QoL scores in domains of leisure and personal relationships.[13]

The level of perceived stress was mild to moderate in the majority (88.9%) of the sample in the present study with a mean PSS score of 16.31. It had been observed that patients with CSU had higher levels of life event stress and perceived stress. Besides, urticaria, apart from being precipitated and exacerbated by stress, can itself be a major cause of stress.[12] In the study by Chung *et al*.,[14] the mean PSS score in chronic idiopathic urticaria was 25.51, and PSS score in patients with chronic idiopathic urticaria was higher than the same noted in patients with allergies.

Limitations

Limitations of our study were a small sample size, single-center design, absence of a control group, bias associated with questionnaires like translation and recall bias, and no engagement of advanced statistical analysis. Since our study was conducted in a tertiary care center, the results cannot be reflected onto the general population.

Conclusion

Patients with a greater severity of disease and angioedema suffer greater disability in terms of QoL and perceived stress in chronic urticaria with specific variables contributing to a negative impact on QoL. This highlights the importance of a multidimensional assessment of QoL in chronic urticaria with important implications for adjunctive stress management approaches in the treatment of chronic urticaria.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Varied presentations of primary cutaneous lymphoma: A case series from a tertiary care center in South India

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Abstract

Background: Recent studies indicate an upsurge of primary cutaneous lymphoma (PCL) in the Indian population. Of late, we too have come across varied presentations of PCL in relatively younger individuals. Hence, we decided to study the clinical and immunohistological profile of patients with PCL in our department.

Methods: All cases diagnosed as PCL from October 2016 to October 2019 were included. Clinical details, complete blood count, peripheral smear, imaging, histopathology, and immunohistochemistry of skin specimens were analyzed. Lymph node biopsy and bone marrow studies were done in most cases. Human T lymphotropic virus-1 (HTLV1) serology was done in 10 cases.

Results: Of the 24 patients with PCL, 12 were below 50 years of age. Twenty-three patients (95.8%) had T-cell lymphoma and only one had B-cell PCL. Mycosis fungoides (MF) (n = 17; 71%) was the most common type of PCL. There were two (8.3%) cases each of adult T-cell lymphoma/leukemia (ATLL) and Sezary syndrome. MF had varied clinical morphology at presentation and variable clinical outcomes. Both cases of ATLL had features of immunosuppression in the form of infective dermatoses.

Conclusion: We observed an increased proportion of T-cell type of PCL, with the age of onset being relatively early. HTLV-1 positivity was noted in three out of the 10 cases tested. More studies are needed to determine the factors responsible for the younger age of onset of PCL and the role of HTLV-1 infection in the development of PCL.

Keywords:
Adult T-cell Lymphoma/Leukemia, HTLV-1, mycosis fungoides, mycosis fungoides with large cell transformation, primary cutaneous lymphoma

Introduction

Primary cutaneous lymphoma (PCL) is a group of extranodal non-Hodgkins lymphoma (NHL) characterized by clonal proliferation of atypical T or B lymphocytes and less commonly of natural killer cells or plasmacytoid dendritic cells.[1] They do not show evidence of non-dermatologic origin at the time of diagnosis.[2] They form the second most common group of extranodal NHL, the first being gastric lymphomas. The 2018 World Health Organization (WHO)–European Organization of Research and Treatment of Cancer (EORTC) classification of cutaneous lymphomas broadly classifies them into T-cell and B-cell types. PCL has

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also been classified based on clinical, pathological, immunopathological, molecular, and cytogenetic findings. Unlike other extranodal lymphomas, T-cell lymphomas form the majority of PCL. Mycosis fungoides (MF), the most common type of primary cutaneous T-cell lymphoma (CTCL), is characterized by distinct clinicopathologic features, but is closely related to other subtypes of CTCL, like Sezary syndrome (SS) and adult T-cell lymphoma/leukemia (ATLL).

Various studies have shown that the site of origin, rather than the tumor morphology of extranodal lymphoma, determines their clinical behavior, prognosis, and appropriate therapeutic approach. The WHO–EORTC classification is based on the site of origin. We report a 3-year retrospective case series of PCL from a tertiary care center in South India. This retrospective study aims to analyze the clinical and immunopathological profile of these cases.

Methods

After obtaining ethical clearance, clinical records of all cases diagnosed as PCL between October 2016 and October 2019 were scrutinized. Clinical details such as age at the time of diagnosis, gender, duration of illness, presence of pruritus or any other symptom, family history of any malignancy, morphological type and distribution of cutaneous lesions, and the presence of lymphadenopathy and hepatosplenomegaly were collected for all cases. Details of treatment and outcome, if available, were collected. Histopathologic examination (HPE) and immunohistochemical (IHC) examination of skin specimens, hemogram, peripheral blood smear, renal and liver function tests, urinalysis, chest X-ray, ultrasonogram of abdomen, and estimation of serum calcium and lactate dehydrogenase (LDH) levels were done in all patients. Bone marrow studies and fine needle aspiration cytology (FNAC) and histopathology of lymph node were done in relevant cases. Due to financial constraints, human T lymphotropic virus-1 (HTLV-1) testing by enzyme-linked immunosorbent assay (ELISA) method was done in 10 cases only. Based on the clinical features and investigations, patients were categorized into an appropriate type of lymphoma according to the WHO-EORTC classification. MF was diagnosed based on the diagnostic algorithm proposed by the International Society for Cutaneous Lymphoma (ISCL).[3] Patients with erythroderma, peripheral lymphadenopathy, and atypical mononuclear cells (Sezary cells) more than 20% of the total lymphocyte count or a total Sezary count of more than 1000 × 10^9/L were diagnosed with SS. Those patients presenting with nodular skin lesions without any extracutaneous involvement and immunohistopathology demonstrating majority of the infiltrate as CD30+ tumor cells were diagnosed as primary cutaneous CD30+ anaplastic large cell lymphoma (ALCL). Patients with diffuse atypical lymphocytic infiltrate restricted to and extending throughout the subcutis without epidermotropism were classified as subcutaneous panniculitis-like T-cell lymphoma (SPTCL). Patients with MF-like presentation and immunohistochemical (IHC) demonstrating CD25+ cells with positive HTLV-1 infection were diagnosed as ATLL. MF and SS were staged based on ISCL/EORTC revision to the classification of MF/SS.[4] PCLs other than MF/SS were staged according to the ISCL/EORTC proposal on tumors, nodes and metastases (TNM) classification of non-MF/SS PCL.[5]

Results

There were 24 patients diagnosed with PCL. Twenty-three (95.8%) had T-cell PCL. There was only one case of B-cell PCL in our series. MF was the most common type of PCL (*n* = 17; 71%). There were two (8.3%) cases each of ATLL and SS. We also had one (4.2%) case each of CD30+ALCL, SPTCL, and diffuse large B-cell lymphoma-leg type (DLBCL-LT).

Age of the patients ranged from 18 to 82 years [Table 1]. Twelve (50%) patients were aged less than 50 years. They included nine cases of MF, two cases of ATLL, and one case of SPTCL. Majority (58.3%) of the PCL cases were men (M:F = 1.4:1) [Table 2]. MF was more (58.8%) among men.

Mycosis fungoides

Majority (53%) of the cases of MF presented before 50 years of age. The youngest patient was a 19-year-old man with hypopigmented MF

Table 1: Age distribution of patients (*n*=24) with primary cutaneous lymphoma

Age (years)	MF	ATLL	SS	CD30+ALCL	SPTCL	DLBCL	Total
<30	1	-	-	-	-	-	1
31-40	4	2	-	-	1	-	7
41-50	4	-	-	-	-	-	4
51-60	2	-	-	1	-	-	3
61-70	6	-	-	-	-	-	6
71-80	-	-	1	-	-	-	1
>80	-	-	1	-	-	1	2
Total	17	2	2	1	1	1	24

ALCL=anaplastic large cell lymphoma, ATLL=adult T-cell lymphoma/leukemia, DLBCL=diffuse large B-cell lymphoma, MF=mycosis fungoides, SPTCL=subcutaneous panniculitis-like T-cell lymphoma, SS=Sezary syndrome

and the oldest was aged 69 years presented with erythematous plaques on the face. Twelve (70.6%) patients had a single type of skin lesion. Psoriasiform MF was the most common (n = 10; 58.8%) type in our series [Table 3]. The other morphological types observed were hypopigmented MF (n = 4; 23.5%), erythrodermic MF (n = 2; 11.8%), and poikilodermatous MF (n = 1; 5.9%) [Figure 1a–c].

Table 2: Gender distribution of patients (n=24) with primary cutaneous lymphoma

	Men	Women
Total (24)	14	10
MF (n=17)	10	7
ATLL (n=2)	1	1
SS (n=2)	2	-
CD30+ALCL	1	-
SPTCL (n=1)	-	1
DLBCL (n=1)	-	1

ALCL=anaplastic large cell lymphoma, ATLL=adult T-cell lymphoma/leukemia, DLBCL=diffuse large B-cell lymphoma, MF=mycosis fungoides, SPTCL=subcutaneous panniculitis-like T-cell lymphoma, SS=Sezary syndrome

The patient with poikilodermatous MF developed large cell transformation later and expired within 6 months. Trunk was the most common site involved in MF. One patient with hypopigmented MF developed epidermodysplasia verruciformis-like lesions and palmar warts. She was later found to be positive for HTLV-1, but had no other features of ATLL.

The most common histopathologic findings in MF were hyperkeratosis (n = 16; 94.1%) and acanthosis (n = 16; 94.1%) [Table 4]. Majority showed epidermotropism (n = 13; 76.5%). Pautrier microabscess was seen in seven (41.2%) cases [Figure 1d]. The seven (41.2%) patients had atypical T-cell infiltrates in both papillary and reticular dermis. The infiltrate was perivascular in seven (41.2%) and periappendageal in four (23.5%) patients.

All cases of MF showed CD3 positivity [Figure 1e]. CD4 positivity was seen in 12 (70.6%) cases [Table 5]. All four cases of hypopigmented MF showed CD8 positivity, and a case of MF with

Table 3: Morphological features in different types of cutaneous lymphomas

Morphological features	MF (n=17)	ATLL (n=2)	SS (n=2)	CD30+ALCL (n=1)	SPTCL (n=1)	DLBCL (n=1)	Total
Macules only	4	-	-	-	-	-	4
Papules only	-	1	-	-	-	-	1
Plaques only	5	-	-	-	-	-	5
Macules and plaques	4	-	-	-	-	-	4
Plaques and nodules	-	1	-	-	1	1	3
Plaques or nodules with ulceration	2	-	-	1	-	-	3
Erythroderma	2	-	2	-	-	-	4

ALCL=anaplastic large cell lymphoma, ATLL=adult T-cell lymphoma/leukemia, DLBCL=diffuse large B-cell lymphoma, MF=mycosis fungoides, SPTCL=subcutaneous panniculitis-like T-cell lymphoma, SS=Sezary syndrome

Table 4: Histopathologic features of primary cutaneous lymphomas

Histopathologic features	MF (n=17)	ATLL (n=2)	SS (n=2)	CD30+ALCL (n=1)	SPTCL (n=1)	DLBCL (n=1)
Hyperkeratosis	16	1	2	1	-	-
Parakeratosis	12	1	2	1	-	-
Acanthosis	16	-	1	1	-	-
Epidermotropism	13	2	2	-	-	-
Pautrier microabscess	7	1	-	-	-	-
Infiltrate						
Diffuse	3	2	2	1	1	1
Nodular	3	-	-	-	-	-
Perivascular	7	-	-	-	1	-
Periappendageal	4	-	-	-	-	-
Extent of infiltrate						
Papillary dermis only	5	-	2	-	-	-
Papillary and reticular dermis	7	2	-	1	-	-
Reticular dermis and subcutaneous	2	-	-	-	-	-
Papillary and reticular dermis and subcutaneous	1		-	-	1	1

ALCL=anaplastic large cell lymphoma, ATLL=adult T-cell lymphoma/leukemia, DLBCL=diffuse large B-cell lymphoma, MF=mycosis fungoides, SPTCL=subcutaneous panniculitis-like T-cell lymphoma, SS=Sezary syndrome

large cell transformation showed CD30 positivity. The mean LDH was 526.1 units/L (normal = 140–280). All patients with hypopigmented MF had normal LDH levels.

Majority (10 out of 17) of the patients with MF came under Stage I. Of these, three were included in Stage IA and seven in Stage IB. There were three patients with Stage IIA MF and two patients with Stage IIB MF. The two patients with erythrodermic MF who did not meet the criteria for SS were classified as Stage IIIA.

Patients with MF (n = 10) with limited skin involvement were treated with narrowband-ultraviolet B radiation (NB-UVB) phototherapy (n = 8) and Psoralen plus ultraviolet A radiation (PUVA) therapy (n = 2) along with topical steroids. All four patients with hypopigmented MF were treated with NB-UVB phototherapy and showed very good response to it. The two patients with erythrodermic MF were managed with total skin electron beam therapy and phototherapy along with systemic chemotherapeutic agents like methotrexate and gemcitabine. The case with large cell transformation had undergone chemotherapy followed by bone marrow transplantation, but relapsed and succumbed to illness within 6 months of bone marrow transplantation.

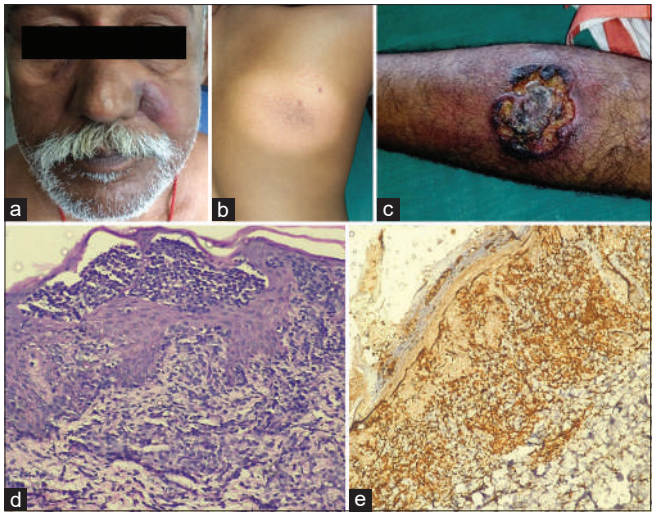


Figure 1: (a) Erythematous plaque on the face of an elderly man with MF. (b) Large hypopigmented patch with the center showing erythema and scaling on the back of a young man with hypopigmented MF. (c) MF presenting as an ulcerated plaque on the lower limb. (d) Epidermotropism with Pautrier microabscess (H and E, ×400). (e) IHC of MF with atypical lymphocytes expressing CD3 positivity (×200). H and E = hematoxylin and eosin, IHC = immunohistochemical, MF = mycosis fungoides

Sezary syndrome

The two cases of SS were men aged 80 and 82 years. Both of them presented as erythroderma

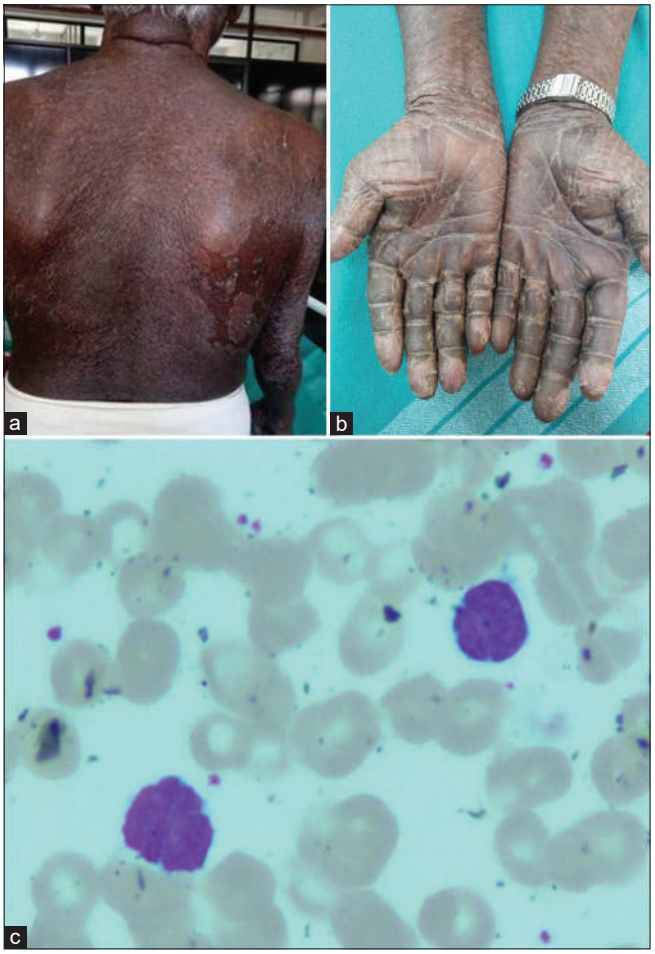


Figure 2: (a) Erythroderma with generalized pruritus and scaling in an elderly man with Sezary syndrome. (b) Painful fissured keratoderma of palms in the same patient. (c) Sezary cells in peripheral smear (H and E, ×100). H and E = hematoxylin and eosin

Table 5: Immunohistochemical features of primary cutaneous lymphoma

Immunohistochemical features	CD3	CD4	CD7	CD8	CD20	CD25	CD30	CD56
MF (n=17)	17	12	-	9	-	-	1	-
ATLL (n=2)	2	2	-	-	-	2	-	1
SS (n=2)	2			-	-	-	-	-
CD30+ALCL (n=1)	-	1	-	-	-	-	1	-
SPTCL (n=1)	1	-	-	1	-	-	-	-
DLBCL (n=1)	-	-	-	-	1	-	-	-

ALCL=CD30+anaplastic large cell lymphoma, ATLL=adult T-cell lymphoma/leukemia, DLBCL=diffuse large B-cell lymphoma, MF=mycosis fungoides, SPTCL=subcutaneous panniculitis-like T-cell lymphoma, SS=Sezary syndrome

and had severe pruritus [Figure 2a]. One of them had depigmented macules, generalized hyperpigmentation, and also extensive dermatophytosis during presentation. Both patients had painful and fissured palmoplantar keratoderma [Figure 2b]. HPE showed atypical cells in a band-like arrangement at a dermo-epidermal junction with no significant epidermotropism. IHC was positive for CD3 and negative for CD20. Serum LDH was markedly elevated (>1000 units/L). Peripheral smear showed Sezary cells and eosinophilia [Figure 2c]. Both cases had significant generalized lymphadenopathy without any visceral organ involvement, and hence were classified under Stage IVA1. One patient was treated initially with daunorubicin, vincristine, and cytarabine. While on maintenance chemotherapy with 6-mercaptopurine and methotrexate, he had a relapse of disease with nodules on the face and was later treated with gemcitabine and oxaliplatin (GEMOX) regimen and went into remission. The other patient died soon after diagnosis, though the exact cause of death could not be ascertained.

Adult T-cell lymphoma/leukemia

There were two cases of ATLL: a 32-year-old man had chronic ATLL and a 30-year-old woman had acute ATLL. The latter had infiltrated papules and plaques on extremities and upper back. She also had extensive tinea corporis and recalcitrant genital warts. The man presented with pruritic papules, nodules, and plaques predominantly involving photo-exposed sites for 3 years and later progressed to acute ATLL [Figure 3a]. He had generalized lymphadenopathy, extensive dermatophytosis, and scabies [Figure 3b and c]. Histopathology of both cases was similar to MF with hyperkeratosis, parakeratosis, epidermotropism, and Pautrier microabscess. CD3, CD4, and CD25 were positive on IHC. One patient had CD56 positivity also [Table 5]. Mean LDH was 1228 units/L (±622.3). Anti-HTLV-1 antibody was positive and peripheral smear showed atypical lymphocytes with flower cell nuclear morphology in both patients [Figure 3d]. Both patients had an advanced stage of disease ($T_{3b}N_2M_1$ and $T_{3b}N_3M_1$, respectively) and succumbed to their disease within 1 year of diagnosis, in spite of receiving chemotherapy.



Figure 3: (a) Multiple erythematous and skin-colored infiltrated papules on the face in a man with ATLL. (b) Extensive tinea corporis in the same patient. (c) Scabies in the same patient. (d) Flower cells in peripheral smear in ATLL (H and E, ×100). ATLL = adult T-cell lymphoma/leukemia, H and E = hematoxylin and eosin

CD30+ ALCL

A 55-year-old man who presented with recurrent ulcerated nodules on the trunk of 2-years duration had CD30+ ALCL. HPE showed large, atypical lymphocytes, which expressed mainly CD30 and were negative for anaplastic lymphoma kinase (ALK). His treatment details could not be obtained as he was lost to follow-up.

Subcutaneous panniculitis-like T-cell lymphoma

A 33-year-old woman who was diagnosed with SPTCL presented with multiple indurated plaques on the face, scalp, chest, abdomen, and arms, mimicking lupus panniculitis [Figure 4a]. HPE showed lobular panniculitis with infiltration by atypical

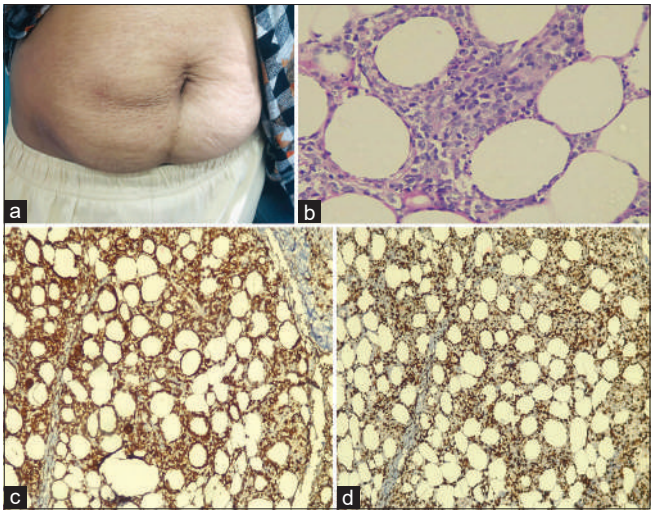


Figure 4: (a) Depressed plaque on the right side of abdomen with peau d'orange appearance in a patient with SPTCL. (b) Atypical lymphocytes in the subcutaneous tissue rimming individual adipocytes (H and E, ×400). (c) IHC of SPTCL showing CD4 positivity (×200). (d) IHC of lymphoma cells showing high Ki67 index (×200). H and E = hematoxylin and eosin, IHC = immunohistochemical, SPTCL = subcutaneous panniculitis-like T-cell lymphoma

lymphocytes surrounding adipocytes [Figure 4b]. The neoplastic cells were CD4 positive with high Ki67 [Figure 4c and d]. She was having an early disease stage ($T_{2b}N_0M_0$) and responded well to six cycles of chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) and was in remission.

Diffuse large B-cell lymphoma

The patient with diffuse large B-cell lymphoma (DLBL) was an 82-year-old woman who presented with erythematous nodules on the lower limbs. We could not get any evidence of extracutaneous disease even after 6 months of initial diagnosis, and it was classified as $T_{2a}N_0M_0$ stage. HPE showed a dense infiltrate of large, atypical lymphocytes with enlarged nuclei and prominent nucleoli in the lower dermis and subcutaneous tissue. IHC revealed positivity for CD20 and Bcl-2. Hence, we made a diagnosis of DLBL-LT. She was treated with Rituximab-CHOP (R-CHOP).

Discussion

Majority (95.8%) of cutaneous lymphomas in our series were of T-cell type. This is similar to several previous hospital-based reports from India.[1,6,7] The low frequency of primary cutaneous B-cell lymphoma in our series was in concordance with studies from other Asian countries like China and Iran.[8,9] But some other reports from Japan, Korea, USA, and certain western countries show the prevalence of B-cell lymphoma to be higher (20%-30%), though it is less common than T-cell lymphoma.[10-12]

There was a bimodal age peak in our series: the first between 31 and 40 years and the second between 61 and 70 years. Half of the patients were less than 50 years of age. A similar trend was reported in some recent studies from India, Korea, and Iran.[1,8,13] In our study, 9/17 (52.9%) cases of MF and all cases of ATLL and SPTCL were below 50 years of age. In 2009, Bradford *et al*.[10] from the USA reported that CTCL showed an exponential increase with age, with a peak around 80 years. A younger age peak in our series could reflect a changing epidemiology of the disease, favoring younger persons, or could be due to earlier diagnosis due to advances in investigation methods. As in previous studies, preponderance of men was noted in our study as well.[1,6] MF was seen more among men, similar to previous reports from India.[1,6] SS was observed exclusively in older men.

In our study, MF was the most common type of PCL (71%). Though 8.3% of patients each had SS and ATLL, it may be premature to conclude that these conditions are more frequent in our population, as this was a short case series. Interestingly, Khader *et al*.[1] from Calicut, which is only about 100 km away from our center, had reported a frequency of 17.1% (6/35) of ATLL in their case series. One woman patient with hypopigmented MF in our study had developed epidermodysplasia verruciformis-like presentation while on phototherapy, with the development of palmar warts and tinea versicolor-like lesions. On further evaluation, she was found to be HTLV-1 positive, but had no other features of ATLL. Though provisionally placed in the group of MF, she is being followed up for possible evolution to ATLL.

Similar to a few other studies from Asia, our series had a relatively high frequency of hypopigmented MF (24%).[1,8,9] Patients with hypopigmented MF were comparatively young.[1,14] The frequency of hypopigmented MF in Caucasian studies is less compared to ours. Some studies report a mixed clinical pattern with areas of erythema within hypopigmented patches.[13] All cases of hypopigmented MF had a very good prognosis in our series. All of them achieved complete remission with NB-UVB phototherapy alone, with no history of relapse till date. In a study on hypopigmented MF by Kanokrungsee *et al*.,[15] 7/11 patients had complete remission with NB-UVB twice weekly and 4/11 had partial remission. Three of them had relapsed after a mean of 10 months. Wongpraparut *et al*.[16] reported that 4/6 patients with hypopigmented MF treated with NB-UVB relapsed within 2 months to 6 years. A study in Egyptian patients with hypopigmented MF showed 86.7% response with phototherapy, 66.7% response with NB-UVB, and 80% response with PUVA.[17]

Another patient with MF later developed large cell transformation with CD30 positivity. This can occur in 20%–50% of advanced MF.[18] MF with CD30+ large cell transformation should be differentiated from other CD30+ lymphoproliferative disorders like primary cutaneous CD30+ ALCL, lymphomatoid papulosis (LyP), and borderline cases, as the treatment outcome varies a lot among them. Primary cutaneous CD30+ ALCL and LyP usually have an excellent outcome. One of our patients with MF deteriorated fast and succumbed to the disease after she developed large cell transformation. Previous studies have shown that MF with CD30+ large cell transformation has a poor prognosis, with a 5-year survival of 28.6%–44.4%.[19,20] MF with coexisting LyP is found in 3% of MF patients and these patients have a favorable prognosis.[21-25] Early large cell transformation in MF (<2 years from the diagnosis of MF), more advanced disease at the time of transformation (Stage IIB–IV), older age (≥60 years), and extracutaneous spread were associated with poor outcomes.[20,26]

Clinicopathologic features of ATLL are often similar to those of MF. Hence, the demonstration of flower cells on peripheral smear and HTLV-1 positivity are mandatory to diagnose ATLL. Mean LDH values were higher in ATLL group than the MF group in our study. Patients with ATLL in our series had a relatively poor prognosis compared to those with MF. HTLV-1 infection is endemic in Japan, the West Indies, and Central Africa. There are some studies showing presence of HTLV-1 infection in India too.[1,27,28] Routine screening for HTLV-1 may be warranted in all cases of suspected cutaneous lymphoma.

We had a relatively higher frequency of SS cases (8%) than that reported in a recent study from South India (5%).[1] Elderly patients with erythroderma should always be evaluated for SS, as many such cases can be missed and managed as primary erythroderma or atopic dermatitis. Repeated cutaneous biopsies and peripheral smear examination should be performed in those cases.

We had just one case of CD30+ ALCL during our study period, which was much lower when compared to previous studies from Asia.[29] A lower frequency of CD30+ALCL was seen in a recent study from India.[1] In our study, the frequency of SPTCL was similar to what is reported in several Asian studies.[29-31] The frequency of SPTCL reported from western countries is less than ours.[13,32,33] SPTCL primarily involves subcutaneous fat tissue with infiltrate composed of CD8+ and cytotoxic T cells with high Ki67 index.

The relatively small number of cases and the inability to do serological testing for HTLV, complete panel of lymphocyte markers, and gene rearrangement studies in all cases due to financial constraints are some limitations of this study. Also, it is difficult to make definite conclusion on the trends about the disease in the general population as the study was conducted in a tertiary care hospital. However, our study indicates an increased frequency of T-cell type of PCL in younger age group. We also noticed several patients with HTLV-1 positivity in our series. More population-based studies with larger sample size are needed to determine the factors responsible for younger age of onset of PCL and the role of HTLV-1 infection in the development of PCL among our population.

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Conflicts of interest

There are no conflicts of interest.

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Dermoscopy of Congenital Hemidysplasia with Ichthyosiform Erythroderma and Limb Defects Nevus with Unilateral Limb Defects

Abstract

Here, we report the dermoscopic findings of congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) nevus with left-sided ichthyosiform erythroderma and left upper-limb aplasia in a 4-month-old baby. The presence of ptychotropism and strict midline demarcation are unique features described in CHILD nevus. Dermoscopy of the CHILD nevus showed linear and dotted vessels with yellowish waxy scales on a pink background. These characteristic dermoscopic findings would also help us to differentiate it from inflammatory linear verrucous epidermal nevus.

Keywords: *Congenital hemidysplasia with ichthyosiform erythroderma and limb defects syndrome, dermoscopy, ptychotropism*

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Introduction

Congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) is a rare X-linked dominant disorder, characterized by unilateral ichthyosiform nevi with a distinct lateralization pattern and strict midline demarcation, as well as an ipsilateral skeletal defect in the form of limb hypoplasia or aplasia.[1] The term CHILD nevus was proposed by Happle *et al*. in the year 1980 due to the unique features distinguishing it from inflammatory linear verrucous epidermal nevus (ILVEN).[1] Here, we report the dermoscopic findings of CHILD nevus with left-sided ichthyosiform erythroderma and left upper-limb aplasia in a 4-month-old baby.

Case Report

A 4-month-old female child, firstborn of a nonconsanguineous marriage, presented with redness and scaling on the left half of the body with complete absence of the left upper limb since birth. There was no history of drug intake or previous miscarriages or abortions in her mother. There was no history of similar illnesses or any other genetic diseases in the family.

On examination, there was a linear erythematous plaque with coarse waxy scales involving the entire left side of the trunk with clear midline demarcation extending to involve the left groin, pubic area, and whole of the left lower limb, with complete sparing of the face [Figure 1a]. There was hypoplasia of the lateral four toes with nail dystrophy [Figure 1b]. The left labia majora showed hypertrophy. Ptychotropism was present in the form of involvement of the vulva and groin on the left side [Figure 1c]. Systemic examination was normal.

Dermoscopy showed linear and dotted blood vessels and large coarse yellowish waxy scales with a pink background [Figure 2a].

Histopathology showed psoriasiform hyperplasia with acanthosis and regular elongation of rete pegs, with few dilated vessels and moderate lymphocytic inflammatory infiltrate in the dermis [Figure 2b].

All routine investigations, echocardiogram, neurosonogram, and ultrasonogram of the abdomen were normal. X-ray whole body showed the absence of the left upper limb [Figure 2c]. ENT and ophthalmology evaluation were normal.

Due to financial constraints, genetic evaluation could not be done. Based on the clinical, histopathological, and radiological evidence, a diagnosis of CHILD syndrome was made. The child was treated with topical emollients and is on follow-up.

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Figure 1: (a) Large erythematous scaly plaque with midline demarcation involving the left half of the body sparing the face with complete absence of the left upper limb. (b) Nail dystrophy and hypoplasia of toes. (c) Ptychotropism with vulval hypertrophy of the left labia majora

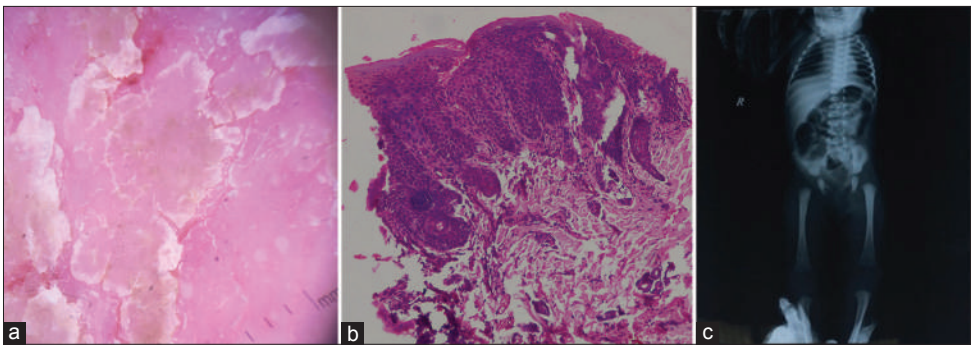


Figure 2: (a) On dermoscopy, linear and dotted blood vessels and large coarse waxy yellowish scales with a pink background (DermLite DL3N). (b) Psoriasiform hyperplasia with acanthosis and regular elongation of rete pegs, with few dilated vessels and moderate lymphocytic inflammatory infiltrate in the dermis (hematoxylin- and eosin-stained section under ×100). (c) X-ray showing absence of the left upper limb

Discussion

CHILD syndrome is due to a mutation in the NAD(P)H steroid dehydrogenase-like protein gene on chromosome Xq28, which encodes for 3-beta-hydroxysteroid dehydrogenase enzyme essential for cholesterol synthesis. Cholesterol deficiency will lead to the accumulation of toxic steroid precursors that will result in cutaneous manifestations in CHILD syndrome. Cholesterol and its precursors are required for the regulation of the sonic hedgehog pathway for skeletal development and its deficiency results in skeletal defects. Mosaicism due to lyonization leads to patchy distribution in CHILD syndrome.[2] In addition to NSDHL gene, emopamil-binding protein gene is also involved in cholesterol biosynthesis, which was initially implicated in CHILD syndrome, and later disproved by König *et al*.[3]

CHILD nevus has to be differentiated from ILVEN as skeletal defects can occur in epidermal nevus syndrome. Presence of ipsilateral skin lesions with clear midline demarcation, ipsilateral skeletal defects and ptychotropism (involvment of body folds) are unique features of CHILD nevus that differentiate it from ILVEN. Histology of CHILD nevus is unique if foamy histiocytes can be seen in the dermis.[4] However, in our case, histopathological features were similar to ILVEN.

Dermoscopy, in our case, showed linear and dotted vessels and yellowish coarse waxy scales on a pink background, whereas dermoscopy of ILVEN shows alternating brown and red glomerular structures over a white background.[5] Other patterns described in ILVEN include cobblestone pattern, cerebriform pattern, and large brown circle.[6] The waxy yellowish scales along with vascular structures over a pink background are possibly unique to CHILD nevus. More studies on ILVEN and CHILD nevus would help us to determine the characteristic dermoscopic patterns differentiating them.

We have advised the patient to use mild cleansers and topical emollients containing ceramides frequently. Topical agents like 2% simvastatin and lovastatin have shown good clinical responses for skin lesions in CHILD syndrome.[7]

The other unique feature of this case is the extensive left-sided involvement of the CHILD nevus. Left-sided involvement is rare[8] and is usually associated with severe visceral anomalies. Our baby presented with left-sided involvement without visceral anomalies.

Declaration of patient consent

The authors certify that they have obtained all appropriate consent forms, duly signed by the parent(s)/guardian(s) of the patient. In the form, the parent(s)/guardian(s) has/have given his/her/their consent for the images and other clinical information of their child to be reported in the journal. The parents understand that the names and initials of their child/children will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Assessment of knowledge regarding sexually transmitted infections among high school students in an educational sub-district in Southern India—A cross-sectional study

Dear Editor,

Sexually transmitted infections (STIs) constitute a challenging health problem among youngsters.[1] According to the World Health Organization (WHO), 20% of persons living with HIV/AIDS are in their 20s. Only a few studies have assessed the level of knowledge about STIs among adolescents.[2,3]

We did a cross-sectional study among 8th, 9th and 10th standard students attending various public and private schools in an educational sub-district in Thrissur, Kerala, with the objective of estimating the level of knowledge about STIs among high school students and their relationship with various socio-demographic parameters after obtaining ethics clearance.

One school each belonging to government, government aided, private and CBSE boards was chosen by the lottery method. Study participants were chosen using multistage stratified random sampling. Divisions from each grade were again chosen by the lottery method. Sample size was calculated based on the proportion of poor knowledge of STI (19.1%) obtained from the previous study and with 95% confidence and 20% allowable error.[2] Sample size obtained was 510. A total of 526 students were recruited over a period of 1 year.

A self-administered questionnaire, prepared by us based on a reference questionnaire, was used as the study tool. Some selected questions from the reference questionnaire were used and few additional questions were added with the help of experts. For the pilot study, we used 50 samples but 10 samples were lost to follow-up. Cronbach's alpha was used to check the reliability of the questionnaire. It showed an alpha value of 0.821 (good internal consistency). Test–retest reliability was assessed every 2 weeks using the Spearman rank correlation coefficient (0.968, a high correlation).

The questionnaire had 9 questions and questions 6, 7, 8 and 9 were given a score of 2 for each correct answer and 1 for each wrong answer. Total score of 36 was divided into 3 parts and a score less than 12 was considered to be poor, a score between 12 and 24 was considered fair and a score more than 24 was considered good knowledge. Because the frequency of students having good knowledge was low, we combined fair and good knowledge into one category for further analysis. Thus, those who scored 12 or less were considered as having poor knowledge and those who scored more than 12 as having good knowledge.

The distribution of our study participants is depicted in Figure 1. The age of the students ranged from 12 to 18 years (mean=15±2.16). Boys outnumbered girls (M:F = 1.4:1). Public talks [439, (83.5%)], posters [420, (79.8%)] and hospital and health workers [382, (72.6%)] were identified to be the common sources of information regarding STIs [Figure 2]. Majority [(n=455(86.5%)] of the students identified HIV/AIDS as an STI [Figure 3]. However, only less than 25% of students were aware of the other STIs like syphilis, gonorrhoea, herpes simplex infections, trichomoniasis and chlamydia. We observed notable misconceptions among students that STI can be transmitted by coughing/sneezing [n = 222(42.2.0%)], sharing of toilets [n = 71 (13.5%)] and sharing of plates [n = 154 (29.3%)] [Figure 4]. Majority of the respondents could not identify the common symptoms of STIs such as weight loss (n= 212, 40.3%), genital discharge (190, 36.1%) and painful micturition (n=158, 30%) [Figure 5]. Only less than 30% of the respondents could identify genital sore and swelling of the groin which are very common symptoms of STIs. Screening of blood and blood products [297 (56.5%)], avoidance of drug abuse [263 (50%)] and use of condoms [226 (43%)] were rightly identified as methods of prevention of transmission of STIs [Figure 6].

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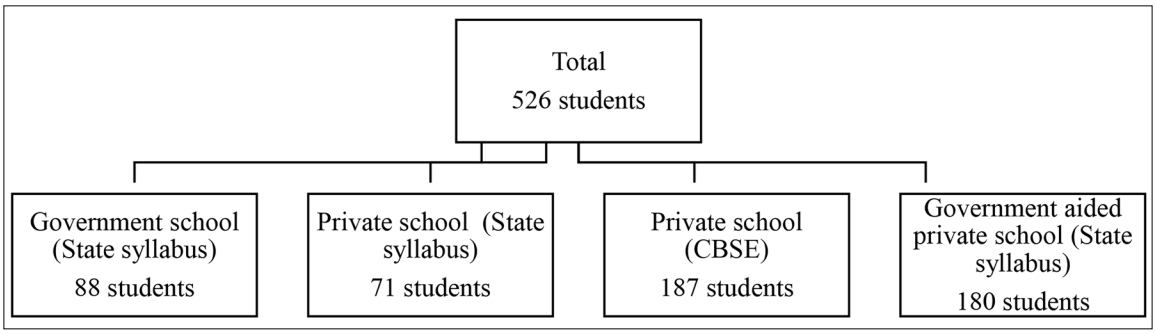


Figure 1: Flowchart depicting the distribution of study participants.

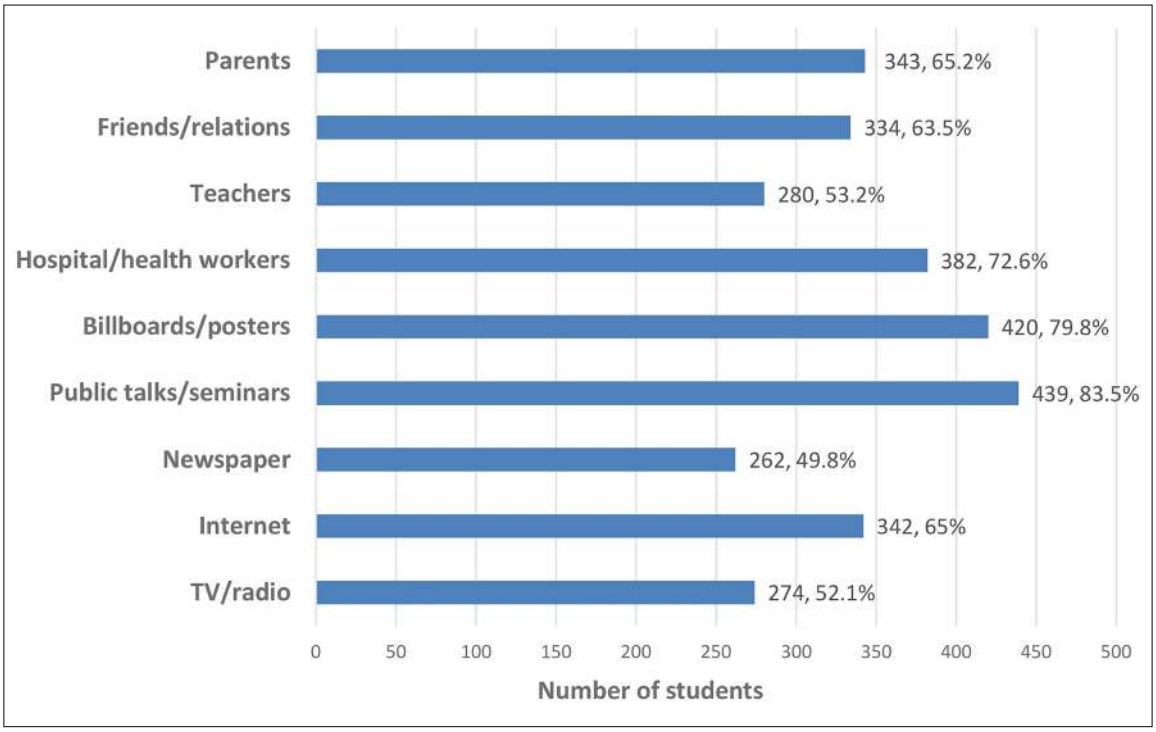


Figure 2: Bar chart showing various sources of information regarding STIs.

A total of 313 (59.5%) students had poor knowledge and 213 (40.5%) had good knowledge of STIs [Table 1]. The factors identified as significant predictors of knowledge regarding STI on univariate analysis were higher age, male gender, CBSE school, higher grade class, parents with higher level of education and acquisition of knowledge from the Internet and health workers [Table 2]. In multivariate analysis, 10th grade class, unaided schools, aided schools, usage of the Internet and health workers were the significant independent factors to influence the level of knowledge [Table 3].

The common sources of information regarding STIs for the students were public talks, posters, hospital and health workers as compared to the Internet, teachers, TV and newspapers. This clearly points out that, despite the widespread use of social media among the current generation, there is a dearth of information on STIs in these media. Studies from Nigeria and Uganda have reported radio/television, newspapers and magazines as important sources of information about STIs.[4] In our study, only less than 25 % of students were aware of the other STIs like syphilis, gonorrhoea, herpes simplex infections, trichomoniasis and chlamydia. This is probably due to lack of awareness campaigns about STIs other than HIV/AIDS in schools. Nguyen et al. also had a similar observation.[5] Significant misconceptions existed regarding mode of STIs transmission, similar to the results of the Nigerian study.[2] Another interesting finding of our study was the lack of awareness of the participants regarding the clinical presentations of STIs. Our results were comparable to another previous study from South India.[3] Respondents correctly identified screening of blood and blood products, avoidance of drug abuse and usage of condoms as methods of prevention of transmission of STIs. This indicates that the students are reasonably well informed about the commoner modes of spread and prevention.

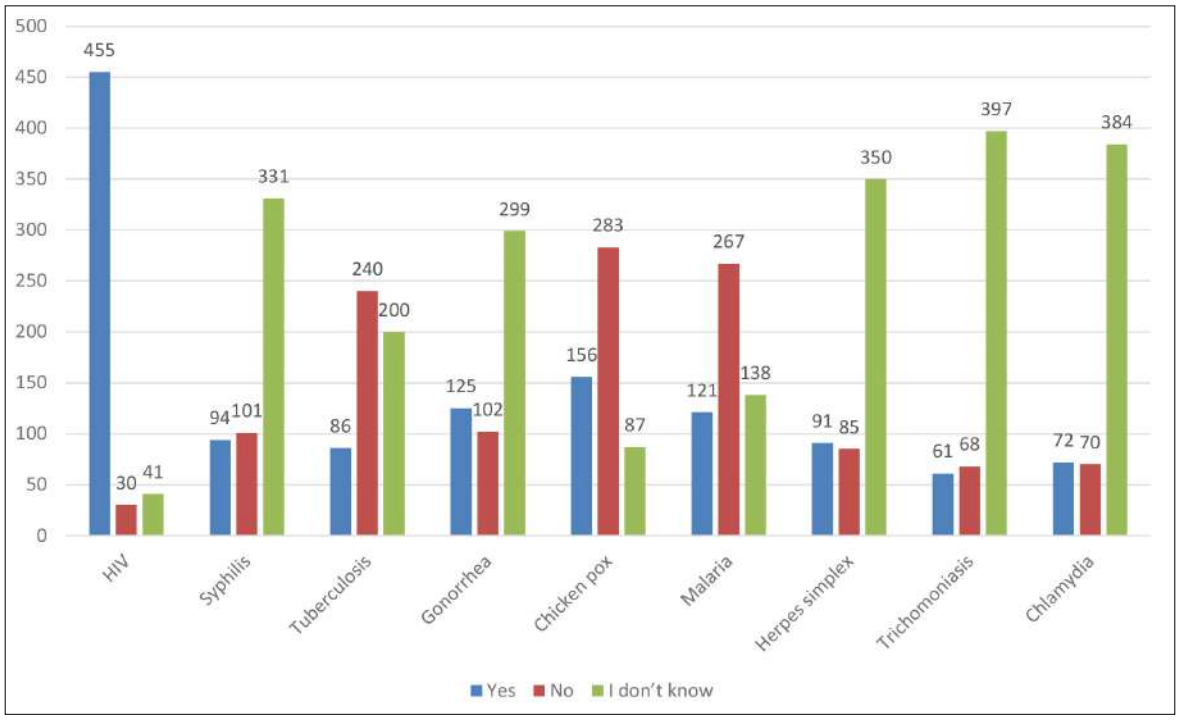


Figure 3: Clustered bar chart showing Identification of various diseases as sexually transmitted diseases by students.

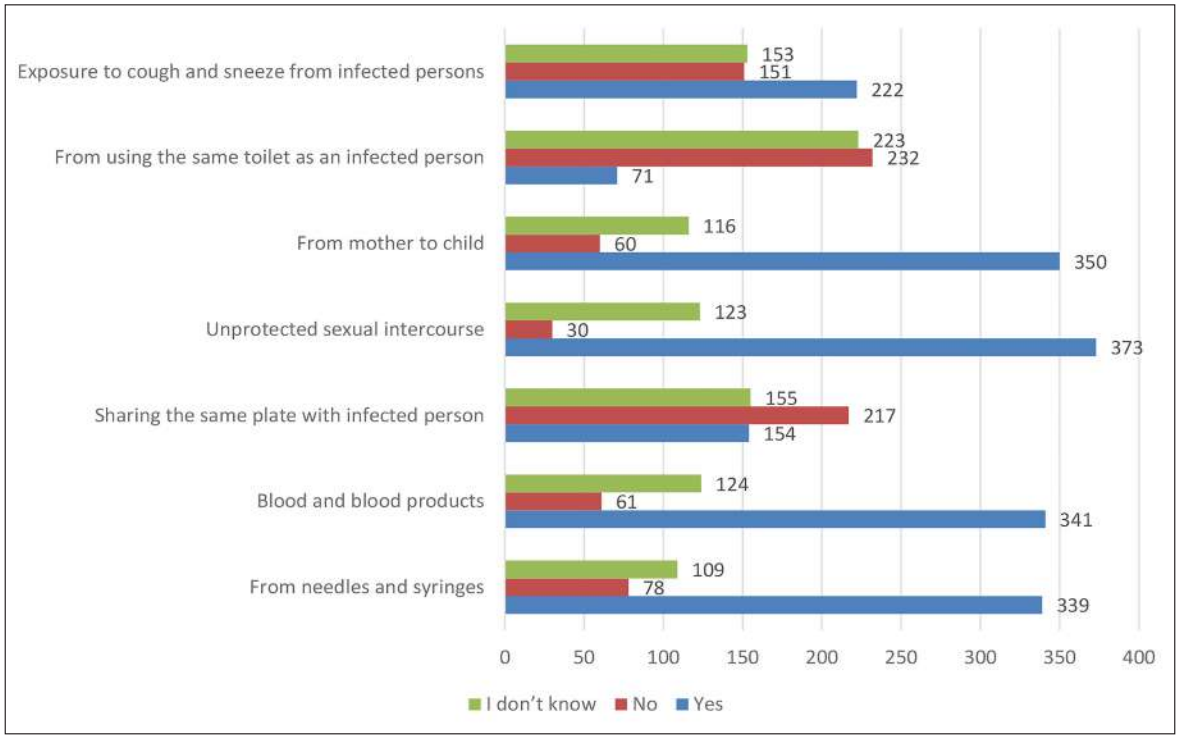


Figure 4: Clustered bar chart showing awareness about the methods of transmission of STI

Older students had better knowledge about STIs. The level of knowledge about STIs varied with the type of school with CBSE students having a statistically significant higher level of knowledge. This could possibly be explained by the sex education classes that they had been exposed to prior to our survey. Boys had a higher level of knowledge as compared to girls (44.1% vs 35.6%) probably due to their increased access to various portals of information.

Following are some of the recommendations that could be made to improve the knowledge about STIs among school students:

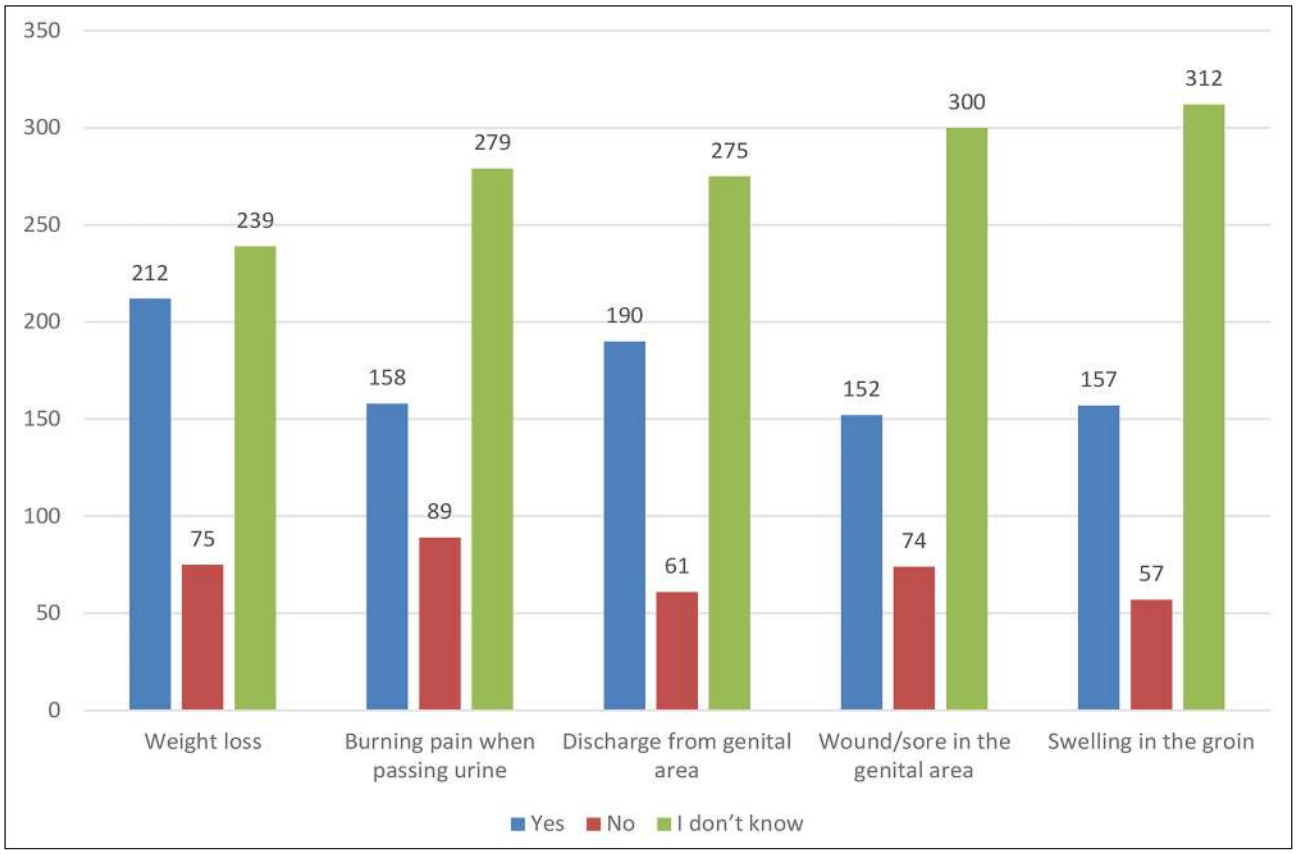


Figure 5: Clustered bar chart showing awareness about the symptoms of STI.

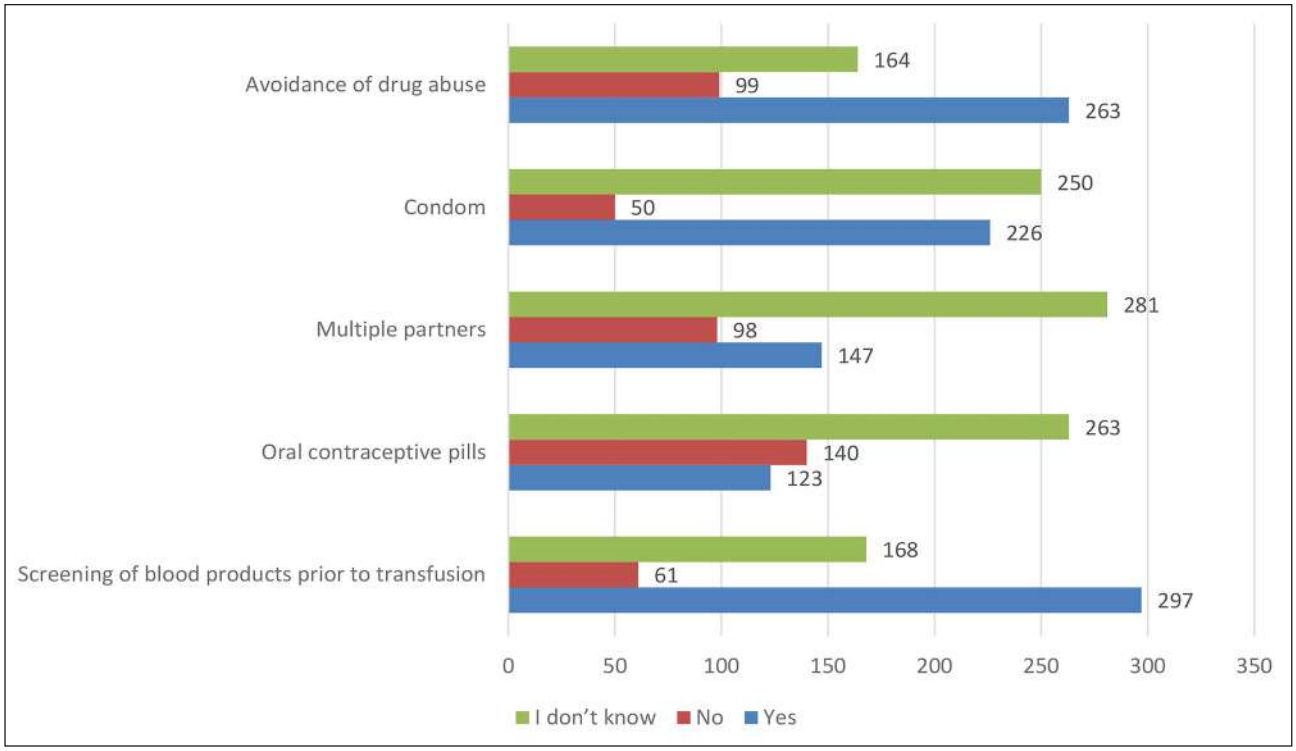


Figure 6: Clustered bar chart showing awareness about the methods of prevention of transmission of STI.

Table 1: Level of knowledge of students from different types of schools about sexually transmitted infections

	Level of Knowledge of STI				
School type	**Poor**	**Good**	**Total**	**Chi-square test**	**p-value**
Government school	45 (51.1%)	43 (48.9%)	88 (100%)		
Unaided school	46 (64.8%)	25 (35.2%)	71 (100%)		
CBSE school	90 (48.1%)	97 (51.9%)	187 (100%)	27.709	0.001*
Aided school	132 (73.3%)	48 (26.7%)	180 (100%)		
Total	313 (59.5%)	213 (40.5%)	526 (100%)		

Table 2: Univariate analysis

Variables	Category	#	Level of Knowledge of STI		OR (95% CI of OR)	p-value
			Poor No. (%)	Good No. (%)		
Age	<14	316	225 (71.2%)	91 (28.8%)	1	<0.001*
	>14	210	88 (41.9%)	122 (58.1%)	3.428 (2.376 – 4.946)	
Class	8th	169	124 (73.4%)	45 (26.6%)	1	0.368
	9th	164	113 (68.9%)	51 (31.1%)	1.244 (0.773 -2.00)	
	10th	193	76 (39.4%)	117 (60.6%)	4.242 (2.713-6.632)	<0.001
Sex	Female	222	143 (64.4%)	79 (35.6%)	1	0.050
	Male	304	170 (55.9%)	134 (44.1%)	1.427 (0.999-2.037)	
Educational status of mother	< Graduate	282	184 (65.2%)	98 (34.8%)	1	0.019
	>Graduate	234	129 (55.1%)	105 (44.95)	1.528 (1.071 – 2.181)	
Education of Father	< Graduate	264	170 (64.4%)	94 (35.6%)	1	0.022
	>Graduate	262	143 (54.6%)	119 (45.4%)	1.505 (1.06–2.136)	
Occupation of mother	Nil	253	139 (54.9%)	114 (45.1%)	1	0.040
	Job	273	174 (63.7%)	99 (36.3%)	0.694 (0.489–0.984)	
Occupation of father	Government job	72	45 (62.5%)	27 (37.5%)	1	0.572
	Non-govt. job	451	266 (59.0%)	185 (41.0%)	1.159 (0.694–1.936)	
Income	<20000	175	114 (65.1%)	61 (34.9%)	1	0.047
	>20000	346	194 (56.1%)	152 (43.9%)	1.464 (1.005-2.134)	
School	CBSE school	187	90 (48.1%)	97 (51.9%)	1	0.642
	Govt. school	88	45 (51.1%)	43 (48.9%)	0.887 (0.534 – 1.472)	
	Unaided school	71	46 (64.8%)	25 (35.2%)	0.504 (0.287–0.887)	0.017
	Aided school	180	132 (73.3%)	48 (26.7%)	0.337 (0.218 – 0.523)	<0.001
Internet	No	184	85 (46.2%)	99 (53.8%)	1	<0.001
	Yes	342	228 (66.7%)	114 (33.3%)	0.429 (0.297 – 0.620)	
Television	No	252	150 (59.5%)	102 (40.5%)	1	1.000
	Yes	274	163 (59.5%)	111 (40.5%)	0.999 (0.705 – 1.415)	
Health worker	No	144	75 (52.1%)	69 (47.9%)	1	0.033
	Yes	382	238 (62.3%)	144 (37.7%)	0.658 (0.447–0.968)	

- Seminars and public talks should be conducted regularly in schools about STIs and their prevention.
- The link between non-HIV STIs and HIV/AIDS should be emphasised. The fact that STIs increase the likelihood of HIV transmission may increase the concern about STIs.
- The right to access age-appropriate confidential sexuality education at home and in school should be granted to all students.

Though the sample size was adequate, one major limitation of this study was the difference in the number of students belonging to different categories of schools. The number of students in different divisions was also not equally distributed. The study was representative of students studying in various types of schools in the sub-district. So, the inference of the study can be expected to represent the status of the students of various socio-economic strata.

To conclude, majority of the high school students have poor knowledge of STIs. It is important for the schools to introduce sex-education programs and incorporate them into the educational curriculum in order to increase student awareness about STIs and preventive methods.

Table 3: Multivariate analysis

Variable	Category	Adjusted Odds Ratio	95% Confidence Interval		p-value
			Lower bound	Upper bound	
Age	<14 year	1			0.698
	>14 year	1.072	0.889	2.074	
Sex	Female	1			0.081
	Male	0.623	0.413	1.189	
Class	8th	1			0.107
	9th	0.244	0.110	0.539	
	10th	1.356	1.024	2.532	0.036
Educational status of mother	<Graduate	1			0.231
	>Graduate	1.026	0.891	1.786	
Education of father	<Graduate	1			0.095
	>Graduate	1.32	0.945	2.104	
Occupation of mother	Nil	1			0.102
	Job	0.786	0.453	1.132	
Income	<20000	1			0.112
	>20000	0.526	0.213	1.243	
School	CBSE school	1			0.356
	Govt. school	0.902	0.634	1.621	
	Unaided school	0.625	0.327	0.912	0.031
	Aided school	0.462	0.118	0.632	0.012
Internet	No	1			0.045
	Yes	0.694	0.235	0.876	
Health worker	No	1			0.023
	Yes	0.732	0.564	0.842	

Declaration of patient consent

Institutional Review Board permission obtained for the study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of Artificial Intelligence (AI)-Assisted Technology for assisting in the writing or editing of the manuscript and no images were manipulated using the AI.

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Net Letter

Multifocal infantile hemangiomas in a 4-month-old female infant

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Dear Editor,

Infantile hemangioma (IH) is the most frequent benign tumor of infancy (with a 3–10% prevalence among newborns) and is more common among girls.[1] Multifocal IH constitutes about 3.6% of all IH.[1]

A 4-month-old female infant presented with asymptomatic discrete reddish raised lesions on the face, trunk, and extremities, noticed one month after birth. Initially, the skin lesions were flat and became raised gradually over three months, along with the appearance of new lesions. There was no history of bleeding or oozing from the lesions.

The baby was born by lower segment cesarean section at 32 weeks of gestation due to fetal distress. Her mother had systemic lupus erythematosus, class 3 lupus nephritis, and expired immediately after delivery due to left ventricular failure. There was no history suggestive of TORCH infections for the mother during pregnancy.

The birth weight of the baby was 1.52 kg. She was admitted to the newborn intensive care unit for prematurity and small for gestational age. She was given formula feeds and gradually gained normal weight. Neck fixation was attained normally at 3rd month. There was no history of seizures.

On examination, the baby was active and playful. There were 12 discrete, partially blanching, reddish, non-tender papules of size varying from 1 mm to 4 mm on the face, trunk, and limbs [Figure 1]. Dermoscopy showed reddish lacunae and cerebriform appearance on a pinkish background [Figure 2]. There were no mucosal lesions. The ophthalmological examination was normal. Systemic examination was normal. There was no hepatosplenomegaly, no tenderness or swellings on the bones, and the joints were normal.

Clinical possibilities of multifocal IHs, blueberry muffin lesions, juvenile xanthogranulomas, and Langerhans cell histiocytosis were considered [Table 1]. Complete blood count, platelet count, bleeding time, clotting time, peripheral smear, liver and renal function tests were within normal limits. TSH was elevated (10 mIU/L). Free T3 and T4 were normal. Subclinical hypothyroidism was considered. Anti–Ro antibody was positive in the ANA profile. There was no evidence of heart block in the electrocardiogram. Echocardiography was normal. Immunoglobulin G and immunoglobulin M antibodies against TORCH infections were negative. Ultrasound of the abdomen was normal; there were no hemangiomas in the liver and no hepatosplenomegaly. Histopathological examination revealed multiple lobules composed of plump endothelial cells lining vascular spaces with inconspicuous lumens and endothelial cell proliferation in the dermis,

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suggestive of IH [Figures 3a and b]. We could not do GLUT-1, which is the specific marker of IH, due to financial constraints. Vascular markers, CD 31 and CD 34 were positive [Figures 4a and b].

A final diagnosis of multifocal IHs was made based on the following features: The appearance of multiple hemangiomas on multiple sites of the skin soon after birth, with a gradual increase in size and number; suggestive features on histopathology and immunochemistry markers of skin lesions.

IHs are classified based on pattern into focal, multifocal, segmental, and indeterminate. The precursor lesions are telangiectasias and ecchymosis. Residual lesions include telangiectasia, scarring, pigment changes, fibrofatty tissue, and atrophic skin. Multifocal IH is multiple discrete focal IHs, usually more than five in number, and they occupy different anatomic sites. It is often associated with hemangiomas in other organs, especially the liver. The complications are high-output cardiac failure and obstructive jaundice.[2]

Prematurity and low birth weight can lead to tissue hypoxia, which, in turn, can trigger disordered angiogenesis mediated by elevated vascular endothelial growth factor.[3] Prematurity and low birth weight might have predisposed to the occurrence of multiple IHs in our child.

Although the Anti-Ro antibody was positive in our child, there were no other features to suggest neonatal lupus erythematosus. Multifocal IHs have also been described in neonatal lupus.[4] Elevated TSH may occur as a part of consumptive hypothyroidism due to increased levels of catalysts of thyroid-inactivating enzymes. It is usually seen in hepatic hemangiomas and reported in cutaneous hemangiomas also.[5]

Treatment of IH depends on the location, morphology, stage of evolution, impact on function, risk of disfigurement, and comorbidities related to IH.[6] Topical treatment options are timolol maleate 0.5% eye drops and becaplermin gel (recombinant human platelet-derived growth factor). Becaplermin gel is indicated in ulcerated IH. In a study conducted among 724 children with superficial IH, topical timolol was noted to be as effective as oral propranolol.[7] Oral propranolol is administered as 1–3 mg/kg/day divided into three equal doses until the clearance of IH with regular cardiac monitoring.[8] The mechanisms of action of propranolol are inducing vasoconstriction, apoptosis of endothelial cells, and curbing of angiogenesis. Timolol and propranolol are beta blockers. The R (+) enantiomers of β-blockers, which could



Figure 1: Reddish, non-tender, partially blanching papules.

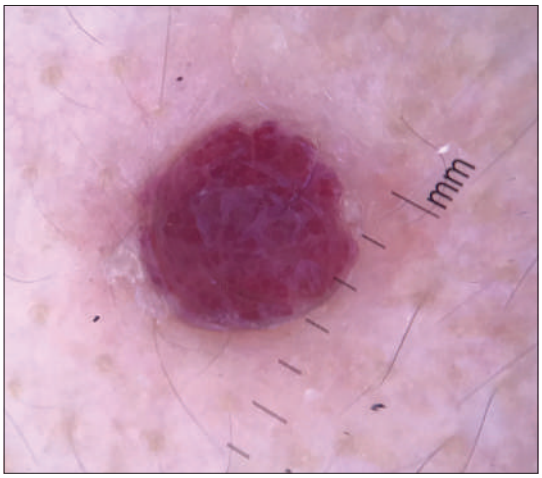


Figure 2: Reddish lacunae and cerebriform appearance on a pinkish background on dermoscopy.

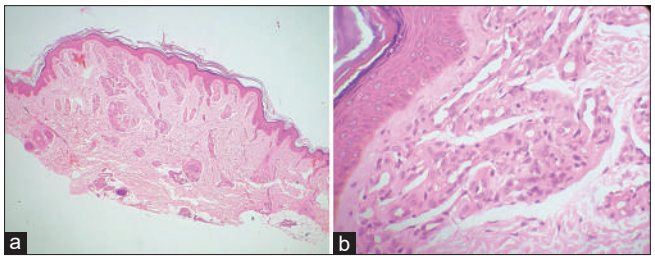


Figure 3: Multiple lobules composed of plump endothelial cells lining vascular spaces with inconspicuous lumens and endothelial cell proliferation in the dermis. (a): Hematoxylin and eosin ×40; (b): Hematoxylin and eosin ×400.

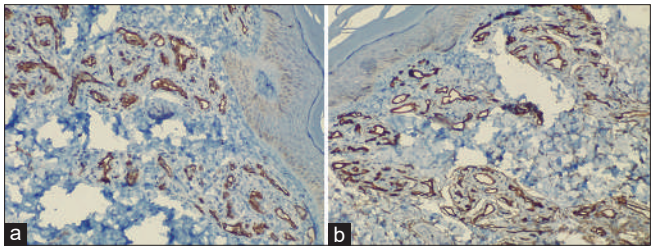


Figure 4 (a): Immunohistochemistry (IHC): CD 31 positive; (b): IHC: CD 34 positive.

Table 1: Differentiating features of clinical possibilities of infantile hemangioma.

Differential diagnosis	Clinical features	Histopathology	Dermoscopy
Blueberry muffin lesions	Erythematous or purple macules, papules, and nodules in the skin	Foci of dermal erythropoiesis	Fine telangiectatic arborizing vessels distributed within a pink background
Multifocal infantile hemangioma	Multiple, discrete, partially blanching reddish papules	Lobules with plump endothelial cells and endothelial cell proliferation	Reddish lacunae and cerebriform appearance
Juvenile xanthogranuloma	Reddish yellow single to multiple papules	Histiocytes in the dermis and Touton giant cells	Setting sun: central yellowish area surrounded by a reddish periphery
Langerhans cell histiocytosis (Hand-Schuller-Christian disease)	Yellow-brown nodules or tumors Associated with lytic bone lesions, exophthalmos, diabetes insipidus	Langerhans cells along the epidermal-dermal junction	Vascular blotch, brown homogenous area, absence of dotted and non-dotted vessels.

increase the efficacy of IH management with fewer adverse effects, are being researched.[9] Indications for pulsed dye laser in IH are ulcerations, post–involution telangiectasis, and erythema. Though multifocal IH has a benign histology, prognosis is determined by the extent of visceral involvement.

Our patient was treated with timolol maleate 0.5% eye drops, one drop on each lesion twice daily. A marked response was noted about three months after therapy. Although extracutaneous hemangiomas were not detected in our baby, follow-up is necessary.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

Dr Neelakandhan Asokan is on the editorial board of the journal.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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Extensive, Adolescent-Onset Inflammatory Linear Verrucous Epidermal Nevus – Treated Successfully with Oral Retinoids

Madam,

Inflammatory linear verrucous epidermal nevus (ILVEN) was first described by Unna in 1896.[1] It is an epidermal keratinocytic nevus, usually appearing during childhood, and manifests as linear, erythematous, pruritic scaly plaques that follow lines of Blaschko.

A 17-year-old girl presented with pruritic papules and plaques on the right side of the body. The lesions first appeared 2 years ago on the right pelvic area [Figure 1a] and gradually extended distally toward the right lower limb [Figure 1b]. No one in the family had similar lesions.

On examination, multiple well-defined discrete and confluent hyperpigmented verrucous papules and plaques surrounded by erythema were presented extensively, covering the entire right pelvic area, that extended toward the posterior part of the right lower limb, in a linear pattern. Hair, nails, and mucosae were normal. Systemic examination was normal. Dermoscopy revealed a brown cerebriform pattern and moderate white scaling suggestive of ILVEN [Figure 2a].[2] A clinical diagnosis of ILVEN was done. It was confirmed by histopathology which showed the presence hyperkeratosis, acanthosis, elongated rete ridges and papillomatosis and perivascular lymphocytic infiltrates, and numerous thick-walled blood vessels in the dermis [Figure 2b].

She was treated with betamethasone dipropionate cream in the morning and tretinoin 0.1% ointment at night for 6 months. Erythema and pruritus came down after topical treatment. As there was no improvement in the lesions, she was started on capsule isotretinoin 10 mg once daily after doing appropriate laboratory investigations including fasting lipid profile and liver function test. Within 2 months, the thickness of the plaques on the pelvic regions decreased [Figure 3a] and the plaques on the right leg completely subsided with postinflammatory hyperpigmentation [Figure 3b]. This response was maintained, at the end of 6 months of therapy and we referred her to the plastic surgery department for further management of lesions on the right pelvic area.

Discussion

ILVEN is caused by genetic mosaicism due to postzygotic mutations. Increased levels of interleukin-1, interleukin-6, and intercellular adhesion molecules in the lesions result in the inflammatory features of ILVEN.[3] A close differential diagnosis of ILVEN is linear psoriasis. The presence of profuse scales, Koebner phenomenon, Auspitz sign, better response to treatment with topical and systemic therapy,

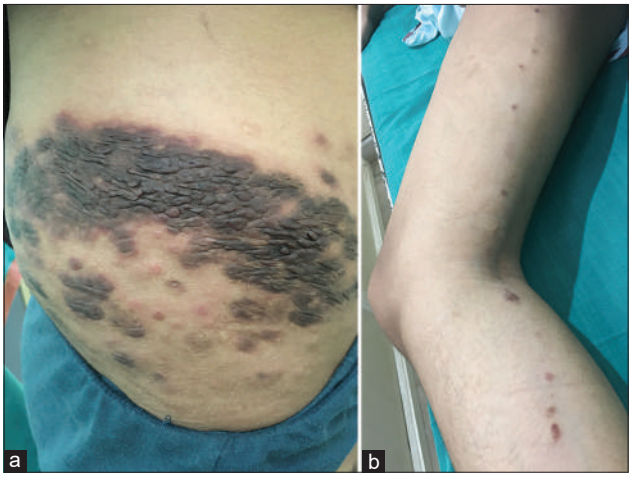


Figure 1: (a) Papules and plaques on the right pelvic area. (b) Papules and plaques on the posterior aspect of the thigh, extending to the leg

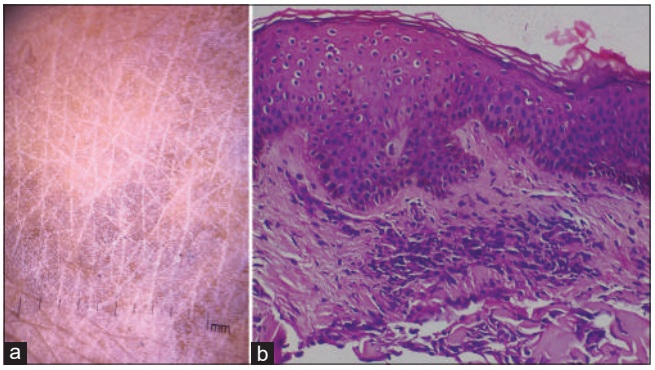


Figure 2: (a) Dermoscopy showing brown cerebriform pattern and moderate white scaling (DermLite DL3N). (b) Hyperkeratosis, acanthosis, elongated rete ridges and papillomatosis, and perivascular lymphocytic infiltrates, and numerous thick-walled blood vessels in the dermis (Haematoxylin and Eosin-stained section under 400)

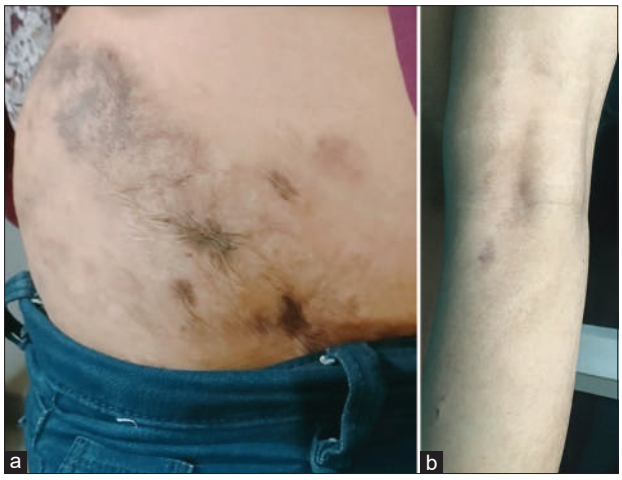


Figure 3: (a and b) Subsidence of skin lesions after treatment with isotretinoin

and distinctive histopathologic characteristics distinguish psoriasis from ILVEN. Lichen striatus and blaschkitis may also have similar clinical presentations. Lichen striatus can be distinguished by the absence of itching and the tendency for spontaneous regression.[4] Blaschkitis is characterized by the presence of pruritic papules and vesicles along multiple lines of Blaschko, especially on the trunk. It follows a relapsing course, with episodes resolving spontaneously within days. Histopathologically, it is distinguished by spongiotic dermatitis.

Topical corticosteroids, topical retinoids, dithranol, cryotherapy, flashlamp-pumped lasers, and tunable dye lasers have been used to treat ILVEN.[5] There are a few reports of the use of oral retinoids in ILVEN.[6,7] Some of them reported excellent responses to acitretin. Response of ILVEN to isotretinoin has been scarcely reported.

Atypical presentation of ILVEN including adult onset and involvement of wide area of the body have been rarely reported.[8] Seventy-five percentage of cases occur in the first 5 years of life, usually in the first 6 months.[9] Our patient developed ILVEN at a slightly older age of 15 years with extensive involvement on the right pelvic area. It is reportedly more common on the left side; in contrast, our patient had lesions confined to the right side. ILVEN is often resistant to treatment. Our patient too was not showing a response to topical corticosteroids or retinoids. However, she showed a good response to oral isotretinoin.

Declaration of consent

The authors certify that they have obtained all appropriate consent forms, duly signed by the parent(s)/guardian(s) of the patient. In the form, the parent(s)/guardian(s) has/have given his/her/their consent for the images and other clinical information of their child to be reported in the journal. The parents understand that the names and initials of their child/children will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Epidermolysis Bullosa Simplex – Dowling-Meara Type: A Case Report in a 10-year-old Boy

Abstract

Epidermolysis bullosa simplex – Dowling-Meara type (EBS-DM) is characterized by the presence of bullae and vesicles with arcuate borders in a herpetiform manner at the trauma-prone areas of the body since birth. Here we report the clinical course of EBS-DM in a 10-year-old boy. We confirmed the diagnosis by antigen mapping which showed clumping of keratin 14 with decreased staining in few areas.

Keywords: *Epidermolysis bullosa simplex, Dowling-Meara, keratin*

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Introduction

Epidermolysis bullosa (EB) is a group of genetically determined skin fragility disorders characterized by blistering of the skin and mucosa in response to minor mechanical trauma. Here, we report the clinical features and disease course in a 10-year-old child with EB simplex – Dowling-Meara type (EBS-DM) since birth.

Case Report

A 10-year-old male child, born of nonconsanguineous parents, after an uneventful pregnancy, presented with recurrent episodes of multiple itchy, clear fluid-filled lesions, and erosions in a grouped manner following minor trauma since birth. These blisters used to rupture leaving erosions that heal without scarring. His parents gave a history of developing oral erosions which used to interfere with oral feeding. Oral erosions subsided by 3 years of age. The frequency and severity of blistering decreased with age. His elder sibling was normal; there was no history of similar lesions or any other genetic disease in the family.

Cutaneous examination revealed multiple tense vesicles and bullae with crusting of size varying from 0.5 cm to 1.5 cm on the nape of the neck, both axillae, popliteal fossa, buttocks, dorsum of the right hand, and heels of both legs in a herpetiform manner [Figure 1a]. Some bullae had an arcuate border and some had surrounding erythema [Figure 1b and c]. There were few bullae on both palms [Figure 1d]. There was no palmoplantar keratoderma. Hair, nails, and mucosae were normal.

A clinical diagnosis of EBS was made based on the nonscarring nature of vesicles and bullae on the trauma-prone areas since birth. The histopathology of the lesion was inconclusive. Immunofluorescence antigen mapping (IFM) showed subepidermal split (due to cytolysis of basal keratinocytes) with clumping of keratin 14 in a few areas and the absence of staining in a few areas [Figure 2a]. Staining with other monoclonal antibodies (laminin 332, Type 1V collagen, and Type VII) was normal and was seen below the split [Figure 2b-d]. The final diagnosis of EBS-DM was made based on the arrangement of vesicles and bullae with immunofluorescence mapping suggestive of keratin 14 mutations.

Discussion

Von Hebra gave EB, the name "erblichen pemphigus" in 1870, and Koebner first proposed the current name "epidermolysis bullosa hereditaria" in 1886. Pearson was the first to classify the condition into distinct types in 1962.[1] Based on the level of cleavage, it is classified as EBS, junctional EB, dystrophic EB, and Kindler syndrome. The most common type of EB is EBS.[2]

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Figure 1: (a) Right axilla showing grouped vesicles with surrounding erythema. (b) Right anterior axillary fold showing vesicles with annular arrangement and arcuate border. (c) Dorsum of right hand showing the annular arrangement of vesicles with some areas of scaling, crusting, and surrounding erythema. Fingernails appear normal. (d) Multiple vesicles and bullae on the right palm

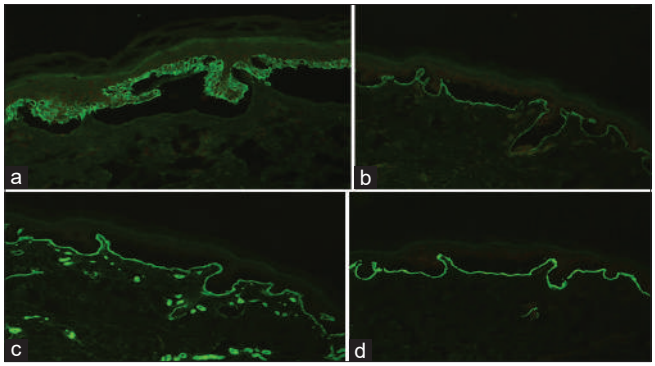


Figure 2: (a) Antigen mapping showing subepidermal split and basement membrane showing clumping of keratin 14 staining in a few areas and decreased staining in a few areas. (b) Normal antigen mapping of basement membrane with laminin 332. (c) Normal antigen mapping of basement membrane with Type IV collagen. (d) Normal antigen mapping of basement membrane with Type VII collagen

EBS-DM also known as EBS herpetiformis is caused by mutations in the genes encoding keratin 5, keratin 14, or both (K5, K14, or both), resulting in blistering in the trauma-prone areas.[3] It is inherited mainly as autosomal dominant manner; autosomal recessive inheritance is rare.[2] Sporadic cases have also been reported, as in our case.[4] EBS herpetiformis has been reported in 38 members of an Arab family in Jerusalem.[5] Most of the other case reports are from European countries.[4] There are reports of varying severity of EBS, even reports of neonatal death in literature.[6]

In our case, the child had bullous lesions from birth limited to trauma-prone and frictional sites with characteristic grouping, arcuate border with surrounding erythema without any scarring or milia formation. He also had oral erosions which subsided completely by 3 years of age. By 10 years of age, skin lesions diminished in number, and these used to heal without scarring within a few days. Our child lacked palmoplantar keratoderma and nail dystrophy which can occur in EB herpetiformis.[4]

EB is diagnosed based on clinical features and confirmed by transmission electron microscopy (TEM), IFM, EB-related monoclonal antibody testing, and mutational analysis.[7] Although IFM showed characteristic findings of EBS in our case, we could not perform TEM or mutation analysis due to financial constraints.

There is no definite management for EB. Avoidance of risk factors is the mainstay of management. Heat and humidity are the main provoking factors for blister formation in EBS in addition to trauma.[7] Several *in vivo* and *ex vivo* gene-targeting therapies have been introduced for EB, especially for junctional and dystrophic types.[8,9] Diacerein, an anti-inflammatory compound isolated from rhubarb root, has been shown to increase skin stability in EBS. In classical EBS, keratin 5 and 14 mutations cause aggregation of the intermediate filament cytoskeleton and cause cell fragility.[9] Topical diacerein, a prodrug of the interleukin-1-converting enzyme inhibitor rhein, is effective in reducing blistering in EB, in a study conducted in Austria.[10] Topical sirolimus, an mammalian target of rapamycin (mTOR) inhibitor, has also shown to be effective in EBS.[9] We treated our patient with supportive measures, and he is under regular follow-up.

Conclusion

EBS-DM although common is probably underreported, especially from the Indian subcontinent. The 10-year follow-up of this case enabled us to know about the progression of skin and mucosal lesions. The complete resolution of oral lesions along with the absence of palmoplantar keratoderma and nail dystrophy suggests a milder variant of EBS-DM with K14 mutation.

Declaration of patient consent

The authors certify that they have obtained all appropriate consent forms, duly signed by the parent (s)/guardian (s) of the patient. In the form, the parent (s)/guardian (s) has/have given his/her/their consent for the images and other clinical information of their child to be reported in the journal. The parents understand that the name and initials of their child/children will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Treatment response of hidradenitis suppurativa with apremilast

Dear Editor,

Hidradenitis suppurativa (HS) is a chronic recurrent inflammatory skin disorder that affects the apocrine gland-bearing areas of the body, predominantly the axilla, groin, and anogenital regions.[1] The usual age of onset is postpubertal, between the second and third decades of life. Its pathogenesis is multifactorial. Treatment of HS is challenging because of the wide range of clinical manifestations of the disease and its complex pathogenesis. Here, we report a case in which apremilast showed a good therapeutic response in a patient with severe HS.

There are limited literature reviews on the effectiveness of apremilast for mild-to-moderate HS.[2-4]

A 32-year-old chronic smoker and alcoholic and otherwise healthy individual presented with recurrent episodes of multiple painful papules, nodules evolving to ulcers, and discharging sinus tracts in both axillae for 2 years duration, similar lesions in the groin and buttocks of 1-year duration. In addition, he developed bilateral knee joint pain and swelling for 1 month. Over the first 2 months, he received multiple systemic antibiotics and steroids, with little response. The results of the general examination were unremarkable. Cutaneous examination revealed ulcers measuring 10 cm × 5 cm × 6 cm–3 cm × 6 cm × 3 cm, open pseudocomedones, keloidal-type scars involving both axillae [Figure 1a and b], multiple nodules, and sinus tracts involving the groin and buttocks [Figure 1c]. Pathergy test results were negative.

A provisional diagnosis of HS Hurley stage 3 with secondary infection and arthritis was made. Pyoderma gangrenosum, scrofuloderma, autoinflammatory syndromes such as pyogenic arthritis, acne, and HS; pyogenic arthritis, pyoderma gangrenosum, acne, and HS; and cutaneous Crohn's disease were considered clinical differentials. Investigations revealed anemia (Hb 8.1 gm/dL), elevated acute-phase reactants (erythrocyte sedimentation rate = 30 mm/h), and hypoalbuminemia. Biopsy showed multiple sinus tracts surrounded by granulation tissue and multinucleated giant cells of the foreign body type, which was consistent with HS [Figure 2]. Acid-fast bacilli (AFB; Ziehl-Neelsen staining) and periodic acid shift staining results were negative. Tissue AFB, fungal culture, and cartridge-based nucleic acid amplification test results were negative. Ultrasound of the lesional area revealed multiple hypoechoic collections with sinus formation [Figure 3a and b]. Magnetic resonance imaging fistulography detected multiple fistulous tracts and infective spondylodiscitis. The rheumatoid arthritis factor was negative. No obvious fluid collection was observed in the ultrasonography knee. Abdominal contrast-enhanced computed tomography and sigmoidoscopy findings were normal. Autoinflammatory syndromes were ruled out by clinical, histopathological, and sonographic evaluation. A final diagnosis of HS Hurley stage 3 with secondary infection and seronegative arthritis was considered.

Management was initially directed toward control of the superposed infection for which systemic antibiotics were administered based on the culture and sensitivity

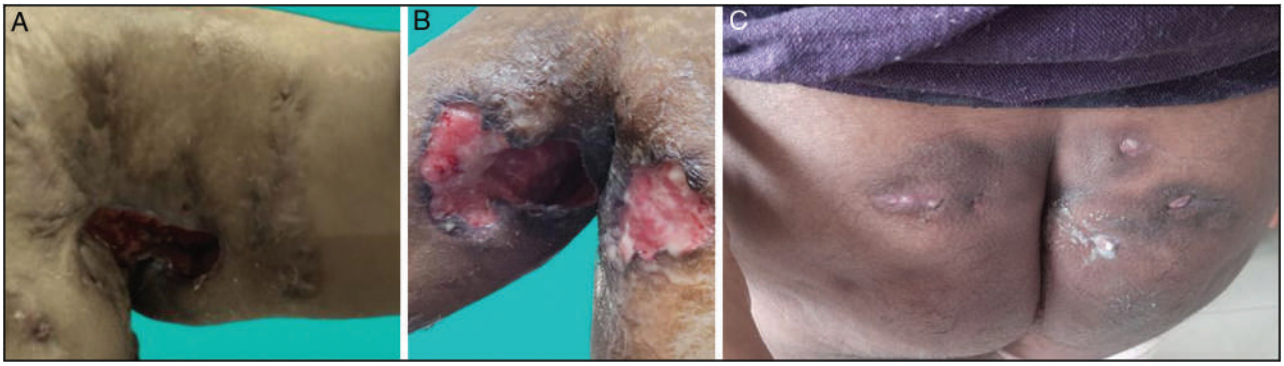


Figure 1: (a) Left axilla showing multiple ulcers with purulent exudate and open pseudocomedones. (b) Right axilla showing multiple ulcers with purulent exudate and open pseudocomedones. (c) Multiple nodules and sinus tracts involving both groin and buttocks

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reports. Specific treatment measures opted for a short course of steroids and doxycycline (100 mg twice daily (BD)] for approximately 4 months. Acitretin 25 mg once a day was administered for about 7 months. Split-skin grafting was also performed. There was no response, and the patient was readmitted twice, with worsening of the lesion. A parallel workup for adalimumab was performed, but it had to be deferred due to infective spondylodiscitis.

Based on previous reports of successful treatment of HS with phosphodiesterase 4 (PDE4) inhibitors, we prescribed apremilast 30 mg BD daily.[3,4] Response was assessed by calculating the International Hidradenitis Suppurativa Severity Scoring System (IHS4) and dermatology life quality index (DLQI) before and 16 weeks after therapy. A 7-point reduction in IHS4 and 10 point reduction in DLQI (at initiation IHS4-11 DLQI-17, 16 weeks posttherapy IHS4-4 DLQI-7) was noted with no adverse effects of medication [Figures 4a and b & 5a and b].

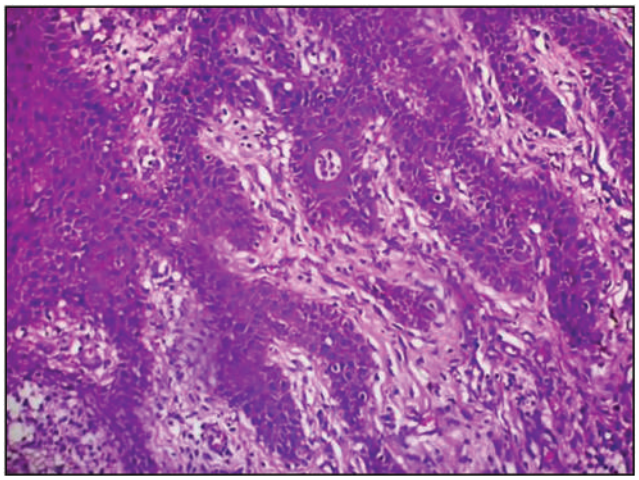


Figure 2: Dense neutrophilic infiltrates forming abscesses, sinus tracts lined by stratified squamous epithelium surrounded by granulation tissue formation, and multinucleated giant cells of foreign body type and histiocytes favoring HS (HPE 10×)

Apremilast is a small-molecule drug that inhibits phosphodiesterase and modulates the expression of several inflammatory cytokines. The off-label use of apremilast has been reported to successfully treat patients with mild to moderate HS, as evidenced by previous studies. Vossen *et al.*[2] did a randomized controlled trial in 2018 to determine the efficacy of apremilast in moderate HS and found a significant reduction in abscess and inflammatory count and a numerical rating scale for pain 16 weeks posttherapy. A case series study by Garbayo-Salmons *et al.*[3] showed a >1 point reduction in physician global assessment (PGA) in 29% of patients ($P = 0.157$), >30% reduction in DLQI in 43% of patients ($P = 0.043$), a significant reduction in IHS4 ($P = 0.068$), and >2 point reduction in the Visual Analog Scale (VAS) in 57% of patients ($P = 0.042$) at 12 and 24 weeks posttherapy.[3] Kerdel *et al.* performed a prospective open-label phase 2 study in 2019 to determine the efficacy of apremilast in mild to moderate HS and observed a significant reduction in Sartorius score ($P \leq 0.001$), PGA ($P \leq 0.01$), VAS pain score ($P < 0.05$), and DLQI ($P < 0.01$) 24 weeks posttherapy.[4]

Our case provides clinical evidence of the role of PDE4 in severe HS. The significant reduction in nodules, abscesses, and fistulous tracts underscores the effect of PDE4 in increasing the levels of proinflammatory cytokines, such as interleukin-17, tumor necrosis alpha, and interferon-gamma, majorly involved in HS.

In conclusion, the major brunt of HS is the psychosocial distress associated with the disease attributed to pain and disfigurement affecting day-to-day activities, especially in severe HS, and the dramatic response to apremilast in our patient with severe HS opens doors to a new promising modality for severe HS. Apremilast may not be uniformly effective in all patients with HS, as the pathogenesis of HS is multifactorial.

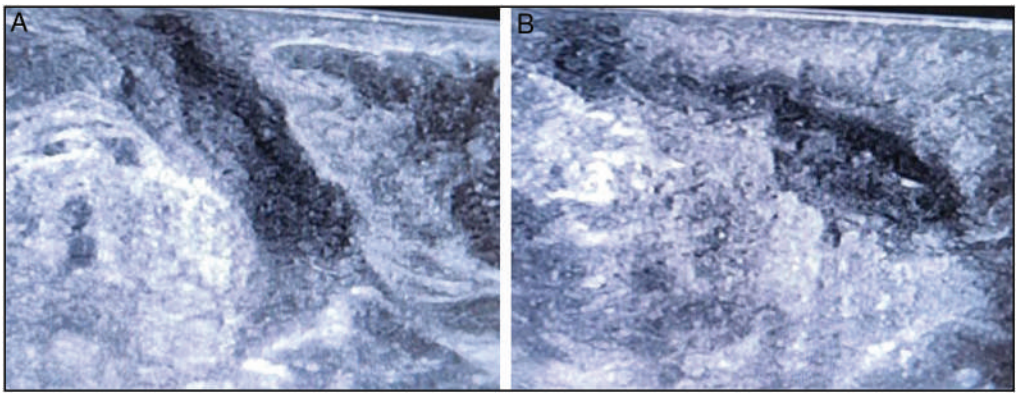


Figure 3: (a) Multiple superficial subcutaneous hypoechoic collection with sinus formation involving the left axilla. (b) Multiple superficial subcutaneous hypoechoic collection with sinus formation involving the right axilla

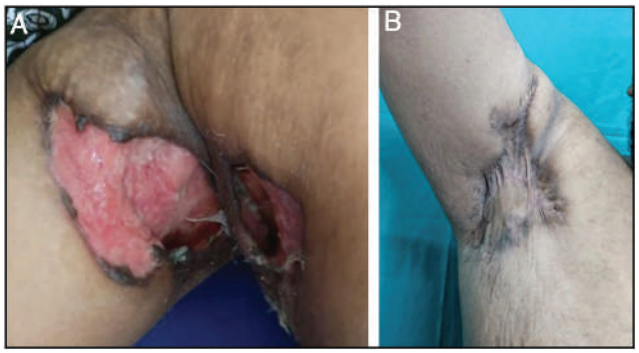


Figure 4: (a) Right axillary lesion before commencing apremilast therapy (IHS4-11 DLQI-17). (b) Right axillary lesion after commencing apremilast therapy (IHS4-4 DLQI-7)

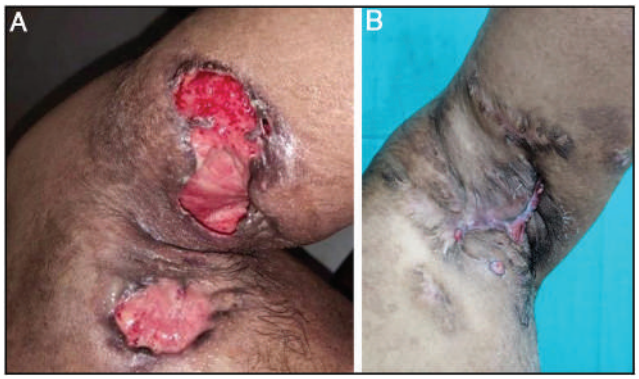


Figure 5: (a) Left axillary lesion before commencing apremilast therapy (IHS4-11 DLQI-17). (b) Left axillary lesion after commencing apremilast therapy (IHS4-4 DLQI-7)

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Conflicts of Interest

There are no conflicts of interest.

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Case Letter

Non-pruritic lichen planus in sickle cell anemia: Is there a role for hydroxyurea?

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Sir,

Herein, we report a case of non-pruritic lichen planus in a 21-year-old male who had been on treatment with hydroxyurea for sickle cell anemia since nine years of age.

A 21-year-old male was admitted with multiple non-pruritic, hyperpigmented, raised lesions in a generalized distribution of three weeks' duration. He was diagnosed to have had sickle cell anemia since nine years of age and had been on treatment with hydroxyurea 500 mg daily and iron and folic acid supplements since then. On examination, he had pallor, bilateral pitting and pedal edema, and there were generalized, bilaterally symmetrical, well-defined, violaceous, and hyperpigmented discrete and confluent papules and plaques of sizes varying from 0.5 x 0.5 cm to 2 x 2 cm with adherent grayish-white scales and Koebner's phenomenon (Figs. 1a and 1b). The mucous membranes and nails were normal. The differential diagnosis considered were acute generalized lichen planus and lichenoid eruption to hydroxyurea.

Peripheral blood smear revealed microcytic hypochromic anemia with poikilocytes such as elliptocytes, pencil-shaped cells, target cells, and some sickle cells. Sickling test was positive. Serology for syphilis, HIV, hepatitis B, and hepatitis C were negative. Histopathological examination of the lesional skin in low power showed acanthosis, focal hypergranulosis, saw toothing of rete ridges, basal cell degeneration, and band-like lymphoplasmacytic infiltration in the dermo-epidermal junction (Fig. 2a). Civatte bodies and pigment incontinence were seen in high power view (Fig. 2b). The diagnosis of acute generalized lichen planus was made. Due to the generalized and extensive nature of the disease, systemic steroids were initiated. As the sickle cell disease was active and histopathology showed no features of lichenoid eruption, hydroxyurea was not discontinued. The skin lesions resolved with hyperpigmentation and there was no recurrence on stopping systemic steroids (Fig. 3).

There are several reports of lichenoid eruption to hydroxyurea [1]. However, in this case, there were no clinical or histopathological features to suggest lichenoid eruption. Furthermore, there was no exacerbation or recurrence of skin lesions in spite of continuing hydroxyurea. Itching is one of the



Figure 1: (a) Generalized, bilaterally symmetrical, well-defined, violaceous and hyperpigmented, discrete and confluent papules and plaques of sizes varying from 0.5 x 0.5 cm to 2 x 2 cm with adherent grayish-white scales and Koebner's phenomenon on the trunk. (b) Bilaterally symmetrical, well-defined, violaceous and hyperpigmented, discrete and confluent papules and plaques of sizes varying from 0.5 x 0.5 cm to 2 x 2 cm with adherent grayish-white scales on the legs.

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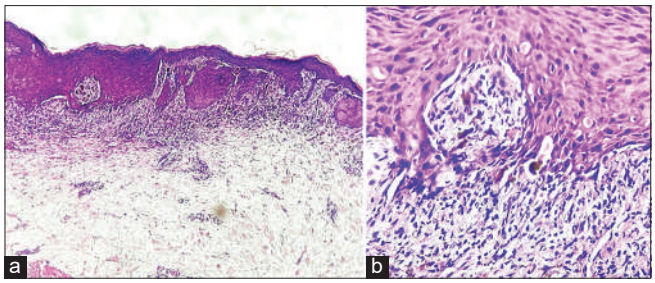


Figure 2: (a) Epidermis showing acanthosis, focal hypergranulosis, saw toothing of rete ridges, basal cell degeneration, and band-like lymphoplasmacytic infiltration in the dermo-epidermal junction (H&E, 40x). (b) Epidermis showing acanthosis, focal hypergranulosis, saw toothing of rete ridges, basal cell degeneration, and band-like lymphoplasmacytic infiltration in the dermo-epidermal junction with Civatte bodies and pigment incontinence (H&E, 100x).



Figure 3: Skin lesions subsided with hyperpigmentation.

important symptoms of lichen planus. It is produced when pruritogenic stimuli activate primary afferent C fibers. Endogenous pruritogens, such as histamine, kinins, proteases, neurotrophins, some opioids, and cytokines produced by keratinocytes, leukocytes, mast cells, fibroblasts, endothelial cells, and cutaneous nerves directly activate the itch-sensitive C-fibers or indirectly induce the release of pruritogenic mediators and modulators from other cells. Some of the newer pathogenetic factors for itch in lichen planus include increased levels of IL-31 and TNF-α; increased expression of IL-31 receptors and protease activated receptors; and the activation of μ-opioid receptors and toll-like receptors (TLRs) [2].

Hydroxyurea has anti-inflammatory action by decreasing the levels of TNF-α and IL-6. Treatment with hydroxyurea leads to a significant decrease in neutrophil-to-lymphocyte ratio, which is positively correlated with serum levels of CRP, TNF-α, and IL-6 [3]. In our patient, hydroxyurea could have made the lichen planus non-pruritic by decreasing the levels of the chemical mediators of itch. This needs to be confirmed by further studies. Drugs such as hydroxychloroquine, dapsone, PUVA, phenytoin, and isotretinoin known to cause lichenoid eruption or trigger lichen planus have found a place in the treatment of the same [4,5]. Whether hydroxyurea like these drugs have a therapeutic role (for pruritus) in lichen planus also needs to be explored.

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Role of histopathology and HLA-DR expression in predicting lepra reactions: A retrospective analysis

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Summary
Objectives To assess the role of histopathology and HLA-DR expression in skin lesions of leprosy in predicting lepra reactions.
Methods Archived skin biopsy specimens from January to December, 2019, showing leprosy granulomas (at the time of diagnosis) were studied for features of lepra reaction and HLA-DR expression. Information on subsequent clinical manifestations of lepra reaction were collected from case records.
Results We studied the archived skin biopsy specimens from 27 patients. Twelve patients (12/27, 44%) had clinically evident Type 1 lepra reaction (T1R) at diagnosis. Six patients who had no clinically evident lepra reaction at diagnosis manifested clinical features of T1R (5 patients) or T2R (1 patient) within 3 months of starting multidrug therapy (MDT). Four of the five (80%) patients who developed T1R and the lone patient who developed T2R after initiating treatment had histological features of the respective reactions in the biopsy specimen at diagnosis. All five patients who later developed T1R showed a moderate-to-strong expression of HLA-DR along the basal layer of the epidermis; a weak HLA-DR expression was noted along the epidermal basal layer of the lesional specimen of the patient who subsequently developed T2R.
Conclusion A combination of histopathology and immunohistochemical analysis of HLA-DR expression in lesional specimens at the time of diagnosis of leprosy may help to identify patients at risk for T1R while on MDT. We need further studies to gather information on whether the added benefit of immunohistochemistry to predict patients at risk of lepra reaction is limited to T1R alone.

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Keywords: Leprosy, type 1 lepra reaction, type 2 lepra reaction, histopathology, HLA-DR

Introduction

Lepra reactions – Type 1 (T1R) and Type 2 (T2R) – assume importance because of their ability to induce nerve function impairment (sensory and/or motor) and disability due to leprosy.[1]

The main cause of nerve function impairment and nerve palsy in lepra reaction is the neuritis and pressure effect on the nerves caused by oedema induced by the reaction. Early administration of systemic corticosteroids can reverse these effects and limit or prevent permanent nerve damage.[2,3]

Ridley, while describing the histopathology of lepra reactions, described a prodromal phase in which patients without clinical evidence of lepra reaction would show histological evidence of the same.[3] He also opined that not all those who showed histological evidence of lepra reaction would manifest a full blown reaction later on.[3] Lockwood et al found that a significant portion of patients manifesting histological evidence of reaction without any clinical features went on to develop clinically evident reaction later on.[4] Similar findings were reported by others as well.[5] In addition, previous authors have observed the expression of HLA-DR in lesional specimens from leprosy patients as a feature of a strong immune response and reversal reaction.[6–8]

HLA-DR (human leukocyte antigen-DR) is a major histocompatibility complex (MHC) class II cell surface receptor that plays an important role in antigen driven immune response.[7] HLA-DR expression is a prerequisite for lymphocyte-macrophage interaction and thus is of significance in the immune response directed against *M leprae*.

We aimed to assess the role of histopathology and HLA-DR expression in lesional specimens at the time of diagnosis of leprosy in predicting lepra reactions.

Materials and methods

The institutional ethics committee approved the study. We retrieved archived skin biopsy specimens from January to December, 2019, which showed leprosy granulomas (at the time of diagnosis).

Exclusion criteria: Histology specimens of poor quality (despite preparing fresh slides from the paraffin-embedded specimens) were excluded. We also excluded the specimens of patients who opted for treatment from other centres after receiving the diagnosis of leprosy.

The skin biopsy specimens were studied for features of lepra reaction and HLA-DR expression. Clinical details of patients at diagnosis of leprosy and during follow up were retrieved from case records, using a pre-set proforma. The pathologist who was blinded as to whether the patients had clinically evident lepra reaction or not at the time of the biopsy, re-evaluated the histology slides for features of T1R/T2R and recorded the findings. When the histology slide was of poor quality, a fresh slide was prepared from the paraffin-embedded specimen and re-stained.

The pathologist evaluated the specimens using a preset proforma, documenting data on the appearance of granuloma (compact or diffuse), type of giant cells, inflammatory cells constituting the granuloma (abundance of lymphocytes/neutrophils or epithelioid cells/-macrophages), dermal/intragranuloma oedema, vascular dilatation, spaces in the dermis or

around the granuloma, the presence of necrosis, the arrangement of dermal collagen (whether separated or not), and acid fast bacilli (AFB).

A histological diagnosis of T1R was made when the histology showed at least two of the following features — granulomas with extracellular or intracellular oedema, dilated vascular channels, separation of dermal collagen, intense delayed-type hypersensitivity response manifested as abundance of lymphocytes, epithelioid cells or giant cells or as necrosis within the granuloma.[9–11]

We made a histological diagnosis of T2R when neutrophil infiltration was noted on the background of macrophage granuloma with or without vasculitis, dermal oedema, intragranuloma oedema or separation of dermal collagen.[9–11]

Immunohistochemistry staining of specimens for HLA-DR expression was performed with prediluted rabbit IgG antibody to HLA-DRα from BIOCYC GmbH&Co, using standard protocols. Bleaching of sections was done prior to immunohistochemistry to remove melanin pigment, which may interfere with interpretation. Intensity of HLA-DR expression was classified into strong, moderate and weak. Based on the number of positively stained cells, we classified the specimens into those showing HLA-DR positivity in many cells and those showing HLA-DR positivity in a few cells. Specimens showing 10 or more positively stained cells for HLA-DR per average high power field after examining 5 high power fields were considered as those showing HLA-DR positivity in many cells and the rest were considered as those showing HLA-DR positivity in a few cells.

The data collected from case records (the institution documents follow up data till completion of multidrug treatment or treatment of lepra reactions whichever is later) were carefully analyzed to identify those patients who developed T1R/T2R at the time of biopsy and later during multidrug therapy. Data were entered in Microsoft Excel and analyzed. Categorical variables were expressed as numbers and percentages. The relation between histopathology findings and HLA-DR expression at diagnosis and subsequent development of lepra reaction was assessed.

Results

As per histopathology features, there were 21 patients with BT leprosy (Figure 1), one each with TT and BL and 4 patients with LL leprosy (Table 1).

Table 1. Classification of study participants based on clinical/histological features of lepra reaction

Type of leprosy	No clinical or histology findings of T1R/T2R at diagnosis (n = 6)	Clinical features of T1R/T2R; no histology findings of the same (n = 6)	Histology findings of T1R/T2R; no clinical findings of the same (n = 9)	Both clinical and histology findings of T1R at diagnosis (n = 6)
*Tuberculoid leprosy (n = 1, 100%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)
Borderline tuberculoid leprosy (n = 21, 100%)	6 (28.6%)	4 (19%)	6 (28.6%)	5 (23.8%)
Borderline lepromatous leprosy (n = 1, 100)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
Lepromatous leprosy (n = 4, 100%)	0 (0%)	2 (50%)	2 (50%)	0 (0%)

*Probably secondary tuberculoid leprosy.

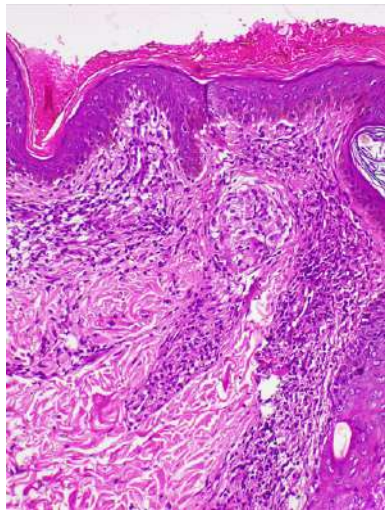
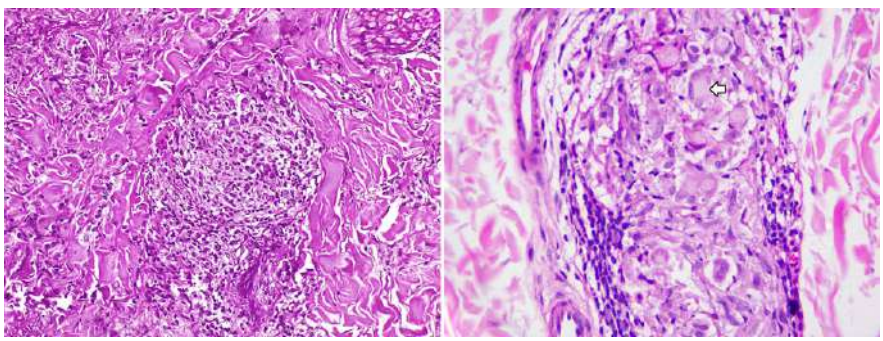


Figure 1. Epithelioid granuloma with no intragranuloma edema or giant cells – borderline tuberculoid leprosy (H and E, ×100).

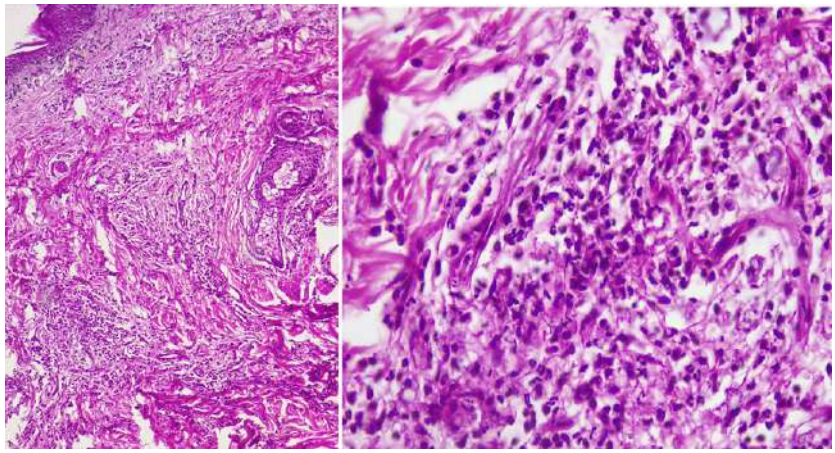


(a) (b)

Figure 2. (a) Epithelioid granuloma with intragranuloma edema-borderline tuberculoid leprosy in Type 1 lepra reaction (H and E, ×200); (b) higher magnification of the same showing separation of dermal collagen, intragranuloma edema and Langhan giant cell (white arrow) (H and E, ×400).

At the time of diagnosis, clinically evident T1R was noted in 12 patients (12/27, 44%). None of the patients showed clinically evident T2R. Only 50% (6/12) of the 12 patients with clinically evident T1R showed histopathology evidence of the same (Figure 2). Six patients (6/27, 22%) manifested no evidence of reaction clinically or histologically at the time of diagnosis.

Nine patients (9/27, 33%) showed histological findings of reaction at diagnosis (T1R in eight and T2R in one) (Figure 3), but no clinical findings of the same. Thus out of the 15 patients who showed histopathology evidence of reaction at diagnosis, 9 (9/15, 60%) lacked any clinical features of the same and six (6/15, 40%) showed both clinical and histology features of T1R.



(a) (b)

Figure 3. (a) Macrophage granuloma showing intragranuloma edema – lepromatous leprosy in reaction (H and E, ×40); (b) neutrophil infiltration and intragranuloma edema in the background of macrophage granuloma (H and E, ×400).

As per case records, six of the 15 patients (6/15, 40%) who had no clinical features of lepra reaction at diagnosis developed T1R (5 patients) or T2R (1 patient) within the succeeding three months. Four out of the five (80%) patients who developed T1R and the lone patient who developed T2R while on treatment had manifested histopathology evidence of the respective reaction at the time of diagnosis despite having no clinical features of the same. In other words 5/9 (56%) patients who had histopathological evidence of lepra reaction (without any clinical features to suggest the same) at diagnosis developed a clinically evident reaction subsequently, whereas 1/6 patients (17%) who lacked both clinical and histological evidence of reaction at diagnosis went on to develop lepra reaction while on MDT (which was a Type 1 reaction).

Analysing HLA-DR expression, we noted a moderate-to-strong expression of HLA-DR in many cells in the granulomas of all specimens irrespective of the type of leprosy or the presence of clinical or histopathological features of reaction. However, HLA-DR expression along the basal layer of the epidermis varied from weak to strong in different specimens.

Thirteen specimens (13/27, 48%) showed absent/weak expression of HLA-DR in the basal layer of the epidermis (Figure 4) and a moderate-to-strong expression was noted in the remaining 14 (14/27, 52%). Most of the specimens (11/14, 79%) that showed a moderate-to-strong expression of HLA-DR (Figure 5) had histopathological features of reaction. All 5 patients who had no clinically evident T1R at diagnosis and who subsequently developed T1R had shown a moderate-to-strong HLA-DR expression along the basal layer of the epidermis at the time of diagnosis; however, the lone patient who had histological evidence of T2R in the lesional specimen (and later developed clinically evident T2R) showed weak HLA-DR expression (Figure 6) in a few cells in the basal layer. HLA-DR expression relationships are summarised in Table 2.

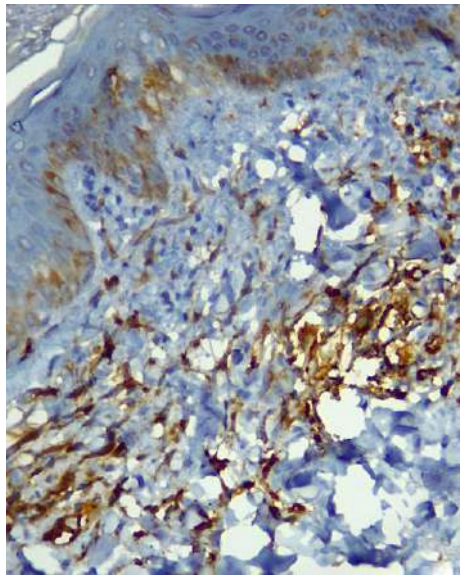


Figure 4. Immunohistochemistry showing strong HLA-DR expression in granuloma and weak expression in a few cells in epidermis in a lesional specimen of borderline tuberculoid leprosy (HLA-DRα, ×200).

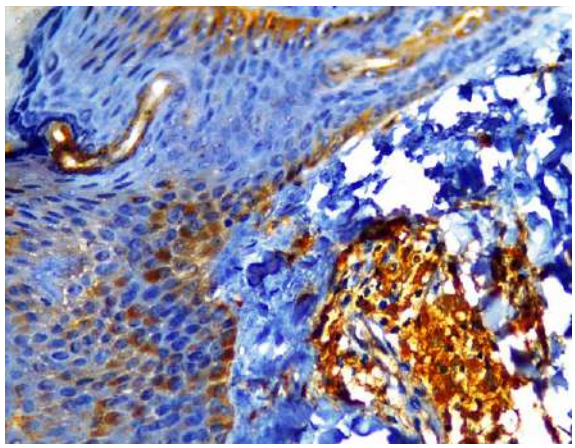


Figure 5. Immunohistochemistry showing strong HLA-DR expression in granuloma and moderate/strong expression in many cells in epidermis in a lesional specimen of borderline tuberculoid leprosy (HLA-DRα, ×200).

Discussion

Our finding of four out of the five patients (80%) who went on to develop T1R while on MDT manifesting histopathology evidence of T1R in the pre-treatment biopsy (despite not showing any clinically evident reaction) was concordant with the findings of others.[4,5]

Our observation of six patients with clinically evident T1R, not manifesting the same histologically was also consistent with previous reports.[5,9] Lockwood et al. in a cohort study of 303 newly registered MB cases, observed clinical and histological agreement of absence

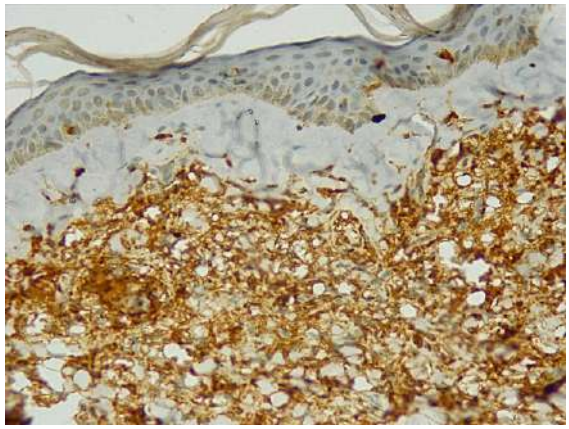


Figure 6. Immunohistochemistry showing strong HLA-DR expression in entire granuloma and scattered cells showing weak expression in the epidermis in a lesional specimen of lepromatous leprosy (HLA-DRα, ×200).

Table 2. HLA-DR expression along the basal layer of epidermis in lesional specimens of leprosy

Clinical and histology findings of lepra reaction	HLA-DR expression along the basal layer	
	Intensity of expression	*Number of positively staining cells
No clinical or histological evidence of reaction (n = 6, 100%)	Weak expression - 4 (66.7%) Moderate expression 1 (16.7%) Strong expression - 1(16.7%)	Positive staining in many cells - 4 (66.7%) Positive staining in a few cells - 2 (33.3%)
Clinical evidence of reaction; no histological findings to suggest the same (n = 6, 100%)	No staining - 1 (16.7%) Weak expression - 4 (66.7%) Strong expression - 1 (16.7%)	Positive staining in many cells - 4 (66.7%) Positive staining in a few cells - 1 (16.7%)
Histological evidence of reaction; no clinical evidence of the same (n = 9, 100%)	Weak expression - 3 (33.3%) Moderate expression - 4 (44.4%) Strong expression - 2 (22.2%)	Positive staining in many cells - 7 (77.8%) Positive staining in a few cells - 2 (22.2%)
Both clinical and histological evidence of reaction (n = 6, 100%)	Weak expression - 1 (16.7%) Moderate expression - 5 (83.3%)	Positive staining in many cells - 3 (50%) Positive in a few cells - 3 (50%)

*Positive staining in more than 10 cells/average high power field after examining five high power fields was considered as positive staining in many cells.

and presence of reaction in 109 and 53 cases respectively.[9] They noted that 60 patients with a histological diagnosis of T1R had no clinical features of the same while 43 patients with a clinical diagnosis of reaction showed no histological evidence (as in our study).[9] A previous study from our institution that assessed the role of histopathology in predicting T1R in 40 patients with BT leprosy, documented that 2 patients with clinically evident T1R lacked histology findings to support the same.[5] It is suggested that often it is difficult to distinguish clinically between BT and BT with T1R.[9] Four of the six patients (67%) who had clinically evident T1R with no histological evidence of the same in our study, manifested BT (Table 1). In addition, dermal/intragranuloma oedema, which is an important histological finding in lepra reaction, may subside by the time of biopsy when there is a delay between onset of reaction and

biopsy, in turn leading to a histological misdiagnosis.[12] Since the current study was carried out in a tertiary referral centre, a time delay between onset of reaction and skin biopsy can not be ruled out.

Cells that express HLA-DR serve as effective antigen-presenting cells to evoke an immune response.[7] Ridley and Ridley in 1982, using the indirect peroxidase method, showed that lesional skin of all patients with polar tuberculoid leprosy (TT) and 50% of those with near-tuberculoid disease in reaction showed HLA-DR expression, while none of the patients within the BT-LL leprosy spectrum showed the same.[6] They suggested that HLA-DR expression could be a marker for the TT group.[6] Some years later, Collings et al, by immunofluorescence staining, showed that 'the amount of HLA-DR measured per unit area in the tuberculoid type of granuloma was significantly higher than that present in the borderline lepromatous leprosy specimens, which in turn was higher than the same observed in lepromatous leprosy specimens'.[7] The HLA-DR expression was noted in the epidermis as well as on non-lymphoid mononuclear cells.[7] A later study that assessed serial biopsies documented HLA-DR expression in both tuberculoid and lepromatous cases and noted an increase in HLA-DR expression after initiation of MDT.[8] The authors also noted that all patients who developed a reversal reaction while on MDT had already shown a strong HLA-DR expression in the pre-treatment lesional specimen. The authors attributed the increase in HLA-DR expression to an improved immune response and suggested that the patients who show a stronger response manifest reversal reactions.[8]

Our finding of all five patients who developed T1R while on treatment showing moderate to strong expression of HLA-DR in basal layer of epidermis at the time of diagnosis was consistent with the literature, though we noted a uniformly strong HLA-DR expression in granulomas in all specimens. The previous authors, except Collins et al have not specifically mentioned the distribution (in the granuloma or along basal layer of epidermis) of HLA-DR expression. However, we did not observe a similar association for T2R. The patient who showed histology evidence of T2R at diagnosis (without clinical findings to suggest the same) and who went on to develop T2R while on treatment showed weak HLA-DR expression in a few cells in the basal layer of epidermis, indicating that in comparison to T1R, T2R is less efficient in bringing out an immunological upgrading.

Limitations

Small sample size and our inability to collect more data on Type 2 lepra reactions were the major limitations.

Conclusion

Prospective studies with larger sample size may help us to arrive at a conclusion regarding the efficacy of a combination of histology evaluation and HLA-DR expression at diagnosis of leprosy in identifying patients at risk for lepra reaction.

Ethical approval

Ethical review board approval obtained from Institutional Ethics Committee, Government Medical College, Kozhikode. Ref. no. GMCKKD/RP2020/IEC/502 dated 25.9.2020.

A conflict of interest statement

The authors report no conflict of interest

Funding (including statement of independence from funders)

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Contributorship statement including name of guarantor

Sarita Sasidharanpillai, Aparna Govindan and Keerankulangara Devi designed the study. Sarita Sasidharanpillai received the grant for the study from the State board of Medical research, Kerala. Sarita Saidharanpillai, Aparna Govindan, Anagha Sathyan, Jiss Maria Roy and Srilakshmi Yedindas carried out the literature search. Sarita Sasidharanpillai, Anagha Sathyan, Jiss Maria Roy and Srilakshmi Yedindas collected the clinical data. Aparna Govindan analysed the biopsy specimen for histopathology and HLA-DR expression. Sarita Sasidharanpillai, Aparna Govindan, Anagha Sathyan, Jiss Maria Roy and Srilakshmi Yedindas drafted the manuscript, which was reviewed and edited by Keerankulangara Devi. Sarita Sasidharanpillai and Aparna Govindan act as guarantors.

Patient consent statement

No patient consent was required, as study was conducted on archived biopsy specimens and clinical data retrieved from case records (retrospective analysis).

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Circinate balanitis in HLA B27 spondyloarthrithis: A report of two cases

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Abstract

Circinate balanitis is a characteristic mucocutaneous lesion commonly associated with reactive arthritis (ReA), previously described as Reiter's disease. It typically presents alongside other ReA symptoms, including urethritis, conjunctivitis, and arthritis, but can occasionally occur as an isolated finding. We report two cases of circinate balanitis occurring in patients with HLA B27-positive spondyloarthritis, without the classical triad of reactive arthritis. A 32-year-old male presented with recurrent erosions on the glans penis for 2 years, with a history of HLA B27-positive spondyloarthritis. He was on treatment with tofacitinib, deflazacort, and sulfasalazine. A skin biopsy from the scrotum confirmed the diagnosis of psoriasis. MRI spine and sacrum showed anterior syndesmophyte formation and right-sided sacroillitis. The final diagnosis was circinate balanitis in association with HLA B27-positive psoriatic spondyloarthritis. A 41-year-old male presented with recurrent erosions on the glans penis for 4 years with history of HLA B27 positivity, and ankylosing spondyloarthritis. The biopsy from the glans penis showed squamous hyperplasia. MRI spine and pelvis was suggestive of inflammatory spondyloarthropathy of the cervical, dorsal and lumbar spine with bilateral sacroilitis. The final diagnosis was circinate balanitis with primary ankylosing spondylitis. Both cases highlight the diagnostic challenge of distinguishing between different forms of spondyloarthritis in the presence ofcircinate balanitis.

ENT

Original Article

A Study on Clinico Radiological Profile and Treatment Pattern of Patients Admitted with Mucormycosis in a Teaching Institution

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Abstract

Objectives: (1) Primary objective: To study the selected risk factors and clinical and radiological profiles of patients admitted with mucormycosis. (2) Secondary objective: To study the treatment pattern of patients admitted with mucormycosis. **Materials and Methods:** A descriptive cross-sectional study was conducted, which included the data of all patients admitted with the histopathological diagnosis of mucormycosis after undergoing surgery in the Otorhinolaryngology Department, Government Medical College, Thrissur, from January 2020 to September 2021. The risk factors, clinical and radiological profiles along with the treatment pattern of patients admitted with mucormycosis were analyzed. **Results:** Most of the cases belonged to the 40–50 age group, although the mean age was 52.24 with patients ranging from the age of 32–76. The male: female ratio was 2:1. All patients had diabetes mellitus. 89.7% had hypertension, and 76.9% had chronic kidney disease. **Conclusion:** Diabetes mellitus and COVID-19 cause a predilection for mucor to invade the paranasal sinuses and beyond. Aggressive treatment with amphotericin B along with surgical clearance aided by radiological investigation will help in decreasing the morbidity of the disease.

Keywords: Black turbinate sign, COVID-19, COVID-19-associated mucormycosis, invasive fungal sinusitis, modified Denker's approach, mucormycosis

Introduction

Invasive fungal sinusitis is one of the most challenging forms of sinonasal pathology to manage, most commonly presenting in diabetic and immunocompromised individuals. Diagnosis of invasive fungal sinusitis requires histopathological evidence of fungi invading nasal tissue.

Mucormycosis is caused by saprophytic fungi of the order Mucorales. These fungi are widely found in the environment and are commensal in the nasal cavity. The clinical presentations of mucormycosis are rhino-orbital-cerebral mucormycosis (ROCM), pulmonary, gastrointestinal, cutaneous, renal, and disseminated mucormycosis.[1,2] ROCM is the most common form of disease in India followed by pulmonary and cutaneous types.[3,4]

Materials and Methods

This descriptive cross-sectional study was conducted on all patients who were admitted with the histopathological diagnosis of mucormycosis following surgery for acute fulminant rhinosinusitis in the Otorhinolaryngology Department, Government Medical College, Thrissur, from January 2020 to September 2021. There should be the presence of mucor with the invasion of the mucosa, submucosa, blood vessels, or bone on histopathological examination to satisfy the diagnosis of mucormycosis. Data were collected from case sheets in the medical record library after getting permission from the Superintendent and the same were entered in a self-designed pro forma. This study was approved by the Ethics Committee of our institution.

Data analysis

Qualitative data were expressed in percentage and proportion, and the quantitative data were expressed in mean and standard deviation. Data were entered into a Microsoft Excel sheet, and

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analysis of data was done using the SPSS version 16.0 (SPSS IBM, Chicago,USA).

Results

A total of 39 patients were included in the study, 26 males and 13 females. 35.9% of the patients were COVID-19 positive at the time of admission, 25.6% of the patients were post-COVID-19, and 38.5% were COVID-19 negative. All the patients had diabetes, 23.1% had chronic kidney disease (CKD), and 10.3% had hypertension [Figure 1].

Symptoms and signs

Major symptoms and signs of patients are depicted in Table 1.

About 59% of the patients had hemoglobin A1C (HbA1C) between 7 and 10, 28.2% had HbA1C more than 10, and only 12.8% had HbA1C <7. HbA1C distribution is depicted in Figure 2.

Radiological evidence of sinus and adjacent areas involved

Magnetic resonance imaging (MRI) with a contrast of the nose and paranasal sinuses and brain and computed tomography nose and paranasal sinus were done for the assessment of the extent of the disease [Table 2]. Decreased contrast uptake of the right inferior turbinate in magnetic resonance imaging with black turbinate sign is depicted in Figure 5.

Treatment pattern

51.3% of the patients were treated with liposomal amphotericin B, 46.2% were with amphotericin B complex dextrose, and 2.6% with amphotericin B lipid complex [Figure 3]. A Patient with maxillary sinus, orbital, and skin involvement postdebridement is shown in Figure 6.

Depending on the sinuses involved different types of surgical procedures was done as shown in Figure 4.

28.2% of the patients needed endoscopic medial maxillectomy with orbital clearance, 17.9% needed MMA with ethmoidectomy with sphenoidotomy, 12.8% needed endoscopic medial maxillectomy with orbital and PPF clearance, another 12.8% had to undergo partial maxillectomy, and 7.7% needed MMA with endoscopic medial maxillectomy.

Table 1: Major symptoms and signs

Symptoms	Percentage
Headache	95
Nasal obstruction	87
Eye pain	58.9
Facial numbness	58.9
Decreased vision	53.85
Facial swelling	51.3
Nasal discharge	51.3
Diplopia	35.89
Black turbinates	61.54
Ptosis	47.82
Proptosis	38.46
Facial palsy	18.8
Other cranial nerve palsy	7.69

Discussion

Invasive mucormycosis was first found by Meyer in 1815, to be a pathogen. In 1955, ROCM was first named, and it was found that the mucor would first invade the nasal mucosa and then spread to the orbit, eventually invading the brain.[5-7] In this study, 66.7% were male and 33.3% were female. In a

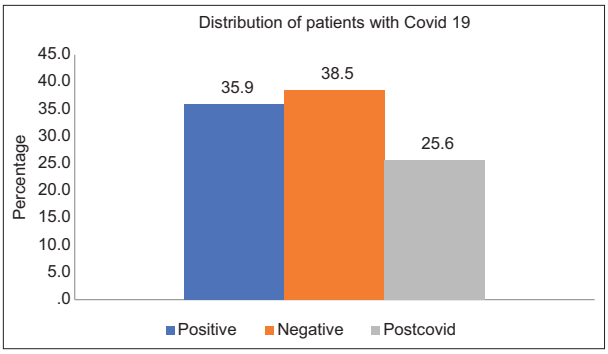


Figure 1: Distribution of COVID-19 among study population

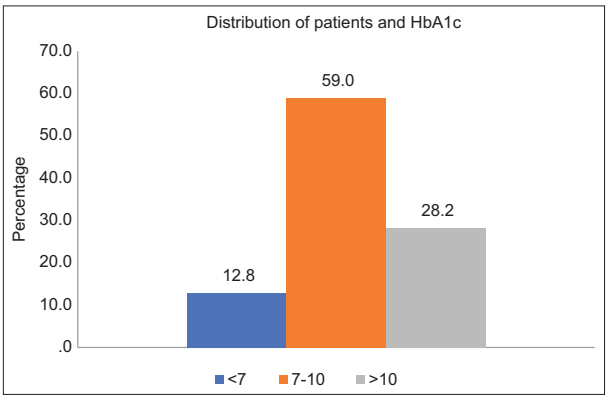


Figure 2: Frequency distribution of hemoglobin A1C among the study population. HbA1C: Hemoglobin A1C

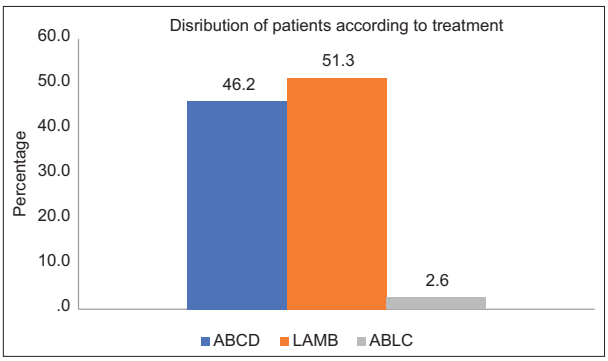


Figure 3: Percentages of patients who received different preparations of amphotericin B

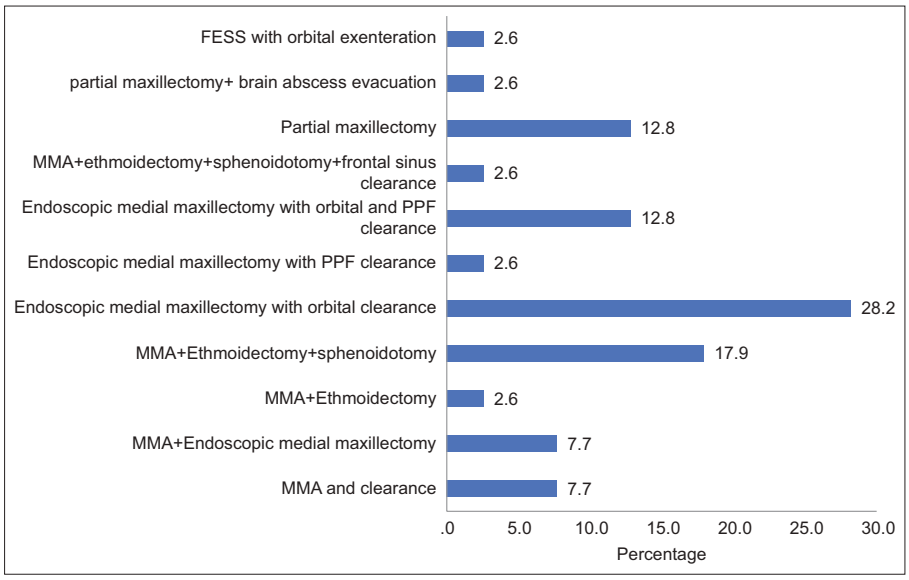


Figure 4: Percentage of patients who underwent different types of surgical procedure

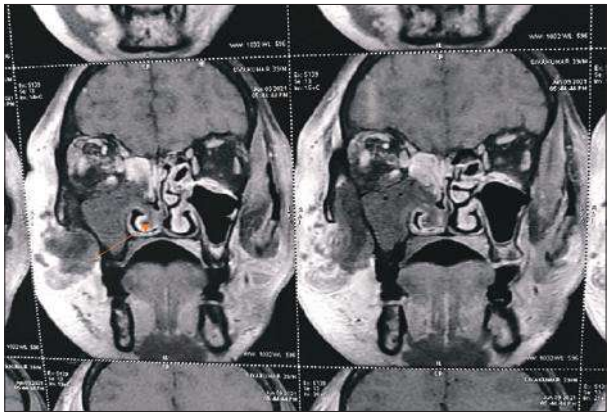


Figure 5: Decreased contrast uptake of the right inferior turbinate in magnetic resonance imaging with contrast-black turbinate (red arrow)



Figure 6: Patient with maxillary sinus, orbital, and skin involvement postdebridement

Table 2: Areas of involvement

Sinus and adjacent areas	Percentage
Maxillary sinus	100
Ethmoid sinus	79.49
Sphenoid	38.46
Frontal	15.4
Orbital involvement	53.8
Pterygopalatine fossa	28.2
Infratemporal fossa	28.2
Intracranial involvement, including cavernous sinus	17.94

study by Arjun *et al*., 76% were male and 24% were female.[8] Most of the patients belonged to the age group 41–50, and the mean age was 52.24. In the OPAI-IJO study by Sen *et al*. on mucormycosis in COVID-19, the mean age was 51.9.[9]

All the patients in our series had diabetes mellitus, 23.1% had CKD, and 10.3% had hypertension. In a study by Arjun *et al*.,[8] all patients had diabetes mellitus. In a study by Ravani *et al*. in IJO (June 2021 Volume 69 issue 6), 96.8% of patients had diabetes mellitus.[10] In a systemic review of literature of COVID-19-associated mucormycosis by Pal *et al*. in the National Library of Medicine, June 2021 edition, 96.7% of patients had diabetes mellitus.[11] In a large collaborative OPAI-IJO study by Honavar *et al*. on mucormycosis in COVID-19 (COSMIC), diabetes mellitus was present only in 78% of the patients.

In our series, 35.9% of patients had COVID-19 at the time of presentation of mucormycosis, 25.6% of patients gave a history of COVID-19, and 38.5% of the patients were COVID-19 negative. In a systemic review of literature of COVID-19-associated mucormycosis by Pal R *et al*.[10] in the National Library of Medicine, June 2021 edition, 37% developed mucormycosis

after recovery from COVID-19 infection. In a study by Ravani *et al*.[11] in IJO, 61.2% of the patients were COVID-19 positive. In a multicenter epidemiological study of coronavirus disease-associated mucormycosis by Patel A *et al*. published in EID Journal Volume 21, among the mucormycosis patients, 65.2% had COVID-19-associated mucormycosis, and the prevalence of COVID-19-associated mucormycosis was 0.27% among hospitalized COVID-19 patients.[12] In COVID-19-infected patients, through the expression of exhaustion markers NK-G2A and PD-1, dysfunction of natural killer cells and T-lymphocytes occurs. This along with decreased fungicidal activity of neutrophils may favor invasive fungal disease in COVID-19 patients.[13] We were not doing COVID-19 antibody testing in our hospital and we may have failed to identify previous COVID-19 infection resulting in more COVID-19-negative patients in our series.

Headache and nasal discharge were seen in almost all patients. The presence of symptoms such as facial swelling (51.3), facial numbness (58.97) along with decreased vision (53.85) in an immunocompromised patient warrants early identification of the diagnosis, institution of amphotericin, and planning of surgery at the earliest. Facial palsy was present in 18.8% of the patients. Intracranial involvement was seen in 17.94% of patients. Intracranial involvement includes cavernous sinus involvement in three patients, brain abscess in two patients (one in the frontal lobe and another in the temporal lobe), and dural involvement in two patients. One patient had a narrowing of the internal carotid artery also. In a review of 929 patients, reported rhino-cerebral disease was 33%, and in a systematic review by Rimesh Pal, the incidence of rhino-cerebral mucormycosis was 24%. In a study published on mucormycosis, orbital involvement was found to be 40%, and in our study, orbital involvement was 53.6%.[14]

Surgical debridement and IV amphotericin B are the mainstay of management. The most common surgeries were endoscopic sinus surgery and orbital clearance (28%). In patients with orbital involvement, whenever possible, disease clearance was done by removing the medial wall of the orbit. When MRI with contrast showed infratemporal fossa and pterygopalatine involvement, in the form of hyperintensity signal on T2 and reduced contrast uptake, the posterior wall of the maxilla was removed and disease clearance was done from these areas. Depending on the extent of involvement of the maxilla, partial maxillectomy and medial maxillectomy were performed.

51% of the patients received liposomal amphotericin B at a dosage of 5 mg/kg for 3–6 weeks, and 2.6% of patients received lipid complex amphotericin B at the same dose and duration. Due to the scarcity of drugs, amphotericin B deoxycholate was given to the rest of the patients at a dosage of 0.5 mg/kg for 3 weeks. All the patients received posaconazole 300 mg for 3–6 months. Six patients expired due to the disease, and the mortality rate was 15%.

Limitation

COVID-19 antibody was not tested in COVID-19 real-time polymerase chain reaction-negative patients. Hence, previous COVID-19 infection was not assessed in the study population. Being a retrospective study, long-term follow-up was not possible.

Conclusion

Diabetes mellitus is the most common predisposing factor of mucormycosis in our study. Rhino-orbito-cerebral disease is the most common form of clinical presentation. A high index of suspicion, early diagnosis, and institution of systemic antifungal antibiotics and surgical debridement are the key points in the management of the disease.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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CASE REPORT

CASE REPORT

An Unusual Case of Airway Obstruction: A Case Report

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Received on: 06 January 2024; *Accepted on:* 22 April 2024; *Published on:* 17 July 2024

Abstract

We report a case of an 88-year-old female who presented to us with dysphagia, change in voice, and stridor, the diagnosis of which turned out to be primary laryngeal lymphoma. It is a rare condition, and repeated biopsies are needed in most of the cases. It has a very good response to radiotherapy and chemotherapy.

Keywords: Amyloidosis, B-cell non-Hodgkin lymphoma, Case report, Chondrosarcoma, Mucosa-associated lymphoid tissue, Neuroendocrine tumors.

International Journal of Phonosurgery & Laryngology (2024): 10.5005/jp-journals-10023-1253

Introduction

When considering the incidence of malignancies that involve the head and neck, lymphoma is second only to squamous cell carcinoma. This level of frequency is attributable primarily to disease involving Waldeyer's ring and cervical nodes. In contrast, primary disease arising in the larynx is unusual. Due to the scarcity of lymphoid tissue in the glottis, most primary lymphomas arise either in the supraglottis or subglottis. Non-Hodgkin lymphoma (NHL) with primary laryngeal presentation is very rare, constituting <1% of all primary laryngeal neoplasms. In a solitary laryngeal lymphoma, radiation therapy may be the sole therapeutic modality necessary to achieve an excellent prognosis.[1,2]

We are reporting this case in view of the diagnostic challenges we faced and the rarity of the condition.

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Conflict of interest: None

Patient consent statement: The author(s) have obtained written informed consent from the patient for publication of the case report details and related images.

Case Description

An 88-year-old female presented with dysphagia for 3 months, a change in voice for 1 month, and breathing difficulty for 3 days. On general examination, stridor was present. Vitals were stable. Oral cavity, oropharynx, and neck examinations were normal. A video laryngoscopic examination was done, and it revealed edema over the left arytenoid, aryepiglottic fold (AEF) with pooling in left pyriform fossa (PFF) and left hemilarynx fixity (Fig. 1). Glottic space was critical. She underwent an emergency tracheostomy under local anesthesia. Contrast-enhanced computed tomography (CECT) scan of the neck was taken, and it showed a fairly defined enhancing soft tissue density lesion of size 2 × 3 × 6.5 cm in left PFF involving AEF, causing supraglottic luminal narrowing with extra laryngeal spread *via* a thyrohyoid membrane and paraglottic extension (Figs 2 and 3). Considering these clinical and radiological findings, a diagnosis of hypopharyngeal malignancy was made.

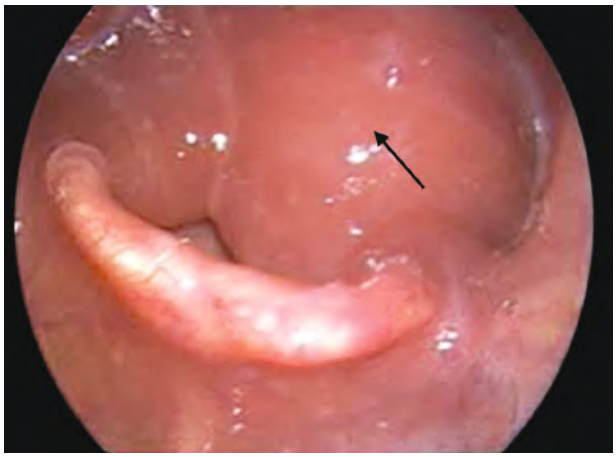


Fig. 1: Video laryngoscopy



Fig. 2: Contrast-enhanced computed tomography neck—section 1

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For confirmation, the patient underwent direct laryngoscopy with biopsy from the supraglottis under general anesthesia (GA), and the specimen was sent for histopathological examination. As the report came out as stratified squamous epithelium with inflammatory infiltrates without any evidence of malignancy, video laryngoscopy (VLS) was repeated, which showed the same previous findings. This led us to repeat the biopsy under GA, but the histopathological report (HPR) report was still negative for malignancy. In view of the high clinical suspicion, we counseled the patient and bystanders for the next attempt, and a third biopsy under GA was done.

This time, the HPR report came out as stratified squamous epithelium with a focal area of diffusely scattered atypical lymphoid cells (Fig. 4). Hence, immunohistochemistry (IHC) was done, and it showed a mild cluster of differentiation 3 (CD3) positivity and strong CD20 positivity (Figs 5 and 6), and this helped us to arrive at a diagnosis as B-cell NHL of the larynx. The patient was then referred to radiation oncology, and she took six cycles of chemotherapy with cyclophosphamide and prednisolone. VLS was done after a follow-up of 3 months and it showed complete resolution of the disease (Fig. 7). Hence, tracheostomy decannulation was done. The patient got symptomatically better, and now she is under regular follow-up.



Fig. 5: Immunohistochemistry—CD3



Fig. 3: Contrast-enhanced computed tomography neck—section 2

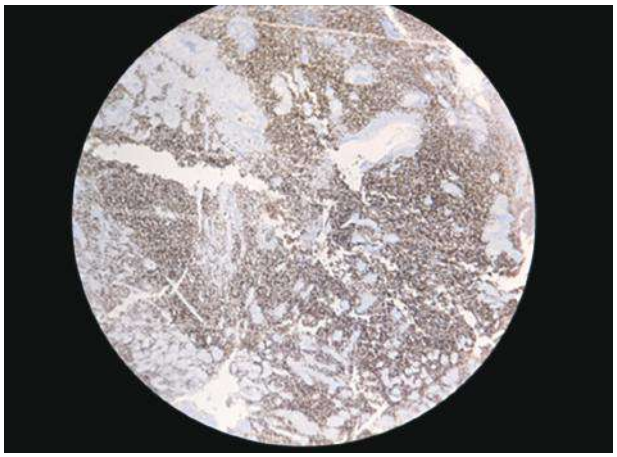


Fig. 6: Immunohistochemistry—CD20

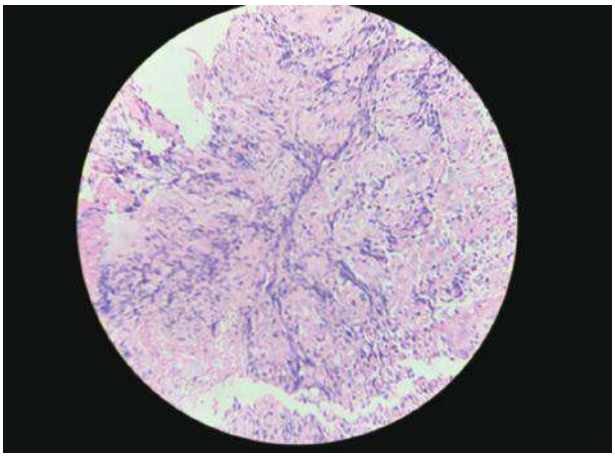


Fig. 4: Histopathology slide—hematoxylin and eosin stain



Fig. 7: Follow-up of VLS

Discussion

Non-Hodgkin lymphoma can occur in extranodal sites in 25% of the cases. NHL with primary laryngeal presentation is very rare, accounting for <1% of primary laryngeal neoplasms. It usually arises from the lymphoid collection of supraglottic lamina propria and ventricle. The most common symptoms are dysphonia and progressive airway obstruction. Usually, B-cell lineage is more common. Clinical and histological diagnosis is difficult most of the time. Repeated deep biopsies are needed for diagnosis. Around <35 cases have been reported in English literature so far.[3] It has a very good response to radiotherapy and chemotherapy. It remains localized for a long duration and then disseminates to other extranodal sites. So, lifelong follow-up and periodic evaluation are mandatory. These lymphomas are predominant in males. Most of the primary low-grade non-Hodgkin's malignant lymphomas belong to the mucosa-associated lymphoid tissue (MALT) type of lymphoma.[4] Some cases of laryngeal lymphoma were associated with extranodal lymphomas elsewhere in the upper respiratory tract.[5] Other differential diagnoses for laryngeal lymphoma are amyloidosis and chondrosarcoma.

Conclusion

Though primary laryngeal lymphoma is very rare, a high index of suspicion is needed when repeated biopsies are negative in laryngeal lesions. Histopathological examination has a very important role in aiding the diagnosis of such rare cases.

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GENERAL SURGERY

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Open Access Case Report

A Serendipitous Histopathological Revelation: An Intriguing Case Report of a Cystic Schwannoma of the Lateral Neck

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Abstract

Schwannomas are rare, benign tumors that arise from Schwann cells, which produce the myelin sheath around peripheral nerves. Cystic degeneration is an uncommon feature of schwannomas, occurring in approximately 4% of cases. The diagnosis of cystic schwannomas can be challenging due to their rarity and nonspecific clinical and radiological features.

A 45-year-old female presented with a two-year history of a gradually enlarging neck mass, which was initially suspected to be a branchial cleft cyst. Computed tomography (CT) scans showed a well-defined cystic lesion in the left supraclavicular region. The patient underwent ultrasound-guided fine-needle aspiration cytology (FNAC), which yielded hypocellular fluid. The patient underwent surgical excision of the mass, which was subsequently diagnosed as a cystic schwannoma based on histopathological examination.

Cystic schwannomas can pose a diagnostic challenge due to their rarity and nonspecific clinical and radiological features. Awareness of the clinical and pathological features of cystic schwannomas is essential for timely diagnosis and effective treatment. Accurate diagnosis is crucial to ensure optimal management and prevent recurrence.

Categories: Neurology, General Surgery, Pathology
Keywords: branchial cyst, cystic degeneration, cystic neck swelling, rare head and neck, schwanoma

Introduction

Schwannomas, also referred to as neurilemmomas, represent rare, benign neoplasms originating from Schwann cells, the neuroectodermal elements responsible for the elaboration of the myelin sheath enveloping peripheral nerves. These tumors are characteristically solitary, well-circumscribed, and encapsulated, often demonstrating a distinct cleavage plane from adjacent anatomical structures. They exhibit a predilection for the head and neck region and the flexor surfaces of the extremities, with approximately one-third manifesting within the cephalocervical domain. Among these, the parapharyngeal space constitutes the most frequently involved site [1].

On cytological examination, schwannomas typically exhibit both Antoni type A and type B tissue patterns. The cytological features generally mirror the histopathology, with Antoni type A areas showing compact, cohesive fascicles of spindle-shaped cells with varying cellularity. These regions often contain dense fibrillary stroma, palisading nuclei, and structures resembling Verocay bodies. The individual tumor cells appear as cohesive spindle or oval cells with tapering ends and indistinct cytoplasmic borders, along with noticeable variability in nuclear size and shape. Antoni type B areas, in contrast, demonstrate loosely arranged, wavy spindle cells dispersed in a myxoid matrix, often accompanied by microcyst formation, histiocytes, and lymphocytes. Immunohistochemical staining for S-100 protein typically shows strong, diffuse positivity. Although schwannomas predominantly exhibit a solid architecture, cystic degeneration is an infrequent histopathological feature, documented in merely 4% of cases [2]. The diagnosis of such lesions remains inherently challenging due to their relative infrequency and the limited diagnostic yield of fine needle aspiration cytology (FNAC) in this context, a modality otherwise instrumental in the evaluation of more common cervical masses.

Of particular diagnostic concern is the potential for schwannomas exhibiting cystic transformation to simulate branchial cleft cysts, both clinically and radiologically. This distinction is of paramount importance, as branchial cysts are prone to recurrence and necessitate long-term surveillance, whereas complete surgical excision of a schwannoma is typically curative, with recurrence being exceptionally rare.

Herein, we delineate the case of a 45-year-old female who presented with a left-sided cervical mass, subsequently identified as a schwannoma with prominent cystic degeneration, underscoring the necessity for heightened clinical vigilance and thorough histopathological evaluation in such diagnostically ambiguous presentations.

Case Presentation

A 45-year-old female presented with a swelling on the left side of her neck, which had been gradually increasing in size over the past two years, with a noticeable increase over the last four months. The swelling was associated with pain, but there were no complaints of dysphagia or breathing difficulty. On clinical examination, a 3×3 cm, mildly tender swelling was noted in the left supraclavicular region, located in the posterior triangle of the neck. The mass had well-defined borders, was firm in consistency, mobile, and not fixed to underlying muscles.

Initially, USG of the neck (Doppler) was done on the 25th of January, 2024, which showed colloid nodules in both lobes of thyroid had Thyroid Imaging Reporting and Data System (TI-RADS) TR 2 lesions, and a cystic lesion in the left supraclavicular region with a possibility of branchial cleft cyst or lymphangioma.

CT neck (plain and contrast study) showed a well-defined cystic lesion in the left side of rgw neck, with a few enhancing soft tissue densities in the peripheries, and the suggested possibilities were lymphangioma, cystic lymph node, and third branchial cleft cyst (Figure *1*).



FIGURE 1: Contrast CT of neck

a) Axial view showing a well-defined cystic lesion on the left side abutting the carotid vessel; b) Sagittal view showing the lesion abutting the paraspinal muscles; c) Coronal view showing a lesion at the root of the neck

Further evaluation with FNAC of the swelling left supraclavicular region, repeated attempts aspirated reddish fluid, and smears show only scattered macrophages, no epithelial cells seen in the smear, suggestive of a cystic lesion. The patient was taken up for surgery. A lateral neck cystic swelling was excised in toto under general anaesthesia (Figure *2*).

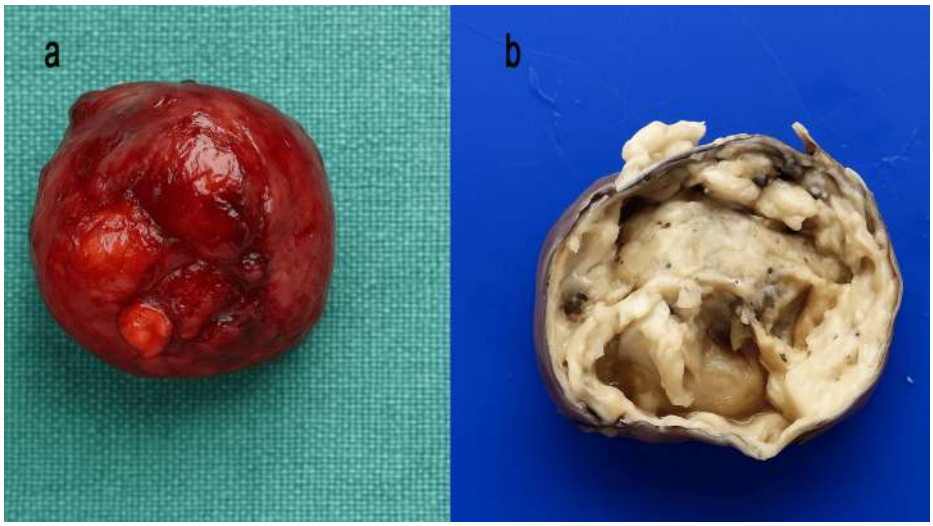


FIGURE 2: Gross morphology

a) Cyst immediately after excision; b) Cut section of the lesion showing cystic spaces

Histopathology revealed a neoplasm composed of hypercellular and hypocellular areas.
Individual cells are narrow, elongated, and wavy with a tapered end, interspersed with collagen fibers, nuclear palisading forming Verocay bodies noted, mitosis infrequent, and finally diagnosed to be Schwannoma (Figure *3*).

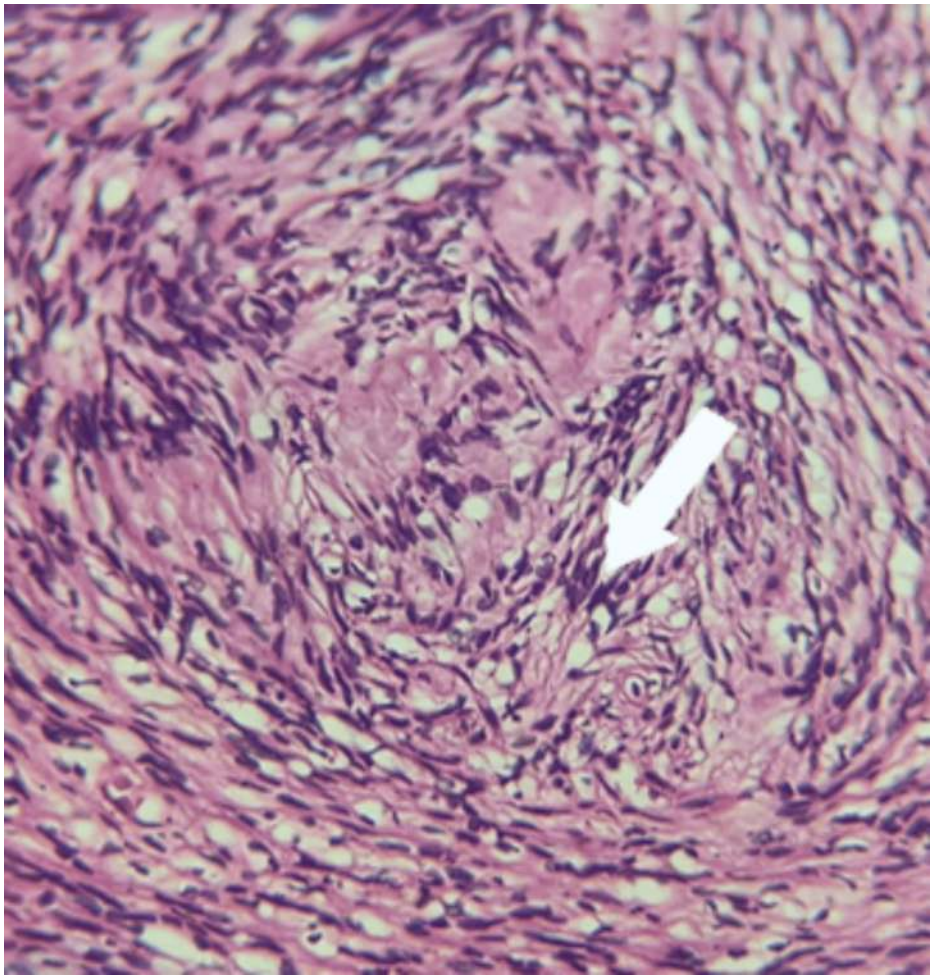


FIGURE 3: Histopathology showing hypercellular areas

Discussion

Schwannomas are benign neurogenic neoplasms arising from Schwann cells, the glial elements responsible for forming the myelin sheath of peripheral nerves. Approximately one-third of these tumors occur within the head and neck region, where they may originate from cranial, peripheral, or autonomic nerves [3]. Among the cranial nerves, the eighth cranial nerve (vestibulocochlear) is most commonly affected. The identification of the nerve of origin in schwannomas can be challenging, with approximately 10-40% of cases remaining indeterminate despite radiological and pathological evaluation [4]. This uncertainty complicates diagnostic efforts, as many of the nerves in the head and neck are small and unnamed, making it difficult to pinpoint the precise origin of the tumor. In this case, the tumor's presentation in the posterior triangle of the neck, where cystic schwannomas are rare, along with the lack of neurological symptoms, added complexity to the diagnosis. The lesion initially appeared to be a benign cystic mass, leading to a delayed recognition of its true nature. This case is noteworthy due to the unusual location of the schwannoma and its atypical presentation, highlighting the importance of considering a broader differential diagnosis and utilizing advanced imaging and pathological tests for accurate diagnosis.

Schwannomas arising in the parapharyngeal space often present as asymptomatic, slow-growing cervical masses along the medial border of the sternocleidomastoid muscle. Clinical diagnosis is frequently delayed due to the indolent nature of these lesions. When symptomatic, hoarseness and paroxysmal cough elicited by palpation may serve as subtle clinical indicators. The differential diagnosis is broad, encompassing branchial cleft cysts, paragangliomas, and malignant lymphomas [5,6].

A subset of schwannomas undergo cystic degeneration, a phenomenon observed in approximately 4% of cases [7,8]. These cystic changes complicate preoperative diagnosis, as they are associated with rapid tumor enlargement and increased lesion size. The pathogenesis of cystic degeneration is attributed to necrosis, mucinous degeneration, hemorrhage, and microcyst formation, particularly within Antoni B areas, which are characterized by loosely arranged spindle cells.

Fine-needle aspiration cytology (FNAC) often yields hypocellular or hemorrhagic aspirates in cases of cystic

schwannoma, thereby limiting its diagnostic utility. The rarity of these lesions, combined with the cytological paucity, renders FNAC alone inadequate for definitive diagnosis. However, ultrasound-guided FNAC may enhance diagnostic accuracy by enabling targeted sampling from hypercellular Antoni A regions, thereby increasing the probability of capturing diagnostic tissue.

Preoperative assessment of schwannomas relies heavily on advanced radiological imaging, with magnetic resonance imaging (MRI) being the modality of choice. MRI provides critical information regarding tumor localization, extent, and relationship to adjacent vascular structures such as the jugular vein and carotid artery. Despite radiological insights, definitive diagnosis hinges on histopathological examination, which classically reveals a biphasic pattern comprising Antoni A and Antoni B areas, palisading spindle cells, and the presence of Verocay bodies. Immunohistochemical staining, particularly diffuse S100 protein positivity, further substantiates the Schwann cell origin of these neoplasms [9].

Occasionally, lymphoid aggregates and scattered lymphocytes may be identified within schwannomas, adding to the diagnostic complexity and mimicking cystic lymphoid lesions. Therefore, in the presence of a cystic lesion with lymphoid components, cystic schwannoma should be considered in the differential diagnosis to avoid misclassification [10].

Accurate distinction between branchial cleft cysts and schwannomas is of paramount importance, given their differing clinical courses and management strategies. Incomplete excision of a branchial cleft cyst predisposes to recurrence, necessitating long-term surveillance. Conversely, complete resection of a schwannoma is typically curative, with recurrence being rare. While surgical excision remains the standard of care, conservative management may be judiciously employed in select, asymptomatic cases [11,12].

Conclusions

In conclusion, schwannomas with cystic degeneration can pose a diagnostic challenge due to their rarity and nonspecific clinical and radiological features. A high index of suspicion and careful histopathological examination are essential to distinguish these tumors from other cystic lesions, such as branchial cleft cysts. Complete surgical excision is the treatment of choice for schwannomas, and accurate diagnosis is crucial to ensure optimal management and prevent recurrence. Awareness of the clinical and pathological features of cystic schwannomas can aid in timely diagnosis and effective treatment.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Ravindran Chirukandath, Tinu Sasi, Hyfa Anan, Arya Rajesh Nair, Saranya Sasidharan

Acquisition, analysis, or interpretation of data: Ravindran Chirukandath, Tinu Sasi, Hyfa Anan, Arya Rajesh Nair

Drafting of the manuscript: Ravindran Chirukandath, Tinu Sasi, Arya Rajesh Nair, Saranya Sasidharan

Critical review of the manuscript for important intellectual content: Ravindran Chirukandath, Hyfa Anan, Arya Rajesh Nair

Supervision: Ravindran Chirukandath, Tinu Sasi, Hyfa Anan, Arya Rajesh Nair, Saranya Sasidharan

Disclosures

Human subjects: Consent for treatment and open access publication was obtained or waived by all participants in this study. Institutional Ethics Committee of Thrissur Medical College issued approval 03/2025. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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Open Access Original Article

Voices From the Field: Stakeholder Perceptions Regarding the District Residency Program Implementation in the State of Kerala, India

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Abstract

Background and rationale

The National Medical Council (NMC) introduced the District Residency Program (DRP) in 2020, mandating a three-month rotational residential work in district hospitals for postgraduate medical students with the aim of revamping the traditional postgraduate medical education system. Despite its potential benefits, the DRP has sparked debate among stakeholders. This study thus aims to evaluate the stakeholder perceptions and challenges in the implementation of the DRP in Kerala using a mixed-method approach. Unlike earlier evaluations from other Indian states, Kerala presents a unique context due to its early and comprehensive implementation of the DRP, strong public health infrastructure, and high stakeholder engagement, making it an ideal setting to generate transferable lessons for national-level policy refinement.

Materials and methods

The study was conducted at Government Medical College, Thrissur, Kerala, with participation from stakeholders across the state. A cross-sectional design was used for the quantitative part of the study, and the Delphi technique was used as a qualitative approach to identify perceptions of implementing officials and their proposed solutions to the issues identified. Informed consent was obtained from all participants before collecting information for the study. A total of 586 stakeholders participated in the study (residents n = 282; Directorate of Medical Education (DME) officials n = 180; Directorate of Health Services (DHS) officials n = 124). Quantitative data were analysed descriptively using IBM SPSS Statistics for Windows version 26, and qualitative insights were collected using a three-round Delphi process with 25 invited senior stakeholders (retention 88%).

Results

A total of 586 stakeholders participated (residents n = 282; DME officials n = 180; DHS officials n = 124). Most residents described district postings as providing diverse clinical exposure but identified gaps in infrastructure and supervision continuity. DME officials acknowledged the program's positive impact on service delivery and training but noted the need for standardized evaluation systems. DHS officials reported improved patient care and staffing at peripheral hospitals, while emphasizing the importance of better accommodation and coordination mechanisms. The District Residency Programme (DRP) was perceived to have a positive impact on postgraduate training by enhancing residents' clinical exposure, independent decision-making, and familiarity with peripheral health systems. However, gaps remained in infrastructure, supervision uniformity, and academic linkage between district hospitals and medical colleges.

Conclusion

The study highlights that while the DRP in Kerala has enhanced postgraduate training and strengthened district-level healthcare delivery, further progress requires investment in infrastructure, specialty-specific postings, and structured monitoring mechanisms to ensure uniform academic and service outcomes across sites.

Categories: Health Policy, Medical Education, Epidemiology/Public Health
Keywords: delphi method, district residency program (drp), health system strengthening, health workforce training, kerala, mixed-method approach, national medical council, postgraduate medical education, stakeholder perceptions

Introduction

In 2020, the National Medical Commission (NMC) launched the District Residency Program (DRP), requiring

postgraduate medical residents to complete a three-month posting in district hospitals as part of their training [1]. This initiative was conceived as part of the broader shift towards competency-based medical education, aiming to strengthen clinical training by exposing residents to district-level healthcare systems.

Although the DRP has the potential to enrich training, it has also generated significant debate. Critics argue that the additional posting reduces valuable time from an already condensed three-year postgraduate curriculum and disrupts academic continuity. Others, however, view the program as a necessary reform that enhances patient exposure, addresses human resource shortages in secondary care hospitals, and bridges gaps between tertiary academic centers and the health services sector [2,3].

Despite ongoing discussions, empirical evidence on stakeholder satisfaction, operational barriers, and the program's impact on postgraduate training remains scarce. Previous assessments have largely relied on administrative reports rather than systematically gathered stakeholder data, leaving a gap in understanding how the DRP functions at the ground level. Kerala provides a unique context for this evaluation due to its early statewide rollout, high health system maturity, and dual administrative control between the Directorate of Medical Education (DME) and the Directorate of Health Services (DHS). Insights from this context can offer transferable lessons for optimizing DRP implementation nationally.

To comprehensively explore this complex program, a mixed-method approach was adopted. The quantitative survey captured broad patterns of stakeholder perceptions, while the Delphi process facilitated expert consensus on key barriers and potential solutions-allowing both breadth and depth of understanding.

Kerala, a state with high literacy rates, strong public health indicators, and strict standards in medical education, was among the first in India to operationalize the DRP. With one full year of implementation completed, the state provides a unique setting to evaluate the successes and challenges of the program.

This study aims to examine the perceptions of stakeholders, including residents, the DME, and the DHS, regarding DRP implementation in Kerala. Using a mixed-methods approach that integrates quantitative and qualitative findings, we sought to identify the strengths and weaknesses of the program and to generate evidence-based insights that may inform its improvement both within the state and nationally. The objective is to assess stakeholder perceptions and identify systemic barriers and facilitators in the implementation of the DRP in Kerala, India, using a mixed-method design integrating quantitative survey and Delphi consensus techniques.

Materials And Methods

Study design and rationale

A mixed-method cross-sectional design was adopted, combining quantitative and qualitative approaches. This study employed a mixed-method design integrating quantitative and qualitative approaches. The quantitative component consisted of a cross-sectional survey conducted among postgraduate residents and officials from the DME and DHS in Kerala to assess their perceptions of the DRP. The qualitative component involved a series of iterative Delphi rounds among selected experts from both directorates to achieve consensus on key challenges and potential solutions related to DRP implementation. This design enabled triangulation of numerical trends with expert consensus to provide a comprehensive understanding of the program's functioning.

Study setting and population

The study was conducted at Government Medical College, Thrissur, Kerala, with participation from stakeholders across the state. The study population comprised three groups: (i) postgraduate residents who had undergone DRP postings; (ii) officials from the DME, including heads of departments, professors, and institutional DRP nodal officers; and (iii) officials from the DHS, including superintendents, DRP nodal officers, and directors associated with DRP centers.

Sampling and recruitment

The quantitative survey component used convenience sampling to include the maximum possible number of postgraduate residents and health administrators actively involved in DRP implementation during the study period (January-June 2024). Based on DME records, approximately 720 postgraduate residents across all government medical colleges in Kerala were eligible for the DRP postings during this period. Of these, 282 residents responded to the survey (estimated response rate ≈39%). Among administrative stakeholders, approximately 260 DME officials and 190 DHS officials were eligible; responses were received from 180 DME and 124 DHS officials.

The qualitative Delphi component used purposive sampling to recruit experts with prior experience in DRP implementation or supervision, ensuring representation from both DME and DHS hierarchies. A total of 25 experts were invited, and 22 completed all three Delphi rounds (retention 88%).

The sample size was determined pragmatically, based on feasibility and expected response rates from prior statewide stakeholder surveys, rather than on formal statistical power calculation, since the study aimed for descriptive rather than inferential analysis.

We acknowledge that convenience and purposive sampling introduce potential selection bias and may limit generalizability. However, these approaches were necessary to capture diverse stakeholder views across Kerala within logistical constraints. To mitigate bias, participation invitations were disseminated through official DME and DHS communication channels statewide, and responses were accepted from all districts to ensure wide geographic representation.

Inclusion and exclusion criteria

All postgraduate residents who had completed at least one DRP posting in Kerala during the study period were eligible. For the DME group, the inclusion criteria were faculty members or nodal officers directly responsible for postgraduate training. For the DHS group, the inclusion criteria were senior officials working in DRP-linked centers. Exclusion criteria were non-consenting individuals and those without direct involvement in DRP implementation.

Questionnaire development and validation

The questionnaire was developed following a review of existing literature on postgraduate residency programs and consultation with subject experts in surgery, medicine, and community medicine (see Appendix). A draft version was piloted among 20 residents and 10 faculty members who were not included in the final study. Based on their feedback, minor modifications were made to improve clarity and relevance. Internal consistency was assessed using Cronbach's alpha, which showed good reliability ($\alpha = 0.82$). Content validity was established through expert review by a panel of five senior faculty members from clinical and paraclinical disciplines.

Delphi technique

The qualitative component employed a three-round Delphi technique to obtain consensus among experts from the DME and DHS regarding the challenges and facilitators in DRP implementation. Twenty-five experts were invited, and 22 completed all three rounds (retention 88%).

Round 1

Participants were asked to provide open-ended responses to broad questions such as "What are the major challenges faced in implementing the DRP at district hospitals?", "What strategies have been effective in improving academic supervision?", and "What structural or policy changes could enhance DRP outcomes?" Responses were thematically analyzed to generate an initial list of recurring issues and recommendations.

Round 2

The summarized list of themes from Round 1 (e.g., infrastructure adequacy, supervision quality, rotation planning, accommodation, monitoring mechanisms, interdepartmental coordination) was circulated to the same panel. Experts rated each theme for importance and feasibility on a five-point Likert scale (1 = not important/feasible to 5 = extremely important/feasible).

Round 3

Items that did not achieve consensus in Round 2 were re-circulated with anonymized feedback summaries. Participants were asked to re-rate these items to confirm or revise their earlier responses.

Consensus operationalization

Consensus was defined a priori as ⩾70% agreement among respondents rating an item as "important" or "extremely important" (scores 4 or 5). Themes reaching this threshold were considered to have achieved consensus. Items failing to reach consensus after three rounds were documented but not included in the final priority list.

Thematic synthesis of the final Delphi findings was conducted using NVivo version 12, allowing integration with the quantitative survey results to identify convergent and divergent insights.

Data collection and analysis

Quantitative data were entered into Microsoft Excel (Microsoft Corp., USA) and analyzed using IBM SPSS Statistics for Windows, version 31.0 (released 2025, IBM Corp., Armonk, NY). Only descriptive statistics (frequencies, percentages, and means ± standard deviations) were applied, as the primary objective of this

study was exploratory, to document stakeholder perceptions rather than to test hypotheses or compare predefined subgroups. Inferential statistical testing was therefore deemed inappropriate because the sampling strategy was non-random (convenience-based) and the dataset was not designed for inferential generalization.

Qualitative data from the Delphi rounds and open-ended survey responses were analyzed using thematic analysis in NVivo version 12. Two researchers independently coded the data using a hybrid framework that combined inductive and deductive approaches. The initial coding framework was guided by the study objectives and included domains such as infrastructure, supervision, academic coordination, workload, and administrative support. Additional codes were added inductively as new ideas emerged. Discrepancies between coders were resolved through discussion, and inter-rater reliability was assessed using Cohen's kappa ($\kappa = 0.79$), indicating substantial agreement.

The study followed a convergent mixed-method design, wherein quantitative survey results and qualitative Delphi findings were analyzed separately and then integrated during interpretation. Integration was achieved through a side-by-side comparison of results in a joint display matrix and narrative weaving in the Discussion section. Specifically, quantitative trends (e.g., proportion of residents reporting inadequate supervision or satisfaction with accommodation) were compared with corresponding qualitative themes (e.g., "variable faculty engagement," "need for structured feedback"). Areas of convergence (e.g., recognition of DRP's positive impact on clinical confidence) and divergence (e.g., differing perceptions of monitoring adequacy between administrators and residents) were identified to generate actionable insights on program improvement.

This integrative approach enhanced data validity by triangulating multiple perspectives and aligning stakeholder perceptions with empirical patterns observed in the survey data.

Examples of emergent themes included "limited operative exposure due to inadequate theatre scheduling," "variation in supervision across departments," "need for joint DME-DHS monitoring," and "enhanced clinical confidence after DRP posting." These themes were then synthesized with quantitative findings to identify convergent and complementary insights.

Ethical approval for the study was obtained from the Institutional Ethics Committee, Government Medical College, Thrissur (IEC/GMCTSR/2024/242). Informed consent was obtained from all participants prior to data collection. Since no personal or sensitive data were disclosed, only aggregated findings are presented in the public domain.

Results

A total of 586 stakeholders participated in the study, comprising 282 (48.1%) junior residents, 180 (30.7%) officials from the DME, and 124 (21.2%) officials from the DHS. Among the DHS respondents, 46 (37.1%) were institutional DRP nodal officers, 24 (19.4%) were DRP coordinators, 41 (33.1%) were superintendents, four (3.2%) were deputy directors, five (4.0%) were additional directors, and two (1.6%) were program officers. From the DME side, 122 (67.8%) were heads of departments, 14 (7.8%) were professors, and 30 (16.7%) were institutional DRP nodal officers.

The mean age of the residents was 28.4 ± 2.1 years, with near-equal gender distribution. Most residents were in their second or third year of training. Their specialty distribution included general medicine (22%), general surgery (20%), pediatrics (12%), obstetrics and gynecology (10%), anesthesia (8%), orthopedics (7%), radiology (6%), emergency medicine (5%), pathology (5%), and others (5%). Among DME officials, the mean duration of service was 14.2 ± 5.6 years, while DHS officials reported an average of 17.8 ± 7.2 years of service.

Feedback from DHS officials showed that the DRP was generally well-received at the district level. Most respondents felt the program improved hospital functioning and postgraduate training, while a notable minority pointed to delays in issuing completion certificates and uneven resident distribution across districts. These perspectives include DRP contributions, overall impressions, state-level coordination, and residents' cooperation. DHS officials reported that the DRP contributed positively to hospital functioning and postgraduate academic training, as illustrated in Figure *1*.

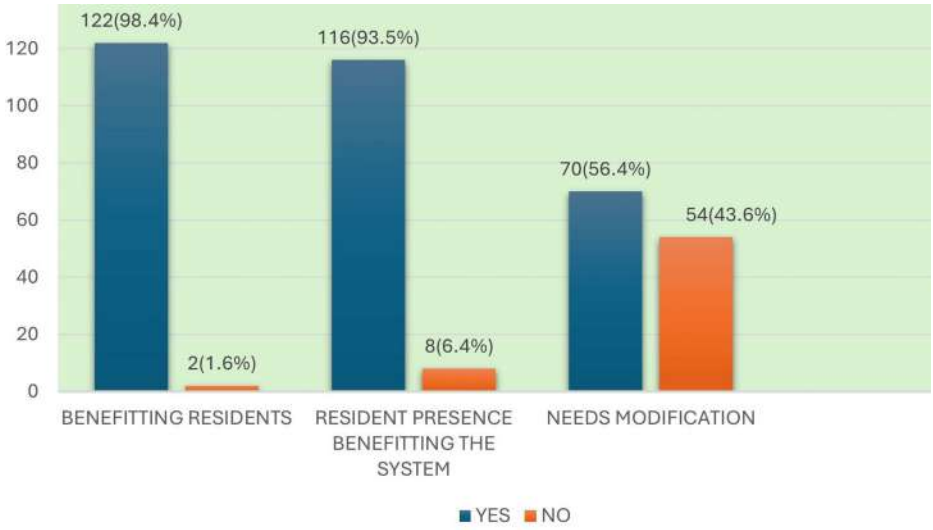


FIGURE 1: District Residency Program (DRP)'s contribution to improved training/academics/hospital work functioning

Image created by the authors with MS Excel (Microsoft Corp., USA)

When asked for an overall appraisal of the program, most DHS respondents expressed a favorable impression of DRP implementation, while a smaller group remained neutral or noted operational difficulties. This snapshot of general sentiment toward the program is summarized in Figure 2.

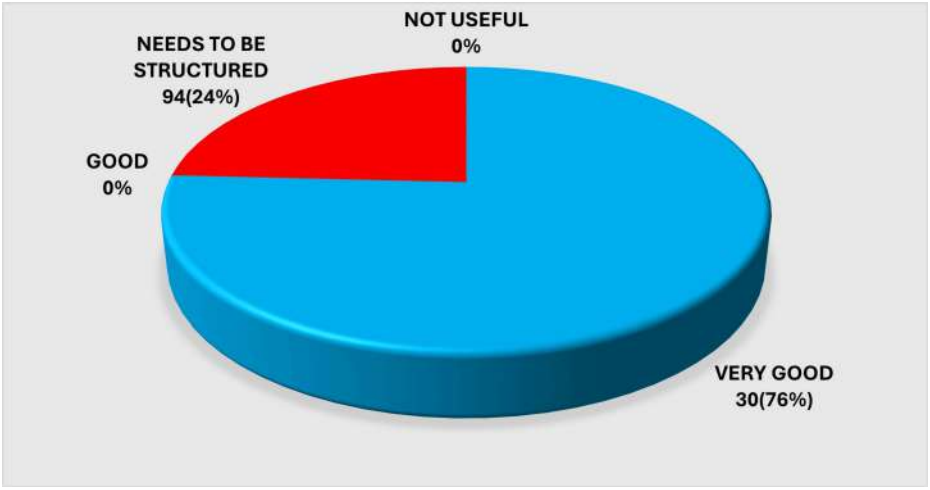


FIGURE 2: Impression regarding the District Residency Program (DRP)

Image created by the authors with MS Excel (Microsoft Corp., USA)

State-level coordination was another key metric assessed by DHS officials. Over two-thirds felt that the communication, scheduling, and administrative oversight provided by the state were good or excellent, although a minority cited delays in certificate issuance. Their detailed ratings of state coordination appear in Figure 3.

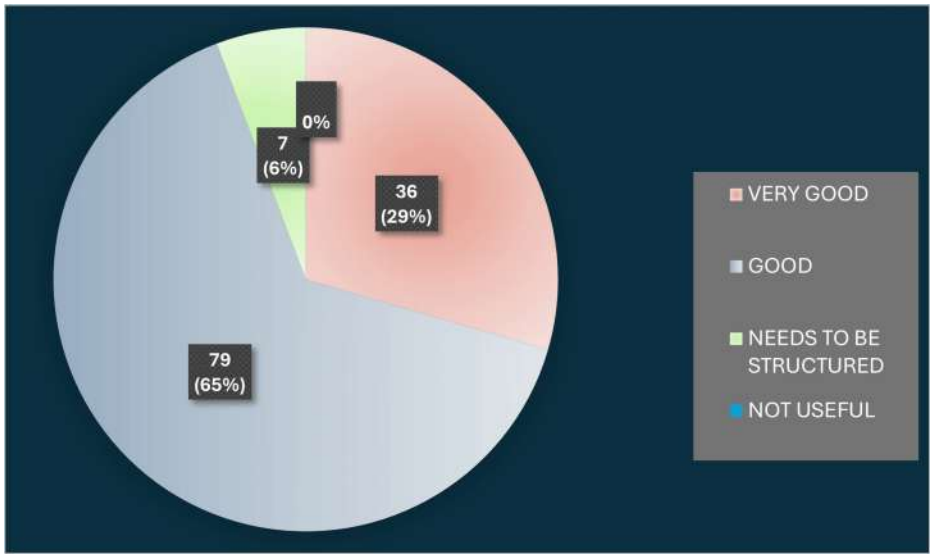


FIGURE 3: State coordination

Image created by the authors with MS Excel (Microsoft Corp., USA)

Cooperation from postgraduate residents was regarded as high, with many DHS respondents commending the residents' professionalism and willingness to adapt to district-level demands. These perceptions of resident cooperation are presented in Figure *4*.

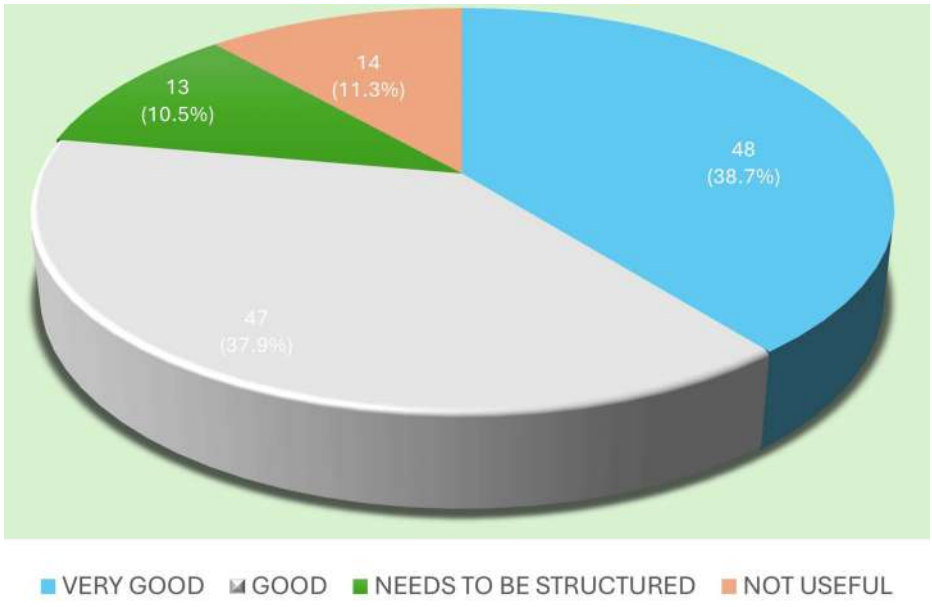


FIGURE 4: Resident cooperation

Image created by the authors with MS Excel (Microsoft Corp., USA)

Feedback from the DME side is depicted in Figures *5*-*8*, which reflect opinions regarding the DRP's impact on postgraduate training, overall impressions, coordination at the state level, and the functioning of DHS institutions hosting DRP residents.

DME officials' views on the DRP's contribution to postgraduate training and hospital academic activities are presented in Figure *5*.

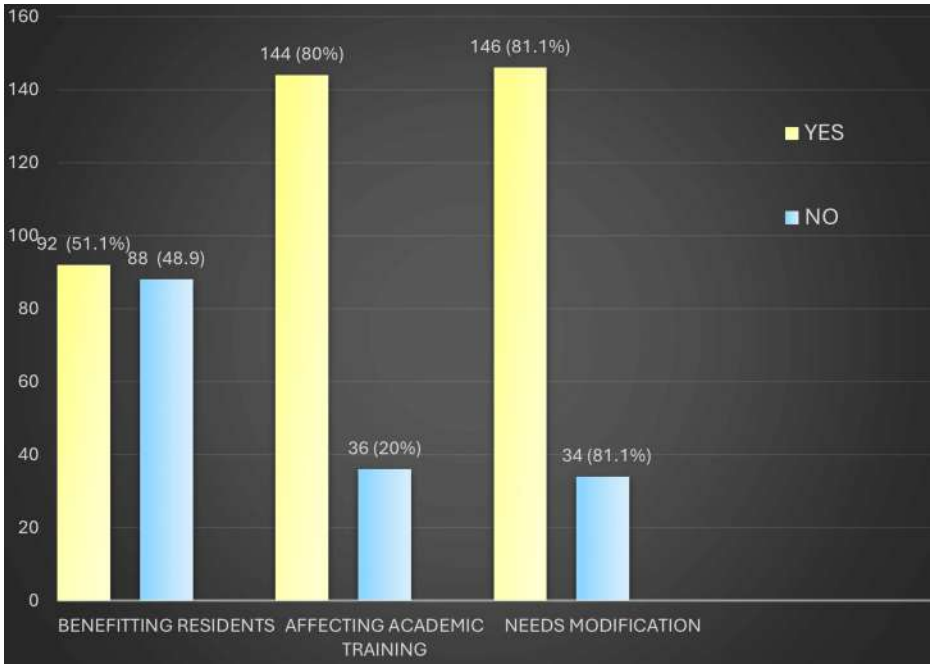


FIGURE 5: District Residency Program (DRP)'s contribution to improved training/academics

Image created by the authors with MS Excel (Microsoft Corp., USA)

DME respondents also provided an overall judgment of the DRP's success. Most rated the initiative positively, while a few pointed to challenges such as limited specialty-specific supervision and uneven resource allocation. These overall impressions are depicted in Figure *6*.

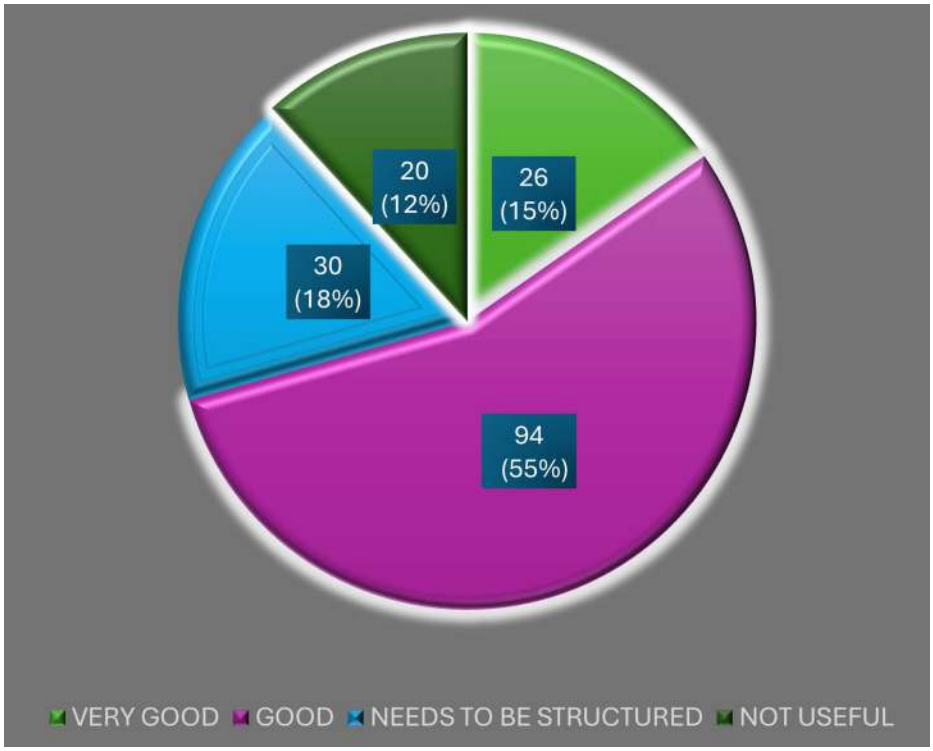


FIGURE 6: Overall impression of the District Residency Program (DRP) as per the Directorate of Medical Education (DME)

Image created by the authors with MS Excel (Microsoft Corp., USA)

Regarding state-level coordination, DME officials reported predominantly good to excellent experiences, citing efficient communication with the Directorate of Health Services and timely administrative support. The distribution of these assessments is illustrated in Figure 7.

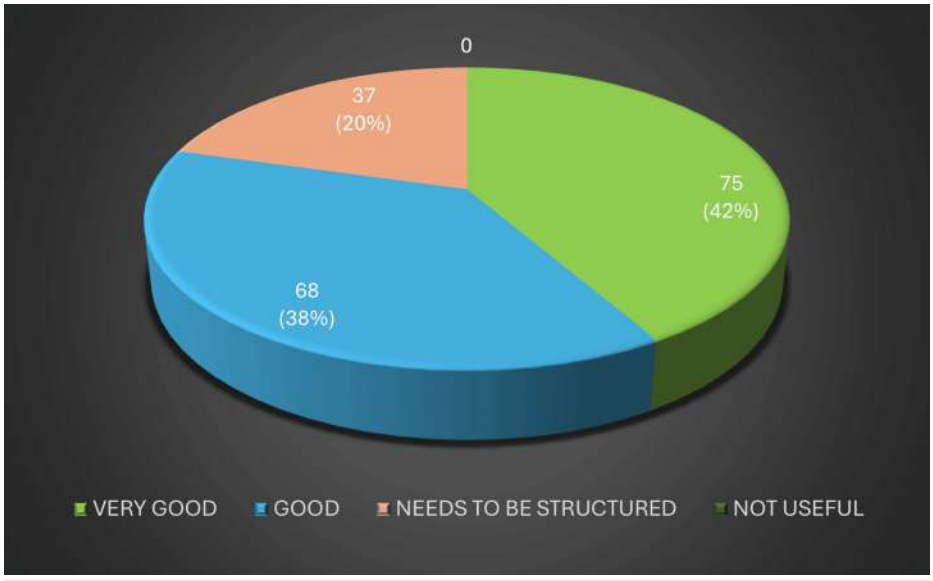


FIGURE 7: State coordination

Image created by the authors with MS Excel (Microsoft Corp., USA)

DME participants further evaluated the performance of DHS institutions that hosted the residents, noting areas of strength like patient volume as well as gaps in specialty coverage and monitoring. Their collective

views on the functioning of DRP centers under DHS are presented in Figure 8.

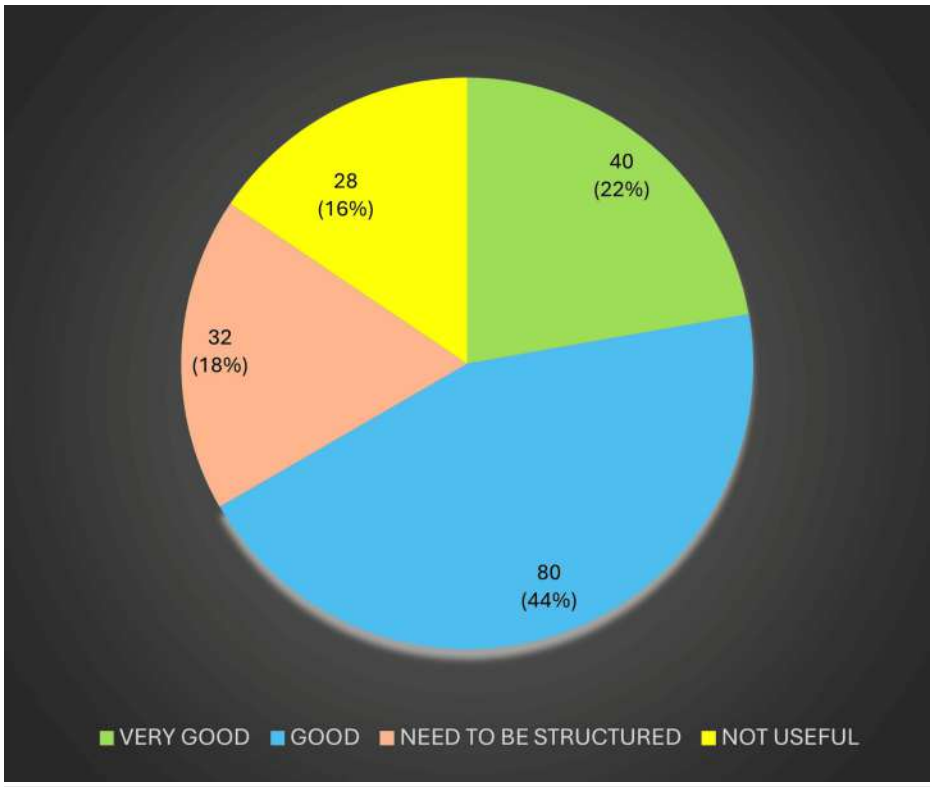


FIGURE 8: Impression regarding institutions under the Directorate of Health Services (DHS) (District Residency Program (DRP) centres)

Image created by the authors with MS Excel (Microsoft Corp., USA)

Junior resident perspectives are presented in Figures 9-12, summarizing their views on the advantages and challenges of DRP, overall impressions of the program, coordination, and experiences at DHS institutions. Junior residents' feedback highlighting the main advantages and challenges of the DRP is depicted in Figure 9.

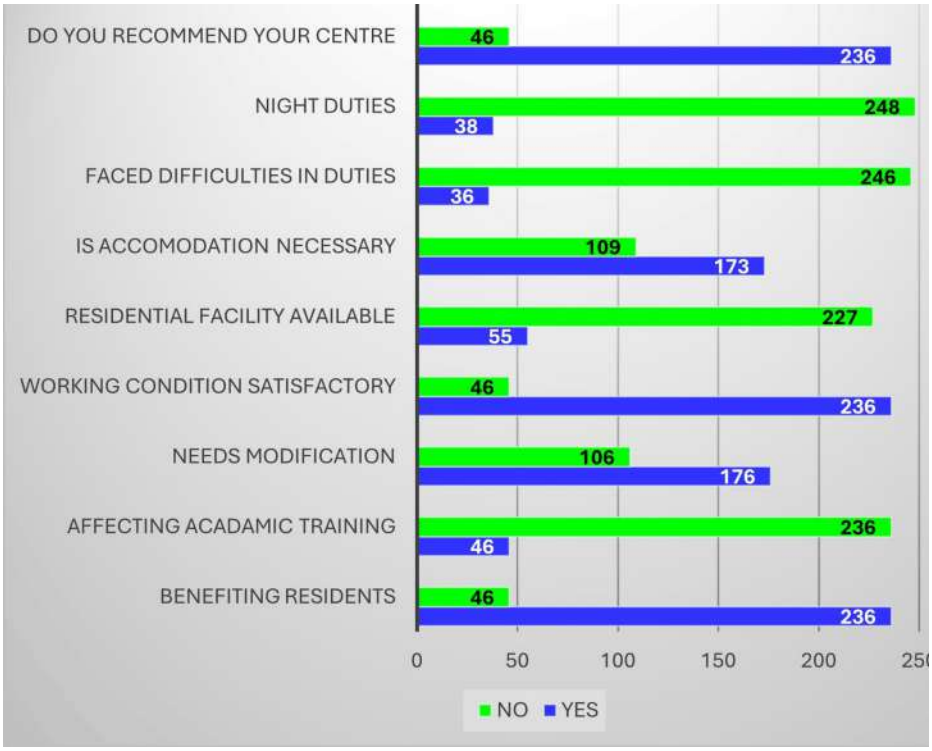


FIGURE 9: Junior resident feedback about the pros and cons of the District Residency Program (DRP)

Image created by the authors with MS Excel (Microsoft Corp., USA)

When summarizing their overall experience, a majority of residents reported satisfaction with the DRP despite the logistical and academic hurdles described above. This overall impression of the program is illustrated in Figure *10*.

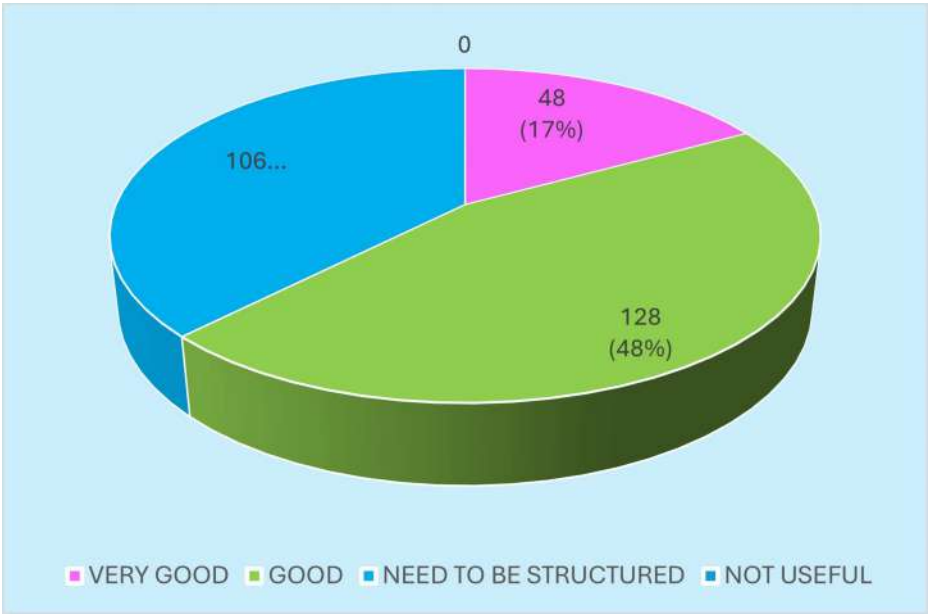


FIGURE 10: Impression regarding the District Residency Program (DRP)

Image created by the authors with MS Excel (Microsoft Corp., USA)

Residents also commented on the efficiency of state-level coordination, with most agreeing that scheduling,

communication, and problem resolution were well managed. Their ratings of coordination quality are summarized in Figure *11*.

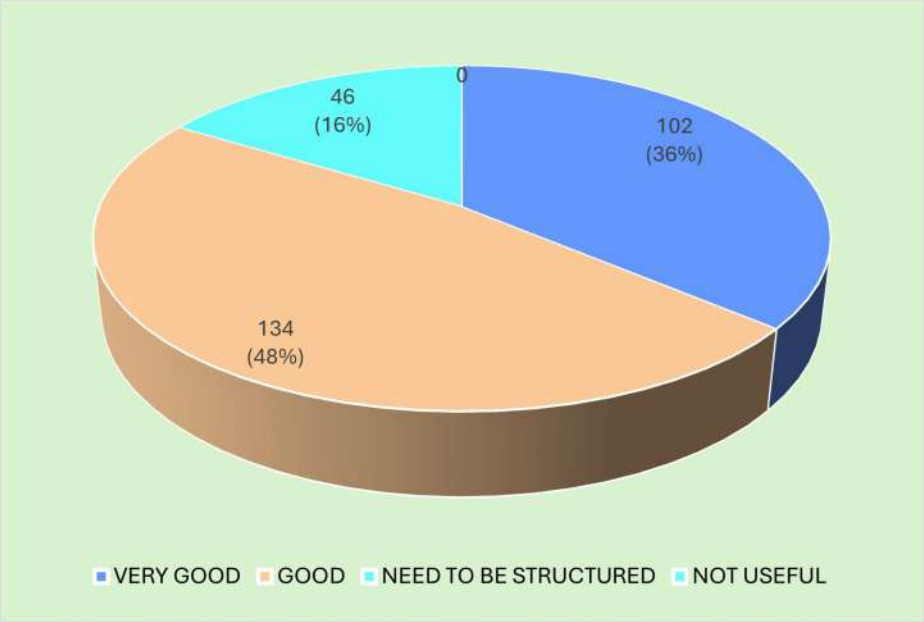


FIGURE 11: State coordination

Image created by the authors with MS Excel (Microsoft Corp., USA)

Finally, residents assessed the DHS institutions where they were posted, discussing factors such as infrastructure, supervision, and staff cooperation. These collective impressions of district centres are presented in Figure *12*.

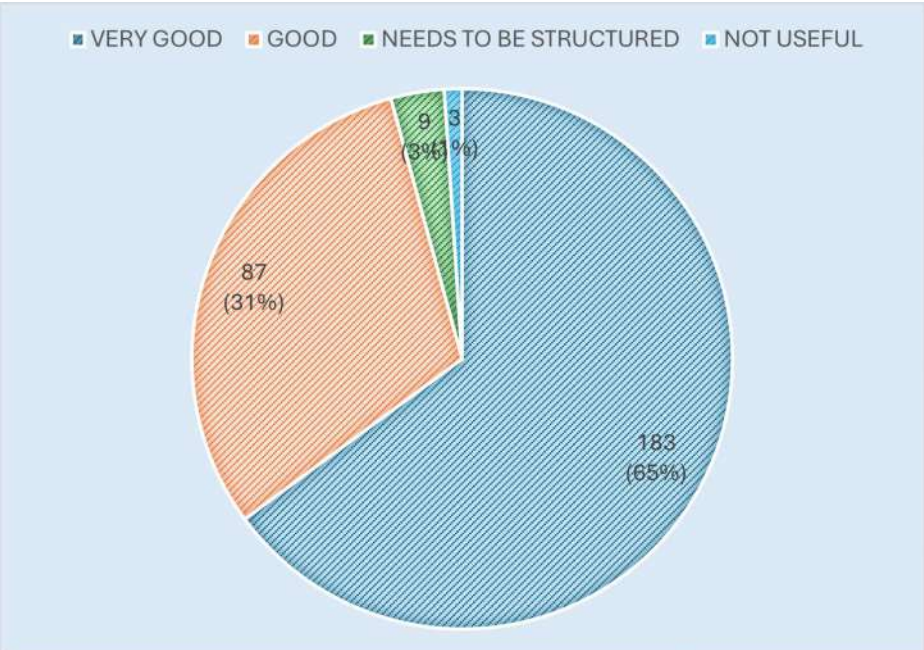


FIGURE 12: Impression regarding institutions under the Directorate of Health Services (DHS) (District Residency Program (DRP) centres)

Image created by the authors with MS Excel (Microsoft Corp., USA)

Qualitative insights (Delphi findings) and Delphi analysis (n=25 participants; 88% retention across three rounds) yielded the following key themes: 1) Structured academic support: The consensus of 20/25 (80%) recommended specialty-specific postings and structured logbooks to ensure adequate training. 2) Monitoring and evaluation: The consensus of 22/25 (88%) suggested unit-level and state-level assessment frameworks to track resident performance and center quality. 3) Infrastructure and logistical support: The consensus of 21/25 (84%) emphasized residential facilities or transport allowances to reduce travel fatigue. 4) Duration and timing of DRP: The consensus of 18/25 (72%) recommended reducing DRP duration to one to two months to minimize disruption to academic schedules. Illustrative quotes include “Without a radiology consultant at the center, residents cannot meaningfully interpret scans.” “Travel expenses consume a significant portion of our stipend, limiting engagement in hospital activities.” In the cross-stakeholder synthesis convergence, both residents and administrators recognized the need for improved supervision, structured academic activities, and equitable postings. For divergence, while administrators rated coordination highly, residents highlighted practical challenges such as travel fatigue, accommodation, and being used for service coverage rather than training. For the integration of mixed methods, quantitative satisfaction rates were supported by qualitative themes, revealing that positive overall ratings co-existed with targeted operational concerns.

System of implementation

Stakeholders reported that the overall coordination of the DRP was satisfactory. Among DHS respondents, 72% rated state-level coordination as good or excellent, while 69% of DME officials expressed similar views. However, challenges in implementation were identified. Over half (54%) of DHS respondents noted delays in issuing completion certificates, and 46% highlighted uneven distribution of residents across districts, with some areas overcrowded and others, such as Wayanad, underserved. Qualitative findings supported these observations. DHS officials emphasized the need for a structured evaluation and monitoring system and recommended equitable posting of residents across districts. One respondent noted, “Some districts have far too many residents, while others struggle with shortages. This creates an imbalance in service delivery.”

Academic impact

Most residents (84%) reported that the DRP did not significantly disrupt their academic training and that working conditions were generally satisfactory. Despite overall satisfaction with the DRP, 41% of residents reported reduced opportunities for structured teaching activities. Faculty respondents, especially from the DME, corroborated this, noting limited hands-on exposure in certain specialties such as radiology, preclinical, and paraclinical departments. Residents frequently expressed that postings in centers lacking specialty-specific consultants constrained their educational experience. These findings underscore the need for structured academic activities, specialty-aligned postings, and supervised clinical engagement to enhance the training value of the DRP. For example, radiology residents reported inadequate training opportunities in centers without qualified consultants, while preclinical and paraclinical residents noted that their laboratory-based learning needs were not met.

Integration of qualitative data highlighted similar concerns. Residents frequently expressed that postings in specialties without corresponding consultants limited the educational value of their training. As one radiology resident explained, “Without a radiology consultant at the center, we could not perform ultrasounds or meaningfully interpret scans.” Faculty echoed this sentiment, recommending specialty-specific postings and structured logbooks to monitor academic activity.

Overall satisfaction and infrastructure

Despite challenges, stakeholders broadly acknowledged the positive impact of DRP. Seventy-six percent of DME officials and 69% of DHS officials agreed that the DRP contributed positively to postgraduate training (Figures *5*-*6*). Among residents, 61% emphasized the need for accommodation facilities (Figure *9*), and 58% reported financial strain due to daily travel costs averaging INR 4,000 per month.

Qualitative feedback triangulated these concerns. Residents repeatedly called for residential facilities or, at a minimum, transportation allowances. One resident remarked, “It is very difficult to travel every day, both physically and financially. Travel expenses consume a significant portion of our stipend.” Others noted that inadequate accommodation limited their ability to participate fully in hospital activities.

Concerns were also raised about residents being treated as substitutes for medical officers. Several respondents reported disproportionate workloads compared with in-house DNB trainees, stating that the original intent of the DRP as a training program was diluted when residents were deployed primarily for service coverage. A resident expressed this sentiment as, “DRP centers should be training institutions, not just places where PGs are used to cover staff shortages."

From the DME respondents, several themes emerged. Pathology residents from private medical colleges were suggested to be posted in district hospitals for autopsy training and in state or regional public health laboratories for laboratory exposure. Concerns were expressed about the limited hands-on experience of radiology residents due to the lack of qualified radiology consultants in DHS centers, while preclinical and

paraclinical trainees were noted to require more laboratory-based training. The need for a structured monitoring system was frequently emphasized, with suggestions for implementing a mentor-mentee framework, maintaining logbooks, recording attendance, preparing detailed activity schedules, and conducting end-of-posting assessments. One respondent remarked that the DRP at times resembled an "extended holiday" owing to the absence of structured supervision. A minority also suggested that the DRP might be more effectively implemented as a mandatory program after completion of postgraduate training, rather than during residency.

Among DHS officials, a recurring concern was the lack of initiative from residents, with some respondents perceiving limited engagement and empathy in patient care. Inequitable distribution of residents across districts was also highlighted, with some districts experiencing overcrowding while others, such as Wayanad, received very few residents. DHS respondents emphasized the importance of a formal evaluation and feedback mechanism, with unit chiefs providing structured assessments of residents, and raised concerns about delays in issuing completion certificates. Many also called for better accommodation arrangements, such as access to government rest houses, and suggested extending the DRP model to include Diplomate of National Board (DNB) trainees.

Resident feedback revealed several important themes. Many called for a reduction in the duration of DRP postings, particularly for non-clinical disciplines such as Anatomy, Physiology, and Pharmacology, where they felt that limited benefit was derived. Residents repeatedly emphasized the need to be posted under consultants from their own specialties, with radiology residents requesting postings in centers with qualified radiology consultants to allow meaningful exposure to imaging, and emergency medicine residents preferring placements in higher-level centers with adequate facilities. Residents from laboratory-based specialties suggested that they should be placed in centers with active laboratory services, while several respondents requested that the duration of postings in public health laboratories be increased to two months.

Concerns regarding academic and research opportunities were widespread. Many residents reported that DRP adversely affected their academic training, and some suggested canceling the program or moving it to the end of the postgraduate course. Others pointed out the potential for research using health data available at the district level, which they felt was underutilized. Accommodation and travel were recurring challenges, with many residents reporting high travel expenses, averaging around INR 4,000 per month, and requesting provision of travel allowances or pooled transport facilities.

Residents also highlighted the need for clear duty guidelines, timely attendance reporting to avoid stipend delays, and specialty-specific digital logbooks. Many expressed dissatisfaction with being used to compensate for staff shortages, reporting that they were often burdened with additional duties compared to in-house DNB residents. Several noted that the original intent of DRP - as a structured training program - was diluted when residents were instead used as substitutes for medical officers. Finally, residents drew attention to workplace dynamics, with some reporting that interactions with other staff could be improved, remarking that "we are residents who came there to help."

Overall, the analysis of responses across all stakeholder groups provides a comprehensive picture of the strengths and challenges of DRP implementation in Kerala, while also offering actionable suggestions for its improvement.

Discussion

The findings of this study highlight both the strengths and challenges of the DRP in Kerala, echoing concerns reported in other parts of India. A study from Rajasthan found that only 17% of residents felt the learning objectives of the DRP were fulfilled, while nearly 60% reported feeling isolated from their academic departments. More than half were not posted within their own specialties, 80% expressed concerns about safety, and over 75% were dissatisfied with basic amenities [4]. Similarly, a study from Moradabad identified strengths such as enhanced patient exposure for residents from private institutions and support for peripheral human resource needs, but also weaknesses, including residents replacing medical officers, inadequate orientation, insufficient resources, and perceptions of postings as "leisure assignments" [5].

These concerns resonate with our findings in Kerala. Residents frequently reported inadequate specialty-specific training opportunities and highlighted the need for structured academic activities during postings. Officials from the DME and DHS confirmed these gaps, emphasizing inequitable distribution of residents across districts and insufficient monitoring mechanisms. Previous literature also points to additional challenges, including reduced time for thesis work, disruption of academic schedules, transport difficulties, and inadequate amenities at district centers [6]. The consistency of these themes across studies suggests that the challenges associated with DRP implementation are widespread and systemic rather than isolated to a single state.

Our study strengthens the evidence base by incorporating perspectives from multiple stakeholder groups, rather than focusing solely on residents. The combination of quantitative surveys and qualitative Delphi

analysis allowed triangulation of findings, providing both measurable trends and nuanced insights. For example, while 61% of residents indicated that accommodation was necessary, qualitative responses elaborated on the financial strain and travel fatigue associated with daily commuting. Similarly, although more than two-thirds of officials rated state-level coordination positively, open-ended feedback revealed frustrations with delays in certificate issuance and inconsistent supervision. This mixed-method approach thus provided a more comprehensive and balanced view of the DRP's current status.

Analytical depth: understanding the findings

Reduced structured teaching (41% of residents) linked to the absence of specialty-specific consultants and variability in DHS institutional resources.

Positive overall satisfaction may reflect strong state-level coordination and resident adaptability, but resource constraints and uneven supervision explain residual dissatisfaction.

Discrepancies between DME and DHS perceptions (e.g., monitoring adequacy, academic engagement) highlight institutional communication gaps.

Integration of mixed-method findings

Quantitative satisfaction rates (e.g., 84% reporting satisfactory working conditions) align with the Delphi consensus that residents are generally cooperative and that DRP improves hospital functioning.

Qualitative insights add nuance: despite overall satisfaction, logistical issues, accommodation, and specialty-specific gaps limit training quality.

Contextualization: Kerala's unique setting

High literacy, robust public health system, and effective state-level coordination may explain higher satisfaction rates compared to Rajasthan and Moradabad.

Kerala's district hospitals have better staffing ratios and infrastructure, yet challenges persist in specialty coverage and supervision, underscoring structural limits even in well-resourced states.

Recommendations linked to evidence

Administrative recommendations include streamlining certificate issuance, implementing structured monitoring, and equitably distributing residents (supported by DHS feedback on delays and overcrowding).

Academic recommendations include specialty-aligned postings, structured teaching sessions, mentor-mentee framework, and digital logbooks (supported by residents and DME faculty reporting limited hands-on exposure).

Infrastructural recommendations are provision of accommodation, transportation allowances, and improved laboratory and clinical facilities (supported by residents' qualitative feedback on travel burden and lack of resources).

Cautious interpretation

Claims about generalizability or evidence contribution are tempered, acknowledging convenience/purposive sampling and descriptive study design.

Findings provide state-level insights for Kerala while offering a framework for other states to adapt, rather than claiming national generalizability.

Several recommendations emerged from the study. Many stakeholders felt that the duration of the DRP could be reduced to one or at most two months to limit disruption of postgraduate academics. It was widely agreed that specialty-specific learning objectives should be clearly defined and standardized at the national level, ideally through a committee constituted by the National Medical Commission. The preparation of structured modules and mandatory orientation for district-level doctors were suggested as means to improve uniformity in training. Respondents also recommended the introduction of digital logbooks and a centralized certification system to improve accountability and streamline documentation.

Infrastructure and support systems were also highlighted as essential areas for improvement. Provision of residential facilities at DRP centers, or alternatively transportation allowances, was strongly recommended by both residents and administrators. Stakeholders also suggested periodic appraisal of DRP centers by a state-level team, with the authority to include or exclude centers based on compliance with training standards. Finally, several respondents proposed extending DRP to DNB trainees, noting that the program could strengthen their training while also enhancing the health system.

By addressing these challenges and implementing targeted reforms, the DRP could evolve into a more structured and impactful program that balances service delivery with postgraduate education. In its current form, the program demonstrates promise but requires adjustments to fully realize its dual goals of strengthening health services and enriching resident training.

Limitations and future directions

This study has several limitations. The use of convenience and purposive sampling may limit representativeness, and reliance on self-reported perceptions introduces the possibility of social desirability bias. Only descriptive statistics were applied, precluding inferential testing or hypothesis-driven comparisons. Despite these limitations, the integration of quantitative and Delphi-derived qualitative data provides a detailed snapshot of stakeholder experiences. Future research should include longitudinal evaluation of DRP outcomes, including residents' skill acquisition, clinical competence, and patient care metrics. In addition, Delphi feedback can inform structured monitoring frameworks, enabling systematic assessment of training quality, specialty-specific supervision, and administrative coordination in district hospitals. Comparative studies across states may further identify best practices and guide national-level DRP optimization.

Conclusions

The DRP in Kerala demonstrates strong state-level coordination and resident cooperation, yet implementation would benefit from systematized monitoring and equitable resident distribution to address observed gaps in supervision and certificate issuance. While clinical residents generally maintained satisfactory academic engagement, non-clinical and specialty-specific postings experienced inconsistent integration of structured learning opportunities, highlighting the need for targeted academic frameworks and mentor-guided activities. Finally, infrastructural and logistical improvements, including provision of accommodation, transportation support, and enhanced specialty-specific supervision, are essential to ensure sustainability and optimize both training quality and service delivery in district hospitals.

Appendices

A structured questionnaire was developed to capture stakeholder perceptions of DRP implementation. It included sections on (i) general information (stakeholder category, specialty, experience), (ii) perceptions of DRP (contribution to training, impact on academic work, state-level coordination, resident cooperation), (iii) implementation challenges (infrastructure, supervision, workload, monitoring), and (iv) suggestions for improvement (duration, specialty-specific postings, inclusion of DNB trainees). Questions were a mix of Likert-scale, multiple-choice, and open-ended formats.

Target respondents: postgraduate students, faculty members, and administrators involved in the DRP

District Residency Programme: stakeholder perception questionnaire

Section A: Demographic Profile

1. Name (optional): _____
2. Designation:
☒ Postgraduate Student
☒ Faculty
☒ Head of Department
☒ Administrator
3. Specialty: _____
4. Institution Type:
☒ Government Medical College
☒ District Medical Office
5. Years of postgraduate teaching experience:
☒ <5 years
☒ 5-10 years
☒ >10 years

Section B: Awareness and Understanding

1. I am aware of the objectives of the District Residency Programme.
☒ Strongly Agree ☒ Agree ☒ Neutral ☒ Disagree ☒ Strongly Disagree
2. The DRP was adequately introduced and explained to all stakeholders before implementation.
☒ Strongly Agree ☒ Agree ☒ Neutral ☒ Disagree ☒ Strongly Disagree
3. I understand the expected outcomes and competencies to be gained during the DRP posting.
☒ Strongly Agree ☒ Agree ☒ Neutral ☒ Disagree ☒ Strongly Disagree

Section C: Implementation Experience

4. The process of posting residents to district hospitals was smooth and well coordinated.
☒ Strongly Agree ☒ Agree ☒ Neutral ☒ Disagree ☒ Strongly Disagree
5. The infrastructure and facilities in district hospitals were adequate to support residency training.
☒ Strongly Agree ☒ Agree ☒ Neutral ☒ Disagree ☒ Strongly Disagree
6. Faculty supervision and mentorship at district hospitals were satisfactory.
☒ Strongly Agree ☒ Agree ☒ Neutral ☒ Disagree ☒ Strongly Disagree
7. There was effective communication between parent institutions and district hospitals.
☒ Strongly Agree ☒ Agree ☒ Neutral ☒ Disagree ☒ Strongly Disagree
8. The duration of the district posting (3 months) was appropriate.
☒ Strongly Agree ☒ Agree ☒ Neutral ☒ Disagree ☒ Strongly Disagree

Section D: Perceived Benefits

9. The DRP improved the residents' exposure to secondary-level healthcare.
☒ Strongly Agree ☒ Agree ☒ Neutral ☒ Disagree ☒ Strongly Disagree
10. The program enhanced residents' clinical decision-making and independence.
☒ Strongly Agree ☒ Agree ☒ Neutral ☒ Disagree ☒ Strongly Disagree
11. The DRP strengthened teamwork and community-oriented learning.
☒ Strongly Agree ☒ Agree ☒ Neutral ☒ Disagree ☒ Strongly Disagree
12. The program contributed to improved healthcare delivery at district hospitals.
☒ Strongly Agree ☒ Agree ☒ Neutral ☒ Disagree ☒ Strongly Disagree

Section E: Challenges Faced

13. Lack of basic facilities or equipment affected the quality of training.
☒ Strongly Agree ☒ Agree ☒ Neutral ☒ Disagree ☒ Strongly Disagree
14. Accommodation and logistics were satisfactory during the district posting.
☒ Strongly Agree ☒ Agree ☒ Neutral ☒ Disagree ☒ Strongly Disagree
15. Communication gaps existed between district hospital and parent medical college.
☒ Strongly Agree ☒ Agree ☒ Neutral ☒ Disagree ☒ Strongly Disagree
16. Workload at district hospitals was manageable and appropriate for training purposes.
☒ Strongly Agree ☒ Agree ☒ Neutral ☒ Disagree ☒ Strongly Disagree

Section F: Suggestions and Way Forward (Qualitative Section)

1. What were the most positive aspects of the District Residency Programme in your experience?
2. What were the major challenges you encountered during DRP implementation?
3. How do you think faculty and institutional support can be improved?
4. In your opinion, how can the DRP posting be made more beneficial for postgraduate residents?
5. Any additional comments or suggestions for policy-level improvement:

Section G: Overall Perception

17. Overall, I consider the DRP a valuable component of postgraduate training.
☒ Strongly Agree ☒ Agree ☒ Neutral ☒ Disagree ☒ Strongly Disagree
18. I would recommend continuation of the DRP with necessary modifications.
☒ Strongly Agree ☒ Agree ☒ Neutral ☒ Disagree ☒ Strongly Disagree

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Institutional Ethics Committee of Government Medical College, Thrissur issued approval IEC/GMCTSR/2024/242. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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A Paradigm for Optimal Management: Traumatic Neck Injuries at a Tertiary Care Centre in South India

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Abstract

Introduction: Traumatic neck injuries represent a critical emergency in surgical practice due to the high concentration of vital structures within the cervical region. These injuries can be classified into blunt and penetrating types, each presenting unique challenges in diagnosis and management. While advances in trauma care have improved patient outcomes, the mortality and morbidity associated with neck injuries remain significant, especially in resource-limited settings.

Materials and methods: A retrospective cohort study was conducted at Government Medical College, Thrissur, analyzing the patterns, management, and outcomes of traumatic neck injuries from January 2022 to December 2024. The study included patients aged 13-79 years, with data collected from medical records, trauma registers, and operative reports. Patient demographics, injury type, anatomical location, management strategies, and clinical outcomes were assessed.

Results: A total of 72 traumatic neck injuries were reviewed, with the majority being young males (n=57, 79%). Blunt trauma (n=45, 62%) was more common than penetrating trauma (n=27, 38%), with road traffic accidents (n=32, 44%) and falls (n=20, 28%) being the leading causes of blunt injuries, while stabbing injuries accounted for most penetrating trauma (n=20, 73%). Emergency neck exploration was required in 17 cases (24%), and the overall mortality rate was seven cases (10%), primarily due to exsanguination (n=5, 67%) and vascular damage (n=2, 33%). The highest mortality was observed in penetrating Zone II injuries (n=5 deaths, 13%), often involving major vascular damage. Complications occurred in 13 survivors (18%), including wound infections (n=6, 8%), pneumonia (n=4, 5%), and neurological deficits (n=4, 5%). Night-time injuries were reported in 43 cases (60%), with a peak incidence during festive seasons and weekends, showing a significant association with alcohol consumption.

Discussion: The findings align with global trends, where penetrating injuries, especially in Zone II, carry a significantly higher risk of mortality. The study underscores the importance of early airway management, rapid surgical intervention, and the role of imaging-based triage for blunt trauma cases. The association of neck trauma with alcohol consumption, especially during nighttime hours, highlights the need for targeted public health measures and enhanced trauma response.

Conclusion: This study provides valuable insights into the epidemiology, management strategies, and outcomes of traumatic neck injuries in a South Indian tertiary care center. The findings emphasize the critical role of early intervention, particularly in penetrating injuries involving vascular structures, and suggest that public health interventions and improved trauma care systems could optimize outcomes in this high-risk population.

Categories: General Surgery, Trauma, Health Policy
Keywords: general trauma surgery, neck vascular injury, penetrating injuries, road traffic injuries, stab injury

Introduction

Traumatic neck injuries are among the most critical emergencies encountered in surgical practice due to the concentration of vital structures within the confined cervical region. The neck houses major neurovascular bundles, the airway, the esophagus, and the spinal cord, making injuries in this area potentially life-threatening. Even seemingly minor trauma can lead to significant morbidity if underlying damage is not promptly identified and managed [1]. The complexity of these injuries necessitates a meticulous approach to diagnosis, triage, and treatment.

Neck trauma is broadly classified into penetrating and blunt injuries, each with distinct etiological factors and clinical implications [2]. Penetrating injuries, often caused by stab wounds, gunshot wounds, or industrial accidents, carry a higher risk of direct vascular or airway compromise. In contrast, blunt trauma, typically resulting from road traffic accidents (RTAs), falls, or assaults, can lead to airway obstruction,

laryngeal fractures, or vertebral injuries with secondary neurological deficits. The decision to intervene surgically depends on multiple factors, including hemodynamic stability, radiological findings, and the presence of hard or soft signs of vascular injury [3].

Despite advancements in trauma care, mortality and morbidity associated with neck injuries remain significant. Penetrating trauma carries a higher immediate mortality risk due to exsanguination or airway obstruction, whereas blunt injuries often lead to delayed complications, including cervical spine instability, airway edema, and neurological impairment. Reported mortality rates vary widely based on injury severity and access to timely medical intervention. In resource-limited settings, delays in diagnosis and surgical intervention further contribute to poor outcomes.

The management of traumatic neck injuries has evolved from a predominantly surgical exploration-based approach to a more selective, evidence-driven strategy [4]. Advances in imaging, particularly CT angiography, have enabled better delineation of vascular and aerodigestive injuries, allowing for nonoperative management in select cases. However, the need for immediate neck exploration remains crucial in patients presenting with active hemorrhage, expanding hematoma, airway distress, or neurological deterioration. Surgical decision-making is often influenced by institutional protocols and available expertise.

In South India, the burden of traumatic neck injuries is rising due to increasing RTAs, interpersonal violence, and workplace accidents. However, regional data on injury patterns, management strategies, and patient outcomes remain limited. Understanding the epidemiology and outcomes of neck trauma in this setting is essential for optimizing treatment protocols and resource allocation.

This study aims to analyze the patterns, mechanisms, and outcomes of neck injuries managed at a tertiary care center in South India over a three-year period. By examining the proportion of penetrating versus blunt injuries, mortality and morbidity rates, and the role of surgical versus conservative management, we hope to provide valuable insights that can guide future trauma care policies and protocols.

Materials And Methods

This retrospective cohort study was conducted in the Department of General Surgery, Government Medical College, Thrissur, a tertiary care center receiving a significant volume of trauma cases. This study was approved by the Institutional Ethics Committee (IEC) of Government Medical College, Thrissur, under IEC number IEC/GMCTSR/2024/235, ensuring adherence to ethical guidelines in the conduct of the research. The objective was to analyze the patterns and outcomes of traumatic neck injuries, differentiating between blunt and penetrating trauma, and to evaluate the anatomical distribution of injuries. The study included all patients aged 13 to 79 years who presented with traumatic neck injuries to the emergency and trauma department between January 2022 and December 2024. Pediatric patients below 13 years and elderly patients above 79 years were excluded.

Patient data were collected retrospectively from operative records, trauma registers, and histopathology reports. Key parameters analyzed included patient demographics (age, sex), injury patterns (blunt vs. penetrating trauma), anatomical location of injuries, management strategies (surgical vs. conservative), and clinical outcomes in terms of morbidity and mortality. The pattern of clinical presentation was also assessed. Data were recorded using a standardized proforma, entered into Microsoft Excel (Redmond, WA, USA), and analyzed using SPSS software (IBM Corp., Armonk, NY, USA). Qualitative variables were expressed as percentages and analyzed using the chi-squared test.

Each case was categorized based on the type of trauma (blunt vs. penetrating), the anatomical zone of injury (Zone I, II, or III), and the management approach (operative vs. non-operative). Imaging modalities, including CT angiography, were used for diagnostic evaluation in stable patients, while hemodynamically unstable patients underwent immediate surgical intervention as per standard trauma protocols. Surgical interventions included neck exploration, vascular repair, tracheostomy, and airway stabilization. Non-operative management involved close monitoring, serial imaging, and conservative measures such as antibiotics and wound care.

Data analysis was conducted using descriptive statistics, with comparisons made between different injury patterns and management outcomes. The study adhered to ethical guidelines, with institutional ethics committee approval obtained prior to data collection. Efforts were made to ensure data accuracy and completeness, though limitations inherent to retrospective studies, such as missing data and selection bias, were acknowledged.

One of the limitations of this study is the potential for incomplete clinical records, which may impact data accuracy. Additionally, as a retrospective analysis, missing data variables could not be controlled.

Results

A total of 72 cases of traumatic neck injuries were analyzed. The majority of patients were young males (n = 57, 79%), with a mean age of 39.6 years (range: 20-75 years). More than n = 43 (60%) of cases occurred at night, correlating strongly with RTAs and violent assaults. A statistically significant association was observed between nighttime injuries and alcohol consumption ($\chi^2 = 12.33$, $p < 0.001$, df = 1, Cramer's V = 0.414), indicating a strong correlation between alcohol use and nighttime trauma.

Blunt trauma (n = 45, 62%) was more common than penetrating trauma (n = 27, 38%), but mortality was significantly higher in penetrating injuries. Among blunt trauma cases, RTAs (n = 32, 44%) and falls (n = 20, 28%) were the most frequent causes, whereas stabbing injuries (n = 20, 73%) dominated the penetrating trauma category (Figure *1*). One rare case involved a hanging wire wrapping around the neck while riding a bike, resulting in tracheal transection, which required tracheal repair.

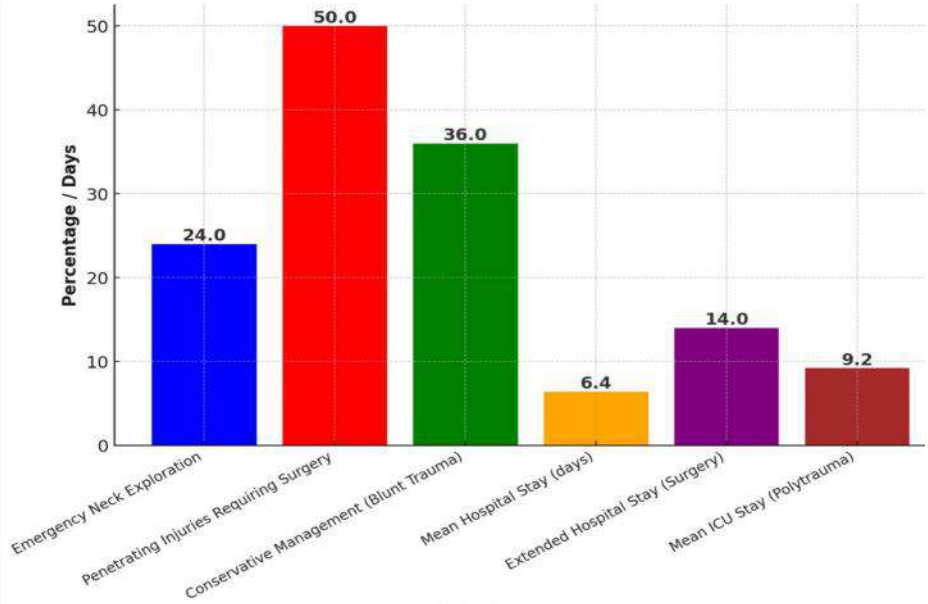


FIGURE 1: Key Findings in Neck Injury Management

Emergency neck exploration was performed in n = 17 (24%) of cases, primarily for expanding hematomas, airway compromise, and suspected major vascular injuries. Among penetrating injuries, n = 13 (50%) required immediate surgical intervention, with vascular repair and tracheostomy being the most common procedures. Conservative management was successful in n = 16 (36%) of blunt trauma cases, particularly those with stable hematomas and minor soft tissue injuries. The mean hospital stay was 6.4 days, but patients requiring surgery had an extended stay of up to 14 days. Prolonged ICU admissions were noted in polytrauma patients and those with associated cervical spine injuries, with an average ICU stay of 5.2 days.

Mortality was observed in n = 7 (10%) of cases, with exsanguination (n = 5, 67%) and vascular damage (n = 2, 33%) being the primary causes. The highest fatality rate was seen in penetrating zone II injuries, where vascular involvement was a major predictor of poor outcomes. A chi-square analysis demonstrated a trend toward higher mortality in penetrating injuries compared to blunt trauma ($\chi^2 = 3.56$, $p = 0.059$, df = 1, Cramer's V = 0.189), suggesting a clinically relevant but not statistically significant difference. Among survivors, n = 13 (18%) developed complications, including wound infections (n = 6, 8%), pneumonia (n = 4, 5%), and neurological deficits (n = 4, 5%). Patients requiring tracheostomy had a higher incidence of pneumonia ($p < 0.05$).

An interesting seasonal trend was noted, with a peak incidence of neck trauma observed during festive seasons and weekends, likely due to increased travel and alcohol-related incidents. A sub-analysis of patients with alcohol-related injuries revealed that n = 19 (70%) had penetrating trauma, predominantly stab wounds. Comparative analysis with national and international studies suggests that while overall mortality rates align with global data, the proportion of penetrating injuries leading to fatal outcomes was higher than expected, emphasizing the need for rapid intervention in such cases.

A chi-square analysis evaluating the relationship between surgical management and complication rates showed a moderate effect but did not reach statistical significance ($\chi^2 = 3.38$, $p = 0.066$, df = 1, Cramer's V = 0.217), suggesting that complications were not significantly different between surgical and conservative management groups.

In this study of 72 traumatic neck injuries, the distribution of injuries across the different zones of the neck

was as follows:

In Zone I (lower neck), n = 15 (20.8%). Blunt trauma was the leading cause, with n = 8 cases due to RTAs, n = 4 to falls, and n = 3 to industrial accidents. Surgical intervention was required in n = 7 (47%), primarily for tracheal or esophageal injuries. The mortality rate in Zone I was 13% (n = 2), with deaths caused by severe respiratory failure and hemorrhage. A chi-square test showed no statistically significant difference in mortality between blunt and penetrating injuries in Zone I ($\chi^2 = 2.14$, p = 0.143, df = 1, Cramer's V = 0.229).

In Zone II (mid-neck), n = 45 (62.5%). This zone had the highest proportion of injuries, with n = 25 (56%) from RTAs, n = 12 (27%) from violent assaults, and n = 8 from falls and industrial accidents. Vascular injuries were most common in this zone. Emergency neck exploration was performed in n = 15 (33%), mostly for airway compromise and expanding hematomas. Among penetrating injuries, which dominated in Zone II (n = 20, 73%), all required surgical intervention. The mortality rate in Zone II was 13% (n = 5), primarily due to exsanguination and vascular damage. A chi-square analysis showed a significant association between vascular injury and mortality ($\chi^2 = 9.47$, p = 0.002, df = 1, Cramer's V = 0.385).

In Zone III (upper neck), n = 12 (16.7%). Violent assaults were the most frequent cause (n = 5, 42%), followed by RTAs (n = 4, 33%). Penetrating trauma dominated (n = 8, 70%), with stab wounds being the predominant injury. Emergency neck exploration was necessary in n = 5 (42%). The mortality rate in Zone III was 8% (n = 1), caused by vascular injury and subsequent hemorrhage. No significant difference was found in mortality rates between surgical and non-surgical cases in Zone III ($\chi^2 = 0.84$, p = 0.358, df = 1, Cramer's V = 0.176) (Figure 2).

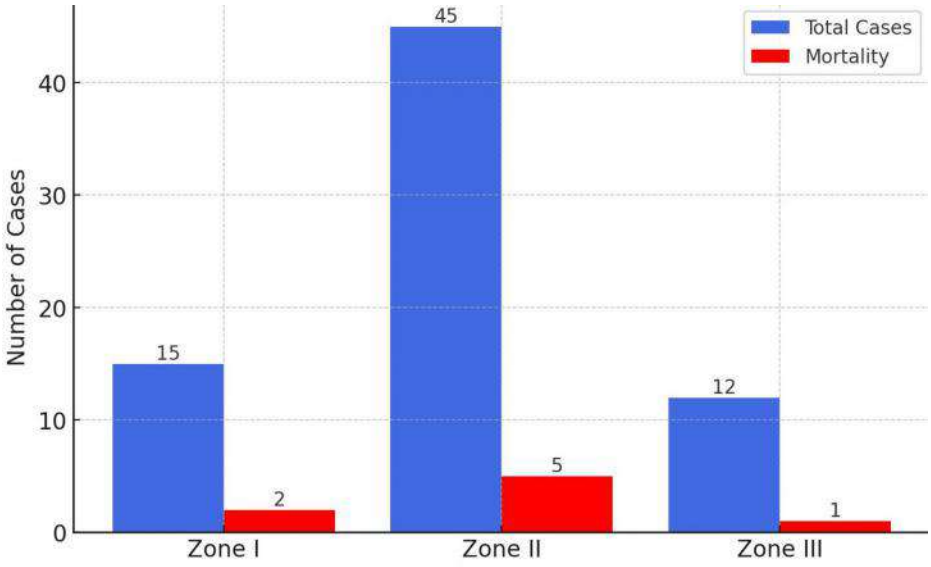


FIGURE 2: Injury Zones and Mortality Rates

Discussion

Neck injuries, whether from blunt or penetrating trauma, present a significant challenge to trauma surgeons due to the complex anatomy and high risk of morbidity and mortality. This study provides a comprehensive analysis of the patterns, management strategies, and outcomes of traumatic neck injuries treated at a tertiary care center in South India over a three-year period.

Demographics and injury patterns

Our findings show that young males (79%) were disproportionately affected, with a mean age of 39.6 years. This aligns with global trauma epidemiology, where young adult males are at higher risk due to greater exposure to RTAs, interpersonal violence, and occupational hazards. The predominance of blunt trauma (62%) over penetrating trauma (38%) mirrors trends seen in other studies from India, Southeast Asia, and Europe, where RTAs remain a leading cause of injury [5].

In contrast to Western data, where firearm-related injuries constitute a significant proportion of penetrating trauma, our study found that stab wounds accounted for 73% of such injuries. This discrepancy reflects differences in social and legal factors governing weapon access. For instance, in the United States, gunshot wounds represent a considerable proportion of penetrating trauma, whereas in European countries, stab wounds are more prevalent [6].

Mortality and morbidity trends

Our study's finding of a higher mortality rate in penetrating neck injuries, particularly those affecting Zone II with vascular involvement, aligns with existing literature [7]. Mortality rates for penetrating neck injuries can reach up to 10%, with vascular injuries being a significant contributor to fatal outcomes. Specifically, arterial injuries occur in approximately 25% of such cases, with carotid artery involvement seen in about 80% of these instances. This underscores the critical importance of early recognition and rapid intervention in managing penetrating neck trauma.

Among survivors, 18% developed complications, with wound infections, pneumonia, and neurological deficits being the most frequent. The presence of neurological deficits in 5% of cases was predominantly observed in patients with cervical spine involvement, underscoring the need for early spinal assessment in neck trauma cases. Prolonged ICU stays were observed in polytrauma patients, further emphasizing the importance of a multidisciplinary approach to trauma management.

Management strategies and surgical outcomes

In our cohort, emergency neck exploration was performed in 24% of cases, mostly for expanding hematomas, airway compromise, and suspected major vascular injuries. This aligns with current trauma guidelines recommending immediate surgical exploration for unstable patients with penetrating injuries, particularly those involving vascular structures. The success of conservative management in 36% of blunt trauma cases, especially those with stable hematomas, reflects a growing trend toward non-operative management in select patients. Recent literature suggests that imaging-based triage, particularly with CT angiography, can help avoid unnecessary surgical interventions while ensuring timely intervention for critical injuries [8].

A key finding in our study was that 80% of penetrating injuries required immediate surgical intervention, with vascular repair and tracheostomy being the most commonly performed procedures. This is in line with data from North American and European trauma centers, where early airway protection and vascular control are paramount in penetrating neck trauma [9]. Our findings further reinforce the role of damage control surgery in cases with severe hemorrhage, emphasizing the need for rapid airway control, hemostasis, and staged surgical interventions in unstable patients [10].

A proportion of patients in our study were managed non-operatively, particularly those with stable hematomas, minor vascular injuries, and soft tissue involvement without airway compromise. These cases were closely monitored with serial clinical assessments and imaging to identify any progression requiring intervention. The success of non-operative management highlights the importance of careful patient selection and the role of imaging in guiding treatment decisions. Our findings align advocate for a more selective approach to surgical intervention, reducing unnecessary procedures while ensuring patient safety and favorable outcomes.

Time trends and seasonal variations

Interestingly, our data revealed a peak in neck injuries during festive seasons and weekends, suggesting a correlation with increased alcohol consumption, travel-related accidents, and interpersonal violence. This pattern has been previously documented in trauma literature, where alcohol-related trauma surges are reported during major holidays [11]. These findings underscore the potential benefits of targeted public health interventions, stricter enforcement of road safety measures, and community awareness programs during high-risk periods.

Another notable trend was the predominance of nighttime injuries (60%), particularly among RTA-related cases. Studies have shown that reduced visibility, fatigue, and alcohol intoxication contribute significantly to nighttime crashes [12]. This highlights the need for improved road lighting, stricter enforcement of driving regulations, and better trauma response preparedness during nighttime hours.

Our study findings are consistent with reports from Indian and global trauma registries, where blunt trauma remains predominant [13], but penetrating injuries carry higher morbidity and mortality. However, unlike Western countries, where firearm-related penetrating injuries are more prevalent, stab wounds and industrial accidents were the leading causes of penetrating trauma in our cohort. This difference highlights the need for region-specific trauma management strategies tailored to local injury patterns.

The success of non-operative management in select blunt trauma cases aligns with a growing body of evidence suggesting that CT angiography-based decision-making can significantly reduce unnecessary surgeries without compromising outcomes [14]. However, our study also reinforces the fact that timely surgical intervention remains the cornerstone of management in unstable penetrating injuries, particularly those with vascular or airway involvement.

The distribution of zones underscores the significant burden of Zone II injuries, which made up the majority of cases, particularly due to the prevalence of penetrating trauma. The association of Zone II injuries with

higher mortality due to vascular involvement highlights the critical need for rapid surgical intervention. In contrast, Zone I and Zone III injuries, while less common, still posed significant challenges, particularly in terms of airway management and vascular damage.

Clinical implications and future directions

The findings of this study have several important clinical implications. First, the high mortality in penetrating Zone II injuries suggests a need for more structured trauma protocols, including early vascular imaging and pre-hospital airway management. Second, the high proportion of nighttime and alcohol-related injuries highlights the potential impact of targeted public health interventions, stricter traffic regulations, and enhanced trauma response systems during high-risk periods.

Studies have shown that the use of CT angiography as a first-line imaging modality improves diagnostic accuracy and facilitates timely decision-making, thereby reducing unnecessary surgical interventions [15]. Additionally, advancements in endovascular techniques have provided an alternative to open surgery in select vascular injuries, demonstrating improved outcomes in recent trauma studies [16]. Moreover, the implementation of standardized trauma protocols, including Advanced Trauma Life Support (ATLS) guidelines, has been associated with a reduction in mortality and morbidity in major trauma centers globally [17].

Moving forward, prospective multicenter studies are needed to further evaluate the role of imaging-based triage in blunt trauma cases and refine criteria for non-operative management. Additionally, efforts should focus on improving pre-hospital trauma care, including early airway protection, hemorrhage control, and rapid transport to definitive care centers.

Limitations

Despite its valuable insights, this study has certain limitations. First, as a single-center retrospective study, the findings may not be generalizable to all healthcare settings. Selection bias is a potential concern, as only patients presenting to our tertiary care center were included, potentially underrepresenting cases managed in peripheral hospitals. Additionally, variations in pre-hospital care and transport times may have influenced mortality and morbidity outcomes. The reliance on medical records for data collection introduces a risk of missing or incomplete information. Finally, while statistical analyses were performed to identify associations, causation cannot be definitively established due to the observational nature of the study. Future prospective, multi-center studies with larger sample sizes and standardized data collection protocols are recommended to validate our findings.

Conclusions

This study provides valuable insights into the patterns and outcomes of traumatic neck injuries in a tertiary care setting in south India. While blunt trauma remains more common, penetrating injuries pose a significantly higher risk of mortality, particularly when involving vascular structures in Zone II of the neck. The findings emphasize the importance of early airway management, rapid surgical intervention, and the role of imaging-based triage in blunt trauma cases. Given the peak incidence of trauma during festive seasons and nighttime hours, targeted public health measures and improved pre-hospital trauma response could further optimize patient outcomes.

The study's limitations include its retrospective design, single-center setting, and potential for selection and reporting bias. Additionally, incomplete follow-up data and variability in trauma management may affect the generalizability of findings.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Consent for treatment and open access publication was obtained or waived by all participants in this study. Institutional Ethics Committee, Government Medical College, Thrissur issued approval IEC/GMCTSR/2024/235. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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Unraveling the Enigma: A Five-Year Comprehensive Analysis of Hurthle Cell Tumors in South India's Tertiary Care Center

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Abstract

Background: Hurthle cell tumors of the thyroid gland constitute a rare and enigmatic group of neoplasms, characterized by the presence of Hurthle cells exhibiting abundant eosinophilic cytoplasm and numerous mitochondria. Despite their low incidence, they pose diagnostic challenges and display diverse clinical outcomes. This study aims to provide a comprehensive analysis of the clinicopathological profile of Hurthle cell tumors within a tertiary care center in South India.

Methods: Through a retrospective approach, we analyzed cases of Hurthle cell tumors diagnosed and treated at a tertiary care center over a five-year period. Clinical, radiological, and histopathological data were meticulously collected and scrutinized. The study focused on examining demographic details, presenting symptoms, imaging features, cytological findings, surgical management, and postoperative outcomes of the patients.

Results: A total of 32 cases of Hurthle cell tumors were identified during the study period. The majority of patients were female (84%), with a mean age of 49.6 years for Hurthle cell carcinoma. Thyroid enlargement and neck mass were the most common presenting complaints. Fine-needle aspiration cytology showed characteristic features suggestive of Hurthle cell tumors in 33% of cases. Total thyroidectomy remains the mainstay surgical approach. Histopathological evaluation confirmed 62.5% of cases as benign adenomas and 37.5% as malignant carcinomas. Among malignant cases, 67% showed capsular invasion and 33% demonstrated vascular invasion. Of the patients, 33.3% received adjuvant radiotherapy. The overall survival rate was 100%. In our study, we found that thyroid nodules larger than 3 cm demonstrated a higher propensity for Hurthle cell carcinoma.

Conclusion: Our findings support the multidisciplinary approach in managing Hurthle cell tumors, with a focus on tailored treatment plans for each patient based on individual characteristics. By recognizing the female predominance, assessing nodule size, and employing a combination of thyroidectomy and ablative therapy, clinicians can optimize patient care and contribute to better long-term prognosis and quality of life for those affected by Hurthle cell tumors. Continued research and collaborative efforts are necessary to advance our understanding and refine treatment strategies, paving the way for improved outcomes and enhanced patient management in the future.

Categories: Pathology, General Surgery, Oncology
Keywords: hurthle cell carcinoma, tumor surgery, adjuvant radiation therapy, thyroid, thyroid nodule size, hurthle cell neoplasm

Introduction

Hurthle cell tumors of the thyroid gland, also known as oncocytic tumors, represent a distinct subgroup of thyroid neoplasms. They are characterized by the presence of Hurthle cells, which are large, granular, and eosinophilic cells with abundant mitochondria [1]. Hurthle cell tumors account for approximately 3-5% of all thyroid neoplasms [2], and they can exhibit a spectrum of clinical behaviors ranging from benign adenomas to malignant carcinomas.

Despite their relative rarity, Hurthle cell tumors present diagnostic challenges and therapeutic dilemmas due to their morphological heterogeneity and uncertain biological behavior. The differentiation between Hurthle cell adenoma and carcinoma has been a subject of variation, with researchers employing diverse criteria for this purpose. Additionally, many have proposed different morphologic characteristics to distinguish between benign and malignant Hurthle cell tumors [3]. Recent molecular studies have shed light on the distinct oncogenic features of Hurthle cell carcinomas, suggesting that they represent a separate pathological entity from both Hurthle cell adenomas and follicular cell carcinomas [4,5].

The accurate preoperative diagnosis of these tumors is essential for appropriate management decisions. Fine-needle aspiration cytology (FNAC) is the primary diagnostic modality; however, due to the overlapping cytological features with other thyroid lesions, definitive diagnosis can be challenging [6]. Numerous studies have provided evidence of the effectiveness of fine-needle aspiration (FNA) in identifying Hurthle cell neoplasms among thyroid nodules [7]. However, accurately classifying Hurthle cell neoplasms as either benign or malignant based solely on FNA data can pose challenges [8].

Furthermore, the management of Hurthle cell tumors remains controversial. The optimal extent of surgical resection, the role of adjuvant therapy, and the long-term outcomes in terms of recurrence and survival are subjects of ongoing debate [9]. Studies exploring the clinicopathological features and outcomes of Hurthle cell tumors are crucial for a better understanding of this entity and to guide evidence-based management strategies.

The clinical course of Hurthle cell carcinoma has been a subject of varying interpretations among researchers. Some have reported a very favorable clinical outcome for this tumor, while others have regarded it as a relatively aggressive malignancy of the thyroid gland [10]. This diversity of perspectives highlights the complexity of understanding and managing Hurthle cell carcinoma, warranting further investigation and consensus-building to improve patient outcomes.

This study aims to provide a comprehensive analysis of the clinicopathological profile of Hurthle cell tumors of the thyroid gland in a tertiary care center in South India. By evaluating the demographic characteristics, presenting symptoms, radiological features, cytological findings, histopathological characteristics, surgical management approaches, and postoperative outcomes, we aim to contribute to the existing knowledge regarding the management of Hurthle cell tumors and provide insights into their clinical behavior in our population.

Materials And Methods

The study encompassed a retrospective analysis set in the Department of General Surgery at Government Medical College, Thrissur. Ethical clearance was sought and obtained from the Institutional Ethics Committee, Government Medical College, Thrissur (IEC/GMCTSR/2023/058). It involved meticulous examination of the operative and histopathology records for all Hurthle cell tumor cases operated on an elective basis from January 2018 to March 2023. The aim was to delineate the various subtypes of Hurthle cell tumors and their demographic distribution, including age patterns and sex ratio, clinical presentation, and anatomical locations.

Inclusion and exclusion criteria

The study defined clear inclusion and exclusion criteria to maintain focused research parameters. Included were elective cases diagnosed with Hurthle cell tumors across a wide age range, specifically from 13 to 70 years, that presented to the Department of General Surgery at the said medical college within the designated study period. In our hospital, we only treat patients aged 13 years and above, in general surgery, thus excluding data for younger patients. Conversely, exclusions encompassed patients outside of the age range considered (under 13 and over 70 years).

Materials for the study were drawn from patients' surgical records and the associated histopathological findings post-resection. The methodology revolved around collating a comprehensive dataset that included both neoplastic and non-neoplastic lesions, as well as classifying them into benign or malignant categories.

Data were meticulously collected, encompassing demographics, clinical symptoms, radiological and cytological findings, surgical management, and postoperative outcomes. The analysis focused on constructing a comprehensive clinicopathological profile, reviewing imaging findings for nodule characteristics, and ensuring the accuracy of cytological diagnosis, which is done by assessing the concordance between the cytological findings and the final pathological diagnosis. All patients primarily underwent total thyroidectomy, and surgical details, along with the postoperative course, were closely documented. Histopathological examination by experienced pathologists identified benign and malignant cases based on specific criteria such as capsular and vascular invasions. Furthermore, the study tracked postoperative care, including adjuvant therapy administration and long-term follow-up to assess recurrence and overall survival, adhering to the rigorous ethical standards set forth by the Institutional Ethics Committee.

Data management

The collected data were systematically categorized according to different age groups and genders using a predefined proforma. The recorded details included the nature of the lesion, patient demographics, and clinical outcomes. This dataset was subsequently entered into Microsoft Excel (Microsoft Corporation, Redmond, WA), and statistical analysis was conducted using SPSS software (IBM Corp., Armonk, NY). The qualitative data, represented as percentages, were primarily examined using the chi-square test for any significant associations or trends.

During the period from January 2018 to March 2023, we conducted a retrospective review and got 32 patients diagnosed with Hurthle cell tumors. For all patients, we obtained detailed thyroid function profiles, including FT3, FT4, thyroid-stimulating hormone (TSH), and serum thyroglobulin. In parallel, ultrasonography data were accrued for all participants in the study. Each patient underwent FNAC for a thyroid nodule or neck node evaluation. A reported finding of a "follicular lesion" on FNAC was considered indicative of a potential malignancy, prompting surgical intervention. In instances where cervical lymph node involvement was detected either via preliminary imaging or during surgical examination, cervical lymph node dissection was performed.

The tumors were histopathologically classified into "carcinoma" if evidence of vascular or capsular invasion was present, or "adenoma" in the absence of such invasion. Tumor size information, critical for comprehensive assessment, was typically sourced from the surgical specimens, supplemented by imaging reports and clinical examination notes. The initial tumor extent was defined in concordance with the TNM (tumor, node, and metastasis) staging classification standards. All diagnosed invasive carcinomas were managed post-surgery with radioactive iodine therapy. Cases exhibiting metastatic disease underwent repeated radioactive iodine treatments. Following the primary treatment protocol, every patient embarked on levothyroxine TSH-suppressive therapy to aid in postoperative management and reduce the risk of recurrence.

Ultimately, this approach was chosen to ensure a thorough and ethically compliant investigation into the clinicopathological attributes of Hurthle cell tumors, seeking to enhance the overall understanding and clinical management of these neoplasms.

Results

The study included 32 patients, with 27 females and five males (Table *1*). Out of these, 20 cases were diagnosed as Hurthle cell adenoma, and 12 cases were identified as Hurthle cell carcinoma upon final histopathological examination (Figure *1*).

Variables	Hurthle cell adenoma	Hurthle cell carcinoma
Number of patients	20	12
Male, n (%)	1 (20%)	4 (80%)
Female, n (%)	19 (70%)	8(30%)
Mean nodule size on histology (cm) (mean ± SD)	22.25 ± 1.09	30.2 ± 1.55
Bethesda cytologic diagnosis		
II	10	1
III	0	0
IV	10	11
VI	0	0
TI-RADS category*		
2	0	0
3	16	0
4	4	1
5	0	11

TABLE 1: Baseline characteristics of patients with Hurthle cell nodules

* Thyroid Imaging Reporting and Data System (TI-RADS) category: 2 = not suspicious; 3 = mildly suspicious; 4 = moderately suspicious; 5 = highly suspicious.

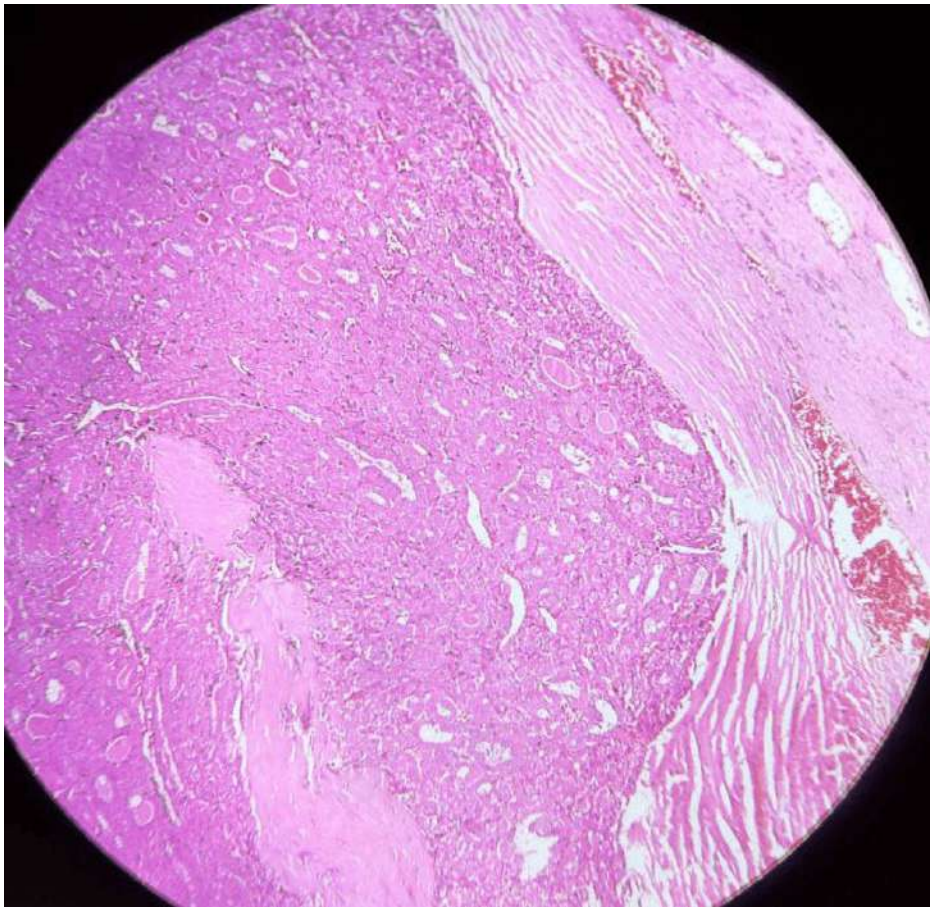


FIGURE 1: Low-power microscopy showing Hurthle cell with vascular and capsular invasion

The median age of patients with adenoma was 43 years, ranging from 20 to 60 years, while the median age of patients with carcinoma was 52 years, ranging from 32 to 86 years. A total of 26 patients presented with neck swelling, one patient had a retrosternal extension, and in five patients, it was incidentally detected on neck imaging. No family history of malignancy was reported in any of the cases.

Prior to surgery, thyroid hormone levels were within the normal range for all patients. Out of the 32 patients studied, two exhibited elevated thyroglobulin levels preoperatively, with subsequent final reports confirming the diagnosis of Hurthle cell carcinoma. Conversely, the thyroglobulin levels in the remaining patients were within normal ranges. Ultrasonography (USG) revealed multiple nodules in both lobes in 15 cases, while 17 cases showed a solitary nodule. FNAC results indicated follicular neoplasm in 21 cases, colloid nodule in 10 cases, and one case exhibited lymphocytic thyroiditis.

All 32 patients underwent total thyroidectomy. The mean diameter of the tumor was 23.3 mm in Hurthle cell adenoma patients and 30.2 mm in Hurthle cell carcinoma patients. In our study, thyroid nodules measuring less than 2 cm exhibited a 13% propensity for Hurthle cell carcinoma while for nodules more than 3 cm, it was 60% (p-value = 0.01; Figure *2*).



FIGURE 2: Nodule size in various subjects

The Y-axis represents nodule size measured in millimeters, while the X-axis represents individual subjects.

HCA: Hurthle cell adenoma; HCC: Hurthle cell carcinoma.

Eight patients with Hurthle cell carcinoma had multifocal lesions. One patient had neck node involvement. Eight cases of Hurthle cell carcinoma showed capsular invasion and four cases showed vascular invasion.

None of the Hurthle cell invasive carcinoma cases showed distant metastases during the I-131 whole body examination. Ten cases showed radio uptake at the thyroid bed (Figure *3*).

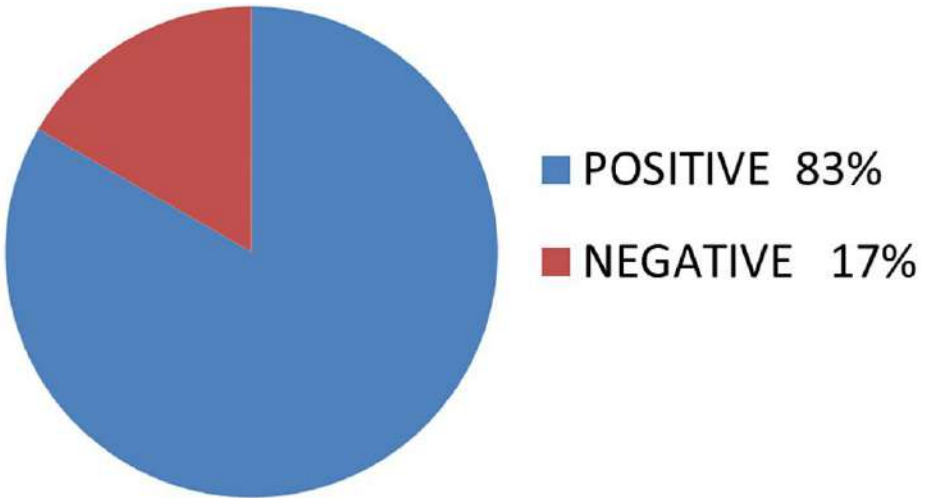


FIGURE 3: Hurthle cell carcinoma with I-131 uptake

Throughout the follow-up period, all cases were meticulously monitored, and there was no evidence of metastasis or mortality related to Hurthle cell carcinoma and no cases of relapse were observed in any of the patients.

Discussion

The demographic characteristics and clinical presentation of patients with Hurthle cell tumors provide valuable insights into the epidemiology and diagnostic challenges associated with this rare thyroid neoplasm. In our study, we observed a female predominance among the patients, with 84% females and 16% males, aligning with previous literature that suggests a higher prevalence in women [10,11]. The median age of patients diagnosed with Hurthle cell adenoma was 43 years, while those with carcinoma had a median age

of 52 years. These findings are consistent with other studies that have reported the occurrence of Hurthle cell tumors in middle-aged to older adults [11]. With the Surveillance, Epidemiology, and End Results (SEER) dataset, there were several clinically significant predictors of poorer outcomes in Hurthle cell carcinoma, including male sex, increasing tumor size, and advancing patient age. Consequently, patients exhibiting these characteristics should be considered for more aggressive treatment strategies [12].

Previous reports on thyroid nodules with Hurthle cell cytology have highlighted nodule size as a crucial parameter influencing the probability of cancer in these nodules [13]. In our study, nodules smaller than 2 cm exhibited a cancer rate of 13%, with all cancers being minimally invasive. However, as nodule size increased, the likelihood of cancer also escalated. For nodules sized more than 3 cm, the cancer rate increased to 60%. The observed increase in cancer rate with larger nodule sizes underscores the importance of considering nodule size as a critical factor when assessing the preoperative risk of cancer in Hurthle cell nodules [14].

Differences in experiences have given rise to a controversial debate regarding the optimal treatment approach for Hurthle cell carcinoma. Some researchers advocate for conservative management of these cancers, while others advocate for more aggressive treatment strategies [15]. Total thyroidectomy was the most frequently performed surgical intervention in our study, consistent with previous literature advocating for aggressive resection for Hurthle cell carcinomas [16].

In the existing literature, there has been a widely accepted paradigm [17,18] stating that Hurthle cell thyroid carcinoma (HCTC) does not accumulate radioactive iodine (RAI). Consequently, reports describing effective radioiodine therapy for HCTC [19] were often regarded as anecdotal evidence [20]. However, contradicting this paradigm is the observation made by Samaan et al. [21] in patients with HCTC treated at MD Anderson Cancer Center and by a study conducted at the Institute of Oncology in Ljubljana, Slovenia, from 1972 to 2000 [12]. In our study, we found that 10 cases exhibited RAI uptake in the thyroid bed, corroborating previous findings in other studies that indicate Hurthle cells are capable of taking up iodine. These findings challenge the conventional understanding and warrant further investigation into the potential use of RAI therapy for certain subsets of HCTC patients.

Hurthle cell carcinoma is a relatively rare tumor, and consequently, there is limited large-scale data available concerning the long-term survival of patients with this condition. Existing research presents conflicting findings, with some studies suggesting a relatively benign course and prolonged survival, while others indicate aggressive behavior and poor expected survival rates [3].

Although the follow-up duration was relatively short in this study population, factors such as age, sex, size of the tumor, extra-glandular invasion, neck node involvement, and major capsular invasion were not found to have significant prognostic value in patients with Hurthle cell carcinoma. Interestingly, none of these risk factors were associated with case mortality or disease-specific mortality. The conflicting viewpoints highlight the need for further research and consensus to guide the best course of action for patients with Hurthle cell carcinoma.

Limitations of this study

Given the focused nature of the study, various limitations may be acknowledged. Firstly, the sample size of 32 cases limits the generalizability of the findings. The study is also confined to a single tertiary care center in South India, which may not reflect the broader population demographic and could influence the clinical presentation and management outcomes observed. Furthermore, the longitudinal follow-up was not done, potentially obscuring the long-term prognosis and recurrence rates. To strengthen future research, a larger, multicentric study with a prospective design and longer follow-up period is recommended to validate these findings and better understand the behavior of Hurthle cell tumors on a wider scale.

Conclusions

Our study provides valuable insights into the clinicopathological profile of Hurthle cell tumors in South India. Despite their rarity, Hurthle cell tumors present diagnostic challenges and require multidisciplinary management. Our findings contribute to the existing literature and underscore the importance of accurate preoperative diagnosis, individualized surgical approaches, and informed decision-making regarding adjuvant therapies for better patient outcomes. Our study findings suggest that Hurthle cell carcinoma did not demonstrate aggressive behavior, which contrasts with observations reported by other researchers. The relatively indolent nature of Hurthle cell carcinoma observed in our study provides important insights into the disease's behavior in this particular cohort. Collaborative efforts among institutions and the accumulation of larger datasets will further enhance our understanding of these enigmatic tumors and aid in optimizing patient care.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Institutional Ethics Committee, Government Medical College Thrissur issued approval IEC/GMCTSR/2023/058. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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Outcomes of the Electrothermal Bipolar Vessel Sealing Device and Electrocautery in Modified Radical Mastectomy Patients

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Abstract

Introduction

With the rising trends in breast cancer throughout the world, the traditional modus of intraoperative tissue dissection using a scalpel, scissors, or electrocautery needs to be re-evaluated in the wake of newer modalities, such as electrothermal bipolar vessel sealing (EBVS) devices, which may theoretically reduce the postoperative complications and morbidity in these patients.

Aim and objective

The objective of this study is to compare an EBVS device to electrocautery (diathermy) in modified radical mastectomy (MRM), based on selected intraoperative and postoperative outcomes.

Study procedure

This was a comparative cross-sectional section study that included 60 patients with operable breast cancer (stages I and II, TNM classification, and post-neoadjuvant stage III disease). Patients were divided into two groups for surgery: one group underwent an MRM using the EBVS device (Group A), while the other group had the procedure performed using conventional electrocautery (Group B), as per the surgeon's choice depending on theatre slot and equipment availability. Intraoperatively, the total operative time, time for raising the flaps, time taken for breast tissue dissection, time for axillary dissection, and blood loss were recorded. Postoperative parameters included total drainage volume, number of days of drainage, seroma formation, and other complications. Patients were followed up for one month after surgery, with early postoperative complications such as wound infection, upper limb lymphedema, seroma, flap necrosis, and nerve injuries being documented.

Results

The groups were found to be comparable in terms of the age distribution, TNM staging, stage grouping, and nodal status of the patients. The EBVS device group demonstrated statistically significant advantages in total operative time, axillary dissection time, flap raising time, breast tissue dissection time, intraoperative blood loss, total drainage volume, and days of drainage. However, no statistically significant difference was found between the two devices in terms of seroma formation, early postoperative complications, and duration of postoperative stay at the hospital.

Conclusion

While the use of EBVS in MRM provides a considerable decrement in the total operative duration, duration of the various steps of surgery, intraoperative blood loss, and postoperative volume and duration of drainage, these devices do not offer an evident advantage in terms of the postoperative complications or morbidity.

Categories: General Surgery, Healthcare Technology
Keywords: vessel sealing devices, bipolar diathermy, ebvs, electrosurgery, mastectomy, breast

Introduction

Breast carcinoma is the most common cancer amongst women worldwide, accounting for 22% of all cases of malignancies in women, and is the single leading cause of cancer deaths in women worldwide [1]. In India, breast cancer is the most dominant cancer amongst women, with age-adjusted incidence rates as high as 25.8 per 100,000 women and a mortality of 12.7 per 100,000 women [2]. In Indian women, it has shown a steadily rising trend over the years [3]. It becomes of paramount importance to find better treatment modalities, as well as reduce complications associated with these treatment methods.

Surgical resection remains the keystone of breast cancer therapy, even though the specific approach for each case depends on the stage and type of tumor, and includes a multidisciplinary tactic involving surgery, radiation, and chemotherapy. It is crucial to prevent common surgical complications to avoid unnecessary delays in adjuvant treatment and to offer a better recovery period to these ailing patients.

Modified radical mastectomy (MRM) is considered the most common operative procedure performed for advanced breast cancer [4]. Early complications in breast cancer surgery have always been attributed to excessive postoperative drainage, prolonged hospital stay, seroma formation, blood loss, hematoma formation, skin necrosis, and nerve injury [5].

Traditionally, raising the skin flaps, dissecting the breast from the pectoral wall, and performing axillary lymph node dissection have been accomplished using either a scalpel (sharp dissection) or electrocautery. Recently developed methods include the use of UltraCision dissection (harmonic scalpel) and tissue response generation using electrothermal bipolar vessel sealing (EBVS) devices in raising these flaps.

This study was done to evaluate if the theoretical benefits and drawbacks of using EBVS devices in MRM are reflected in the outcomes experienced by patients in a practical setting.

Materials And Methods

This prospective observational study, aimed at evaluating the differences in outcomes of using electrocautery against EBVS devices, was conducted between September 2019 and September 2020 in a single unit in the Department of General Surgery and Surgical Oncology in the tertiary care setup of Government Medical College, Thrissur, India, with a total of 60 participants with operable breast cancer.

After taking a detailed history, conducting a complete physical examination, and performing relevant investigations, consent was obtained from all patients for both the MRM and their participation in the study. All patients underwent mammography or ultrasound of both breasts, along with a metastatic workup to rule out metastasis. Preoperatively, each patient also had a fine needle aspiration cytology (FNAC) or Tru-Cut needle biopsy performed. They were separated into two equal groups, either to undergo MRM using the EBVS device (Group A) or to undergo it using conventional electrocautery (Group B), as per the surgeon's choice, depending on theater slot and equipment availability.

The total operative time, time for raising the flaps, time for dissecting the breast tissue, time for axillary dissection, and blood loss were measured intraoperatively. All major intraoperative events were meticulously recorded. Postoperative parameters included total drainage volume, days of drainage, seroma formation, and other complications.

Results

The average age of the subjects in the study population is 52.6 ± 9.4 years with a range between 34 and 70 years. The mean age in the electrocautery group was 52.5 ± 9.081 years and 52.7 ± 9.396 years in the EBVS group.

The distribution of patients with node positivity in each device group was found to be comparable amongst the study subjects ($p = 0.302$). This is in line with other similar studies that have emphasized keeping nodal positivity rates similar amongst both case and control groups.

The average total intraoperative time for the study population was found to be 62.7 ± 8.579 minutes. Of those who underwent the procedure using electrocautery, the average total intraoperative time was found to be 70.2 ± 3.899 minutes, whereas those patients who underwent the procedure using the EBVS device had their procedures completed in 55.2 ± 4.262 minutes. The result was found to be statistically significant ($t = 14.223$; $p < 0.001$).

The average time taken for raising flaps was found to be 24.2 ± 3.729 minutes for the study population. For those who underwent MRM using electrocautery, the average time taken for raising the flaps was found to be 27.37 ± 2.008 minutes, whereas those patients who underwent MRM using the EBVS device had their flaps raised in 20.97 ± 1.752 minutes. This finding proved to be statistically significant ($t = 13.155$; $p < 0.001$) (Figure *1*).

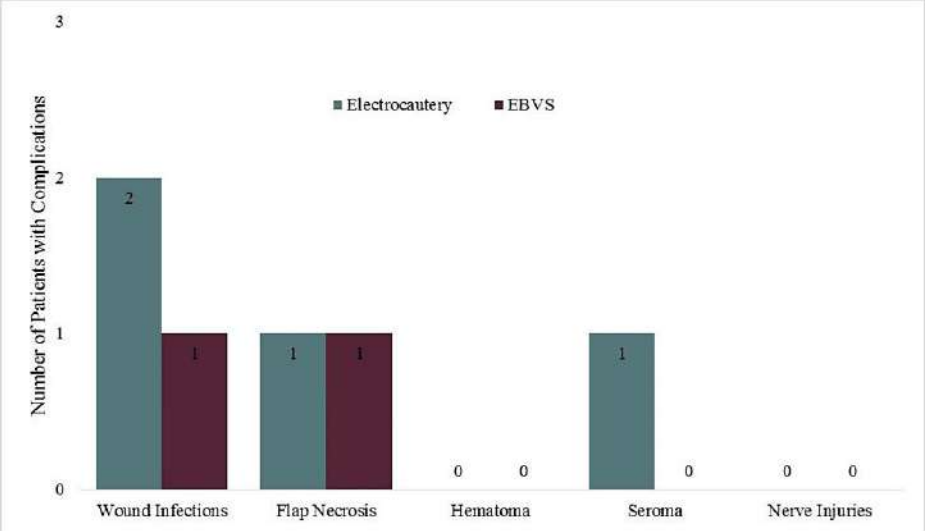


FIGURE 1: Comparison of average operative time for various steps of MRM

MRM: modified radical mastectomy; EBVS: electrothermal bipolar vessel sealing

The key area of concentration was axillary dissection among the study population. The average time taken for axillary dissection was found to be 25.82 ± 3.039 minutes. The duration was found to be 28.33 ± 1.470 minutes for those who underwent the procedure using electrocautery. In contrast, for those who underwent MRM using the EBVS device, the average time taken for axillary dissection was 23.3 ± 1.878 minutes. This was determined to be statistically significant (t = 11.559; p < 0.001) (Table *1*).

Device	Mean total operative time in minutes (SD)	Mean time for raising flaps in minutes (SD)	Mean time for axillary dissection in minutes (SD)	p-value
Electrocautery	70.2 (3.899)	27.37 (2.008)	28.33 (1.470)	
EBVS device	55.2 (4.262)	20.97 (1.752)	23.30 (1.112)	<0.001
Study population	62.7 (8.579)	24.20 (3.729)	25.82 (3.039)	

TABLE 1: Intraoperative timings at various strategic steps

EBVS: electrothermal bipolar vessel sealing

The average intraoperative blood loss for the study population was found to be 187.5 ± 42.888 mL. For those who underwent the procedure using electrocautery, it was found to be 222.67 ± 24.485 mL, while for those patients who underwent the procedure using the EBVS device, the average intraoperative blood loss was found to be 152.33 ± 24.166 mL. This result was found to be statistically significant (t = 11.198; p < 0.001; mean difference = 70.333 mL; dF = 58) (Table *2*).

Device	Mean intraoperative blood loss (mL)	SD
Electrocautery	222.67	24.485
EBVS device	152.33	24.166
Study population	187.5	42.888

TABLE 2: Average intraoperative blood loss

The average duration of postoperative hospital stay for the study population was found to be 2.83 ± 1.564

days. For those who underwent the procedure using electrocautery, the average duration of postoperative hospital stay was found to be 2.93 ± 1.837 days, whereas for those patients who underwent the procedure using the EBVS device, the average postoperative hospital stay was found to be 2.73 ± 1.258 days. This was found to be statistically insignificant (t = 0.492; p = 0.625).

The volume of drainage in the postoperative period for the study population was found to be 625.67 ± 93.905 mL. For those who underwent the procedure using electrocautery, the average volume of drainage was found to be 659.33 ± 86.181 mL, whereas for those patients who underwent the procedure using the EBVS device, the average volume of drainage was found to be 632.00 ± 90.379 mL. This was found to be statistically insignificant. The duration of drainage in the postoperative period for the study population was found to be 11.38 ± 2.108 days.

The overall incidence of surgical complications in the study population was only 10%. There were four incidences (13.33%) of surgical complications in the group operated using electrocautery and only two incidences (6.67%) of surgical complications in the group operated using the EBVS device. This was not found to be statistically significant (c2 = 0.741; p = 0.389) (Figure *2*).

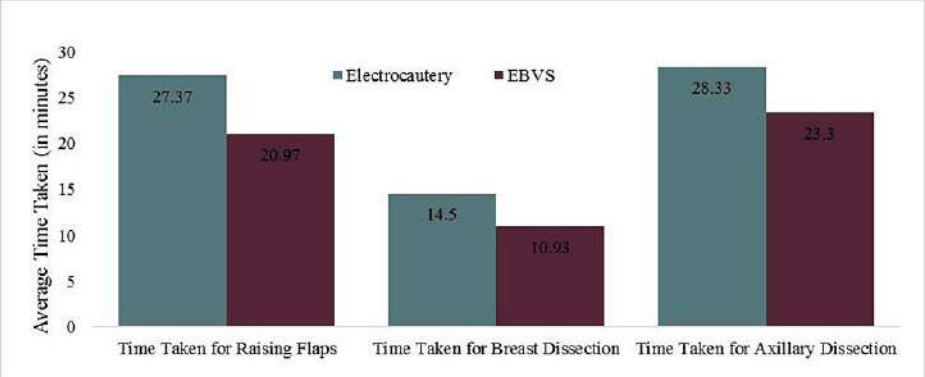


FIGURE 2: Comparison of surgical complications by device

EVBS: electrothermal bipolar vessel sealing

The commonest complication was wound infection, with two incidences (6.67%) in the electrocautery group and one incidence (3.33%) in the EBVS group. There was no statistical difference in terms of the incidence of wound infections in either group (c2 = 0.351; p = 0.554).

There was a single incidence (3.33%) of seroma formation in the electrocautery group which was not observed in the EBVS device group. This was not found to be statistically significant (c2 = 1.017; p = 0.313).

The incidence of flap necrosis was equal in both groups with a single incidence (3.33%) in each group. Nerve injuries and hematoma formation were not observed amongst any of the study subjects in either group.

Discussion

Surgical resection remains the keystone of breast cancer therapy, even though the specific approach for each case depends on the stage and type of tumor and includes a multidisciplinary tactic involving surgery, radiation, and chemotherapy. MRM is considered the most common operative procedure performed for advanced breast cancer [4]. Early complications in breast cancer surgery have always been attributed to excessive postoperative drainage, prolonged hospital stay, seroma formation, blood loss, hematoma formation, skin necrosis, and nerve injury [5]. In conventional practice, the elevation of skin flaps, removal of breast tissue from the pectoral wall, and axillary lymph node dissection have typically been conducted using either a scalpel for sharp dissection or electrocautery. Recently developed methods include the use of UltraCision dissection (harmonic scalpel) and tissue response generation using EBVS devices in raising these flaps.

The distribution of patients with node positivity in each device group was found to be comparable amongst the study subjects (c2 = 1.067; p = 0.302). This is in line with other similar studies that have emphasized keeping nodal positivity rates similar among both case and control groups, like the study by Chang et al. [6].

The key factor that determines the overall outcome is the comparison of total operative time, and devices with the ability to coagulate and cut play a significant role in reducing time and increasing the pace of surgery significantly [6].

This study revealed a difference of around 15 minutes in the total operative duration ($p < 0.001$), which is significant in terms of the time needed for general anesthesia and related complications. Correspondingly, statistically comparable timings were noticed in the various steps of MRM, which include the time taken for raising the flaps, the time taken for dissection of the breast tissue, and the time taken for dissection of the axilla [6].

The most rate-limiting step of this procedure is the axillary dissection due to the anatomical significance and nodal dissections. It was found that the use of these devices has a significant impact on the overall timings and the time taken for axillary dissection ($p < 0.001$ in each scenario). This is the key step in which these devices have an advantage over the other gadgets.

Few studies have analyzed the average intraoperative blood loss by various devices, and it was found of a significant reduction in total blood loss in the EBVS group ($t = 11.198$; $p < 0.001$) [7].

To evaluate the impact of energy devices on systemic inflammatory response, we measured the concentration of CRP on the third postoperative day. Our findings revealed that while CRP levels exhibited a typical increase in all patients, this elevation was not associated with the specific device utilized. This indicates that the type of electrosurgical device used for tissue dissection does not influence the systemic inflammatory response [8,9].

The rates of overall postoperative surgical complications, which include wound infections, flap necrosis, seroma formation, hematoma formation, and nerve injuries, were not found to be significantly different between the two device groups ($p = 0.389$) (Table *3*).

Complications	Device	This study	Study by Chang et al. [6]
Wound infections/skin necrosis	Electrocautery	3	12
	EBVS device	2	4
	p-value	0.640	0.264
Seroma formation	Electrocautery	1	7
	EBVS device	0	3
	p-value	0.313	0.734
Overall complications	Electrocautery	4	22
	EBVS device	2	7
	p-value	0.389	0.051

TABLE 3: Comparison of the surgical complications in various studies

EBVS: electrothermal bipolar vessel sealing

Limitations of the study

This is studied as a cross-sectional observational study, and the sample size is less. A more structured approach with a randomized study will benefit to come out with a better analysis of the outcome comparison.

Conclusions

While the use of EBVS in MRM provides a considerable decrement in the total operative duration, duration of the various steps of surgery, intraoperative blood loss, and postoperative volume and duration of drainage, these devices have comparable outcomes in terms of postoperative complications or morbidity. These findings underscore the potential benefits of utilizing EBV to optimize surgical outcomes and improve patient care in MRM procedures.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Institutional Ethical Committee, Government Medical College, Thrissur, Thrissur, India issued approval IEC/GMCTCR/2020/042. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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Difficult Terrains of Research Publications Faced by Researchers: A Cross-Sectional Study

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Abstract

Background

The publication of scholarly work in peer-reviewed journals is a well-established method for disseminating knowledge and findings to a global audience. However, the publishing process is constantly evolving and encountering various obstacles that hinder progress. Despite a significant increase in the number of research projects undertaken, there are few studies evaluating the challenges faced by investigators in publishing their research. This study aims to identify the factors and elements that influence the publication process after the completion of research.

Methods

This study included 759 projects approved by the Institutional Ethics Committee (IEC) from 2016 to 2021 at a tertiary care centre in South India. A list of these approved projects was analysed for overall output in terms of publication and completion. Investigators were contacted and interviewed using a validated, 15-question survey to identify various factors influencing scientific publications.

Results

A total of 759 projects approved by the IEC from 2016 to 2021 were analyzed. It was found that only 36.72% of studies were completed by faculty members, and the publication conversion rate was 34.24%. A single-point analysis showed a statistically significant lower conversion rate for resident articles ($p = 0.032$). The 15-point analysis detailed the factors influencing publication conversion, revealing that the majority of researchers publish based on academic and research interests (68.89% and 72.12%, respectively). Various deterrents to publication, such as study design, statistical analysis, journal selection, and knowledge about journal submission, were identified. Notably, 98.4% of researchers expressed a desire to publish more in the future, highlighting the importance of this study.

Conclusion

The study highlights areas that require attention to facilitate and augment research. It identifies the real gaps in the publication process and suggests points of intervention needed to enhance the research environment, increase publication rates, and establish demand-based research support units in the medical education sector.

Categories: Medical Education, Quality Improvement, Health Policy
Keywords: academics, journals, medical education, publications, research

Introduction

The publication process in India is still evolving, with multiple barriers impeding the successful dissemination of research findings. Despite a significant increase in the number of research projects undertaken, the rate of resulting publications remains limited. There is a scarcity of studies evaluating the challenges faced by investigators in publishing their research [1,2]. Numerous factors influence the quality of scientific publications, including rigorous methodology, valid results, significance of findings, journal reputation, peer review process, funding sources, collaboration, timeliness, and writing quality [3,4].

A detailed analysis of the difficulties encountered by investigators in publishing their research and the factors influencing the publication output of approved research projects has not been thoroughly explored in India, particularly in Kerala. This study aims to identify the possible factors and elements that influence the publication process following the completion of research. It focuses on the challenges and factors affecting the publication of research findings from projects approved by the Institutional Ethical Committee (IEC) at Government Medical College in Thrissur, Kerala, India.

The study seeks to address the obstacles faced by investigators in publishing their research and identify the factors influencing the publication output of approved research projects. It includes a comprehensive review of the challenges encountered during project execution and publication, the study setting, research questions, and the methodology employed. The study examines the role of institutional support, availability of resources, and training in research methodology as potential barriers to successful publication. It also investigates the influence of external factors such as journal selection criteria, peer review processes, and publication costs. By identifying these factors, the study aims to propose strategies to enhance the research environment and improve the publication rate of approved projects. Additionally, the study will provide recommendations for policy changes at institutional and governmental levels to support researchers in overcoming these barriers. The ultimate goal is to foster a culture of research and publication, thereby contributing to the advancement of medical science and improving healthcare outcomes in the region.

Materials And Methods

We conducted a cross-sectional study of all projects approved by the IEC over six years, spanning from January 2016 to December 2021, at Government Medical College in Thrissur, a tertiary-level institution in central Kerala, India. The IEC of Government Medical College Thrissur issued approval to conduct the study (approval number: IEC/GMCTSR/234/2021). A total of 759 projects were analyzed. The primary objective was to quantitatively assess the publication status of these approved research projects and identify the factors influencing researchers in the scientific publication of their work.

A comprehensive list of IEC-approved projects from the specified period was examined for overall output in terms of publication and completion. We compiled all studies approved by the IEC, and the principal investigators (PIs) were contacted. Data were collected through direct or telephonic interviews using a validated 15-item questionnaire designed to identify various factors influencing scientific publications. The inclusion criteria encompassed all 759 projects approved between January 1, 2016, and December 31, 2021. We included PIs who could be contacted directly or via telephone. Exclusion criteria consisted of PIs who could not be reached or were unwilling to participate in the study.

Data collection was conducted using a standardised proforma. The data were then collated and analysed using Epi Info software (Centers for Disease Control and Prevention, Atlanta, GA). A master chart was created to facilitate detailed analysis and presentation of the results.

Results

In this interview-based study, we incorporated a total of 759 studies approved by the IEC between 2016 and 2021 (Figure *1*). However, data were successfully obtained from only 321 principal investigators. The majority of the approved studies were conducted by junior residents, comprising nearly 69% of the total, followed by faculty members. Notably, medical students and resident interns also demonstrated significant interest in participating in research activities.

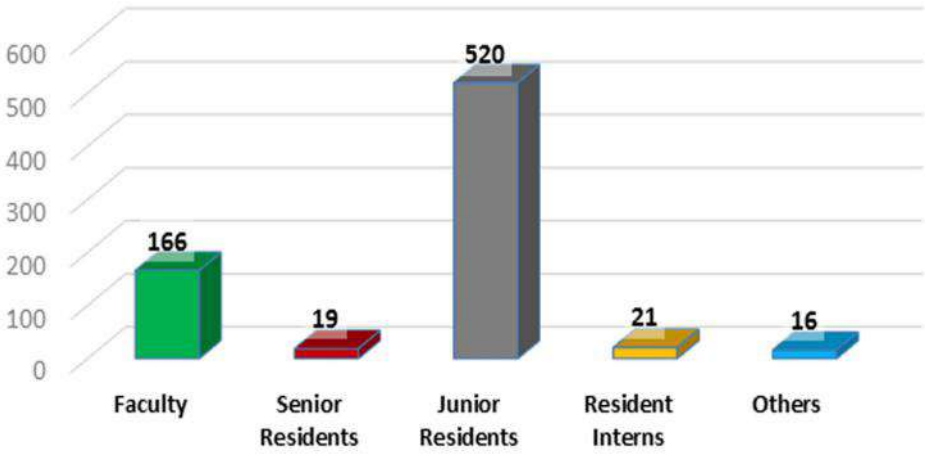


FIGURE 1: A break-up of the total projects approved by the Institutional Ethics Committee

Among the 321 principal investigators interviewed it was found that only 189 studies were published. Of these, approximately 62% were published in national journals, with very few appearing in international databases such as PubMed and Scopus (Figure *2*). Faculty studies accounted for only 36.72% of the total approved studies, with a conversion rate of 34.24%.

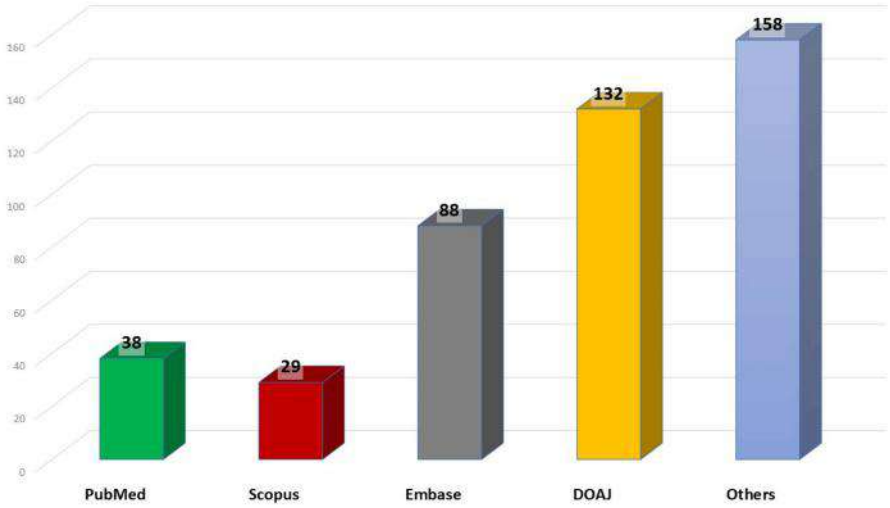


FIGURE 2: Number of publications in various databases

Embase: Excerpta Medica database; DOAJ: Directory of Open Access Journals

The resident group demonstrated a statistically significant lower rate of converting studies into publications ($p = 0.0032$). The majority of researchers published based on academic and research interests, with 68.89% and 72.12%, respectively. When asked about their desire to publish, 98.4% of investigators expressed a wish to do so.

The difficulties in publishing research were analysed under two categories: project execution and project publication. During project execution, the most challenging aspect was protocol writing and submission, accounting for nearly 62% of the problems faced by investigators, followed by Institutional Research Committee (IRC) clearance. Other issues included completing office formalities and obtaining IEC clearance (Figure *3*).

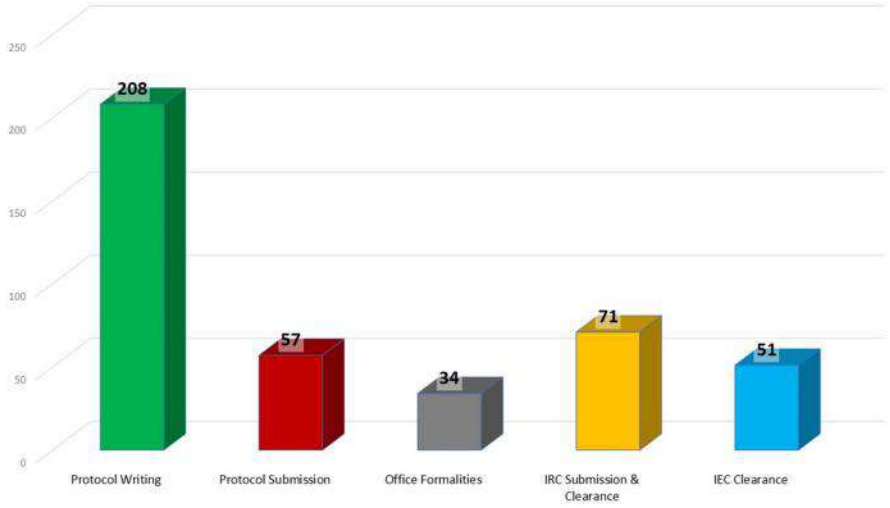


FIGURE 3: Difficulties faced during project execution

IRC: Institutional Research Committee; IEC: Institutional Ethics Committee

The major hindrance to paper publication was performing a proper statistical analysis. Other significant factors included paper writing and journal selection. Investigators noted that even if they could write a good paper with accurate statistical analysis, selecting an appropriate journal and following up was difficult (Figure *4*).

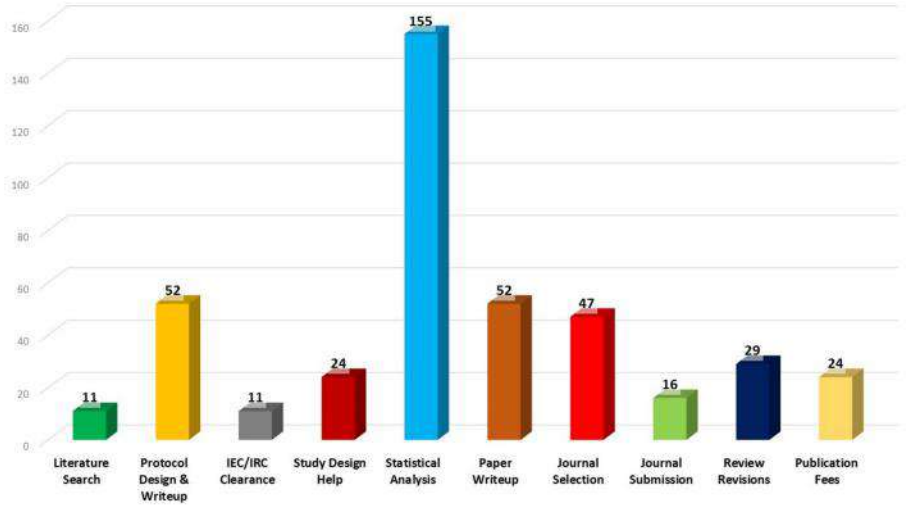


FIGURE 4: Difficulties faced in project publication

The majority of investigators expressed a desire to publish again, indicating the need for mechanisms to improve the research environment, motivation, and assistance (Figure *5*). Additionally, they said needed to select topics oriented towards publication.



FIGURE 5: The answers to the question "Do researchers want to publish?"

Discussion

This study analysed the publication status of 759 research projects approved by the IEC between 2016 and 2021. The findings reveal that only 36.72% of the approved studies were completed, with a publication conversion rate of 34.24%. Additionally, the majority of researchers published based on academic and research interests, with 98.4% expressing a desire to publish more in the future.

The significance of this study lies in its identification of the factors influencing the publication of research findings from approved projects, providing valuable insights into the challenges faced by investigators [5]. By quantitatively analysing the publication status and conducting interviews, the study not only identified barriers but also highlighted the strong inclination of researchers towards future publications [6].

Various reasons contribute to the non-publication of research findings, including ongoing manuscript preparation, studies still in progress, and biases due to negative results, which are clearly unacceptable [7]. Other documented reasons include journal rejections (6%), fear of non-acceptance (12%), lack of motivation, and low prioritisation of publication [8, 9]. The difficulties encountered by investigators during project

execution and publication were substantial. The major hindrance to paper publication was performing proper statistical analysis. Additionally, challenges in project execution included protocol writing and submission, which accounted for almost 62% of the problems faced by investigators. Other issues included obtaining Institutional Research Committee clearance, completing office formalities, and IEC clearance. Further, difficulties in the paper write-up and journal selection were significant obstacles in the publication process.

The analysis of publication output revealed that the majority of publications were in Indian journals and those indexed in The Directory of Open Access Journals (DOAJ), the Excerpta Medica database (EMBASE), Crossref, and other databases. Less than 6.2% of the articles were published in PubMed-indexed journals, likely due to several factors [10]. Time constraints lead researchers to focus on journals with high impact factors, which typically accept articles with positive results [11]. Additionally, poor study designs, repetitive research, and duplication of study results contribute to non-publication in high-impact, PubMed-indexed journals [12].

The Bachelor of Medicine, Bachelor of Surgery (MBBS) curriculum is the primordial point where the fundamentals and outline of research should be introduced. By integrating research education early in the curriculum, we can encourage more students to take advantage of publication opportunities, such as those offered by The Indian Council of Medical Research (ICMR). This early exposure not only promotes a research-oriented mindset but also equips students with the necessary skills to contribute meaningfully to medical science. The study identifies points of intervention needed to enhance the research environment, improve publication rates, and establish demand-based facilitatory research units in the medical education sector [13,14]. Addressing the challenges and barriers faced by investigators during project execution, such as protocol writing, submission, and IRC clearance, as well as obstacles in project publication, including statistical analysis, paper write-up, and journal selection, is crucial.

Furthermore, the study highlights the need for onsite assistance and the desire of most researchers to publish more in the future. These findings underscore the necessity for interventions aimed at improving the publication conversion rate, addressing specific challenges faced by different groups, and fostering a more supportive research environment within the medical education sector [15].

Conclusions

The publication process is still evolving in this country, and multiple barriers impede the process of research publication, including time constraints. The number of research projects being undertaken has increased drastically, but publications are limited. By quantitatively analysing the publication status and conducting interviews, the study not only identified the barriers but also revealed the researchers' strong inclination towards future publications. Ultimately, the findings offer a compelling basis for devising interventions aimed at improving the publication conversion rate, addressing specific challenges faced by different groups, and fostering a more facilitatory research environment within the medical education sector.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Intriguing Insights From 100 Consecutive Colorectal Cancer Cases in Mid-Kerala: Sparse BRAF Gene Mutations and Mismatch Repair Deficiency (MMR-D)

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Abstract

Colorectal cancer (CRC) is among the most prevalent types of cancer globally. It is well established that the development of CRC primarily results from the sequential activation of oncogenes and the simultaneous inactivation of tumor suppressor genes. It has also been noted that after the initial oncogenic mutation, many subpopulations with different mutational profiles are created, causing heterogeneity among the tumors.

This retrospective study analyzed 100 patients diagnosed with CRC through colectomy over an eighteen-month period at a tertiary referral center in mid-Kerala, India. Pathology records and histological slides were reviewed by two pathologists, and clinicopathological data were collected from pathology reports. Immunohistochemical analysis for BRAF mutation and possible microsatellite instability (MSI) (by mismatch repair (MMR) protein study) was conducted on tumor tissue blocks sent to an external center due to the lack of an automated platform at the hospital. The study utilized Roche's Benchmark XT platform for BRAF analysis and assessed MMR protein expression using antibodies for MLH1, MSH2, MSH6, and PMS2.

The mean age of patients was 58.36 years, with a male predominance (58.0%). Most tumors were classified as T3 (71.0%, n-71) and T2/T4a (14.0% each, n-14), while nodal involvement included N0 (35.0%, n-35), N1 (26.0%, n-26), N2 (19.0%, n-19), and NX (20.0%, n-20). Histological examination revealed predominantly well-differentiated tumors (78.0%, n-78), with lymphatic invasion noted in 41.0% (n-41) and vascular invasion in 5.0% (n-5) of cases. Left-sided tumors predominated (33.0%, n-33), followed by rectal carcinoma (37.0%, n-37), and right-sided colon cancers (30.0%, n-30).

Genetic profiling showed sparse BRAF mutations (1.0%, n-1) and MSI (1.0%, n-1), with some cases exhibiting loss of MMR proteins (MLH1, PMS2, MSH2, and MSH6) by immunohistochemistry (IHC). The study highlights the rarity of BRAF mutations in this cohort and emphasizes the diverse pathological and molecular characteristics observed.

The discussion focuses on the implications of these findings, suggesting that CRC in this population exhibits unique clinicopathological features potentially influenced by factors beyond genetic mutations. Further multicentric studies are warranted to comprehensively explore these factors and refine risk stratification and treatment strategies for CRC patients in similar demographics.

Categories: Pathology, General Surgery, Oncology
Keywords: molecular behavior, msi, braf, oncogenesis, colorectal cancer

Introduction

Colorectal cancer (CRC) ranks among the most prevalent types of cancer globally. It's widely known that sequential activation of oncogenes and concomitant inactivation of tumor suppressor genes is the principle process behind the development of CRC [1]. It has also been noted that after the initial oncogenic mutation, many subpopulations with different mutational profiles get created, causing heterogeneity among the tumors [2].

BRAF gene mutation is an example of such a heterogenic event in colorectal carcinogenesis and is seen in about 10% of the CRC cases in Western literature [3]. The BRAF mutation confers poor prognosis and resistance to anti-epidermal growth factor receptor (anti-EGFR) therapy. Treatment of CRC with BRAF mutations has changed rapidly in the last few years, with new combinations and targeted therapies.

Very few studies have evaluated the prevalence and association of BRAF mutations with clinicopathological

features in the Indian population. BRAF mutation frequency ranges from 2% to 7% in Indian CRC patients [4-6]. Although the BRAF mutation does not seem to be prevalent in the Indian population, it was noted to be associated with advanced stages [6]. Understanding the frequency of somatic mutations in a particular population is important in deciding the targeted therapy.

Another putative biomarker with clinical and therapeutic potential is the presence of microsatellite instability (MSI) detected by polymerase chain reaction (PCR) or its equivalent by looking for mismatch repair (MMR) proteins by immunohistochemistry (IHC). Microsatellites are multiple repeats of 1-5 base pairs occurring at microsatellite loci, widely dispersed throughout the genome. MSI has been frequently observed in several types of cancer, including endometrial and colorectal carcinomas [7].

We retrospectively analyzed the presence of BRAF and MMR aberrations and their correlation with the clinicopathological factors in 100 colorectal cancers of the 100 cases analyzed for BRAF and MMR.

Materials And Methods

The study was conducted at Government Medical College, Thrissur, Kerala, India. We conducted a retrospective study in 100 patients diagnosed with CRC through colectomy during the period of one and a half years. Pathology records and histological slides with a diagnosis of CRC were reviewed by two pathologists. Clinicopathological information and patient history were collected from pathology reports.

Immunohistochemical analysis for BRAF mutation and MMR status was performed on blocks of tumor tissue collected during the study period. As the standardized, automated platform for immunohistochemistry (IHC) is not available in the hospital, the blocks were sent for IHC analysis to another center. The approved system for IHC studies on BRAF is Roche (Ventana) Medical System's Benchmark XT platform and Opti View DAB IHC Detection Kit. Samples were tested using the anti-BRAF V600E (VE1) antibody on the Benchmark XT platform, and protein expression was detected using the Opti View DAB IHC Detection Kit.

MMR protein expression by IHC is a widely accepted test that identifies an affected gene by detecting the loss of protein products. The MMR protein expression profile was assessed using the Roche platform using antibodies to look for specific mismatch gene products, MLH1, MSH2, MSH6, and PMS2. Each of the markers will be analyzed for their nuclear expression (normal/abnormal).

The intensity of BRAF expression in tumor cells was assessed using a scale ranging from 0 to 3. Strong cytoplasmic staining received a score of 3, medium cytoplasmic staining was scored as 2, weak cytoplasmic staining as 1, and absence of staining as 0. Scores of 1 to 3 indicated positive staining, while scores below 1 were considered negative staining.

The results were categorized based on the immunohistochemical profile of each case. The pathological and molecular characteristics of the tumor tissue, along with the tumor stage, were established based on the American Joint Committee on Cancer (AJCC) tumor/node/metastasis criteria [8].

Different clinicopathological parameters, including age, sex, location, size, differentiation, and histology, were analyzed and correlated with the IHC profile of BRAF.

The data on these mutations and their correlation with the different clinicopathological features in the Indian cohort is inadequate.

Results

The study was conducted on 100 consecutive colorectal cases operated on for 18 months at a tertiary referral center in mid-Kerala, India.

The mean age in our study was 58.36±11.49 years, and out of 100 participants, 58 (58.0%) were male and 42 (42.0%) were female.

Most of the patients underwent radical colectomy and, hence, constituted the majority. In our study, the prevalence of each stage was found to be as follows: T3 (71.0%), T2 (14.0%), and T4a (14.0%). Early tumors T1 (1.0%) were sparse and constituted only 1% of the total resected specimens. The majority of resected tumors (35%) were lymph node-negative specimens, which may be due to unstandardized resections. The rest was made up of N1 (26.0%), NX (20.0%), and N2 (19.0%) (Table *1*).

TNM stage	Frequency (n=100)	Percentage
T1	1	1%
T2	14	14%
T3	71	71%
T4a	14	14%
NX	20	20%
N0	35	35%
N1	26	26%
N2	19	19%
MX	100	100%

TABLE 1: Distribution of TNM stage

TNM: tumor, node, metastasis

The tumors were analyzed for the degree of differentiation and lymphovascular invasion (LVI), wherein 41% of tumors exhibited lymphatic permeation but vascular emboli were seen only in 5%. Tumor differentiation also had a significant predilection for low-grade tumors, with 78% of the tumors exhibiting good differentiation and 9% exhibiting poor differentiation. These factors point to the fact that these tumors were less aggressive on the basis of their pathological behavior (Table *2*, *3*).

Pathological diagnosis	Frequency (n=100)	Percentage
Large vessel invasion	5	5.0%
Lymphatic invasion	41	41.0%

TABLE 2: Distribution of pathological diagnosis

Histological grade	Frequency	Percentage
Well differentiated	78	78.0%
Moderate	13	13.0%
Poor	9	9.0%

TABLE 3: Distribution of histological grading

Location-wise, most of the tumors were left-sided colonic (33%). Rectal carcinoma constituted 37.0%, and right-sided tumors contributed to 30% of the tumors.

Loss of MSH2 and MSH6 protein expression with normal MLH1, PMS2, and BRAF was seen in three patients. There were two cases with loss of MLH1 and PMS with no aberrations of MSH2, MSH6, or BRAF. There was only one case of positive BRAF with normal MLH, MSH, and PMS status (Figure *1*). There is no significant presence of genetic mutations, with just 6% of MSI mutations and BRAF mutations occurring in just 1% (Table *4*).

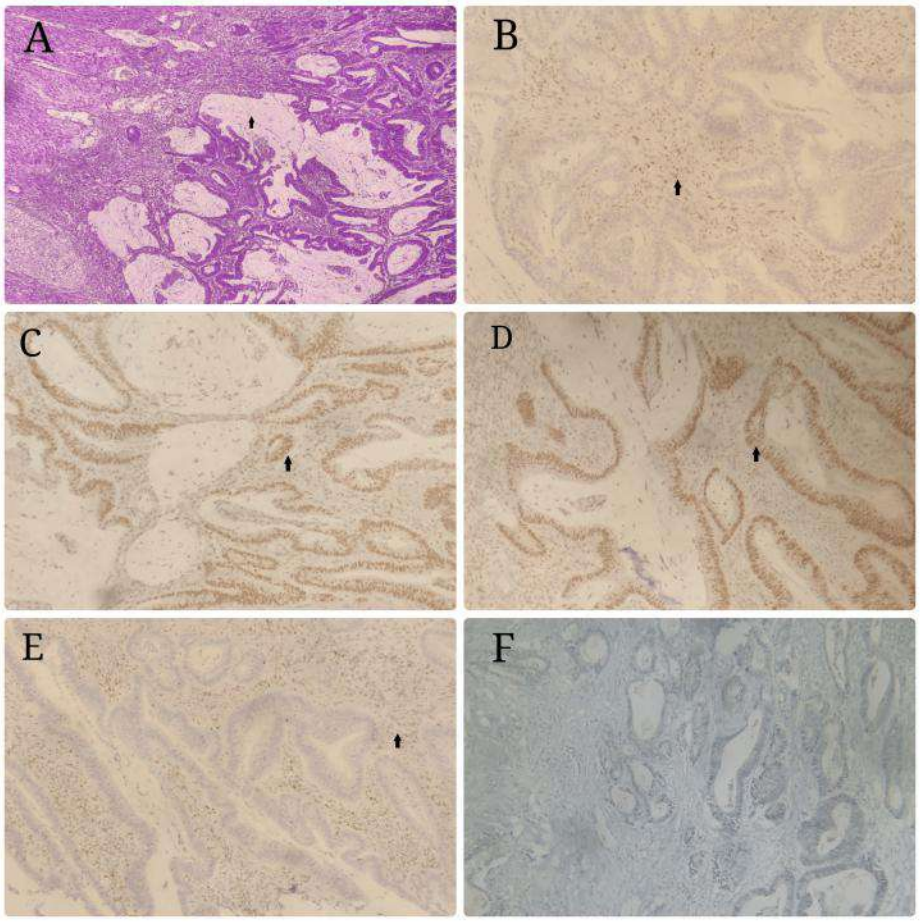


FIGURE 1: Genetic mutation and histopathology

A: colonic carcinoma with peritumoral lymphocytic reaction; B: loss of nuclear expression of MSH 6; C: intact nuclear expression of PMS2; D: nuclear expression of MLH 1; E: loss of expression of MSH 2; F: BRAF negative

Genetic profile	Frequency	Percentage
BRAF MUTATION	1	1.0%
MMR IHC	1	1.0%
MLH 1	1	1.0%
MSH2	1	1.0%
PMS 2	1	1.0%
MSH 6	1	1.0%

TABLE 4: Distribution of genetic profile

Discussion

Colorectal cancer ranks as the third most diagnosed cancer globally, with approximately 1.4 million new cases each year. Tumors in the colorectal region that exhibit BRAF mutations and microsatellite stability (MSS) are linked to unfavorable outcomes in patients [9]. Therefore, combined testing for microsatellite instability high (MSI-H) and BRAF mutations could potentially aid in risk assessment, especially for patients diagnosed with stage II tumors [10].

Carcinogenesis in CRC can occur through multiple pathways. Unlike the classic adenoma-carcinoma

sequence, where APC inactivation is the initiating event [11], the serrated pathway is driven by BRAF mutations, with serrated polyps serving as the precursor lesions [12].

Serrated tumors typically do not exhibit chromosomal instability but often show extensive DNA methylation of CpG islands. This methylation can occur in the MLH1 promoter (a gene involved in the mismatch repair system), leading to a 'sporadic' microsatellite instability (MSI) phenotype. [13]. In 60% of sporadic MSI CRC cases, there is an association with BRAF mutations. However, BRAF mutations are not found in Lynch syndrome, where microsatellite instability arises through a different mechanism involving germline mutations in mismatch repair genes.

BRAF mutations are more common in tumors of the proximal colon and are associated with unique pathological features, including poorer differentiation, mucinous histology, MSI, and larger primary tumors [14]. The metastatic pattern also differs from BRAF wild-type (BRAF-WT) tumors, showing a higher incidence of peritoneal metastasis and fewer liver and lung metastases.

BRAF negativity in this series points to the fact that colorectal cancer etiology and behavior are influenced by other factors. The various factors that emerged from this study pointed out that the majority of the tumors studied were early-stage, left-sided, well-differentiated tumors with a low nodal load and fewer lymph vascular emboli.

The mitogen-activated protein kinase (MAPK) cascade is pivotal in tumor cell proliferation and survival. Increasing evidence indicates that mutations in the BRAF oncogene are not only tied to a poorer prognosis but also correlate with reduced efficacy of anti-epidermal growth factor receptor antibodies in treating metastatic colorectal cancer (mCRC) [15].

Importantly, the study highlights that colorectal cancer's etiology in our population is influenced by a broader spectrum of factors beyond genetic mutations. The predominance of early-stage, left-sided tumors with well-differentiated histology, low nodal load, and minimal lymph vascular emboli suggests alternative pathogenic mechanisms. This finding calls for further multi-centric, structured analyses to comprehensively evaluate these variables and their contributions to CRC development and progression [16].

The study points to the fact that colorectal cancer in our population has diverse etiologies and factors other than genetic mutations. The factor of divergent causation needs to be further analyzed by a multi-centric analysis with a more structured approach looking at various variables.

Limitations of the study

This study has several limitations, including its retrospective design, small sample size, and single-center data, which limit the generalizability and causality of the findings. The lack of an automated IHC platform requires sending samples to an external center, potentially introducing variability, and the focus on a limited set of genetic markers may overlook other relevant genetic alterations. Additionally, the absence of long-term follow-up data might affect the assessment of prognostic implications and pathological staging.

Conclusions

This research underscores the complexity and heterogeneity of colorectal cancer (CRC) etiology and progression, emphasizing the role of genetic and epigenetic alterations. The identification of BRAF mutations and microsatellite instability (MSI) as markers associated with adverse patient outcomes highlights the importance of integrating molecular diagnostics into risk assessment, particularly for early-stage CRC patients. Insights into tumor biology suggest that BRAF mutations contribute to more aggressive disease phenotypes and may influence therapeutic responses, particularly regarding anti-epidermal growth factor receptor antibody treatments in metastatic CRC.

In conclusion, while genetic markers such as BRAF mutations and MMR/microsatellite status provide critical insights into CRC prognosis and therapeutic strategies, a more nuanced understanding of the diverse etiological factors is essential. Such efforts could pave the way for more personalized and effective diagnostic, prognostic, and therapeutic strategies for managing colorectal cancer.

Additional Information

Author Contributions

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Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Institutional Review Board of Thrissur Medical College issued approval IEC/GMCTSR/2023. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Concealed cause, critical consequences: Internal hernias and small bowel obstruction

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ABSTRACT

Background: Internal hernias are potentially devastating condition that can manifest as intestinal obstruction and often present with nonspecific symptoms. This vagueness can lead to delayed diagnosis and management challenges. Therefore, clinical vigilance, prompt recognition, and timely intervention are crucial in preventing catastrophic complications associated with this under-recognized condition. **Aims and Objectives:** The objective is to underscore the imperative of prompt diagnostic interventions in patients presenting with intestinal obstruction. Moreover, fostering awareness among nascent surgeons regarding this clinical entity is essential, as it can precipitate a paradigm shift in the long-term prognosis. **Materials and Methods:** A retrospective analysis of data extracted from the emergency operative room register at GMC Thrissur, spanning a 5-year period. **Results:** Sixteen cases underwent emergency laparotomy, with internal hernias diagnosed either preoperatively through contrast-enhanced imaging or encountered intraoperatively as an unexpected finding. Conversely, two patients underwent elective laparotomy. For all patients, the hernia was reduced and internal defect repaired. Six patients had the need for resection of gangrenous bowel segment with primary anastomosis, while none required the need for ileostomy. Post-operative period for all of the patients was uneventful. **Conclusion:** The non-specific nature of clinical presentations inherent to internal hernias renders diagnosis exceedingly challenging. Prompt surgical intervention and early detection remains the sole viable treatment modality for this pathology. Early diagnosis is significantly facilitated by a comprehensive understanding and awareness of this rare yet formidable cause of intestinal obstruction. This cognizance serves as a catalyst for expedited decision-making and action, thereby playing a pivotal role in mitigating complications and profoundly influencing the outcome.

Key words: Internal hernia; Laparotomy; Bowel obstruction; Contrast computed tomography abdomen

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INTRODUCTION

Internal hernias are characterized by the protrusion of abdominal viscera, predominantly small bowel loops, through a pre-existing or acquired peritoneal or mesenteric defect into the abdominal or pelvic cavity. The hernial orifice may be an anatomical defect, such as the Foramen of Winslow, or a pathological defect of congenital or acquired origin.

Internal hernias constitute one of the rarest and most insidious causes of small bowel obstruction, frequently remaining undetected until catastrophic complications arise. The clinical presentation is often nebulous, manifesting as a wide range of non-specific symptoms, thereby rendering this condition a "silent iceberg." The indeterminate nature of internal hernias poses a significant diagnostic challenge, leading to delayed recognition and, consequently, a high incidence of strangulated small bowel obstruction.[1]

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This potentially devastating outcome often necessitates major resections and stomas, which could be avoided with early diagnosis. Here, we present a series of nine cases, wherein patients initially presented with vague abdominal complaints, only to ultimately develop full-blown small intestinal obstruction, culminating in a diagnosis of internal hernia.

This series analyzed 16 cases operated at the department of surgery medical college. Thrissur was undertaken to create awareness among young surgeons and patients about this entity and highlight the necessity of early investigations in patients with intestinal obstruction with no significant history. This retrospective series analyzed the clinical presentation, investigations and varying presentations and to emphasize the need for early intervention to avoid long-term complications.

Aims and objectives

The aim of this study is to highlight the significance of early diagnosis and timely surgical intervention in managing internal hernias causing small bowel obstruction, thereby improving patient outcomes and minimizing morbidity. The objectives include analyzing the clinical presentation and diagnostic challenges associated with internal hernias, assessing the role of contrast-enhanced CT imaging in early detection, and evaluating surgical management strategies and their outcomes. Additionally, this study seeks to raise awareness among young surgeons about internal hernias as a rare but critical cause of intestinal obstruction and emphasize the importance of early intervention in preventing complications such as bowel strangulation and necrosis.

MATERIALS AND METHODS

A retrospective analysis of data extracted from the emergency operative room register at GMC Thrissur, spanning a 5-year period, yielded a cohort of 18 patients. Sixteen of these patients, devoid of any prior laparotomy history, underwent emergency laparotomy for internal hernias, either pre-diagnosed through contrast-enhanced imaging or encountered intraoperatively as an unexpected finding. Conversely, two patients underwent elective laparotomy for pre-diagnosed internal hernias, identified on contrast-enhanced computed tomography (CECT) scans performed to investigate chronic abdominal pain.

RESULTS

In the emergency setting, all 16 patients who underwent emergency laparotomy presented with a primary complaint of obstipation, lasting 4–7 days, accompanied by vomiting and reduced appetite for 2–3 days. Notably, six out of eight patients with the left paraduodenal and transmesenteric hernias reported a 6-month history of intermittent bloating and nausea. Two patients with the right preduodenal hernias presented with a 4-month history of chronic periumbilical pain, without any significant medical history. In addition, two patients with paracecal hernias had undergone evaluations for recurrent right iliac fossa pain at a local hospital over 3 months.

In contrast, the patient who underwent elective laparotomy presented with a 2-month history of dyspepsia and upper abdominal pain, which persisted despite treatment with proton-pump inhibitors and analgesics. Preliminary investigations, including ultrasound and upper gastrointestinal endoscopy, yielded normal results.

Regarding the emergency management, ten out of 16 patients underwent direct emergency exploratory laparotomy due to the presence of toxic clinical features, including tachycardia, dehydration, hypotension, low urine output, and significant air-fluid levels on plain

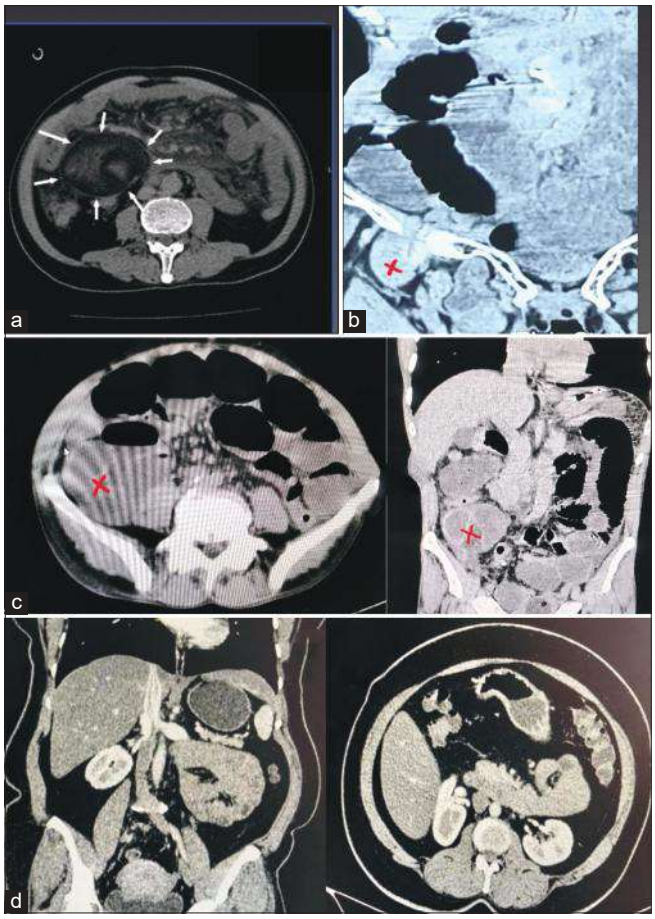


Figure 1: (a) Cluster of bowel loops in the right lumbar region-transmesenteric hernia; (b) cluster of bowel loops through obturator foramen-obturator hernia; (c) cluster of bowel loops in RIF-paracecal hernia; and (d) cluster of bowel loops in continuation with jejunal loops in the anterior pararenal space on the left side-left paraduodenal hernia

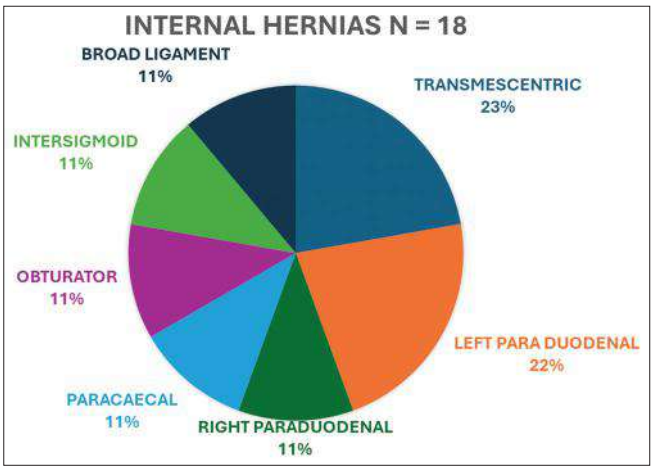


Figure 2: Distribution of cases

X-ray abdomen in erect and supine positions. In contrast, six out of 16 patients with stable vital signs underwent emergency CECT scan of the abdomen, which revealed evidence of internal hernia, followed by exploratory laparotomy.

All patients were investigated with contrast CT scan and the findings came in concordance with the pre-operative findings confirming the sensitivity and specificity of contrast (Figure 1).

The distribution of cases is depicted in Figure 2.

All 18 patients underwent exploratory laparotomy and the primary identification of hernial sac, reduction was done in all cases 6/16 cases developed gangrene of the small bowel and needed resection and anastomosis 37.5% of the total emergency cases. The elective cases needed just the release of the sac, reduction, and repair of the internal defects (Figure 3).

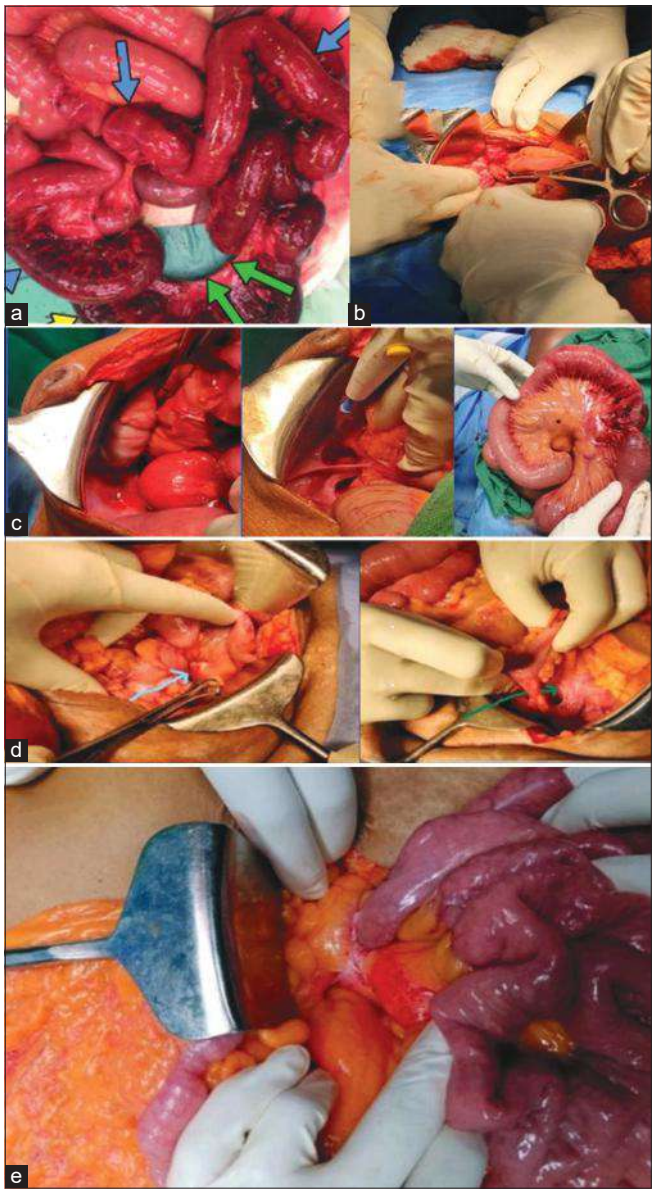


Figure 3: (a) Gangrenous bowel after reduction of transmesenteric hernia, (b) obturator hernia, (c) gangrenous bowel after reduction of paracecal hernia, (d) intersigmoid hernia reduction, and (e) mesenteric defect through which small bowel herniating-paraduodenal hernia

DISCUSSION

Internal hernias are a rare yet potentially devastating cause of intestinal obstruction, accounting for approximately 1–4% of all cases.[2,3] Despite their rarity, internal hernias pose a significant diagnostic challenge due to their non-specific clinical presentation.

There are numerous classifications of internal hernias, and one of the most acceptable ones is suggested by Welch, who divides internal hernias into eight types. The clinical manifestations of internal hernias can vary widely, but often include symptoms such as abdominal pain, nausea, vomiting, and obstipation.[4,5]. In our series, all 16 patients presented with obstipation, accompanied by vomiting and reduced appetite. Notably, six out of eight patients with the left paraduodenal and transmesenteric hernias reported a 6-month history of intermittent bloating and nausea.

The diagnosis of internal hernias is often delayed due to their non-specific presentation and the lack of pathognomonic signs.[6] Imaging studies, such as CECT scans, can aid in the diagnosis, but may not always be conclusive.[7] In our series, 16 out of 16 patients underwent emergency CECT scans, which revealed evidence of internal hernia. Due to limited clinical awareness, internal hernias are frequently underdiagnosed, leading to small bowel obstruction, which remains the most common clinically diagnostic manifestation.

CECT of the abdomen is the imaging modality of choice for diagnosing internal hernias, offering a sensitivity of 94–100% and specificity of 90–95%. Characteristic features on CECT include: Cluster of dilated loops or a "sac-like appearance" of crowded small bowel loops within the hernia sac at an abnormal anatomic location.

Diagnostic laparoscopy is a supportive diagnostic modality, particularly when CECT fails to detect any anomalies. Laparoscopy offers both diagnostic and therapeutic benefits, enabling repair of internal defects in the same sitting, if present.

The management of internal hernias is primarily surgical, with emergency laparotomy being the treatment of choice.[8,9] In our series, ten out of 16 patients underwent direct emergency exploratory laparotomy due to the presence of toxic clinical features.

Early diagnosis and prompt surgical intervention are crucial in preventing complications and improving outcomes.[10,11] In our series, two patients with the right preduodenal hernias presented with a 4-month history of chronic periumbilical pain, highlighting the importance of considering internal hernias in the differential diagnosis of chronic abdominal pain.

Internal hernias are a rare yet potentially devastating cause of intestinal obstruction. A high index of suspicion, combined with prompt imaging studies and surgical intervention, is essential in preventing complications and improving outcomes.

Limitations of the study

The limitations of this study include its retrospective design, which may introduce selection bias and limit the completeness of data collection. The relatively small sample size restricts the generalizability of findings to a broader population. Additionally, as the study was conducted at a single tertiary care center, variations in surgical expertise and institutional protocols may affect the reproducibility of outcomes in different settings. The reliance on imaging for preoperative diagnosis, while effective, may have led to underdiagnosis in cases where subtle internal hernias were missed. Furthermore, long-term follow-up data on patient outcomes, recurrence rates, and post-operative complications were not extensively analyzed, limiting the assessment of long-term prognosis.

CONCLUSION

The blurry nature of this disease makes it difficult for physicians to diagnose it at an early stage, leading to furthermore complexities in managing the condition in the form of major resections and stomas that can be possibly avoided with more clinical awareness and upscaling the diagnostic investigations in patients with recurrent nonspecific abdominal complaints.

Prompt recognition and timely intervention are crucial in mitigating the morbidity associated with internal hernias, underscoring the imperative of heightened clinical vigilance, expedited imaging evaluation, and judicious employment of diagnostic laparoscopy to facilitate optimal patient outcomes.

ACKNOWLEDGMENT

None.

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Juxtaposing pedagogical paradigms: the efficacy of peer-assisted learning (PAL) versus faculty-assisted learning (FAL) in the refinement of surgical proficiency

Santhosh Thekkoot Vijayan[1*], Jithin Joshy Kattuparambil[1], Praveen Thichur Mani[1], Ravindran Chirukandath[1] and Manoj Antony[1]

Abstract

Background Skill training in medical education poses significant challenges. The traditional "see one, do one " approach is increasingly seen as outdated and inconsistent with modern adult learning principles. The 2019 Medical Council of India (MCI) skill training module recommends Peyton's four-step method for psychomotor skill training is designed for a 1:1 teacher-to-student ratio. However, this ratio is often impractical due to faculty shortages. Peer-assisted learning (PAL) has emerged as a potential solution, yet its effectiveness in teaching suturing skills using Peyton's method remains underexplored in our context.

Objectives To compare the effectiveness of PAL using Peyton's method with faculty-assisted learning (FAL) for surgical skill training and to evaluate students' perceptions of their learning experiences through validated feedback forms.

Materials and methods Sixty second-year MBBS students were randomized into two groups: one trained in basic suturing techniques (interrupted, vertical mattress, and continuous suturing) by peer tutors (PAL group) and the other by faculty members (FAL group). Peer tutors, trained by senior faculty members, used Peyton's four-step method to teach suturing techniques in a skill lab using manikins. Post-training, proficiency was assessed using a 15-point OSCE checklist, and students' perceptions were evaluated through a questionnaire.

Results Both groups achieved mean proficiency scores exceeding 80% (> 12/15) across all techniques, with no statistically significant difference between groups. Students in both groups reported high satisfaction with their training experience. Notably, the PAL group demonstrated significantly higher confidence in performing suturing both in the skill lab and on real patients ($p < 0.05$).

Conclusion Peer-assisted learning is as effective as faculty-assisted learning for surgical skill training using Peyton's method. PAL can be recommended as a viable adjunct to traditional teaching methods for skill instruction.

Clinical trial number Not applicable.

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Keywords Peer-assisted learning, Faculty-assisted learning, Surgical skills, Peyton's method, Undergraduate medical education

Introduction

Teaching and mastering surgical skills remain complex and multifaceted challenges in medical education. There is a growing concern that current training methods often fail to meet expectations [1, 2], primarily due to the lack of structured, evidence-based curricula and a critical shortage of adequately trained teaching professionals [3–5]. Traditional methods, such as the "see one, do one" approach, have long been a cornerstone of surgical education but are increasingly criticized for being outdated and misaligned with contemporary adult learning principles [6, 7].

To address these concerns, Peyton's four-step approach has gained prominence as the gold standard for teaching psychomotor skills. This method involves demonstration, deconstruction, comprehension, and performance, providing a structured framework that fosters effective skill acquisition [8]. Endorsed by the Indian Medical Council, Peyton's method is widely recommended for skill training [9]. However, its ideal implementation requires a 1:1 teacher-to-student ratio [10], which is rarely feasible in the current landscape of medical education, characterized by faculty shortages and the increasing workload of existing educators [5]. This gap necessitates innovative strategies to sustain the quality of surgical training.

One such solution is Peer-Assisted Learning (PAL), a collaborative learning approach where students gain knowledge, skills, and understanding from their peers at the same or varying academic levels [11, 12]. PAL promotes a range of competencies, including critical thinking, clinical reasoning, problem-solving, and professional development, by leveraging peer exploration, argumentation, and mentorship [13]. Unlike faculty-led methods, PAL not only alleviates the burden on teaching staff but also fosters a sense of mutual growth and accountability among students.

Despite the potential of PAL in addressing faculty shortages, its application in surgical skill training, particularly when integrated with Peyton's methodology, has been underexplored. A recent meta-analysis highlighted the potential benefits of PAL combined with Peyton's method but also pointed to significant limitations, such as small sample sizes and heterogeneity among studies [14]. This underscores the need for robust research to determine the efficacy of PAL as an alternative or adjunct to faculty-assisted learning in surgical education.

Research question

Can peers teach peers basic surgical skills via Peyton's method as effectively as faculty do?

Hypothesis

We hypothesize that PAL by Peyton's method is as effective as FAL by Peyton's method in basic surgical skill training of undergraduates in medical education via Peyton's 4-step method.

Objectives

Primary objective To compare the effectiveness of peer-assisted learning via Peyton's method with that of faculty-assisted learning in the surgical skill training of phase 2 MBBS students via the OSCE.

Secondary objective To assess the perceptions of students about their learning experience via validated feedback forms.

Materials and methods

Settings

It was a quasi-experimental study conducted at Government Medical College Thrissur. After obtaining Institutional Research Board permission (IRB No: IEC/GMCTSR/2024/056 Dated 09/04/2024) consented medical students from second phase of the MBBS program were recruited.

The study period was three months

Ethical considerations The study participants were enrolled only after obtaining informed consent and they were free to opt out of the study at any point of the study period, irrespective of whether they had completed the assessment or not. The results of the assessment would not influence their formative or summative assessments in any way. Allocation of each participant to a particular group was done by simple random sampling using lottery system, therefore each enrolling participant had an equal chance of being assigned to a particular group. No monetary benefit was provided to the participants. All participant-related information was kept confidentially.
Confidentiality statement: The confidentiality of the data gathered was maintained. The names of participants were not be entered in proforma.

Sample size for the was calculated using the formula

$$n = \frac{(z_\alpha + z_\beta)^2 \times 2 \times sD^2}{d^2}$$

Zα = 1.96: At 5% error (level of significance).
Zβ = 0.84: At 80% power of the study.

$$SD^2 = \frac{SD_1^2 + SD_2^2}{2}$$

SD1=0.65
SD2=0.79
d = 0.57
n = 25

The required sample size (n) is 25 participants in each group.
We have taken 30 participants for each group.
The value for mean and standard deviations were taken from a previous study done by Ong MN et al. [15].

This study was conducted at National Emergency Life-Support Skill (NELS) centre at the campus of Government Medical College, Thrissur. The basic suturing skills training module was structured based on skill training module for undergraduate curriculum by National Medical Commission, India [9]. The training protocol was summarised in Fig. 1.

Training of peer tutors

Six, Phase 2 MBBS students who were willing to be peer tutors and have good communicative skills were selected. They were trained by senior authors (TVS, RC, JJK) individually in basic suturing techniques using the same training module prepared for the study using Peyton's 4 step approach. After training they were assessed by faculty members of the Department of Surgery for proficiency using OSCE (Objective Structured Clinical Examination) Checklist (Appendix 1) [16]. They should score 15/15 on the checklist which was the maximum possible score to be selected as peer tutors.

Five faculty members who were not below the rank of Assistant Professor from the Department of Surgery were selected as faculty trainers. They were also trained via Peyton's method with the same checklist for uniformity.

Selection of trainees and intervention

From the 160 phase II medical students, sixty students who had no previous experience with basic suturing and consented for study were selected by simple random method by lottery system. Then they were divided into two equal groups to receive basic surgical skills training either by faculty (faculty-assisted learning—FAL group) or peer tutors (peer-assisted learning—PAL group). This was also done by lottery system.

The surgical skill training module developed based on surgical skill training module by NMC [9]. Total training consists of six hours divided into two sessions.

The first session was of two hours duration. It was mainly a didactic session about wound care, different types of wounds, suture materials, and the handling of surgical instruments like needle holder, forceps and Mayo's suture cutting scissor. This was by one of the senior authors himself.

After the first session each group subdivided into smaller groups of 15 for convenience of training and assessment This was consisted of 4 h. In this session students were instructed and practiced interrupted, vertical and continuous suturing and instrument knotting with 2 – 0 silk on a mannequin (Opsys 3-layer suture practice pad OP-25, Opsys Simulations India) using needle holder and Adson's forceps.

Peyton's four-step approach was used to teach the suturing skills. It has 4 steps: [8]

1. Demonstration -faculty/peer teacher demonstrates suturing techniques on a mannequin at normal pace without any comments.
2. Deconstruction- The tutor then repeats the procedure once again, describing all necessary steps.
3. The comprehension-faculty/peer teacher repeats the procedure on the mannequin following the instructions of the trainee while all other trainees are watching.
4. Performance-- trainee performs the procedure while all other trainees are watching. Then, given feedbacks.

Training was conducted at a teacher-to-student ratio of 1:3 in both groups. After instruction, the students have given time to practice on the mannequin, and each student has practiced correctly at least 6 times in the skill lab.

Assessment of skills

Students' proficiency in suturing skills were assessed via objective structured clinical examination (OSCE). At the skill station, the students were instructed to demonstrate the wound closure technique and knot tying using instrument. There were 3 stations, one for interrupted suturing, the second for vertical mattress suturing and the third for continuous suturing. Each station consisted of 5 min. First and second stations students were instructed to perform minimum 3 suturing and best one selected. In the 3rd station they must close 3 cm wound using continuous suturing. Each student was assessed for proficiency using a validated checklist based on NMC skill training module [9]and a previous study by Yap etal(Appendix 1) [16]. It has an internal consistency (Cronbach α) of 0.61 to 0.77 [17]. The maximum score was 15. Students who could not achieve a score of 12 (< 80% score) were given remedial sessions by the faculty and were reassessed. The assessors of the procedural skills were faculty members in the department of surgery who were not involved in the training of participants and they were ignorant of the training the students had received.

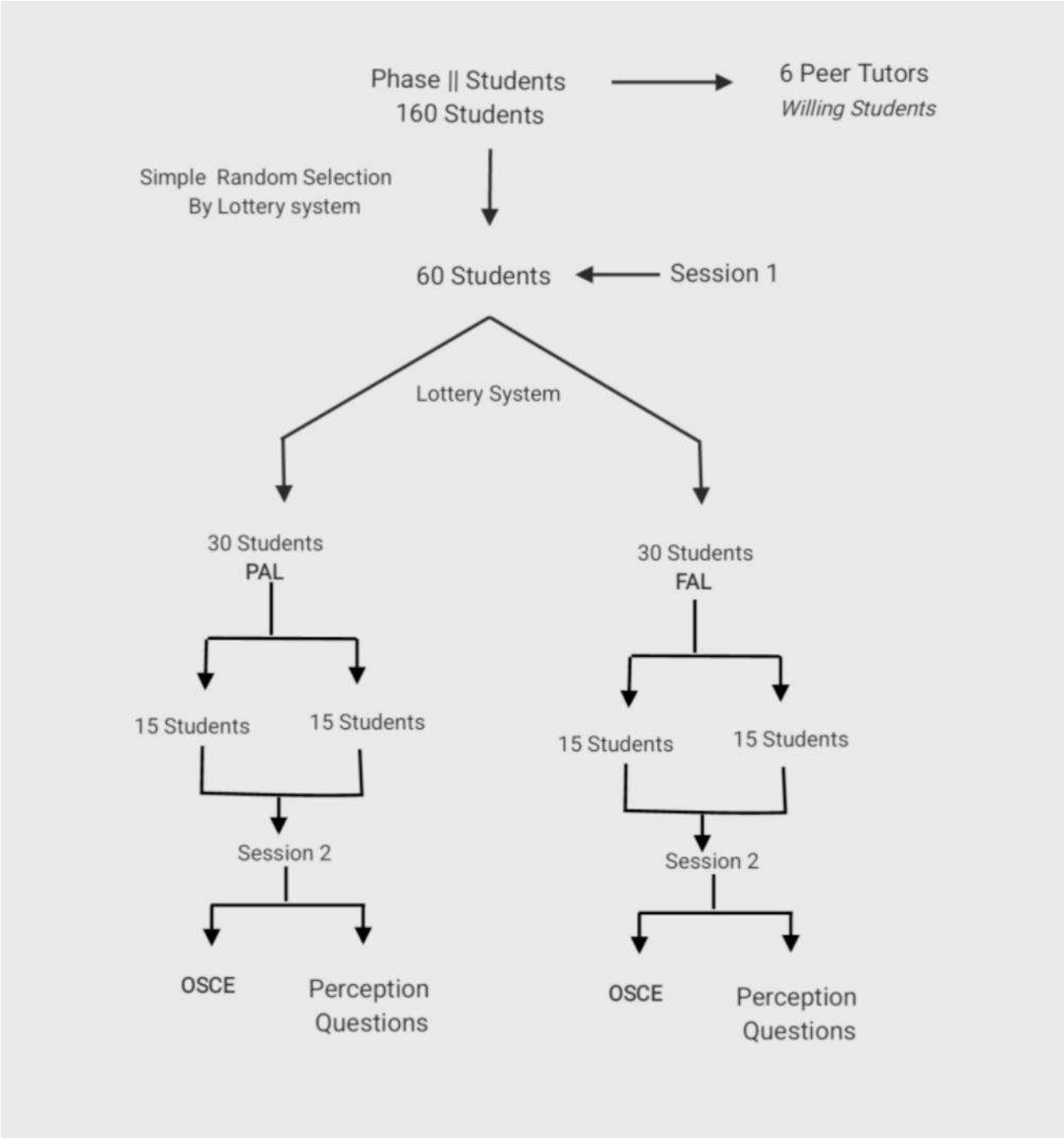


Fig. 1 Study design and training protocol

Following the training feedback from tutees on their perceptions of their learning experience was collected via a questionnaire [Appendix 2] [18]. The perceptions of groups on (1) skill development and (2) overall student satisfaction will be measured on a four-point Likert scale.

Data analysis

Statistical analysis was performed via the Epi Info TM Version 7.2, CDC, Atlanta, Georgia. The OSCE scores summarized as mean standard deviations and was compared via independent t-test. the perceptions were summarised as median and Mann–Whitney test U-test was used to compare the median scores of perceptions. The

Table 1 Comparison of the interrupted, vertical mattress and continuous suturing techniques

Suturing skills (Mean ± SD)			
Groups	**Interrupted**	**Vertical mattress**	**Continuous**
FAL($n=30$)	14.20 ± 0.66	13.67 ± 0.66	13.47 ± 0.629
PAL($n=30$)	14.00 ± 0.8	13.90 ± 0.75	13.57 ± 0.679
P value*	0.32	0.20	0.55
95% CI	-0.20-0.60	-0.60-0.13	-0.43-0.23

*(Independent t test, $P<0.05$ considered statistically significant)

Table 2 Opinion about skill lab training

Learning procedures at skill lab is a better alternative to learning at patient's bedside	**FAL *n* (%)**	**PAL *n* (%)**	**Mann–Whitney U**	***P* value**
Strongly agree	23 (76.7	18 (60.0)	525.00	0.169
Agree	7 (23.3)	12 (40.0)		
Disagree	0	0		
Strongly disagree	0	0		
Total	30 (100.0)	30 (100.0)		
Median	Strongly agree	Strongly agree		

Table 3 Learning experience in skilled labs

Learning experience at skill lab was satisfactory	**FAL *n* (%)**	**PAL *n* (%)**	**Mann–Whitney U**	***P* value**
Strongly agree	26 (86.7)	26 (86.7)	450.00	1.000
Agree	4 (13.3)	4 (13.3)		
Disagree	0	0		
Strongly disagree	0	0		
Total	30 (100.0)	30 (100.0)		
Median	Strongly agree	Strongly agree		

Table 4 Overall experience in the skilled lab

How will you rate the overall experience in skill laboratory?	**FAL *n* (%)**	**PAL *n* (%)**	**Mann–Whitney U**	***P* value**
Excellent	29 (96.7)	27 (90.0)	480.00	0.305
Average	1 (3.3)	3 (10.0)		
Below average	0 (0.0)	0 (0.0)		
Not good at all	0 (0.0)	0 (0.0)		
Total	30 (100.0)	30 (100.0)		
Median	Excellent	Excellent		

level of significance was fixed at $p<0.05$ for statistical tests.

Results

The study included 60 phase 2 medical students. The participants were randomized into two groups. They were assessed via a 15-point OPSE checklist. The mean competency score in both groups was above 80%, i.e., > 12 out of 15. The mean competence score did not differ significantly between the two groups for all three procedures assessed. (Table 1).

Additionally, we gathered information regarding students' perceptions of their skill lab experience and skill acquisition. Every student took part in the questionnaire. Both groups were happy with the facilities offered and firmly felt that the skilled lab was a superior option to bedside learning for training. Everyone agreed that the chosen procedure was extremely pertinent. Everyone has the chance to practice at least three times. Everyone was quite happy with their overall educational experience. The groups' satisfaction levels did not significantly differ from one another.

The participants in the PAL group expressed significantly more confidence in their ability to complete the procedure at the skill lab and perform on real patients. (Fig. 2). A few students in both groups faced some difficulties in the learning process. These students expressed some technical difficulties in handling the instruments, mainly needle holders (Table 5).

Discussion

The implementation of the Competency-Based Medical Education (CBME) curriculum in India in 2019 emphasized the importance of skill training as a cornerstone of undergraduate medical education [19]. However, significant barriers hinder its effective execution, primarily due to resource constraints, faculty shortages, and the demanding workloads of medical educators [5]. In this context, Peer-Assisted Learning (PAL) has emerged as a potential solution to address these challenges [11]. PAL, defined as the process of gaining knowledge, understanding, or skill from peers at the same or different academic levels, is known to promote critical thinking, problem-solving, and professional development through collaborative learning [12, 13].

Traditional methods like "see one, do one" have been criticized for being outdated and for compromising patient safety [20]. Peyton's four-step method has gained recognition as a structured and student-centric alternative for teaching psychomotor skills [21]. This method, endorsed by the Medical Council of India, includes demonstration, deconstruction, comprehension, and performance, providing a framework that enhances both cognitive and mechanical skills [22, 23]. However, the teacher-to-student ratio required for Peyton's method poses a challenge in resource-constrained settings, making PAL a viable and practical alternative [5, 11].

This study aimed to evaluate the efficacy of PAL versus Faculty-Assisted Learning (FAL) in teaching surgical skills using Peyton's methodology. The findings revealed no significant difference in the acquisition of suturing skills between the PAL and FAL groups, with both achieving comparable mean scores of over 80%.

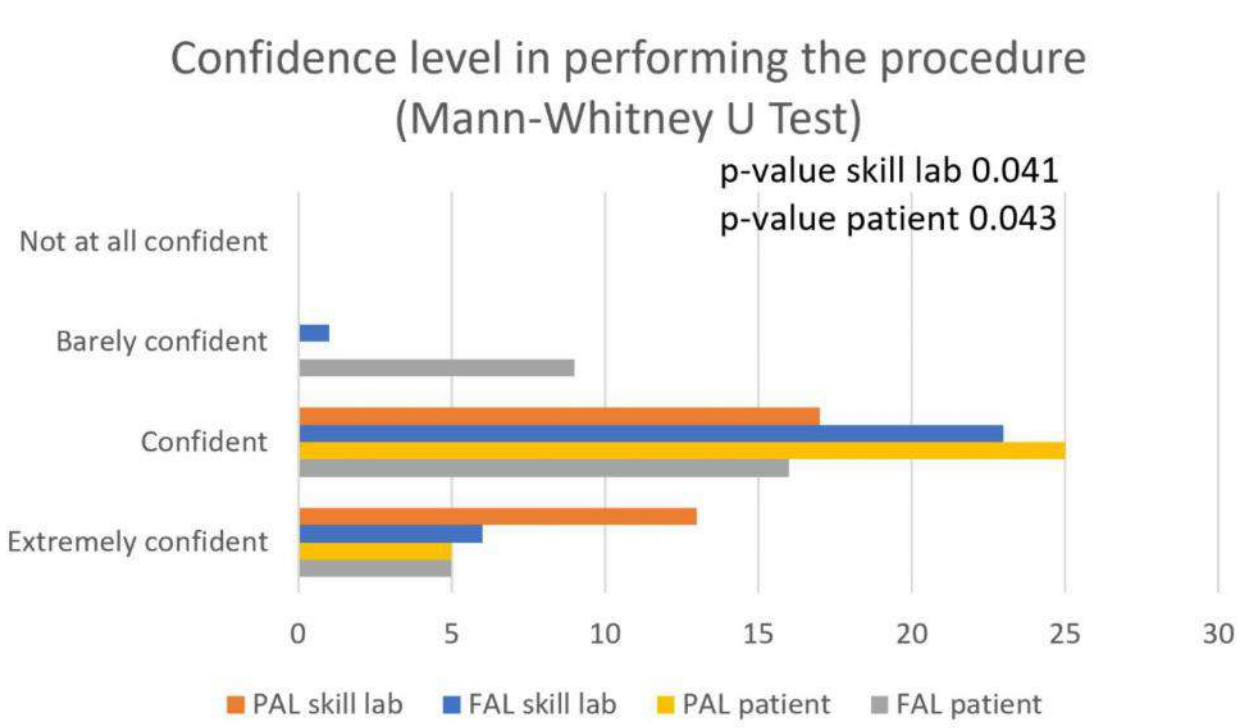


Fig. 2 Confidence level in a skilled lab and a real patient

Table 5 Difficulty faced during the learning process

Any difficulties or problems perceived during the learning process?	F	P	Mann-Whitney U	*P* value
Yes	5 (16.7)	3 (10.0)	480	0.451
No	25 (83.3)	27 (90.0)		
Total	30 (100.0)	30 (100.0)		
Median	No	No		

Interestingly, students in the PAL group reported greater confidence in applying their skills in both the skills lab and real-life scenarios. This underscores the non-threatening, collaborative environment fostered by PAL, which may alleviate stress and enhance learning outcomes, a notion supported by similar findings in nursing education [24].

Existing literature corroborates these findings, highlighting the efficacy of PAL in surgical skill training. For instance, studies by Preece et al. and Pintre et al. demonstrated that students trained by peers achieved comparable or even superior outcomes compared to those trained by faculty. These studies emphasize the role of peer instructors in creating a learner-centric environment conducive to skill acquisition and confidence building [25, 26]. Additionally, randomized trials have shown that PAL can effectively teach basic surgical skills, with learners achieving similar or better proficiency levels than their faculty-taught counterparts [15, 27, 28].

While PAL has garnered widespread support, some criticisms persist. Certain studies have questioned its effectiveness in teaching complex skills, such as aseptic techniques, attributing this limitation to the inherent difficulty of the tasks [29]. Furthermore, concerns have been raised about whether PAL's positive impact on learners' perceptions translates into actual examination performance [30]. However, recent meta-analyses favor PAL, concluding that it is as effective, if not more so, than FAL in skill development [31–33].

This study contributes to the limited literature on combining PAL with Peyton's method for surgical skill training. The results demonstrate that trained peers can teach techniques like suturing as effectively as faculty, providing a sustainable solution to faculty shortages. Additionally, the successful integration of Peyton's method into the PAL framework further validates its utility in psychomotor skill training. While existing meta-analyses have explored Peyton's method and peer teaching [14], this study uniquely focuses on their combined application in surgical skill training, offering valuable evidence for future educational strategies.

In conclusion, PAL represents a promising alternative to FAL, particularly in resource-limited settings, and can effectively employ structured methodologies like Peyton's. Future research should aim to expand the evidence base by exploring PAL's applicability to more complex surgical skills and conducting randomized trials

to establish its long-term impact on competency-based medical education.

Conclusion

The comparative analysis of Peer-Assisted Learning (PAL) and Faculty-Assisted Learning (FAL) in surgical skill training underscores the unique merits and challenges associated with each pedagogical approach. PAL fosters a collaborative and less intimidating learning environment, encouraging active participation, peer mentorship, and confidence-building among trainees. It effectively cultivates critical thinking and problem-solving skills while enhancing camaraderie and team dynamics. However, its efficacy may be limited by the variable expertise of peer tutors, potentially leading to inconsistent knowledge dissemination or perpetuation of errors.

On the other hand, FAL offers structured, expert-led guidance, ensuring the dissemination of standardized, evidence-based surgical techniques. Faculty mentorship allows for immediate correction of errors, personalized feedback, and a deeper exploration of complex surgical concepts. However, its reliance on resource-intensive faculty involvement may pose logistical challenges, especially in institutions with constrained faculty availability. A blended approach, leveraging the strengths of both PAL and FAL, could provide a balanced and effective model for surgical education, ensuring skill acquisition while promoting self-directed and collaborative learning.

Limitations

Motivated and passionate peer tutors play an important role in the success of peer teaching. In this study, both the instructors and the students were chosen voluntarily. Usually, highly motivated and enthusiastic students volunteer to participate in the study as both peer tutors and trainees. A selection bias might be introduced as a result [34]. 34So, while generalizing the data, one must exercise caution. Second, we were not given a long-term assessment of the PAL. We were also not evaluated on the peer tutors' views of the training. We also did not compare sub competencies like as instrument handling, suturing abilities, tissue handling, or instrument knotting. Except for tissue handling, a study by Ong MN et al. that looked at these factors found no discernible differences between PAL and FAL. They trained using a bench model made of chicken skin [15].

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12909-025-06827-2.

Supplementary material 1

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Author contributions
Conception and Design STV, JJK, PTM, RC, MA. Analysis and interpretation of data STV, JJK, PTM, RC, MA. Drafting of article STV. Critical Revision of Article for important intellectual content STV, JJK, PTM, RC, MA.

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Data availability
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was reviewed and approved by the Institutional Ethics Committee GOVERNMENT MEDICAL. COLLEGE THRISSUR, KERALA, INDIA (Reg. No. EC/NEW/INST/2022/KL/0176, dated 20.10.2022) under. IRC Protocol No. IEC/GMCTSR/2024/056. The study, titled *"Effectiveness of Peer Assisted Learning (PAL) versus Faculty Assisted Learning (FAL) in Surgical Skill Training"*, underwent an expedited review process. The documents reviewed and approved include the application form, research proposal, and consent form. Written informed consent was obtained from all participants involved in the study. This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. All procedures were conducted in accordance with national regulations and ethical guidelines.

Consent for publication
Consent for publication was obtained from all participants involved in the study.

Competing interests
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CASE REPORT

Cureus

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Navigating the Cervico-Axillary Canal: A Rare Encounter With Double Dumbbell Space Sarcoma Involving the Neck and Axilla

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Abstract

Space sarcomas are exceedingly rare neoplasms, and double dumbbell space sarcoma in the cervicoaxillary canal has not been previously reported. We present a case of a 63-year-old male who presented with a swelling in the neck and axilla of four years' duration, which rapidly increased in size over the last three months. Clinical examination and imaging revealed a multiseptate mass extending from the posterior triangle of the neck to the right axilla and chest wall through the cervicoaxillary canal. This lesion encased major vessels and components of the brachial plexus but did not infiltrate them. A trucut biopsy confirmed the diagnosis of well-differentiated liposarcoma. Surgical intervention was performed, achieving complete resection with preservation of neurovascular structures. This case highlights the unique challenges and complexities associated with managing double dumbbell space sarcomas in the cervicoaxillary canal. Additionally, it underscores the importance of a multidisciplinary approach to achieving successful outcomes while preserving limb function and minimizing complications. Long-term follow-up is essential for monitoring potential recurrences.

Categories: Oral Medicine, General Surgery
Keywords: lipo sarcoma, space sarcoma, sarcoma, dumb bell, cervico axillary canal

Introduction

Liposarcoma stands as one of the most prevalent soft-tissue sarcomas found in adults, making up approximately 20% of all soft-tissue malignancies [1]. Typically, its occurrence is observed in the retroperitoneum and lower extremities, particularly within structures like the intermuscular fascia [2]. Extracompartmental space sarcoma is rare, and we present an unusual occurrence of liposarcoma in the neck and axilla that arose from a pre-existing, long-standing lipoma. At the outset, individuals diagnosed with well-differentiated liposarcomas in their extremities typically have a more favorable prognosis. As a result, the primary treatment approach should involve wide excision. Even in situations where the lesions are in close proximity to major nerves or blood vessels, conservative resection techniques that preserve these crucial structures and maintain limb function have demonstrated remarkable effectiveness, resulting in minimal recurrence and metastasis rates [3].

Case Presentation

A 63-year-old gentleman presented with a swelling in his right neck and axilla, which had been persisting for four years but had significantly increased in size over the last three months. The patient had no prior history of comorbidities or surgical procedures. Physical examination revealed a distinctive dumbbell-shaped mass measuring 20 cm × 15 cm in the root of the neck and 15 cm × 10 cm in the right axilla (Figure *1*). The neck lesion was mobile and displayed varying consistency with both soft and hard areas, while the chest lesion was subpectoral. There was no palpable axillary lymph node enlargement, focal neurological deficits in the right arm, or muscle weakness.



FIGURE 1: Dumb bell tumor in neck and axilla

An MRI scan demonstrated a 24 cm × 18 cm × 11 cm multiseptate lesion extending from the posterior triangle of the neck to the right axilla and chest wall through the thoracic inlet (Figure *2*). The lesion abutted the internal jugular vein superiorly, the trapezius muscle posteriorly, the paraspinal muscles medially, and the sternocleidomastoid muscle laterally, maintaining fat planes. Notably, the lesion encased the subclavian vessels and components of the brachial plexus without evidence of infiltration.

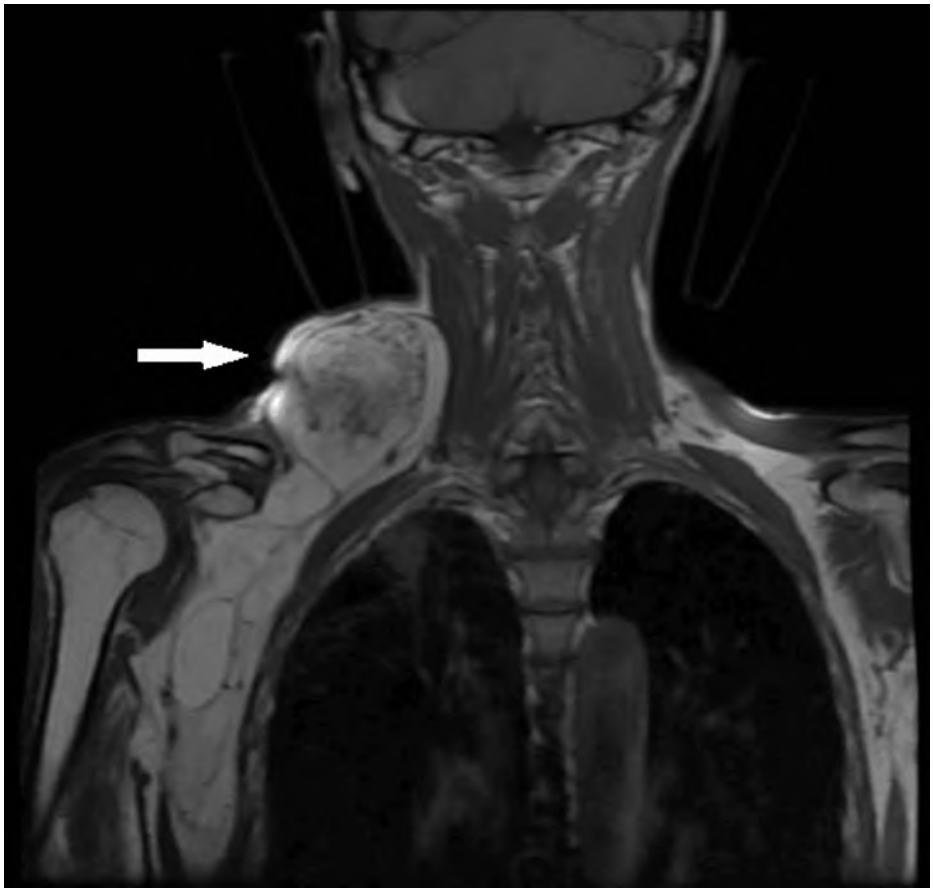


FIGURE 2: MRI showing space sarcoma in the cervicoaxillary canal

A trucut biopsy performed on solid areas of the lesion suggested a diagnosis of well-differentiated liposarcoma. Given the rarity of double dumbbell space sarcomas and the unique location and relationship of this lesion with major vessels, surgical intervention was deemed necessary.

Surgical excision was undertaken using two incisions, one in the neck and another in the axilla. The lesion was first mobilized from the neck, dissecting it from the trapezius, sternocleidomastoid, and paraspinal muscles. Subsequently, through the axillary incision, the axillary part of the lesion was mobilized after careful taping of the brachial plexus and subclavian vessels (Figure *3*). An extracapsular dissection was performed without tumor spillage, preserving the integrity of vessels and nerves and achieving an R0 resection (Figure *4*). Postoperatively, the patient did not display any neurovascular deficits or weakness. The dumbbell tumor specimen submitted for histopathological examination exhibited the gross characteristics of a soft, fleshy mass with extensive areas of hemorrhage and necrosis (Figure *5*). Microscopic analysis revealed liposarcoma, manifested by sheets of large pleomorphic cells featuring vesicular hyperchromatic nuclei, prominent mitotic activity, and infiltration into the thick capsule, indicative of the tumor's aggressive nature (Figure *6*).

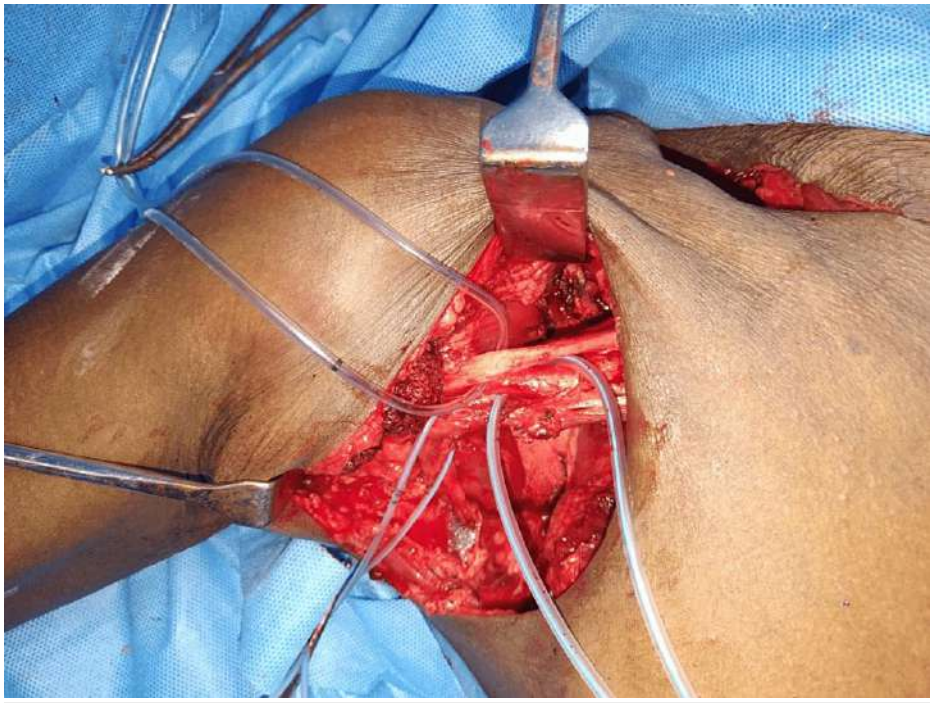


FIGURE 3: Taped brachial plexus and subclavian vessels



FIGURE 4: Dumbbell tumor



FIGURE 5: Gross image of the lesion

Cut surface showing yellow, fatty tissue with interspersed fibrous septae, areas of necrosis, and hemorrhage

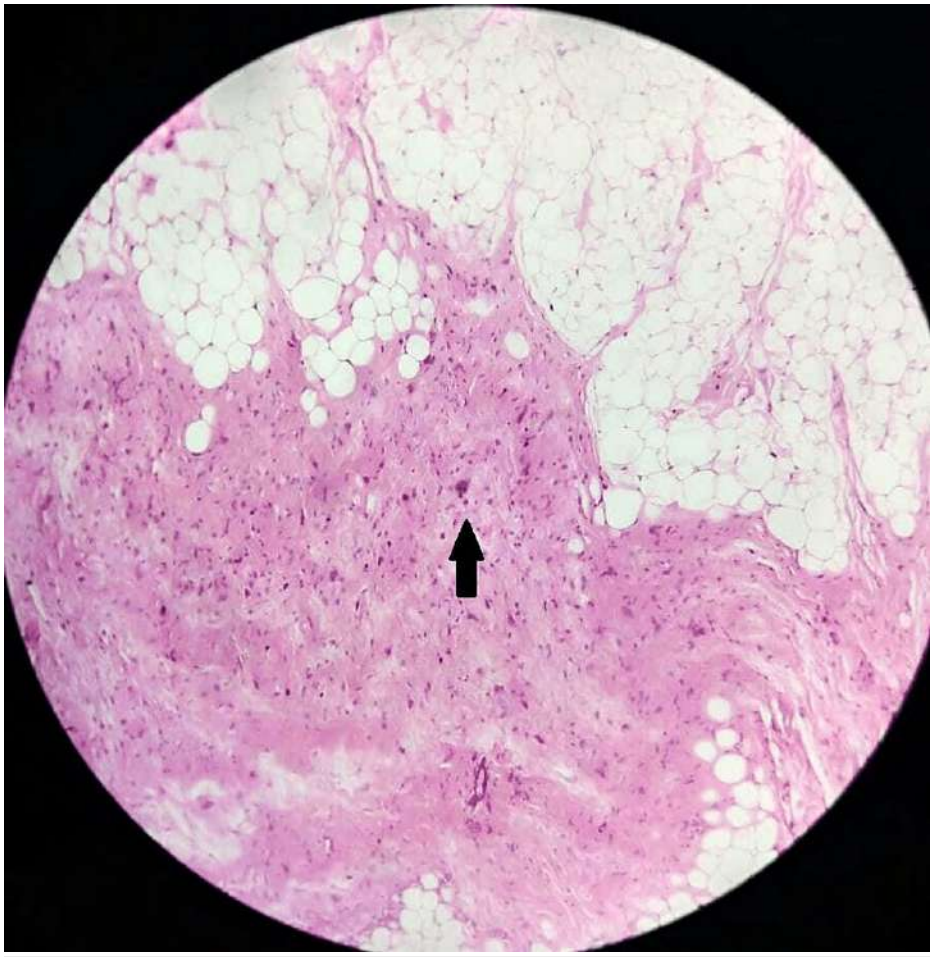


FIGURE 6: Microscopy of the lesion

Microscopy showing adipocytes with hyperchromatic pleomorphic nuclei and multinucleated tumor cells

Discussion

The thoracic outlet is precisely defined as the region in the lower neck situated between the thorax and axilla, serving as the conduit through which the subclavian vein, subclavian artery, and brachial plexus traverse from their central origins to their peripheral destinations. This anatomical region is demarcated by the clavicle anteriorly, the first thoracic rib posteriorly, the insertion point of the pectoralis minor muscle, and the humerus laterally. Functionally, it is partitioned into three distinct areas: the scalene triangle situated above the clavicle, the costoclavicular space, or cervicoaxillary canal, located between the clavicle and the first rib, and the subcoracoid or pectoralis minor space positioned below the clavicle [4,5]. This spatial zone encompasses the primary subclavian artery, subclavian vein, and brachial plexus. This is a narrow and confined space, and any space-occupying lesion within this canal presents a significant challenge for surgical removal.

Soft tissue sarcomas (STS) originating in extra-compartmental spaces exhibit distinctive features. These tumors possess the capacity to extend over a significant distance both proximally and distally, encountering fewer anatomical constraints. As a consequence, tumors arising within these spaces tend to be closely situated within the neurovascular bundle, often leading to early involvement [6-8]. The cervicoaxillary canal's limited dimensions make the removal of any space-occupying lesion within it a demanding surgical task.

Wide excision surgery produces excellent results in the treatment of massive liposarcomas of the extremities in terms of not only a low recurrence rate but also good limb function [9]. Space sarcomas involving the cervicoaxillary canal are exceptionally uncommon. The location of this lesion, with its proximity to major vessels and the brachial plexus, adds a significant level of complexity and interest to the case. A trucut biopsy performed on solid areas of the lesion suggested a diagnosis of liposarcoma, prompting surgical intervention.

The objectives of resection for soft tissue sarcomas in the extremities encompass achieving a wide excision

of the tumor with clear, negative resection margins, all while preserving the optimal function of the affected limb. Intra-compartmental tumors typically entail resection of both the tumor and the surrounding muscle to accomplish this goal. In contrast, space tumors, despite their close proximity to blood vessels, may sometimes be resected with negative margins while sparing the neurovascular bundle. However, in other instances, the behavior of these tumors may lead to vascular involvement, necessitating their resection in accordance with the extent of vessel involvement [10].

Conclusions

An understanding of the anatomy of the cervicoaxillary canal is essential for diagnosing and managing conditions such as double dumbbell space sarcoma. The precise location and relationships of structures within this anatomical region can greatly impact surgical planning and outcomes. Careful dissection, preservation of neurovascular structures, and attention to maintaining fat planes are crucial aspects of successful management in this challenging anatomical space.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Acquisition, analysis, or interpretation of data: Ravindran Chirukandath, Ireddy Sandeepreddy, Priyanka Mittra

Drafting of the manuscript: Ravindran Chirukandath, Sumin V. Sulaiman, Saheer Neduvanchery, Ireddy Sandeepreddy, Priyanka Mittra

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Disclosures

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Section: General Surgery

Case Report

FROM CRIMSON CLUES TO THE UNSEEN ENEMY: NAVIGATING THE THERAPEUTIC MAZE OF URACHAL CARCINOMA – A COMPELLING CASE REPORT

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Abstract

Background: Urachal carcinoma is a rare, aggressive form of bladder cancer, representing only 0.01% of all adult malignancies. Due to its embryonic origin from the allantois, it often presents late with nonspecific symptoms, complicating timely diagnosis and treatment. This case report outlines the clinical presentation, diagnosis, surgical management, and histopathological findings of a high-grade urachal adenocarcinoma. **Case Presentation:** A 64-year-old male presented with lower abdominal pain, hematuria, and increased frequency of micturition. Examination revealed a firm, non-tender midline mass in the suprapubic region. Imaging suggestive of mass infiltrating the bladder dome with polypoid growth into the lumen and abutting the anterior abdominal wall. Cystoscopy revealed a large proliferative growth, and biopsy indicated high-grade noninvasive papillary urothelial carcinoma. The patient underwent umbilicectomy, urachal cyst excision, partial cystectomy, and bilateral pelvic lymph node dissection. Histopathology confirmed adenocarcinoma of urachal origin characterized by glandular structures with mucin production. **Conclusion:** Early recognition of urachal carcinoma symptoms, combined with imaging and histological confirmation, is critical for appropriate surgical intervention. Comprehensive resection remains the cornerstone of treatment, with ongoing research needed for adjuvant therapies to improve long-term survival.

INTRODUCTION

Urachal carcinoma is a rare and aggressive type of bladder cancer, accounting for only about 0.01% of all adult malignancies. Originating from remnants of the embryonic allantois, it often presents at an advanced stage with vague, nonspecific symptoms, making early diagnosis and treatment challenging. This case report describes the clinical presentation, diagnostic workup, surgical management, and histopathological characteristics of a high-grade urachal adenocarcinoma.

CASE REPORT

A 64-year-old male who is a known hypertensive, presented with complaints of lower abdominal pain, hematuria and increased frequency of micturition. On physical examination, an ill defined firm, and non tender mass was palpable, in the midline of suprapubic region.

Initially ultrasound abdomen was done, revealed a 6x7cm solid cystic lesion in relation to superior wall of urinary bladder. Subsequent contrast CT showed a well defined solid cystic lesion abutting the dome of urinary bladder towards the midline, 6.6x4.5x7.4cm in size, solid component showed contrast enhancement. Lesion seen infiltrating the urinary bladder with polypoidal growth into the bladder lumen. Anteriorly, lesion is abutting the abdominal wall with maintained fat plane.



Figure 1: Axial image, contrast-enhanced CT scan of the abdomen and/or pelvis demonstrates well defined solid cystic lesion abutting the dome of urinary bladder.lesion seen infiltrating the urinary bladder with polypoidal growth into the lumen, anteriorly lesion abutting abdominal wall with maintained fat plane

Following which, cystoscope was done, detected a large proliferative growth over the anterior wall of bladder, towards the apex. Biopsy was taken and the result came as Noninvasive papillary urothelial carcinoma high grade. The patient underwent Umbilectomy, urachal cyst excision, partial cystectomy and bilateral pelvic lymph node dissection.

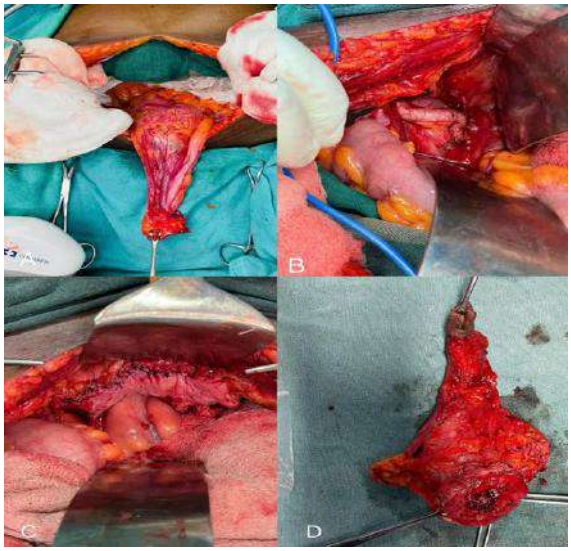


Figure 2: A. Intraoperative picture showing the tumor, B.Intraoperative view after pelvic lymph node dissection, C.Intraoperative appearance of residual bladder after partial cystectomy, D. Resected urachal tumor with umbilicectomy and partial cystectomy

Histopathology showed adenocarcinoma of urachal origin NOS.pT3A

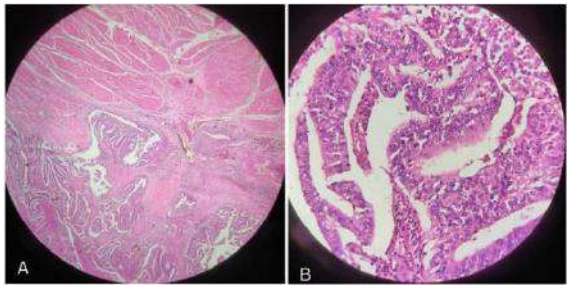


Figure 3. Histopathological picture showing infiltrating neoplasm composed of cells arranged in glandular pattern (A.Low resolution B. High resolution).

DISCUSSION

The urachus is a fibrous remnant of the allantois, an embryological structure that initially connects the fetal bladder to the umbilicus, facilitating the drainage of urine. In the adult, the urachus typically transforms into a fibrous cord known as the median umbilical ligament. This remnant is located in the space of Retzius, positioned between the transversalis fascia anteriorly and the peritoneum posteriorly. During fetal development, part of the urogenital sinus gives rise to the bladder and the prostatic urethra, while the allantois initially remains open but eventually obliterates as the urachus matures. This anatomical progression is vital to understanding the origin of urachal malignancies.

Urachal cancer, first described by Hue and Jacquin in 1963, is a rare and often aggressive malignancy. It accounts for an estimated 0.01% of all adult cancers and 0.5%-2.0% of all bladder malignancies, representing a significant but infrequent cause of bladder cancer. Urachal adenocarcinoma, in particular, makes up 20%-40% of primary bladder adenocarcinomas, further distinguishing it from more common urothelial bladder carcinomas. The clinical course of urachal carcinoma is typically marked by late presentation, a tendency for early local invasion, and a high propensity for distant metastasis, all contributing to a dismal prognosis. Patients diagnosed with locally advanced or metastatic disease have a mean survival of only 12-24 months, with a 5-year survival rate of approximately 43%.[1] The delayed symptom onset and aggressive behaviour of the disease make early detection and intervention challenging.

Urachal carcinomas primarily arise from the epithelial lining of the urachus. Although the urachal remnant is normally lined with urothelium, these carcinomas often exhibit histological features distinct from conventional bladder cancer. In contrast to most bladder carcinomas, which are predominantly urothelial carcinomas, urachal carcinomas are more often adenocarcinomas. These adenocarcinomas are typically mucin-producing and frequently display focal signet ring cell differentiation. These histological features distinguish urachal adenocarcinomas from typical

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urothelial carcinomas, which usually present as noninvasive papillary tumors that do not invade the muscular wall of the bladder. In contrast, urachal adenocarcinomas tend to infiltrate the muscularis propria and perivesical soft tissues, underscoring their more aggressive nature. Histological subtypes of urachal adenocarcinoma include mucinous, intestinal, and mixed types, with mucinous adenocarcinoma being the most common. Sarcomas, small-cell carcinomas, and transitional cell carcinomas are rare in this context.[2]

One of the major challenges in managing urachal carcinoma is its tendency to remain asymptomatic in the early stages. Symptoms typically develop only when the tumor invades the bladder wall, leading to common clinical signs such as hematuria, irritative voiding symptoms, and mucous-like discharge. Hematuria is present in approximately 90% of patients and is a key indicator of malignancy, increasing the likelihood of cancer by 17-fold, particularly in patients over 55 years of age.[3] Abdominal symptoms such as umbilical pain or discharge may also be reported, particularly in the later stages. These nonspecific symptoms often result in diagnosis at an advanced stage, complicating treatment and limiting the available therapeutic options.[4]

Imaging plays a crucial role in the diagnosis and staging of urachal carcinoma. A combination of ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) is typically employed to assess tumor size, location, and extent of local and distant spread. Ultrasound is frequently the first modality used and can detect the presence of a soft tissue mass with heterogeneity and calcification. Doppler imaging may sometimes reveal internal vascularity, although this is nonspecific. CT scans are particularly useful in visualizing the mixed solid and cystic nature of the tumor, with cystic components often representing mucin. CT also has high sensitivity for detecting calcifications, which are commonly observed in urachal adenocarcinomas. In terms of tumor positioning, 88% of these tumors are found outside the bladder lumen.[5] MRI is valuable for assessing the extent of local invasion, including lymph node involvement, and provides detailed imaging of peritoneal or visceral spread. MRI typically demonstrates high signal intensity on T2-weighted images and post-contrast enhancement, which is attributed to the mucin content and calcifications within the tumor.

Surgical resection remains the cornerstone of treatment for localized urachal cancer. The optimal approach typically involves partial cystectomy along with removal of the urachal ligament and, in many cases, umbilectomy. This combined approach has been shown to result in better outcomes compared to cystectomy alone, as it reduces the risk of recurrence and preserves the patient's quality of life.[6] Studies have consistently demonstrated that this comprehensive surgical approach offers superior survival outcomes. A retrospective case series by Bruins et al,[7] highlighted lymph node metastasis as an independent prognostic factor associated with reduced overall survival (OS). However, there was no significant survival difference between patients who underwent pelvic lymph node dissection (PLND) and those who did not, suggesting that lymph node dissection may not have a significant impact on survival outcomes, at least in the context of this disease.

Recurrence after surgery is common, with reported recurrence rates as high as 40%.[8] This recurrence often manifests within the first two years following surgery, primarily as local recurrence (in the pelvic lymph nodes, peritoneum, or omentum) or distant metastasis, particularly to the lungs and liver.[9] While there is no consensus regarding the use of adjuvant or neoadjuvant chemotherapy, chemotherapy is generally recommended for patients with lymph node involvement, distant metastasis, or positive surgical margins.[10] Radiotherapy is rarely used, with less than 1% of patients receiving it as a monotherapy, and its role remains unclear in the management of urachal carcinoma. The decision to use chemotherapy or radiation therapy should be individualized based on the patient's clinical stage and overall prognosis.

Although follow-up protocols for urachal carcinoma remain somewhat controversial, the high recurrence rate necessitates intensive surveillance. Cross-sectional imaging, particularly CT scans, is commonly employed for routine post-operative surveillance, similar to the follow-up protocol for muscle-invasive bladder cancer. Additionally, cystoscopy is recommended due to the risk of tumor seeding, particularly in patients who have undergone partial cystectomy for noninvasivetumors. Pinthus et al. identified tumor seeding into the lower urinary tract in 8.3% of patients, even after partial cystectomy, suggesting that cystoscopic surveillance is an essential component of post-operative care.[11] Given the significant risk of recurrence and metastatic relapse, an intensive follow-up strategy should be employed, incorporating both imaging and cystoscopy, to ensure early detection of recurrence and to guide subsequent treatment.

CONCLUSION

In conclusion, urachal carcinoma is a rare and aggressive malignancy that poses significant diagnostic and therapeutic challenges. Early detection remains difficult due to its often asymptomatic nature in the early stages. A high level of clinical suspicion, along with comprehensive imaging and histopathological analysis, is essential for diagnosis. Surgical resection remains the mainstay of treatment, with the addition of chemotherapy in cases with advanced disease. Given the high risk of recurrence, close post-operative monitoring, including imaging

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and cystoscopy, is necessary to detect relapses and guide subsequent management.

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Open Access Case Report

A Serendipitous Histopathological Revelation: An Intriguing Case Report of a Cystic Schwannoma of the Lateral Neck

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Abstract

Schwannomas are rare, benign tumors that arise from Schwann cells, which produce the myelin sheath around peripheral nerves. Cystic degeneration is an uncommon feature of schwannomas, occurring in approximately 4% of cases. The diagnosis of cystic schwannomas can be challenging due to their rarity and nonspecific clinical and radiological features.

A 45-year-old female presented with a two-year history of a gradually enlarging neck mass, which was initially suspected to be a branchial cleft cyst. Computed tomography (CT) scans showed a well-defined cystic lesion in the left supraclavicular region. The patient underwent ultrasound-guided fine-needle aspiration cytology (FNAC), which yielded hypocellular fluid. The patient underwent surgical excision of the mass, which was subsequently diagnosed as a cystic schwannoma based on histopathological examination.

Cystic schwannomas can pose a diagnostic challenge due to their rarity and nonspecific clinical and radiological features. Awareness of the clinical and pathological features of cystic schwannomas is essential for timely diagnosis and effective treatment. Accurate diagnosis is crucial to ensure optimal management and prevent recurrence.

Categories: Neurology, General Surgery, Pathology
Keywords: branchial cyst, cystic degeneration, cystic neck swelling, rare head and neck, schwanoma

Introduction

Schwannomas, also referred to as neurilemmomas, represent rare, benign neoplasms originating from Schwann cells, the neuroectodermal elements responsible for the elaboration of the myelin sheath enveloping peripheral nerves. These tumors are characteristically solitary, well-circumscribed, and encapsulated, often demonstrating a distinct cleavage plane from adjacent anatomical structures. They exhibit a predilection for the head and neck region and the flexor surfaces of the extremities, with approximately one-third manifesting within the cephalocervical domain. Among these, the parapharyngeal space constitutes the most frequently involved site [1].

On cytological examination, schwannomas typically exhibit both Antoni type A and type B tissue patterns. The cytological features generally mirror the histopathology, with Antoni type A areas showing compact, cohesive fascicles of spindle-shaped cells with varying cellularity. These regions often contain dense fibrillary stroma, palisading nuclei, and structures resembling Verocay bodies. The individual tumor cells appear as cohesive spindle or oval cells with tapering ends and indistinct cytoplasmic borders, along with noticeable variability in nuclear size and shape. Antoni type B areas, in contrast, demonstrate loosely arranged, wavy spindle cells dispersed in a myxoid matrix, often accompanied by microcyst formation, histiocytes, and lymphocytes. Immunohistochemical staining for S-100 protein typically shows strong, diffuse positivity. Although schwannomas predominantly exhibit a solid architecture, cystic degeneration is an infrequent histopathological feature, documented in merely 4% of cases [2]. The diagnosis of such lesions remains inherently challenging due to their relative infrequency and the limited diagnostic yield of fine needle aspiration cytology (FNAC) in this context, a modality otherwise instrumental in the evaluation of more common cervical masses.

Of particular diagnostic concern is the potential for schwannomas exhibiting cystic transformation to simulate branchial cleft cysts, both clinically and radiologically. This distinction is of paramount importance, as branchial cysts are prone to recurrence and necessitate long-term surveillance, whereas complete surgical excision of a schwannoma is typically curative, with recurrence being exceptionally rare.

Herein, we delineate the case of a 45-year-old female who presented with a left-sided cervical mass, subsequently identified as a schwannoma with prominent cystic degeneration, underscoring the necessity for heightened clinical vigilance and thorough histopathological evaluation in such diagnostically ambiguous presentations.

Case Presentation

A 45-year-old female presented with a swelling on the left side of her neck, which had been gradually increasing in size over the past two years, with a noticeable increase over the last four months. The swelling was associated with pain, but there were no complaints of dysphagia or breathing difficulty. On clinical examination, a 3×3 cm, mildly tender swelling was noted in the left supraclavicular region, located in the posterior triangle of the neck. The mass had well-defined borders, was firm in consistency, mobile, and not fixed to underlying muscles.

Initially, USG of the neck (Doppler) was done on the 25th of January, 2024, which showed colloid nodules in both lobes of thyroid had Thyroid Imaging Reporting and Data System (TI-RADS) TR 2 lesions, and a cystic lesion in the left supraclavicular region with a possibility of branchial cleft cyst or lymphangioma.

CT neck (plain and contrast study) showed a well-defined cystic lesion in the left side of rgw neck, with a few enhancing soft tissue densities in the peripheries, and the suggested possibilities were lymphangioma, cystic lymph node, and third branchial cleft cyst (Figure *1*).

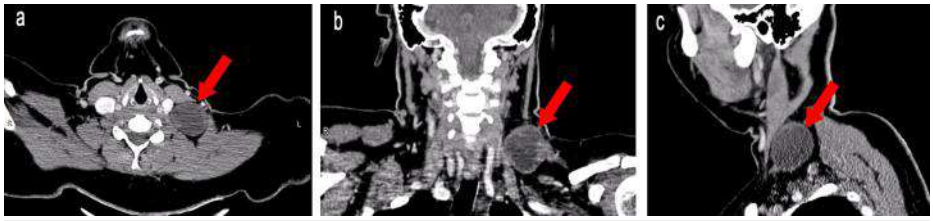


FIGURE 1: Contrast CT of neck

a) Axial view showing a well-defined cystic lesion on the left side abutting the carotid vessel; b) Sagittal view showing the lesion abutting the paraspinal muscles; c) Coronal view showing a lesion at the root of the neck

Further evaluation with FNAC of the swelling left supraclavicular region, repeated attempts aspirated reddish fluid, and smears show only scattered macrophages, no epithelial cells seen in the smear, suggestive of a cystic lesion. The patient was taken up for surgery. A lateral neck cystic swelling was excised in toto under general anaesthesia (Figure *2*).

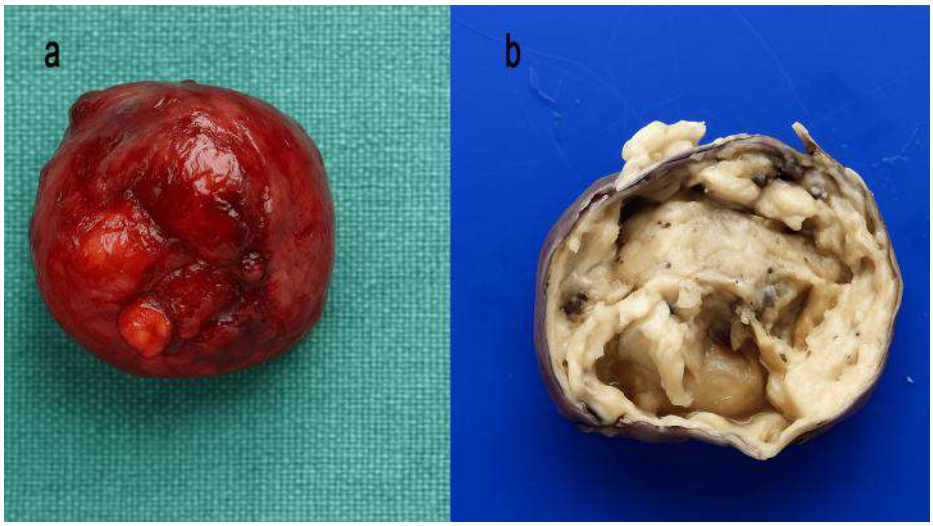


FIGURE 2: Gross morphology

a) Cyst immediately after excision; b) Cut section of the lesion showing cystic spaces

Histopathology revealed a neoplasm composed of hypercellular and hypocellular areas.
Individual cells are narrow, elongated, and wavy with a tapered end, interspersed with collagen fibers, nuclear palisading forming Verocay bodies noted, mitosis infrequent, and finally diagnosed to be Schwannoma (Figure *3*).

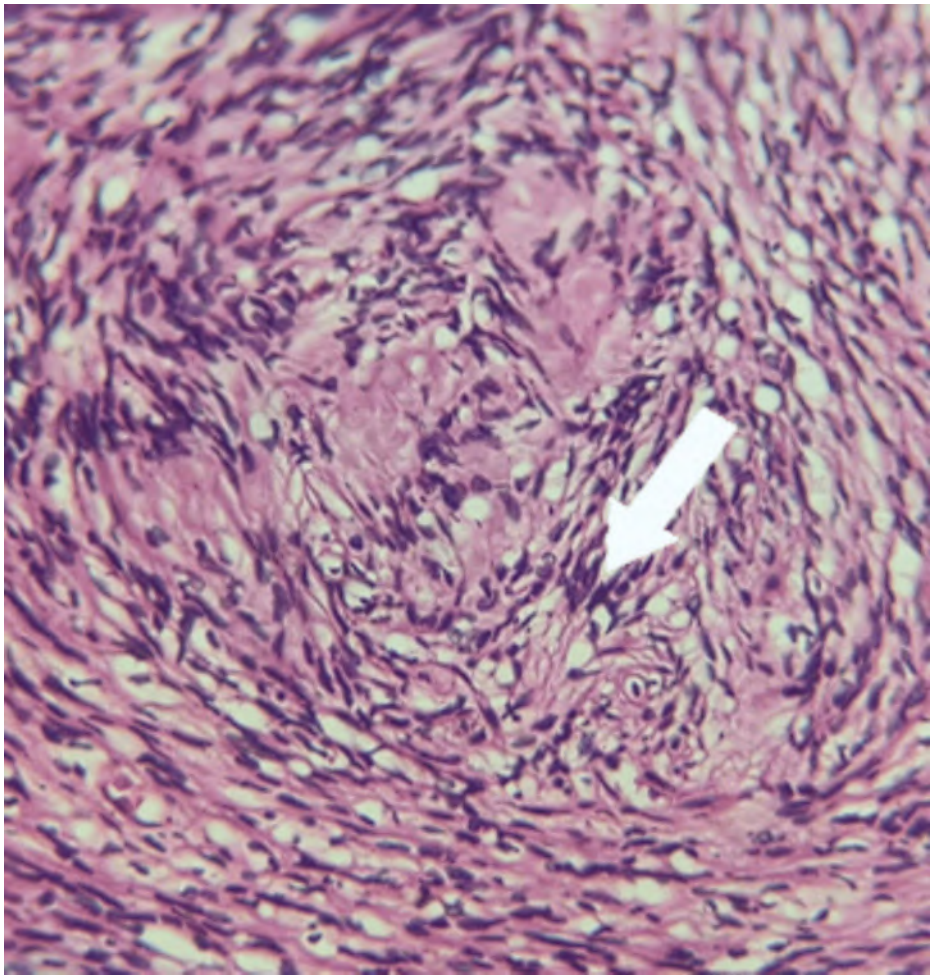


FIGURE 3: Histopathology showing hypercellular areas

Discussion

Schwannomas are benign neurogenic neoplasms arising from Schwann cells, the glial elements responsible for forming the myelin sheath of peripheral nerves. Approximately one-third of these tumors occur within the head and neck region, where they may originate from cranial, peripheral, or autonomic nerves [3]. Among the cranial nerves, the eighth cranial nerve (vestibulocochlear) is most commonly affected. The identification of the nerve of origin in schwannomas can be challenging, with approximately 10-40% of cases remaining indeterminate despite radiological and pathological evaluation [4]. This uncertainty complicates diagnostic efforts, as many of the nerves in the head and neck are small and unnamed, making it difficult to pinpoint the precise origin of the tumor. In this case, the tumor's presentation in the posterior triangle of the neck, where cystic schwannomas are rare, along with the lack of neurological symptoms, added complexity to the diagnosis. The lesion initially appeared to be a benign cystic mass, leading to a delayed recognition of its true nature. This case is noteworthy due to the unusual location of the schwannoma and its atypical presentation, highlighting the importance of considering a broader differential diagnosis and utilizing advanced imaging and pathological tests for accurate diagnosis.

Schwannomas arising in the parapharyngeal space often present as asymptomatic, slow-growing cervical masses along the medial border of the sternocleidomastoid muscle. Clinical diagnosis is frequently delayed due to the indolent nature of these lesions. When symptomatic, hoarseness and paroxysmal cough elicited by palpation may serve as subtle clinical indicators. The differential diagnosis is broad, encompassing branchial cleft cysts, paragangliomas, and malignant lymphomas [5,6].

A subset of schwannomas undergo cystic degeneration, a phenomenon observed in approximately 4% of cases [7,8]. These cystic changes complicate preoperative diagnosis, as they are associated with rapid tumor enlargement and increased lesion size. The pathogenesis of cystic degeneration is attributed to necrosis, mucinous degeneration, hemorrhage, and microcyst formation, particularly within Antoni B areas, which are characterized by loosely arranged spindle cells.

Fine-needle aspiration cytology (FNAC) often yields hypocellular or hemorrhagic aspirates in cases of cystic

schwannoma, thereby limiting its diagnostic utility. The rarity of these lesions, combined with the cytological paucity, renders FNAC alone inadequate for definitive diagnosis. However, ultrasound-guided FNAC may enhance diagnostic accuracy by enabling targeted sampling from hypercellular Antoni A regions, thereby increasing the probability of capturing diagnostic tissue.

Preoperative assessment of schwannomas relies heavily on advanced radiological imaging, with magnetic resonance imaging (MRI) being the modality of choice. MRI provides critical information regarding tumor localization, extent, and relationship to adjacent vascular structures such as the jugular vein and carotid artery. Despite radiological insights, definitive diagnosis hinges on histopathological examination, which classically reveals a biphasic pattern comprising Antoni A and Antoni B areas, palisading spindle cells, and the presence of Verocay bodies. Immunohistochemical staining, particularly diffuse S100 protein positivity, further substantiates the Schwann cell origin of these neoplasms [9].

Occasionally, lymphoid aggregates and scattered lymphocytes may be identified within schwannomas, adding to the diagnostic complexity and mimicking cystic lymphoid lesions. Therefore, in the presence of a cystic lesion with lymphoid components, cystic schwannoma should be considered in the differential diagnosis to avoid misclassification [10].

Accurate distinction between branchial cleft cysts and schwannomas is of paramount importance, given their differing clinical courses and management strategies. Incomplete excision of a branchial cleft cyst predisposes to recurrence, necessitating long-term surveillance. Conversely, complete resection of a schwannoma is typically curative, with recurrence being rare. While surgical excision remains the standard of care, conservative management may be judiciously employed in select, asymptomatic cases [11,12].

Conclusions

In conclusion, schwannomas with cystic degeneration can pose a diagnostic challenge due to their rarity and nonspecific clinical and radiological features. A high index of suspicion and careful histopathological examination are essential to distinguish these tumors from other cystic lesions, such as branchial cleft cysts. Complete surgical excision is the treatment of choice for schwannomas, and accurate diagnosis is crucial to ensure optimal management and prevent recurrence. Awareness of the clinical and pathological features of cystic schwannomas can aid in timely diagnosis and effective treatment.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Consent for treatment and open access publication was obtained or waived by all participants in this study. Institutional Ethics Committee of Thrissur Medical College issued approval 03/2025. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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MICROBIOLOGY

Original Article

Free-living amoebic encephalitis – Case series

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Abstract

Introduction: Free-living amoeba is ubiquitous in fresh water, mud, and moist soil; although seldom pathogenic to humans, *Naegleria fowleri*, *Acanthamoeba* spp., and *Balamuthia* spp. are known to cause infections of the central nervous system.

Methods: We report two interesting cases, both of which presented with a rapid-onset and fulminant course. The first case details a 36-year-old male with a history of surgically corrected nasal bone fracture 15 years back, who presented with acute onset of fever, headache and convulsions.

Results: Direct smears of cerebrospinal fluid (CSF) revealed motile trophozoites resembling *N. fowleri* and were later confirmed by molecular diagnosis (polymerase chain reaction [PCR]). Subsequently, the source was identified as water used for religious purposes. Unfortunately, the patient succumbed to cardiac arrest. The second case is that of a 4-year-old boy from Palakkad district, Kerala, who presented with sudden onset of nasal discharge, fever, headache, vomiting, seizures and altered sensorium. His CSF smear examination showed motile trophozoites resembling *Acanthamoeba* spp. While undergoing treatment, he seized thrice before going into cardiac arrest. Despite extensive resuscitation measures, the child could not be revived and passed away. The postmortem CSF sample sent for molecular analysis confirmed infection by *Acanthamoeba* spp.

Conclusion: Rapid progression and lack of definite treatment options make this a highly fatal condition. Although clinical presentations of both patients were indicative of pyogenic meningitis, parasitic infection was suspected when the CSF was found turbid with no bacteria, high protein, and low sugar. High index of suspicion helped us to get an early preliminary diagnosis from direct microscopy.

Keywords: *Acanthamoeba*, free-living amoeba, Naegleria

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INTRODUCTION

Parasitic infection of the central nervous system (CNS) by free-living amoebae is rarely encountered. These free-living amoebae are ubiquitous and worldwide in distribution. Pathogenic species include *Naegleria fowleri* and *Acanthamoeba* spp., which present as primary amoebic meningoencephalitis (PAM) and granulomatous amoebic encephalitis (GAE), respectively.[1] These are well known to inhabit fresh water, tap water, coastal water, sewage, poorly chlorinated swimming pools, artificial lakes, heating and ventilation units.[2]

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N. fowleri infection follows the entry of water-containing amoeba into the nose. It is responsible for a rapidly fatal infection involving the CNS, which occurs most often in healthy young individuals with a recent history of swimming in freshwater. It usually results in death within 72 h of the onset of symptoms. *N. fowleri* induces an intense inflammatory response that results in hemorrhage and lytic necrosis.[3] Most of the cases are misdiagnosed as pyogenic meningitis, with the majority of PAM diagnoses made postmortem.

GAE usually occurs in immunocompromised patients with diabetes mellitus, acquired immune deficiency syndrome, alcoholism and immunosuppressive medication, bone marrow failure, lymphoproliferative and hematoproliferative disorders, renal failure, splenectomy and dysproteinemia.[4,5] GAE can also be seen in otherwise healthy individuals as well.

Rapid progression of the disease with limited awareness among medical professionals makes this disease a diagnostic challenge. Early diagnosis and management may improve the prognosis of the disease.

CASE REPORTS

Case 1

A 36-year-old male who was previously healthy was brought to our hospital casualty with generalized tonic–clonic seizure and altered sensorium. He had a 2-day history of throbbing headache predominantly over frontal areas, associated with nausea, photophobia and high-grade fever not relieved by antipyretics. Probative clinical history included a 15-year-old nasal bone fracture which was corrected surgically.

At initial examination, the patient was drowsy, febrile (39.5°C), with a sluggishly reactive left pupil, and terminal neck stiffness. Examination of all other systems was within normal limits. There was a progressive deterioration of consciousness, following another generalized tonic–clonic seizure, due to which the patient was shifted to the intensive care unit and started on Ceftriaxone, Acyclovir and Steroids (Vancomycin avoided due to a history of patient's allergy). The laboratory workup found is mentioned below [Table 1].

Lumbar puncture was performed which showed a highly turbid cerebrospinal fluid (CSF) sample. Cytological and biochemical analyses were done which showed the following [Table 2].

Gram staining showed numerous pus cells, with no obvious organisms. Fortunately, wet film examination showed motile trophozoites resembling *Naegleria* spp. Figure 1.

CSF sediment culture on nonnutrient agar with a lawn culture of *Escherichia coli* ATCC 25922 yielded motile trophozoite forms of *Naegleria* spp. after 24 h of incubation (Trail sign positive) Figure 2.

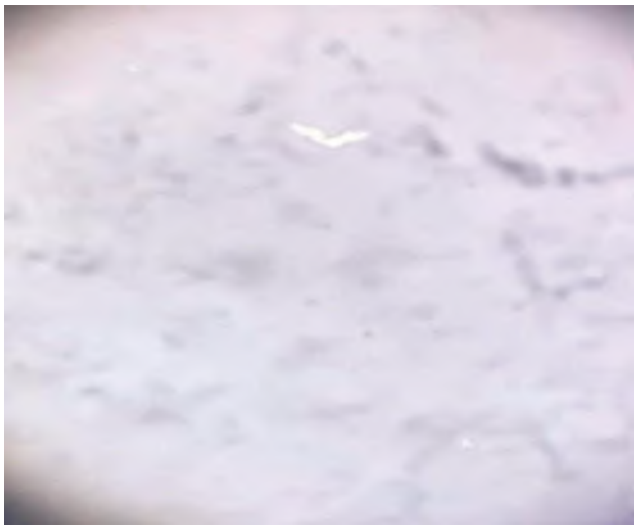


Figure 1: Motile trophozoites resembling Naegleria spp

The critically ill patient desaturated and went into ventricular tachycardia, further developed a myocardial infarction from which he could not be revived.

Immediate to releasing the preliminary laboratory report suggesting *Naegleria* infection, a detailed investigation into the source of infection indicated a suspicious exposure incident with well water through the nasal route for religious purposes. Subsequently, six water samples from the patient's locality (received through FHC Desamangalam), along with his CSF sample was sent to PGIMER, Chandigarh, for confirmation of diagnosis Further, studies of water showed that chlorine levels of the water supply were inadequate.

Case 2

A 4-year-old boy from Palakkad, who had no known comorbidities, presented with altered sensorium and episodes of seizures. He had fever for 4 days associated with nasal discharge and headache, which was followed by vomiting for 3 days. The child destabilized later becoming increasingly drowsy and irritable with excessive crying. Physical examination revealed signs of meningeal irritation. Although empirical therapy with Intravenous Ceftriaxone and Vancomycin along with Dexamethasone was started, within 2 days of admission, seizures recurred and escalated to right hemiparesis.

Laboratory reports gave a picture suggestive of pyogenic infection [Table 3].

The CSF sample received in our microbiology laboratory was visibly turbid and was processed as per protocol. Gram stain showed plenty of pus cells without any bacteria. However,



Figure 2: Positive Trail sign

the unstained wet film revealed the motile trophozoites resembling *Acanthamoeba* spp. Figure 3 Although the boy exhibited mild improvement on Intravenous Amphotericin B, Fluconazole, Cotrimoxazole and Rifampicin subsequent to the initial report, signs of meningeal irritation worsened within the next week. He had an episode of generalized tonic–clonic seizure, following which he passed away due to cardiac arrest. The CSF sediment culture on nonnutrient agar with a lawn culture of *E. coli* yielded the motile trophozoite forms of *Acanthamoeba* spp. after 24 h of incubation (positive Trail sign). The laboratory diagnosis of *Acanthamoeba* spp. was confirmed from CSF samples collected postmortem, by PGIMER, Chandigarh.

The amoebae were identified by the method standardized at PGIMER, Chandigarh.[6] Briefly, samples were subjected to pan-FLA PCR that targets the 18 S rRNA gene sequence. The samples found to be positive for *Acanthamoeba* spp. and *N. fowleri* by pan-FLA PCR were then confirmed by parasite-specific PCR targeting of *Acanthamoeba* spp. and *N. fowleri*. For *Acanthamoeba* spp., the JDP primers targeting the 18 S rRNA gene were used. *N. fowleri* was identified using the genus- and species-specific primers targeting the ITS1 and ITS2 regions. The amplified DNA products were separated on a 1.5% agarose gel and viewed in a gel documentation system (ProteinSimple AlphaImager HP System Automated Gel Imaging, Santa Clara, CA, USA).

DISCUSSION

Amoebic meningitis is a rare, but fatal CNS infection. PAM can mimic acute pyogenic infections and GAE is a chronic progressive disease. Here, we report two cases in previously healthy individuals. Both of them surrendered



Figure 3: Motile trophozoites resembling Acanthamoeba spp

to the disease within a week, despite combination treatment with anti-fungal agents and Rifampicin. The majority of the reported cases gave a history of swimming in contaminated waters, but nasal irrigation with tap water for therapeutic and religious purposes has also been reported in the literature.[7,8]

Less than four cases of PAM are reported per year worldwide, 79% of which were males. Most of them were from Asia and Africa during the warmer seasons, as well as in North America during spring and summer.[9-11] It is uncertain whether nasal surgery done 15 years prior could have had an impact on disease progression in the first case. Although diagnostic confounders such as neutrophilic pleocytosis cytology with low sugar levels indicated a pyogenic cause, high index of suspicion helped us to get a preliminary diagnosis from direct microscopy. We were also able to culture the parasite on non nutrient agar with a lawn of *E. coli* and confirm the diagnosis.[12,13]

Reports of survivors (11 cases) consumed a myriad of antimicrobial combinations of Intravenous and Intrathecal Amphotericin B, Ketoconazole, Miltefosine, Rifampicin and Dexamethasone for a minimum of 3–4 weeks as recommended by the Centers for Disease Control and Prevention (CDC).[13-15]

GAE commonly presents as a subacute or chronic infection and seldom in immunocompetent patients. Khurana *et al.* reported a CNS infection in a 3-year-old malnourished child who recovered without any residual symptoms, contrary to our second case.[16] Of about 30 cases of pediatric GAE reported over the past 40 years, 46% were from India, of whom 87% were previously healthy.[17] History of fresh water swimming may be elicited rarely (20% cases). Definitive diagnosis requires the presence of motile trophozoites in CSF, which may be misidentified as macrophages. Serological tests have a minute advantage in GAE diagnosis over PAE due to the indolent progression of the disease, though molecular confirmation is the currently accepted gold standard for both infections.[6,18] Out of the 20 genotypes of *Acanthamoeba* found in India, T4 is the most common genotype.[19]

Table 1: Laboratory investigations

Test	Result
Total leukocyte count	13,300/mm^3
Neutrophils	93%
Lymphocytes	4%
Eosinophils	1%
Hemoglobin	13.7 g/dL
Sodium	133 mmol/L
Potassium	4.4 mmol/L
Liver function test	Within normal limit
Renal function test	Within normal limit

Table 2: Cytological and biochemical investigtation reports

Test	Result
Total leukocyte count	300/mm^3
Neutrophils	6%
Lymphocytes	39%
Protein	1100 g/dL
Sugar	5 mg/dL

Table 3: Biochemical investigations

Test	Result
Total leukocyte count	33,500/mm^3
Neutrophils	96%
Lymphocytes	3%
Eosinophils	1%
Hemoglobin	10.5 g/dL
Sodium	131 mmol/L
Potassium	4.4 mmol/L
Liver function test	Within normal limit
Renal function test	Within normal limit

Treatment guidelines for both PAM and GAE are poorly elucidated, and therapy is decided based on CDC recommendations, which include Pentamidine, Sulfadiazine, Flucytosine and Fluconazole/Itraconazole, as early as possible. Less than 15% overcome the disease, with the survival rate highest among those who took triple-drug regimen for more than 3 months. However, a quarter of survivors reported long-term neurological sequelae.[20,21]

Environmental surveillance led to the confirmation of local tap water as a source in the first case which directed a rapid response from the public health center to enhance chlorination of all surrounding water supply. The incidence of amoebic meningitis in immunocompetent hosts indicates a critical need for improving water quality and safety to eliminate these water-borne parasites. Periodical and appropriate surveillance for water contamination and implementation of preventive hygienic measures, following the identification of a case and its infective source, is vital to alleviate the incidence of this lethal infection.

Contamination of water with organic material and warm temperatures are ideal for the proliferation of *N. fowleri*.[15] *Acanthamoebae* spp. is distributed in soil, air, water, chlorinated water in pools, sewage, dialysis units, air conditioning units and contaminated contact lens solutions. Free-living amoebae have been isolated from tap water samples, ventilators, air conditioners, hemodialysis units and dental irrigation systems of hospitals.[22] Chlorinated water and salt water significantly decrease the risk of *N. fowleri* infection. Chlorine at 2 ppm is effective against *N. fowleri* but not for *Acanthamoeba* spp. It is necessary that wells be properly maintained with adequate chlorine for *N. fowleri*.[23] Water that has been distilled or purified should be used for sinus rinsing, according to the CDC.[24]

CONCLUSIONS

PAM and GAE are rare fatal diseases involving the CNS, usually found in tropical and subtropical regions. Both are serious public health problems. Prompt identification with timely intervention with an appropriate antimicrobial therapy in the correct dosage is the key.

Public health measures have to be taken for the prevention and control of free-living amoeba including *N. fowleri* and *Acanthamoeba* spp. Better awareness of the disease within the medical community and public health awareness through health education are desirable. Clinical microbiologists should be more aware of the importance of careful examination of CSF wet preparation for diagnosis of *N. fowleri* and *Acanthamoeba* spp. as early treatment may markedly improve the prognosis of the disease.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Demographic trends and antimicrobial susceptibility pattern of *Shigella* species - A 14-year study

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Abstract

Introduction: Shigellosis is the major factor responsible for dysentery among children who are <5 years of age. *Shigella dysenteriae* are responsible for outbreaks and epidemics. *Shigella flexneri* and *Shigella sonnei* are the predominant species known to cause endemic infections in developing and developed countries. One of the main concerns about the increase in *Shigella* infections is their ability to easily acquire antibiotic resistance.

Objective: The objective of the present study was to determine the demography and antibiotic susceptibility pattern of *Shigella* species over 14 years in a tertiary care center in Central Kerala.

Materials and Methods: This was a cross-sectional retrospective study which was conducted in the department of microbiology from January 2009 to November 2022. 4418 stool samples from patients with dysentery were collected and sent for culture. Sixty-six isolates of *Shigella* species were obtained and their antibiotic susceptibility pattern was determined using standard microbiological methods. The data were analyzed using Statistical Package for the Social Sciences (SPSS) Software version 28 (IBM SPSS Statistics version:28.0.0.0 New York, USA) after entering in Microsoft Excel.

Results: Sixty-eight percent of the affected population were children below 15 years. The period prevalence of *Shigella* species in the present study was 1.5%. Among the *Shigella* species, 66% of the isolates were *S. sonnei*, 32% were *S. flexneri*. Forty of the 66 isolates were multidrug resistant.

Conclusion: *S. sonnei* has been found to be the predominant cause of shigellosis in the present study though in tropical countries *S. flexneri* is known to be the most common causative agent. Many isolates were multidrug resistant which highlights the importance of stopping the over-the-counter sale of antibiotics and prescribing antibiotics judiciously.

Keywords: Bacillary dysentery, multidrug-resistant organism, shigellosis

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INTRODUCTION

In middle- and low-income countries, the second major cause of mortality and morbidity due to diarrhea among children <5 years is *Shigella*.[1] *Shigella* is a genus which is included in the family Enterobacteriaceae. *Shigella flexneri*, *Shigella sonnei*, *Shigella dysenteriae,* and *Shigella boydii* are four

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species of *Shigella* which are notorious to cause dysentery. *S. dysenteriae* are known to cause epidemics and outbreaks whereas endemic infections in developed and developing countries are produced by *S. sonnei* and *S. flexneri*. *S. boydii* infections are rare and restricted to India and neighboring countries.[2] Clinical spectra of shigellosis vary from mild diarrhea to fulminant dysentery.[2] Poor hygiene, close personal contact, lack of safe water, and malnutrition contribute to the transmission of *Shigella* infection.[3]

Although a self-limiting disease, shigellosis can cause complications such as encephalopathy.[4] Hence, antibiotic therapy is advised to reduce the diarrheal output, prevent further complications, and limit postsymptomatic fecal shedding.[4] Due to the tendency of *Shigella* to acquire resistance by horizontal gene transfer from other *Enterobacteriaceae*, antibiotics such as sulfonamide, tetracycline, streptomycin, and chloramphenicol have developed resistance since the late 1950s. Ampicillin and co-trimoxazole which were used as alternatives afterward also developed resistance by the 1980s.[4] Ciprofloxacin, cephalosporins, or azithromycin has been recommended by the World Health Organization for the treatment for all cases of pediatric dysentery due to *Shigella* infection.[5,6] Therefore, the antibiotic susceptibility pattern of *Shigella* needs to be constantly monitored to direct the physicians in selecting the most effective treatment. Furthermore, it can also help in strengthening the preventive strategies devised by the public health system.

The present study was carried out to determine the demography and trends in antibiotic susceptibility patterns of *Shigella* species over 14 years in our center.

MATERIALS AND METHODS

This was a cross-sectional retrospective study which was carried out in the clinical microbiology laboratory at a tertiary care teaching hospital from January 2009 to November 2022 after getting clearance from the institutional ethics committee (IEC/GMCTSR/2023/014). Stool samples which were obtained from patients with dysentery in the microbiology labortory were included in the study. Stool samples from patients whose required demographic/antibiotic susceptibility details were not available were excluded. These were inoculated in Selenite F broth for 6–8 h after which they were inoculated on MacConkey agar and were incubated at 37°C overnight. On the next day, colonies which were nonlactose fermenting, stained pink (Gram-negative) upon Gram-staining, and tested negative with oxidase test were characterized biochemically after doing standard bacteriological tests. Those isolates which on biochemical tests showed characteristics of *Shigella* species were serotyped using *Shigella* polyvalent and monovalent antisera. Antibiotic susceptibility testing was done by Kirby–Bauer disc diffusion method according to the Clinical and Laboratory Standards Institute guidelines.[7] The antibiotic discs used were nalidixic acid (30 μg), co-trimoxazole (25 μg), ciprofloxacin (5 μg), ampicillin (10 μg), azithromycin (15 μg), and ceftriaxone (30 μg) (HiMedia Laboratories, India). Multidrug-resistant organisms are defined as an organism which shows resistance to at least one antimicrobial agent in three or more classes of antibiotics.[8]

RESULTS

A total of 4418 stool samples were received during the study period. Sixty-six samples grew *Shigella* species. The period prevalence was 1.5% (confidence interval: 0.01, 0.02). Maximum cases were obtained from the patients of 0–10 year age group (44%) [Figure 1]. Males and females were almost equally affected. Six patients gave a history of travel within the state over the past 2 weeks. Among the *Shigella* species, 44 were *S. sonnei* (66%), 21 were *S. flexneri* (32%), and 1 was *S. dysentriae* (0.01%) [Figure 2]. Out of the 66 isolates, 40 (60%) were multidrug resistant. Most of them were resistant to ampicillin (54%), ciprofloxacin (73%), nalidixic acid (42%), and cotrimoxazole (76%) [Tables 1 and 2].

DISCUSSION

In our country, the prevalence of shigellosis varies from 2% to 6%.[9-11] However, the point prevalence in the present study was 1.5%. The reduction in prevalence in the present study could be due to the reduction in poverty rates, improved quality of life as compared to before, increased awareness about sanitation and hygienic practices, and better prevention strategies adopted by the government against communicable diseases.[12] True prevalence of *Shigella* cannot be estimated accurately as most cases are self-limiting and mild and may not be requiring laboratory testing or medical attention.[9] Forty-four percent of the population affected were children below 10 years of age.

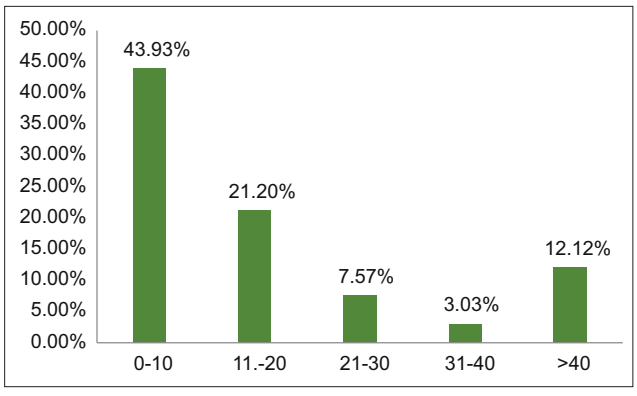


Figure 1: Age-wise distribution of *Shigella* infections (in years)

Table 1: Antibiotic resistance pattern in *Shigella* species

Antibiotics	*Shigella sonnei* (*n*=44; 66%), *n* (%)	*Shigella flexneri* (*n*=21; 32%), *n* (%)	*Shigella dysentriae* (*n*=1; 0.01%), *n* (%)	Total isolates (*n*=66), *n* (%)
Ampicillin	22 (51.16)	12 (57.14)	1 (100)	36 (54.5)
Nalidixic acid	18 (41.86)	8 (38.09)	1 (100)	27 (40.9)
Ciprofloxacin	31 (72.09)	15 (71.42)	1 (100)	48 (72.7)
Co-trimoxazole	32 (74.41)	16 (76.19)	1 (100)	50 (75.7)
Ceftriaxone	8 (18.60)	1 (4.76)	0	9 (13.6)
Azithromycin	12 (27.90)	6 (28.57)	0	18 (27.2)

Table 2: Antibiotic resistance profile of *Shigella* species over 14 years

	Antimicrobial resistance profile of *Shigella* species					Total isolates (*n*=66)
Year	Ampicillin (%)	Ciprofloxacin (%)	Co-trimoxazole (%)	Ceftriaxone (%)	Azithromycin (%)	
2009	100	100	100	0	0	1
2011	100	0	100	0	0	1
2012	0	0	100	0	0	1
2013	50	50	67	0	0	3
2014	50	50	50	0	0	4
2015	60	43	86	29	0	10
2016	29	100	86	13	12	8
2017	0	100	100	0	33	6
2018	60	89	60	20	33	16
2019	100	100	100	50	70	3
2020	0	100	100	0	100	3
2022	44	58	58	28	67	10

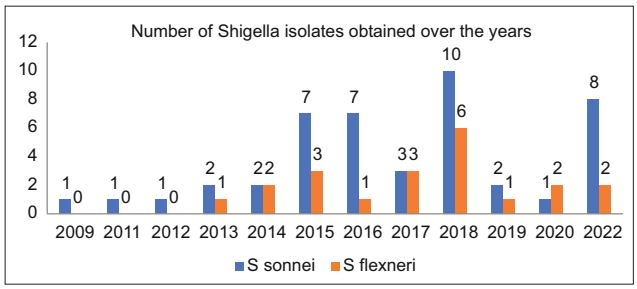


Figure 2: Year-wise distribution of *Shigella* infections

This was similar to the study by Kumar *et al.* where the maximum number of *Shigella* (53%) was isolated in children (0–18 years).[9] Factors such as malnutrition, unhygienic food handling practices, and the ability of even a small inoculum of the bacteria being capable of causing infection could be the reason why children are being more vulnerable to *Shigella* infection.[2] The gold standard test for diagnosis of shigellosis is culture. Out of the 4418 stool samples received, 66 samples grew *Shigella* species. Most of the studies from India have shown *S. flexneri* to be the most common species isolated. About 74.7% of isolates were *S. flexneri* in a study done by Nair *et al.* in Kolkata, 47.6% isolates of *S. flexneri* in the study done by Jain *et al.* in Karnataka, and 57% isolates of *S. flexneri* in the study carried out by Kumar *et al.* in Pondicherry.[9-11] On the contrary to this, in the present study, *S. sonnei* has been found to be the predominant isolate (66%). In the places that had underwent industrialization, the cases due to *S. flexneri* had reduced drastically and the cases due to *S. sonnei* had markedly increased.[13] A similar increase in the isolation rate of *S. sonnei* has been observed in studies from Bangladesh also where the number of reported cases rose from 7% to 25% from 2001 to 2011.[13] In a review article by Thompson *et al.*, it has been proposed that three major environmental pressures had resulted in the dominance of *S. sonnei*.[4] The bacterium, *Plesiomonas shigelloides,* would promote the development of natural passive immunization in those populations which get poor water supply thus protecting them against *S. sonnei* also. Therefore, when the quality of drinking water supplies improves, it would reduce exposure to *P. shigelloides* leading to lesser protection against *S. sonnei* infection. Second, in temperate countries, *Acanthamoeba castellanii*, a species of amoeba which is capable of phagocytosing *S. sonnei* symbiotically, helps the bacteria to tolerate harsh environmental conditions such as chlorination. Finally, *S. sonnei* can acquire antimicrobial resistance genes through horizontal gene transfer from commensal and pathogenic bacteria, more easily than *S. flexneri*.[4]

Many parts of the world, including the USA, Indonesia, Vietnam, China, Iran, India, and Bangladesh, have reported MDR *Shigella* so far.[2,10,14-16] Multidrug-resistant organisms are defined as organisms which shows resistance to at least one antimicrobial agent in three or more classes of antibiotics.[8] Sixty percent of the *Shigella* isolates were multidrug resistant. Nalidixic acid resistance was found in 81% of the isolates, co-trimoxazole resistance in 76%, ciprofloxacin resistance in 73%, and ampicillin resistance in 53%. Many studies have shown *Shigella* species showing extensive resistance to norfloxacin, ofloxacin, and ciprofloxacin.[3,17] In a study by Nair *et al.*, it was found that most of the *Shigella* isolates were

resistant to ampicillin (50%), co-trimoxazole (94%), and ciprofloxacin (90%).[10] As fluoroquinolones are used for the treatment of many other infections such as otitis media, urinary tract infection, and diarrhea, they have become highly resistant due to this overuse.[9] This alarming rate at which drugs such as ciprofloxacin have developed resistance limits our therapeutic options for shigellosis.

CONCLUSION

S. sonnei has been found to be the predominant cause of shigellosis in the present study. Furthermore, there has been a dangerous rise in the number of multidrug-resistant isolates of *Shigella* in the present study. As the majority of the *Shigella* are becoming fluoroquinolone resistant, it is essential to know the changing antibiotic susceptibility pattern of the isolates so that the hospital antibiogram could be modified accordingly.

Limitations

1. All the antibiotics in the antibiotic panel could not be tested due to the limitation of resources in our institute
2. The identification could not be reconfirmed from a reference center as we did not have the facility for long-term storage of isolates in our center.

Author contribution

Concepts, design, and data acquisition – Dr. LSK, Concept, data acquisition, and manuscript preparation – Dr. AB, Concept, manuscript editing, and manuscript review – Dr. VAN.

Data availability statement

The data of the original master sheet is available with the corresponding author which will be available on request through mail.

Conflict of interest statement

There are no conflicts of interest.

Ethics committee approval statement

Ethics committee approval was obtained on January 13, 2023. Approval number is EC/GMCTSR/2023/014.

Patient/participant consent statement

Informed consent was obtained.

Artificial intelligence generated text statement

The authors declare that the manuscript has not been written using the AI-generated text tool.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Proportion of Microbiologically Confirmed Extrapulmonary Tuberculosis among Pathologically diagnosed Extrapulmonary Tuberculosis

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Abstract

Context: Current National Tuberculosis Elimination Program (NTEP) guidelines recommends culture/CBNAAT/molecular test/histopathology examination and drug sensitivity testing for all patients with presumptive Extrapulmonary TB (EPTB). Studies on correlation of CBNAAT with pathological evidence in the diagnosis of EPTB are scarce in our literature. **Aims:** To estimate the proportion of microbiologically confirmed EP TB among the cases with pathological evidence and among those who underwent molecular testing; and to estimate the proportion of EP TB notified who underwent either pathology evaluation (FNAC or Biopsy) or microbiology evaluation (NAAT / Culture) Settings and Design: Record based cross sectional study. **Material and Methods:** Data of EPTB patients registered for treatment from January to December 2022 were collected and triangulated to see what proportion of patients diagnosed / notified in one source can be traced in the other department, and verified report at that department. Statistical analysis used: Proportions were estimated for the tests undergone and the diagnostic yield of each test. **Results:** Among 282 study subjects, 62 (21.98%) cases were microbiologically confirmed. In 118 (41.84%) patients, cytopathology/ histopathology was the basis of diagnosis. 26% of pathologically diagnosed TB had a positive CBNAAT. Yield of NAAT positivity among patients who underwent CBNAAT testing was 52% with high yield of 78% in lymph node TB. For 87 (30.85%) patients, neither microbiological confirmation nor histopathology/ cytological evidence was available. **Conclusions:** Though CBNAAT is integral part of TB diagnosis, only 47% underwent NAAT examination. Whenever NAAT was done, the yield was reasonable (52%).

Keywords: *Cytology, extrapulmonary, histopathology, India, nucleic acid amplification tests, tuberculosis*

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Introduction

Tuberculosis (TB) remains a major public health problem worldwide. The Global TB report 2023 estimated that 10.6 million people fell ill with TB worldwide in 2022. Two-third of the global TB burden is contributed by eight countries, of which India accounts for 27%.[1] The most common presentation of TB is pulmonary TB. TB involving any organ other than lungs is called extrapulmonary TB (EPTB). The sites of EPTB include lymph nodes, pleura, gastrointestinal system, genitourinary system, bones and spine, and central nervous system, although other organs may also be involved. Among these, lymph nodes are most commonly involved, followed by pleura.[2]

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According to the Global TB Report 2020, EPTB constituted 16% of the 7.5 million reported TB cases globally and 19% in Southeast Asia.[3] Over the years, the number of EPTB cases is rising in Kerala. As per the 2010 annual status report of the Revised National TB Control Program of India, the proportion of EPTB among total notified TB cases in Kerala was 26%.[4] However, by 2021, the proportion of EPTB cases among notified TB cases in Kerala had increased to 40%.[5]

EPTB diagnosis and management remain a considerable challenge even with advances in various diagnostic methods/modalities available. Varied and nonspecific symptoms and lack of access to diagnostic tests in peripheral hospitals and health centers make EPTB an underrecognized entity.[6] Paucibacillary nature of bacteria in specimens and the need for invasive procedures to obtain the specimen are the major factors resulting in a delayed diagnosis. The delayed diagnosis worsens the prognosis and increases the morbidity.[7]

The conventional methods employed for diagnosis include fine needle aspiration cytology (FNAC)/histopathology of the affected site and demonstration of acid-fast bacilli (AFB) by Ziehl–Neelsen (ZN) staining. The diagnosis by FNAC has limitations like subjective variation and inability to differentiate between various granulomatous lesions. The limitations of ZN staining are low sensitivity and requirement of at least $10^{[4]}$ bacilli to demonstrate in smears.[7] The diagnosis of TB by culture remains the gold standard, but it takes 4–6 weeks.[8] This necessitates the need for rapid diagnostic modalities. In early 2011, the WHO endorsed a novel, rapid, automated molecular test – cartridge-based nucleic acid amplification test (CBNAAT).[9] This is a very sensitive test, with the added advantage of detecting rifampicin resistance simultaneously.[8] Furthermore, CBNAAT has the ability to detect bacterial load as low as 100–130 bacilli per ml of sample, which is at par with culture as 100 bacilli per sample are needed for culture positivity.[10] In 2014, the WHO has recommended CBNAAT over conventional methods for the diagnosis of TB from paucibacillary samples.[11]

As per the current NTEP guidelines, any person with presumptive EPTB has to be checked for the availability of a tissue-based diagnosis. NAAT and culture, as well as histopathological tests, can provide a tissue-based diagnosis. Microbiological confirmation can be obtained from a positive NAAT or culture positivity. Although microscopy using ZN staining is also a part of microbiological diagnosis, due to less sensitivity and specificity, it seldom forms a basis of microbiological confirmation. Any case of EPTB without microbiological confirmation is regarded as clinically diagnosed EPTB.

The current national tuberculosis elimination programme (NTEP) guidelines suggest nucleic acid amplification testing as the mainstay in diagnosis. As per the WHO meta-analysis, the sensitivity of CBNAAT in diagnosing various EPTB, like lymph node TB, central nervous system (CNS) TB, and pleural TB, was 84.9%, 79.5%, and 43.7%, respectively, as compared to culture and 83.5%, 55.5%, and 17% as compared to composite reference standard (CRS).[12] In TB lymph node, the most common form of EPTB, the diagnosis, in common practice, is made from the histopathological examination (HPE) alone.

A study on EPTB by Nishal *et al*. reported that the sensitivity and specificity of CBNAAT when compared to CRS were 32.3% and 100%, respectively, where CRS defined by clinical, radiological, laboratory, and histopathological findings and treatment response to ATT at the end of 6 months.[6] CBNAAT had a sensitivity of 33.3% and a specificity of 76.9% when compared to HPE. CBNAAT when combined with AFB culture and histopathological evidence together as diagnostic modality gave a sensitivity of 95.5%. In the study, the maximum yield for CBNAAT was for bone and joint TB (35.7%), followed by that for lymph node TB (34%). HPE reported granulomatous inflammation in 92.9% of TB pleural effusion (pleural tissue) and 91.7% of lymph node TB.

Studies on correlation of CBNAAT with pathological evidence in the diagnosis of EPTB are scarce in our literature. The aim of the present study was to estimate what proportion of EPTB cases with histopathological evidence of TB were microbiologically confirmed. We also wanted to find out the proportion of notified EPTB cases who either had a pathological diagnosis or a microbiological confirmation. As part of the study, we also wanted to know the proportion of individual forms of TB (lymph node TB, pleural TB, bone TB, and CNS TB) among the study population.

Methodology

The study aimed to estimate the proportion of microbiologically confirmed EPTB among the cases with pathological evidence and among those who underwent molecular testing as well as to estimate the proportion of EPTB notified who undergo either pathology evaluation (FNAC or biopsy) or microbiology evaluation (NAAT/culture) at the same institution and the yield of each investigation.

A record-based cross-sectional study was done after getting permission from the departments of pulmonary medicine, microbiology, and pathology. The sample size was estimated on the assumption that about 30% of

EPTB is microbiologically confirmed; to estimate this with 95% confidence, a sample size of 224 was needed. We included 281 subjects in the study.

Data of EPTB patients who were registered for treatment from January 2022 to December 2022 were collected. Data from three sources (clinical or laboratory diagnosis) or at pathology or microbiology department were triangulated to note what proportion of patients diagnosed/notified in one source could be traced in the other department and to check what the report was at that department. Based on this analysis, it was determined whether a diagnosis of TB was made clinically, microbiologically, or pathologically and proportions of microbiological confirmation in each group were estimated. All patients notified as EPTB either at NTEP cell (clinical or laboratory diagnosis) or at pathology or microbiology department were included.

Data were entered into Excel and analyzed using Epi Info 7.2.5.0. (CDC, Atlanta, GA, USA). Proportions were estimated for each of the tests and for each form of EPTB.

Clearance was obtained from the ethics committee before the start of the study. Consent waiver was obtained as this was a record-based data collection; confidentiality of the data was strictly maintained with all patient identifiers being removed before analysis. All expenses for the study were borne by the investigators.

Results

Our study involved a total of 281 EPTB patients registered during the period January 2022 to December 2022. The mean age of the study population was 43.9 + 19.1 years. The male-to-female distribution was similar with 138 (49.11%) males and 143 (50.89%) females. 270 (96.09%) patients were newly diagnosed cases of EPTB, whereas 11 (3.91%) were retreatment cases. The most common site involved was lymph node TB (43.4%), followed by pleural TB (17.4%), skeletal TB (13.9%), abdominal TB (13.2%), and central nervous system TB (5.7%).

For all EPTB, pathological evidence was considered as either histopathological evaluation results or the cytology evaluation results. Microbiological confirmation was done by CBNAAT evaluation. The proportions of cases diagnosed either on pathological evaluation or by CBNAAT are shown in Table 1.

As shown in Table 1, the proportion diagnosed by pathological examination was 52% and that by NAAT was 24%.

A significant proportion of patients had not undergone microbiological evaluation as compared to pathological evaluation; hence, the proportion of microbiologically confirmed EPTB among those with pathological evidence was low. Table 2 depicts the proportion of microbiologically confirmed EPTB among those with pathological evidence.

Among the patients with pathologically diagnosed TB, only 26% was microbiologically confirmed. However, this was in part due to the fact that a significant

Table 1: Comparison of yield of pathological examination versus cartridge-based nucleic acid amplification test

Site of EPTB	Total (*n*)	Diagnosed by pathology		Diagnosed by NAAT	
		n	Proportion (%)	*n*	Proportion (%)
Lymph node	122	105	86	38	31
Pleural	49	7	14	7	14
Abdominal TB	37	8	22	9	24
Skeletal TB	39	12	31	7	18
CNS TB	16	1	6	1	6
Others	18	14	78	5	28
Total	281	147	52	67	24

CNS: Central nervous system, TB: Tuberculosis, EPTB: Extrapulmonary TB, NAAT: Nucleic acid amplification test

Table 2: Cartridge-based nucleic acid amplification test positivity of extrapulmonary tuberculosis among those with pathological evidence

Site of EPTB	Diagnosed by pathology (*n*)	Diagnosed by NAAT (*n*)	Proportion (%)
Lymph node	105	21	20
Pleural	7	6	86
Abdominal TB	8	4	50
Skeletal TB	12	4	33
CNS TB	1	1	100
Others	14	2	14
Total	147	38	26

CNS: Central nervous system, TB: Tuberculosis, EPTB: Extrapulmonary TB, NAAT: Nucleic acid amplification test

Table 3: Yield of nucleic acid amplification test in those who actually underwent nucleic acid amplification test

Site of EPTB	Total (*n*)	Number who underwent NAAT	Diagnosed by NAAT	
			n	Proportion (%)
Lymph node	122	49	38	78
Pleural	49	31	7	23
Abdominal TB	37	18	9	50
Skeletal TB	39	10	7	70
CNS TB	16	13	1	8
Others	18	7	5	71
Total	281	128	67	52

CNS: Central nervous system, TB: Tuberculosis, EPTB: Extrapulmonary TB, NAAT: Nucleic acid amplification test

Table 4: Proportion of pathological or microbiological diagnosis in extrapulmonary tuberculosis

Site of EPTB	Total (*n*)	Diagnosed based on Pathology/Microbiology		No positive result on Pathology/Microbiology	
		n	Proportion (%)	*n*	Proportion (%)
Lymph node TB	122	122	100	0	0.00
Pleural TB	49	12	24.49	37	75.51
Abdominal TB	37	13	35.14	24	64.86
Skeletal TB	39	15	38.46	24	61.54
CNS TB	16	1	6.25	15	93.75
Others	18	17	94.44	1	5.56
Total	281	180	64.06	101	35.94

CNS: Central nervous system, TB: Tuberculosis, EPTB: Extrapulmonary TB

proportion did not undergo testing by CBNAAT. A detailed analysis of microbiological confirmation in those who did undergo NAAT is given in Table 3.

EPTB diagnosis is ideally based on tissue-based diagnosis with either pathological evidence or microbiological confirmation. Those having tissue-based diagnosis are compared with those not having either of these as in Table 4.

Investigations done in most patients was pathology, only 128 (45.5%) of samples underwent testing by NAAT. Hence the low proportion of diagnosis by NAAT (as seen in Tables 1 and 2) were thought to be due to NAAT not being performed. Hence the investigators also looked at the diagnostic yield of NAAT in patients whose samples actually underwent testing by NAAT and the results are shown in Table 3.

The yield of NAAT in those who underwent CBNAAT was high in LN TB at 78% and skeletal TB at 70%, whereas it was low in pleural TB at 23% and CNS TB at 8%. The overall yield of CBNAAT in all patients with EPTB who were tested was 52%.

Discussion

In the present study, the mean age of presentation was 43.9 years. This was slightly older than in studies by Chakravorty *et al*. (20–39 years) and Yadhav and Veena (21–30 years).[13,14] The age distribution of TB patients in Kerala was higher than the rest of India, with maximum cases being notified in the 45–54 years' age group.[15] Our study reported a slight female predominance, where the female-to-male ratio was 143:138. Although male predominance was reported in studies from Indian subcontinent, there are studies where female predominance was reported.[13,14] 96.09% of patients were newly registered cases of EPTB, which is comparable to national statistics, where 88.4% of cases were newly diagnosed TB.[3]

The common sites of EPTB involved as per India TB Report 2023 were lymph node (26.3%), pleural (23.3%), abdomen (17.4%), spine (4.8%), meninges (2.8%), bone (excluding spine; 2.7%), and genitourinary tract (1.6%). In our study, the most common site involved in EPTB was lymph node (43.4%), followed by pleura (17.4%). Lymph node TB described as the most common form of EPTB in other studies such as Nishal *et al*., Sharma *et al*., and Komanapalli *et al*.[6,16,17]

This study could estimate the yield of CBNAAT for various sites of EPTB-lymph node (78%), pleural TB (23%), skeletal TB (70%), and CNS TB (8%). The yield of CBNAAT for diagnosing various forms of EPTB varies greatly in different studies. Nishal *et al.* reported the yield of CBNAAT in various forms of EP TB in Trivandrum, India. CBNAAT was diagnostic in 34% 0f cases with lymph node TB, 35.7% of cases with bone and joint TB and 31.7% of cases with pleural effusio.[6] Xpert MTB/Rif assay could detect 76.5% of tuberculous lymphadenitis with histopathological evidence in a study by Haridas *et al*.[18]

Pathological diagnosis can be obtained by cytopathology or histopathology evaluation. Of the total 281 patients, 261 underwent pathological evaluation. In our study, 86% of lymph node TB had a pathological diagnosis. Haridas *et al.* reported that 46.66% of tuberculous lymphadenitis were diagnosed by HPE.[18] A comparative study on various diagnostic modalities on tubercular lymphadenitis reported that histopathology had a sensitivity of 96% and a specificity of 78.5%.[19]

Being a paucibacillary state, pleural fluid examinations often have a low diagnostic potential. However, thoracoscopic pleural biopsy has been reported to have 100% positive diagnostic yield by histopathology and had higher yield in CBNAAT of 45%.[20]

Abdominal TB included both the peritoneal TB and intestinal TB. The yield of HPE for abdominal TB came as 23%. In intestinal TB, only 50%–80% reported demonstrable granuloma on intestinal mucosal biopsies in clinically confirmed cases.[21] The yield of HPE can be improved to 85%–95% with peritoneal biopsy performed by laparoscopic guidance, minilaparotomy, or exploratory laparotomy.[22]

In our study, 55% of cases of skeletal TB were diagnosed by histopathology. For diagnosing spinal TB, HPE has been reported to have slightly higher sensitivity of 90% compared to NAAT (88% sensitivity).[23] In CNS TB, classical pathology included TB meningitis, tuberculoma, or tuberculous abscess where the latter two are associated with characteristic histopathological features.[24] Our study had poor yield (6%) with pathological examination for diagnosing CNS TB as well as for NAAT (8%).

Various forms EPTB showed varying positivity with histopathological evaluation in the study by Nishal *et al*. In this study, lymph node TB showed positivity of 88%, pleural TB 81.2%, abdominal TB 60%, and bone and joint TB 57.1%.[6]

In our study, 35.94% of cases have neither pathological evidence nor microbiological confirmation. The highest proportion of patients who had neither HPE evidence or microbiological confirmation was for CNS TB (93.75%), followed by pleural TB (75.51%). CNS TB is the most severe form of TB with nonspecific clinical features and diagnostic challenges. Since the delay in diagnosis increases the morbidity and mortality, empirical therapy is initiated in many cases without waiting for tissue diagnosis. As per the WHO updates, the sensitivity of CBNAAT for detecting adult pleural fluid is 0.19 and for adult CSF 0.41.[18] It is due to the paucibacillary nature of these conditions. For bone TB, imaging techniques are still popular and MRI and CT have got 100% sensitivity.[24]

The current NTEP guidelines emphasize a tissue-based diagnosis for presumptive cases of EPTB. As per the recommendation appropriate samples taken for microbiological and histological testing, unless diagnostic sampling is deemed to risk undue harm. When CBNAAT is performed for the diagnosis, an early evaluation of rifampicin resistance is also checked simultaneously. Although the diagnostic yield of CBNAAT and histopathology was low in certain forms of EPTB such as CNS TB, abdominal TB and pleural TB, every effort for making a tissuebased diagnosis is essential even in these cases.

This study brings out an important finding that the perception of low yield of NAAT in EPTB by clinicians is often due to the fact that samples were not sent for NAAT testing. The study showed that whenever samples were sent for NAAT, the yield of NAAT in such cases, where testing by NAAT was done, was fairly good, particularly in LN TB and skeletal TB.

Conclusion

Among the EPTB, 26% of pathologically proven cases got microbiological confirmation. 65.04% of EPTB cases got either pathological evidence or microbiological confirmation. Among the various sites involved in EPTB in this study, the highest proportion of patients had lymph node TB (43.4%) and the second highest proportion of patients had pleural TB (17.4%). The overall yield of NAAT was 52%, with the highest yield of 78% in lymph node TB.

Strength of the study

It was carried out as an interdisciplinary study involving microbiologists, pathologists, and clinicians. The study included data for 2022 accounting for 281 patients.

Limitations of the study

Being a retrospective study, clinical follow-up was not possible.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Research Article

Molecular and genomic characterization of *Leptospira* isolates in humans and its relation to disease severity

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Abstract

Objective

The study was conducted with the aim to find out the genomo species and serovars of Leptospira by gene sequencing among blood samples tested positive for Leptospira PCR and to identify the species associated with highest mortality.

Methods

All samples with Ct value less than 35 were included in the study. After *lipL32 PCR* amplification and agarose gel electrophoresis, the amplified products were subjected to gene sequencing. Demographic details and mortality data were obtained from records.

Results

66 out of the 70 samples showed maximum similarity to *L.interrogans* in sequencing. Other species identified include *L.kirschneri* and *L. noguchi* (5 samples). Among those tested positive, 14 patients died. *L.interrogans* was frequently isolated (13/14)from those who died.

The different serovars identified include serovar *canicola/hardjo/copenhageni*, *manilae/bataviaea/lai/icterohaemorrhagiae*. Of these, serovars identified in death include Serovar *canicola/hardjo/copenhageni/ranaram/manila*.

Conclusion

Following sequencing, we identified the predominant species as *L. interrogans* (91 %) with case fatality rate of 19 %. They are found in animal population of our area, pointing the zoonotic potential of Leptospira. This highlights the need for sensitization of those with animal exposure regarding preventive strategies.

Introduction

Leptospirosis is a globally distributed zoonosis with more than one million severe cases and 60,000 deaths per year, the highest incidence being reported from tropical countries [1,2]. It is an emerging public health problem both in developing and developed countries [3]. Study by Basker P et al. in Villipuram district in Tamil Nadu states Leptospirosis is responsible for about 12.7 % of acute febrile

illness attendance at hospitals [4]. The causative agent for the disease belongs to the genus *Leptospira.* Among the different species causing human disease *Leptospira interrogans* is the most frequently isolated one [5]. Humans acquire the infection by direct contact or exposure to soil or water contaminated by the urine of reservoir hosts. The disease has a varied presentation ranging from asymptomatic or mild febrile illness to severe illness resulting in multi organ failure and death [6,7].

For routine diagnosis of Leptospirosis, serological tests such as Enzyme Linked Immuno Sorbent Assay (ELISA) and Microscopic Agglutination Test (MAT) are commonly used. Identifying the infecting serovar has become significant in establishing an epidemiological basis and to adopt public health measures for prevention of the disease [3]. MAT using a suspension of live antigens can provide valuable information on local circulating serovars. Availability of live antigens from the culture suspensions demands a laborious and time-consuming process which may not be adopted by many laboratories. Hence MAT is restricted to specialised laboratories.

Because of the superior sensitivity and ability to establish early and rapid diagnosis of infections, molecular diagnostic methods are becoming more important. There are studies suggesting the use of genotyping for the identification of serovars faster than MAT and sequence based methods for identification of infecting species [3]. PCR based techniques has enabled typing of *Leptospira* serovars in clinical material without the need for isolation of bacteria from pure culture [8].Molecular characterization separates *Leptospira* into 20 species, comprising of nine pathogenic, five intermediate, five saprophytic and one species, *L. meyeri*, consisting of a mixture of putative pathogenic and saprophytic serovars.

Earlier, the classification of genus *Leptospira* into pathogenic species *L. interrogans* and saprophytic *L.biflexa* was made based on phenotypic characteristics. But with the advent of DNA-DNA hybridization studies, molecular classification came into use [8]. Different methods used for molecular characterisation of *Leptospira* include DNA-DNA hybridization studies, Bacterial restriction-endonuclease DNA analysis, Ribotyping, Pulse field Gel Electrophoresis. PCR based methods can be used for both detection and characterisation. Sequence based genotyping is a highly robust and efficient method in identifying ancestral relationships and segregating outbreak associated strains according to their genome species status. This has proved to be useful to identify the strain relatedness isolated from different hosts which can include both human strain and the animal strain. The availability of whole genome sequences enables detailed studies on pathogen evolution and distribution.

As per the study by Lata et al. on human *Leptospira* isolates till date, 654 *Leptospira* sequences have been published, among these most of the sequences (49 %) belong to *L. interrogans*, followed by *L. borgpetersenii* (7 %), *L. santarosai* (6 %) and *L. kirschneri* (5 %) [9]. Another study from France by Linda et al. identified L. *interrogans* serovars *Icterohaemorrhagiae and Copenhageni*, *L. kirschneri* serovar *Grippo typhosa* and *L. interrogans* serovar *Pyrogenes* as the infecting strains [2].

Identification of the *Leptospira* species serogroup as well as serovars is not done as a part of routine diagnostic work up. But it has got epidemiological and diagnostic significance. Severity of the disease and the mortality rates may vary among different serovars. Molecular typing of the *Leptospira* is essential to know about these different serovars. A study on this area is deficient in our literature. Hence it was decided to undertake the current study with the objective to find out the genomospecies and serovars by gene sequencing among samples tested positive for *Leptospira* PCR in our institution. We also wanted to check the association of demographic factors and mortality with

different genomospecies.We hypothesise L. *interrogans* will predominate and will be associated with highest mortality.

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Section snippets

Methodology

A retrospective study was conducted in Virus Research and Diagnostic Laboratory (VRDL), Department of Microbiology, among the blood samples received from patients showing classical symptoms of leptospirosis during the period April 2022 to March 2023. We obtained ethical committee clearance. All samples tested positive for Leptospirosis PCR were included in the study. The sample selection can be summarised as shown in Fig. 1.

We proceeded with genomic sequencing of the *Leptospira* isolates from

Results

During the study period a total of 627 blood samples were received with clinical suspicion of Leptospirosis. Of these, 185 samples turned to be positive for Leptospirosis PCR. Month wise distribution of sample positivity is tabulated in Table 1.

A total of 97 positive samples with Ct/Cq values less than 35 (Fig. 3), were selected after qPCR assays with Mylab Discovery solution's *Leptospira* Detection Kit.

These samples were again confirmed by *lipL32* gene amplification (Fig. 4), and a well

Discussion

Molecular studies are seldom used for routine laboratory diagnosis of Leptospirosis. Genomic studies are becoming important for the characterization of pathogen diversity and pathogenicity [2].

Our study was conducted with the aim to find out the genomospecies and serovars of *Leptospira* by gene sequencing among samples tested positive for *Leptospira* PCR. Out of the 627 blood samples received with clinical suspicion of Leptospirosis, only 185 samples turned to be positive for Leptospirosis

Conclusion

Using sequencing studies, we could identify the infecting species accurately. Though L.*interrogans* is commonly identified as the causative agent, identification of *L. noguchii* and *L. kirschneri* were possible only with molecular characterisation. We identified the predominant species as *L. interrogans* (91 %) with case fatality rate of 19 %. The different serovars identified for *L.interrogans* species include serovar *canicola/hardjo/copenhageni* and *manila.* Among death patients the most common

Limitations

Being a retrospective study, only the basic demographic details of the patients available in the request form could be included, clinical details as well as follow up of patients could not be done. The study was done on human samples only. MAT was not performed to identify the serogroups. The

correlation of genomic studies from animal samples during the same period from same locality and identification of reservoir could not be done.

Strength of study

There are many studies on clinicoepidemiological correlation of Leptospirosis and molecular characterisation of Leptospira isolates in animal population. Studies in this regard are few from human samples. Geographical distribution of circulating genomospecies as well as serovars are useful for developing vaccines. Epidemiology including data on local serovars is crucial to accurately diagnose and treat the infection and for effective control of infection. So the study was useful in identifying

CRediT authorship contribution statement

Anitha Thattamparambil Ravindranathan: Writing – review & editing, Writing – original draft, Validation, Methodology, Data curation, Conceptualization. **Aiswarya Mukundan:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Methodology, Investigation, Conceptualization. **Sithara Nasar Thottathil Puthanpurayil:** Writing – original draft, Methodology, Data curation. **Bijesh Kavuthodi:** Software, Methodology, Data curation. **Sunitha Karunakaran:** Writing – review &

Ethics approval

Study was approved by Institutional Review board and IEC (Institutional Ethics committee) vide IEC/GMCTSR/2023/201.

Funding

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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CORRESPONDENCE

Response to Pyridostigmine in Congenital Myasthenia with LRP4 Mutation

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To the Editor: A baby boy, small for gestation, delivered at term, with hypotonia, poor suck and feeding difficulty with no tongue fibrillations was suspected to have a myopathy in neonatal period. The whole exome sequencing revealed LRP4 (lipoprotein related protein 4) mutation, a pathogenic variant described in congenital myasthenia syndromes. The baby showed dramatic improvement with increased movements of limbs, resolution of ptosis and elicitable reflexes on a trial of pyridostigmine at 1 mg/kg/dose 6 hourly.

With 32 mutations described till date, congenital myasthenia syndromes are genotypically and phenotypically heterogenous group of neuromuscular disorders where there is an impaired neuromuscular transmission [1]. LRP4 is the gene which encodes for a protein which function as receptor for nerve-derived proteoglycan agrin [2]. Agrin binding to LRP4 leads to activation of muscle-specific kinase receptor (MuSK), a transmembrane component of post synaptic neuromuscular junction. Activated MuSK leads to clustering of acetylcholine receptors (AChRs), it also anchors acetylcholine esterase to the neuromuscular junction and thus aids in neuromuscular transmission [3].

COLQ^{-}, LAMB2^{-}, DOK7 and MuSK mutations are known to worsen clinically with pyridostigmine. Salbutamol or ephedrine can be used to treat myaesthenic synfdrome caused by DOK7 and COLQ variants; fluoxetine, quinidine, or quinine may be used to treat slow channel syndrome [4].

There is no definite recommendation of pyridostigmine use in LRP4 mutation. Pyridostigmine being an inhibitor of acetyl cholinesterase acting at post synaptic transmission, could probably explain the response of the patient to the medication. Very few cases of LRP4 mutation are described worldwide; first reported case showed poor response to acetylcholine esterase inhibitor (AChEI) [1]. The treatment option with AChEI may still offer positive hopes in lives of children with LRP4 mutation. We recommend initiation of the drug in this mutation, thus contributing to data pool regarding the condition.

Declarations

Conflict of Interest None.

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A Prospective Observational Study of Short Term Outcome in Preterm Neonates Delivered in a Tertiary Care Hospital

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Abstract

Background Preterm refers to a newborn whose gestational age is fewer than 37 full weeks and it claim the lives of almost 1 million children annually. Disease patterns in preterm newborns differ from location to location and even within a single location. Therefore, in order to create effective strategies to deal with serious preterm morbidities, it is essential to conduct regular neonatal audits. Objective To study the short term outcome of preterm neonates delivered in a level III neonatal intensive care unit. Methods A hospital based prospective observational study was conducted in neonatal intensive care unit, during February 2022 to July 2022 in a in a level III neonatal intensive care unit. All the inborn preterm neonates of less than 37 weeks of gestation were included and assessed for morbidity pattern. Results A total of 192 preterm neonates were included in the study. Ninety seven (50.5%) were male and 95(49.5%) were female. The major morbidities observed in the preterm neonates were respiratory distress syndrome in 62.5 %, apnea of prematurity 36.9 %, hyperbilirubinemia in 27 %, and hypoglycaemia in 18.23%. Other common morbidities seen were retinopathy of prematurity in 12.17%, culture proven sepsis in 9.42% intraventricular haemorrhage in 9.3%, broncho pulmonary dysplasia in 5.26% and patent ductus arteriosus in 5.24%. Conclusions The major short term morbidities of preterm neonates are respiratory distress syndrome, hyperbilirubinemia, hypoglycemia and apnea of prematurity. Keywords: Preterm, short term morbidity, respiratory distress, apnea of prematurity and hyperbilirubinemia.

Neonatal Meningitis Outbreak by *Elizabethkingia*: A Case Series and Epidemiological Investigation Findings

Abstract

This study is a case series (*n* = 7) of neonatal meningitis caused by *Elizabethkingia* at a tertiary-level hospital in South India. All cases occurred in premature and low-birth-weight neonates over a short period of 4 months, constituting an outbreak. The bacterial pathogen was identified in cerebrospinal fluid (CSF) in all cases and was found to be sensitive to vancomycin and ciprofloxacin. All neonates survived, but one developed ventriculomegaly. The outbreak was investigated, but the source of contamination was not identified in the environment. However, new cases ceased to occur after revamping the feeding practices. Hence, it was assumed that the feeding utensils might have been the source of contamination. The study highlights the importance of source elimination and implementing appropriate infection control measures in neonatal intensive care units (NICU).

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Key Words
CTS (Carpel tunnel syndrome), NCS (nerve conduction studies), AAEM (american association of electro diagnostic medicine)

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A Clinical Study on Carpel Tunnel Syndrome in A Tertiary Care Centre in South India

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Abstract
Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy presenting in the neurology clinics. It is due to the compression of the median nerve in the carpal tunnel. It will produce a wide variety of symptoms and signs. This is a retrospective study using the discharge tickets of CTS Patients admitted in neurology ward and out patient's tickets of CTS patients attending in the neurology OPD from August 2019 (01/08/2019 to July 2020 (31/07/2020) at Government medical college, Thrissur. Carpal tunnel syndrome was more common among the females with a female to male ratio of 3.1:1.Majority of the patients belonged to 40-60 age group. Most of the patient had bilateral symptoms and the dominant hand was involved in most of them irrespective of whether it is bilateral or unilateral involvement. Obesity, Diabetes and hypothyroidism were found as common risk factors associated with carpel tunnel syndrome. Phalens tests and Tinel's test were positive in majority of our patients. In our study group, no correlation was observed between the severity of the symptoms and the electro physiological grading of the disease.

INTRODUCTION

Carpel tunnel syndrome (CTS) is the most common entrapment neuropathy encountered by the neurologist. It is due to the compression of the median nerve in the carpel tunnel[1]. It Manifests as various symptoms like paresthesias and numbness. There are many risk Factors for this condition like environmental and medical conditions like diabetics, pregnancy, Hypothyroidism. This condition has got a female preponderance[2].

A Brief Review: Carpal tunnel syndrome is a medical condition in which the median nerve is compressed at the wrist producing various symptoms like numbness and pain. It is the most frequent compression neuropathy found in neurophysiological labs. It is more common in women (506 per 1000000 /year) than in men (139 per 1000/years) (2). It can occur at any age but has a peak incidence of around the age 50[3].

Although most case of CTS are idiopathic, there are still many medical risk factors connected with CTS. Medical risk factors can be divided into extrinsic and intrinsic. Extrinsic factors increase the volume within the carpal tunnel and include factors like pregnancy, menopause, obesity, renal failure, hypothyroidism, use of oral contraceptives and congestive cardiac failure. Intrinsic factors within the nerve increasing the occupied volume inside the tunnel include lumps and tumor like swellings. Neuropathic factors include conditions like diabetes, alcoholism, vitamin deficiency or exposure to toxins[4].

The compression of the median nerve produces the signs and symptoms of CTS. The condition is usually bilateral, the dominant hand seems to be more severely affected. Numbness and paresthesias in the first three fingers are the classical symptoms of CTS. Typically the symptoms present at night and often awakens thee patient from sleep. The other symptoms include numbness, tingling and burning in the median nerve region. In severe instances, weakness in activities such as turning keys while using the hands, opening door knobs or jar lids. Conventional tests for the diagnosis of CTS are Tinels test, Phalens test and median nerve compression test. In the presence of aggrevation of symptoms, these tests are considered to be positive[5].

The most accurate test is nerve conduction studies and EMG. It has a sensitivity of 49-84%and specificity of 95%. Nerve conduction studies (NCS) provide an objective assessment of the physiological condition of the median nerve. Other alternatives diagnosis that should be considered included cervical radiculopathy, peripheral neuropathy, arthritis of the wrist/metacarpal joints, taenosynovitis and ulnar neuropathy[6].

Carpel Tunnel Syndrome was diagnosed if any of the following were present in the nerve conduction studies (criteria by U K Misra and J Kalitha)[7].

Distal median motor latency >4.4ms. (2) Difference between distal motor latency of median and ulnar nerves>1.1ms. (3) Difference between distal sensory latency of median and ulnar nerves>0.2ms (4). (A). Difference between median and ulnar sensory latencies on stimulating fourth digit and recording from wrist at equal distance >0.2ms

Difference between median and radial sensory latencies on stimulating thumb and recording from wrist at equal distance >0.4 ms. (5). Palm wrist conduction: Difference between median and ulnar sensory latencies across 8cm >0.4ms.(6). Inching technique: Latency jump >0.2ms/cm.(7). Comparison of lumbrical (median nerve) and interosseous (ulnar) latencies greater than or equal to 0.6ms.

Patients were Classified Based on NCS Studies as per the AAEM (American Association of Electrodiagnostic Medicine) Criteria[8]: The treatment of CTS depends on the severity. In mild cases the injection of corticosteroids and application of wrist splints are beneficial. In severe cases we may have to release the median nerve by surgery. Females have a higher incidents of CTS. Pregnancy and lactation are increased risk factors and increase in intensity of symptoms is in future pregnancy. Recurrence of CTS after surgery is also common.

Objectives:

- To study the, gender distribution, age of onset and clinical presentation of patient with Carpal Tunnel Syndrome admitted in neurology department of a tertiary care hospital In Kerala coming for follow up in outpatients.

MATERIALS AND METHODS

Study Design: Cross sectional study-Record based

Study Setting: GMC, Department of Neurology Thrissur

Study participants. This is a retrospective study using the discharge tickets of CTS Patients admitted in neurology ward and out patient's tickets of CTS patients attending in the neurology OPD from August 2019 (01/08/2019 to July 2020 (31/07/2020).

Inclusion Criteria: All the patients in the study are diagnosed on clinical features of CTS and on nerve conduction study features.

Exclusion Criteria: Cases of Cervical Radiculopathy, Peripheral Neuropathy, Cervical Rib, Ulnar Neuropathy,

Arthritis of wrist and Metacarpels who do not have the NCS features of CTS are excluded.

Study Period: 3 months

Simple Size: All cases during the period 01/08/2018-31/07/ 2021 are included. Data collection tool-structured proforma

Methodology: Data collection Record based Analysis. Secondary data of patients with CTS will be collected using a structured proforma. Data on clinical presentation, age of onset, gender, progression and clinical test performed and Nerve conduction tests employed will be collected and analysed.

Variables included Age of onset, Gender, Presentation (signs and symptoms), Severity and Duration of symptoms and clinical tests.

Data Analysis: Data entered in MS excel and amp, analyzed using appropriate software like Epi info. Qualitative data was analyzed using proportions. They were tabulated and amp, discussed.

Ethical Consideration: This is a record based study. It was started after getting the approval from the research and ethical committee. Confidentiality of data will be maintained.

RESULTS AND DISCUSSIONS

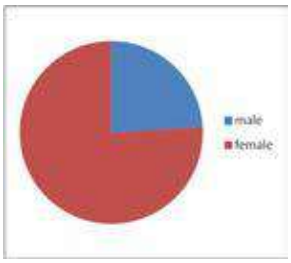


Fig. 1: Gender ratio

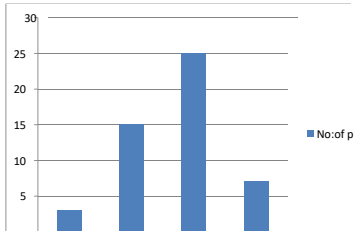


Fig .2: Age wise distribution of patients

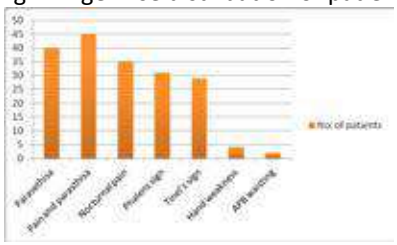


Fig. 3: Clinical Signs and symptoms

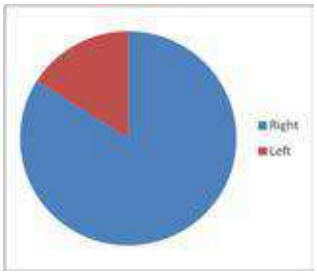


Fig. 4: Handedness of patients

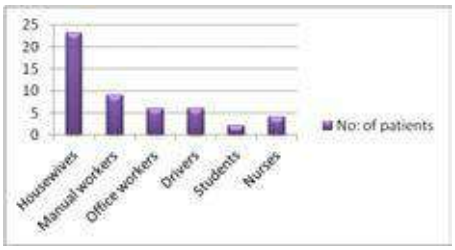


Fig. 5: Occupation of Patients

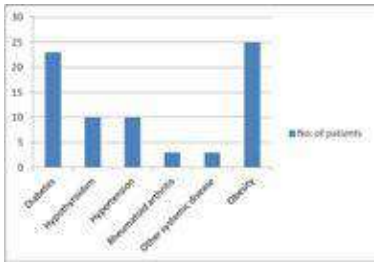


Fig. 6: Incidence of Systemic Disease in Study Group

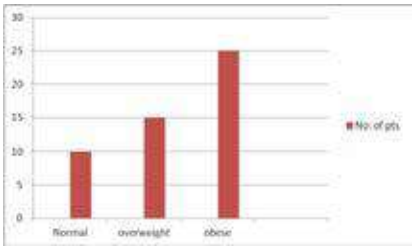


Fig.7: Body Mass Index of Patients

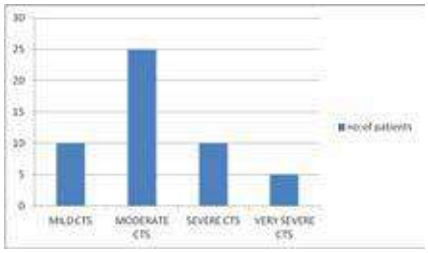


Fig.8: Grading of CTS as per NCS Studies

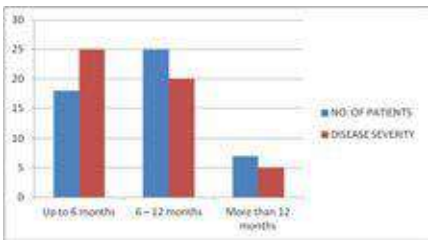


Fig. 9: Correlation between duration of symptoms and severity of symptoms clinically

Table No: 1

Symptoms and signs	No: of patients and percentage
Parasethisa	40 pts (80%)
Pain and parasthisa	45 pts (90%)
Nocturnal pain	35 pts (70%)
Phalens sign	31 pts (62%)
Tinel's sign	29 pts (58%)
Hand weakness	4 pts (8%)
APB waisting	2 pts (4%)

Table no:2

Mild CTS	Mild carpal tunnel syndrome (CTS) is characterized by delayed sensory peak latency and decreasing sensory amplitude.
Moderate CTS	Moderate CTS Abnormal median sensory interaction with addition of motor distal latency prolongation
Severe CTS	Severe carpal tunnel syndrome (CTS) involves a significant prolongation of median nerve motor and sensory distal latency, along with a reduction in both sensory and motor amplitude.
Very severe CTS	In cases of very severe carpal tunnel syndrome (CTS), there are no detectable sensory or motor responses from the median nerve

Table 3

Duration	NO: Of patients
Up to 6 months	18 patients (36%)
6-12 months	25 patients (50%)
More than 12 months	7 patients (14%)

Table 4

Duration	Disease severity as per subjevtive	symptoms
No: of patients	18	25(Mild +Moderate)
Up to 6 months	25	20(Moderate+ Severe)
6 – 12 months	7	5(Very severe)
More than 12 months		

Gender: In our study there were 50 patients, out of which 38 were females and 12 males. Shown in figure no.1

Presentation: Most common symptoms were paresthesias present in 40 patients, followed by pain and paraes thesia and nocturnal pain. Phalens sign and Tinel's sign was positive in 31 patients and 29 patients respectively. Hand weakness was present in 4 patients and Abductor pollicis Brevis waisting was present in 2 patients. Shown in figure No. 3 and Table No. 1

Handedness and Unilateral and bilateral presentation-Symptoms were present in both hands in 35 patients and in one hand only in 50 patients. Dominant hander's more involved in 42 patients while non-dominant hand was more involved in 8 patients irrespective of whether presentation was bilateral or unilateral. Shown in figure no . 4

Occupation of Patients: A detailed occupational history of each patient of in our study was taken. 23 patients were housewives followed by manual workers (9 patients),Office workers (6patients), Drivers (6 patients), Students (2 patients), Nurses (4 patients) shown in figure no.5

Patient's records were scrutinised and the blood routine, blood sugar, Liver function test, renal function test, Thyroid function test and other relevant investigations were analyzed.

Obesity, Diabetes, Hypertension, Hypothyroidism and Rheumatoid arthritis were the common risk factors noted in our study. There were 23 (46%)patients with Diabetes 10 (20%) patients with Hypothyroidism, 10 (20%) patients with Hypertension, 3(6%) patients with Rheumatoid Arthritis, 25 (50%) patients with obesity and 3(6%) patients with Other systemic diseases. Shown in figure no.6

Data on each of these factors were studied in detailed and further analysed. Based on the BMI, patients were classified as normal, over weight and obese as shown in figure no.7

Patients were diagnosed have carpel tunnel syndrome based on the crtiteria laid down by U K Misra and J Kalitha et al.7 Depending upon the NCS finding, they were further classified as mild, moderate, severe and very severe shown in figure no.8

Patients were classified based on NCS Studies as per the AAEM Criteria, which is given in table no. 2 below8

Duration of Symptoms: Patients were classified as per the duration of symptoms and shown in table no. 3

A Correlation between duration of symptoms and clinical disease severity as experience by the patient and the NCS findings are shown in table no. 4. Also shown in figure no.9

Gender-In our study, the female to male ratio was 3.1:1.In the study by Salah El- 2 the female male ratio was found to be 4:1.IN another study by Vishali Kotwal Et al9,there is again a female preponderance with a female to male ration of 3:1.

Age: The maximum number of patients were found in the 40-60years group in our study,25 patients (50%).These findings are consistent with the studies of Vishali Kotwal Et al 9 and Goyal[10].

Presentation: Symptoms were present in both hands in 35(70%) patients and in one hand only in 15 (30%) patients. Dominant hander's more involved in 42 patients while non-dominant hand was more involved in 8 patients in our study. Pawel Dec and Andrzej Zyluk et al have reported bilateral symptoms in 22-87% in their study[11] and the study by Malibary *et al* also found that bilateral involvement was more common[12].Irrespective of the bilateral or Unilateral symptoms, dominant hand was involved more in the studies of vishali kotwal et al9 and in the study by salah el Magzoub M2

Presentation: Most common symptoms were paresthesias present in 40 patients, followed by pain and paraesthesia and nocturnal pain. Phalens sign and Tinel sign was positive in 31 patients and 29 patients respectively. Hand weakness was present in 4 patients and Abductor pollicis Brevis waisting was present in 2 patients involved in 84% of the patients. Similar presentations are seen in the studies of Vishali Kotwal[9]

Signs: Phalens test: in this test, the patient is asked to flex the wrist and maintain it in that position for 60 seconds. If the patient experiences pain or paraesthesia in the distribution of the median nerve, it is considered as a positive test. In our study group, 31 patients (62%) had a positive phalen sign. The sensitivity of Phalens test is reported to be between 67% - 83%[13,14,15]

Tinels's test: It is done by tapping over the volar surface of the wrist, if the patient has paraesthesia in the figures innervated by the median nerve, it is considered as a positive test. In our study, it was positive in 29patients (58%).The specificity of the tinels test is reported to be between 48%-73% in the studies of Kuhlman et al ,Naranjo et al and Amirfeyz R et al.The specificity of the test is between 30%-94% in the same studies[13,14,15] Occupation: In our study, majority of the patients were housewives,23 (46%) .An increased prevalence of CTS was reported among housewives in the study of Vishali Kotwal[9]

Risk factors: There were 23 (46%)patients with Diabetes 10(20%) patients with Hypothyroidism ,10(20%) patients with Hypertension,3(6%) patients with Rheumatoid Arthritis ,25(50%) patients with obesity and 3(6%) patients with Other systemic diseases.

Obesity: In our study, most of the patients were overweight or obese (40 patients) Sharief et al has described that there is a relation between increased BMI and CTS. (Ref no: 16).In obese patients, increased fat accumulation occurs within the carpel tunnel and also there is an increased hydrostatic pressure inside the carpel tunnel. This goes in accordance with the the studies of Becker[17].

Diabetes: 23 patients were diabetic, studies by Wiberg et al has shown a strong correlation of diabetes with CTS.(Ref no: 18).Same observation has been made by Becker[17].

Hypothyroidism: 10 patients had elevated TSH in our study, hypothyroidism has been shown to be one of the causes or risk factors for CTS.In uncontrolled hypothyroidism, there will be deposition of mucopolysaccrorides on the median nerves.A swelling may also develop in the synovial membranes around the tendons in the carpel tunnel. This has been described by Rempel[19]

Electro Physiological Findings: In our study, 10 patients were having mild CTS, 25 patients had moderate CTS, 10 had severe CTS AND 5 had very severe CTS as per the AAEM criteria.

Correlation of Clinical Symptoms with NCS Findings. The duration of symptoms were compared with the clinical severity as per the NCS studies. 18 patients had very severe symptoms clinically and on the basis of NCS, they were categorized as mild and moderate cases but their duration of symptoms was up to 6 months. Another 25 patients had moderate symptoms and they were classified as moderate to severe based on the NCS studies, but their duration of symptoms in these cases was 6-12 months. Another 5 patients had mild symptoms and were classifies as very severe by NCS studies. But, the duration of symptoms was above 12 months and they had mild symptoms clinically.

In our study, more patients are having severe symptoms than detected by nerve conduction studies. So the severity of complaints experienced by the patients were not matching with neither the severity detected by nerve conduction studies nor with the duration of symptoms. In the study by Leighton Chan[20] also there was no statistically significant correlation between the symptom severity of the patients and the

electrophysiological studies. Firosh Khan *et al* has described in his study that the symptoms were more in concordance with psychological factors than NCS findings[20]. Itsubo et al and Longstaff et al have also found similar findings in their studies[22,23].

Truini *et al* has forwarded many postulations for this difference in correlation[24]. In the early course of the CTS, the thin myelinated A delta fibers and the unmyelinated C fibers are involved first. These fibers carry the pain sensation and their dysfunction is not pickup in the nerve conduction studies. The thick myelinated A beta fibers are involved only in the late stages of the disease. The dysfunction of the fibers will produce abnormalities in the nerve conduction studies. Another thing is that the patient who is not accustomed to pain and other sensory symptoms may complain of severe pain and other dysfunction in the early part of the disease, but as the disease progresses he becomes tolerates these symptoms in a much better way. Nunez et al has described that the painful symptoms of CTS are dependent on the general mood and psychological status of the patient[25].

CONCLUSION

Carpel tunnel syndrome is more common among females. Most of the patients belonged to the 20-40 age group. Most of the patients had bilateral symptoms. Symptoms were more pronounced in the dominant hand, irrespective of whether the disease was unilateral or bilateral. Phalens sign and Tinel's sign were found positive in a significant number of our patients. Most of the patients in our study were obese or overweight. Diabetes and hypothyroidism were found as substantial risk factors in our study group. There was no correlation between the severity of the symptoms experienced by the patients and the electrophysiological severity grading of the disease.

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Posterior fossa tuberculosis: Unusual presentations of a common disease and literature review☆

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ABSTRACT

The burden of tuberculosis is very high in our country and though the number of deaths due to tuberculosis has drastically reduced, still the associated morbidities caused by the disease can be very debilitating.[1] Central nervous system tuberculosis is a rare and serious presentation of tuberculosis, the general presentation being hydrocephalus, meningitis, and disseminated miliary lesions.[2] More often than not tuberculosis is associated with immunocompromised status and central nervous system tuberculosis in immunocompetent young individuals with no evidence of systemic tuberculosis is very rare.[3]Association of tuberculosis with ocular manifestations and even blindness is not uncommon, the causes of blindness being causes like uveitis, retinitis, interstitial keratitis, ophthalmitis, and even orbital tuberculosis.[4] Classical teaching in neurosurgery is that a posterior fossa lesion unless proven otherwise is a metastasis. Therefore, here we are discussing three cases of central nervous system tuberculosis in isolation, without any systemic involvement in immunocompetent adults in the posterior fossa region as well as a literature review of cases from across the globe of posterior fossa tuberculosis in immunocompetent adults. The first case is regarding a treatable cause like tuberculoma in an immunocompetent young adult causing blindness which is rare as well as unfortunate. The other two cases highlight the need to keep tuberculosis as a differential even when the clinical features, radiological features, and blood and other investigations are not suggestive.

1. Introduction

Tuberculosis is a great mimicker and most commonly presents as pulmonary disease however other organs can also be affected. 5–15 % of the cases are of extrapulmonary tuberculosis out of which central nervous system (CNS) tuberculosis accounts for 1% of cases.[1–5] The risk factors for developing CNS tuberculosis are pediatric age group, immunocompromised individuals either due to immunosuppressive drugs or HIV co-infection, malnutrition, and malignancy.[6] The common presentation of CNS tuberculosis is tuberculous meningitis, followed by tuberculomas, other pathological findings are cerebral abscess, cerebral miliary tuberculosis, tuberculous encephalopathy, tuberculous encephalitis, and arteritis.[7] Since the infratentorial tuberculomas behave as any other space-occupying lesion in the brainstem and cerebellum with respect to the signs and symptoms, it is difficult to diagnose especially in the absence of associated systemic symptoms or pulmonary symptoms of tuberculosis[8] The diagnosis of central nervous system tuberculosis becomes very challenging, as apart from the symptoms which can mimic a plethora of conditions, the cerebrospinal fluid and other tests yield very little evidence towards a diagnosis and a tissue diagnosis becomes mandatory.[9,10] (see Table 1, Figs. 1–8)

2. Case reports

2.1. Case 1

A 19-year-old male presented to our department with complaints of headache for 4 years, walking difficulty for 3 years with complete loss of vision for 2 years in the right eye, the headache had worsened over the past 1 week and was associated with vomiting for the past 2 days.

On examination, the patient was drowsy, and cerebellar signs were positive with no evidence of cranial nerve involvement, pyramidal tract involvement, or signs of meningitis. On fundoscopic examination, bilateral papilledema was noticed. Vitals were stable with a pulse of 86/min and a blood pressure of 140/90 mm of mercury. The patient was seronegative and the total blood count was 11,000 mm^3, 60%

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Table 1
Review of literature concerning posterior fossa tuberculoma in immunocompetent adults.

Age/sex	Symptoms	Pulm.Tb	Investigations	Site	Hcp	Treatment	outcome
49/F	Headache Gait imbalance Cerebellar signs	No	Normal	Left cerebellar	_	Excision ATT 8 months	good
16/F	Headache Gait imbalance	No	ESR: high CSF: lymphocytosis	Right cerebellar	+	No details	good
28/M	Headache Gait imbalance Vomiting Visual disturbance	No	ESR: high CSF: lymphocytosis	NA	NA	NA	good
42/F	Headache Vomiting convulsion	No	Normal	NA	_	Excision ATT 9 months	good
35/F	Headache Ptosis	No	Normal	Bilateral cerebellar	_	Excision ATT 15 months	Good
34/F	Headache Neck pain Vomiting	No	Normal	Right cerebellar	+	Excision Ventriculostomy ATT on going	good
20/F	Fever Headache Vomiting	Yes	ESR: high	NA	NA	ATT 12 months	good
45/M	Headache Photophobia	No	Normal	NA	NA	Excision ATT 12 months	Good
59/M	Headache Gait imbalance Vomiting	No	NPCR + ve	+	+	ATT 24 months	good

Abbreviations Pulm: pulmonary; Tb: tuberculosis; hcp: hydrocephalus; ATT: anti tubercular treatment; ESR: erythrocyte sedimentation rate; NPCR; nested polymerase chain reaction; NA: not available.

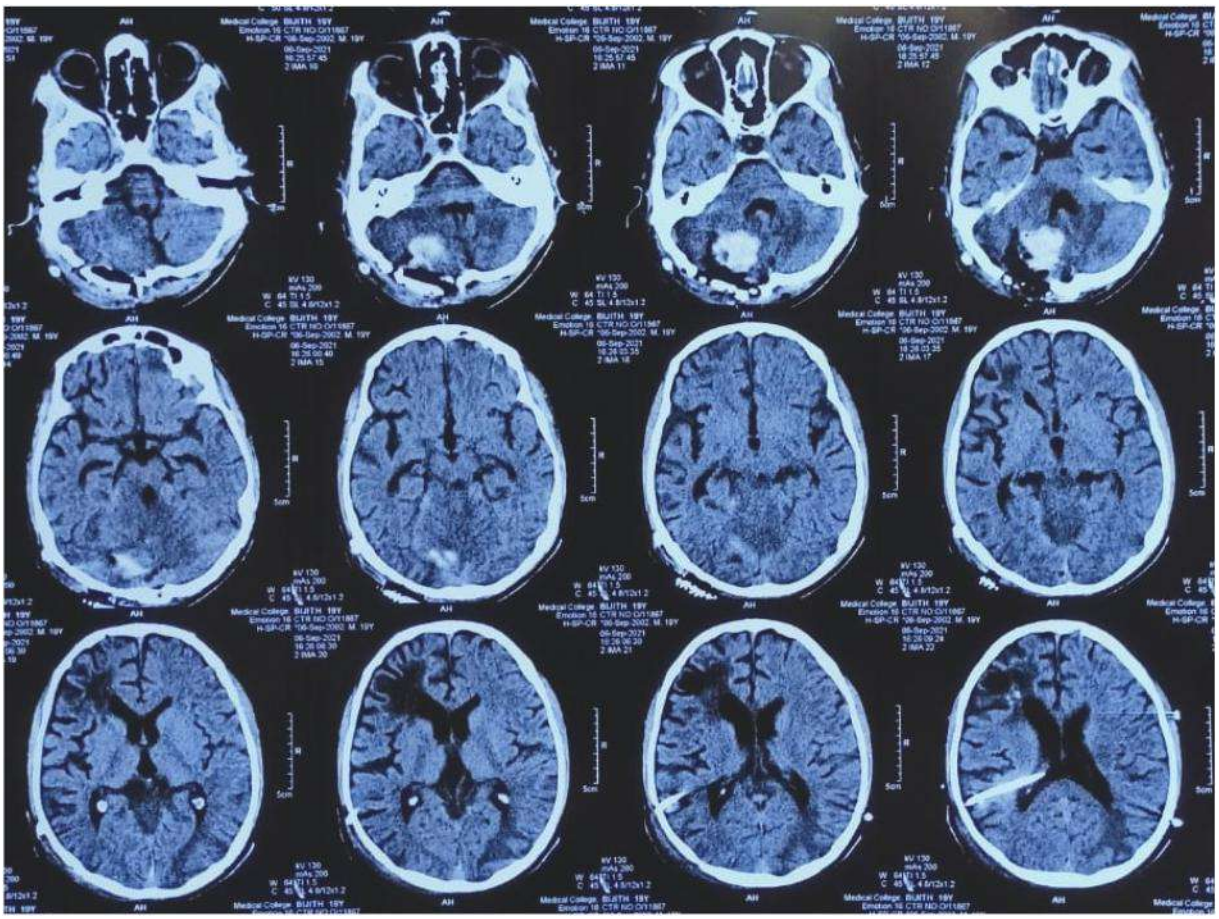


Fig. 1. non contrast enhanced computed tomography of brain, post ventriculoperitoneal shunt and craniotomy and excision of right cerebellar tuberculoma, occipital lesion and ventriculoperitoneal shunt in the right lateral ventricle.

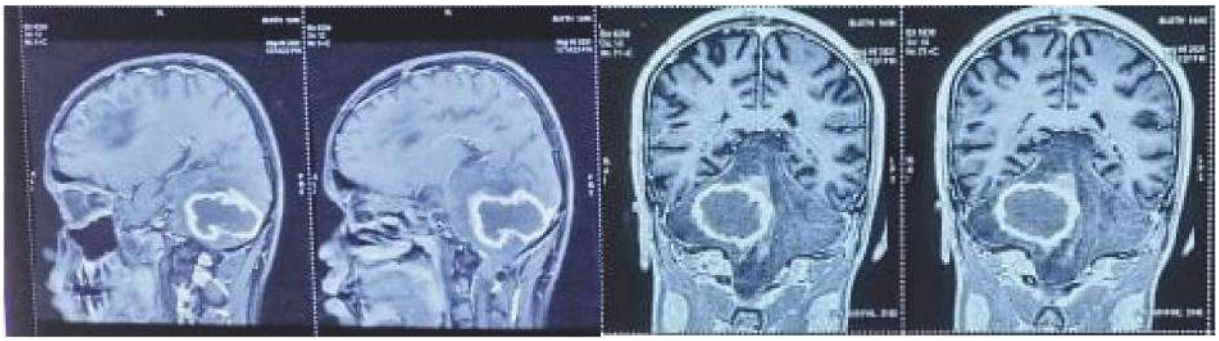


Fig. 2. contrast enhanced magnetic resonance imaging of brain showing a ring enhancing lesion in the right cerebellum.

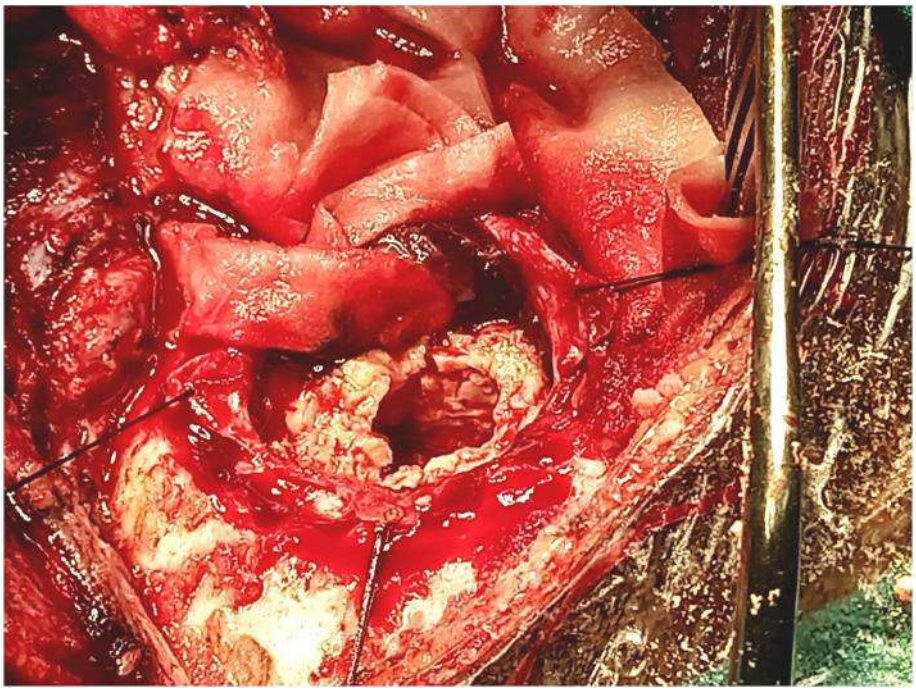


Fig. 3. intraoperative picture showing the rubbery, minimally vascular, flaky lesion suggestive of a tuberculoma.

neutrophils, and 40% lymphocytes. Haemoglobin was 13.1 gm/dl and ESR was 40 at the end of 1 h.

Computed tomography was done which showed a 4.3 × 3.9 cm lesion on the right cerebellum associated with perilesional edema, mass effect, and dilatation of the ventricles suggestive of obstructive hydrocephalus.

The patient underwent emergency ventriculoperitoneal shunt insertion and was planned for excision of the cerebellar mass after further evaluation. CSF studies showed mild pleocytosis with no evidence of tuberculosis. Further studies were done and an MRI brain was taken which corroborated the findings of the CT. Evaluation of vision showed complete and permanent loss of vision in the right eye.

The patient underwent right suboccipital craniotomy and excision of the right cerebellar. The lesion was firm to rubbery with the thick fibrous wall, minimally vascular with flakes. Near total excision of the lesion was done with good hemostasis. Specimen sent for frozen section showed granulomatous caseating lesion. Histopathology showed brain tissue with extensive areas of caseous necrosis, focal granulomatous inflammation composed of epithelioid cells, Langerhan's and foreign body giant cells and lymphocytes and CBNAAT showed the presence of tuberculosis which was sensitive to rifampicin. The patient was started on antitubercular drugs along with steroids. Post post-operative period was uneventful and the patient showed good response to the antitubercular drugs however the vision showed no improvement whatsoever. The patient tolerated the antitubercular drugs well and was on follow-up for 2 months following which the patient was subsequently lost to follow-up.

2.2. Case 2

A 47-year-old male patient presented to our outpatient department with complaints of headache, projectile vomiting, and slurring of speech for 5 days.

On examination patient was conscious and obeying with no associated weakness of upper or lower limbs, signs of meningitis, or cranial nerve involvement. Fundoscopy showed no evidence of papilledema. Vitals were stable with a pulse of 80/minute and blood pressure of 110/70 mm of mercury. Total leucocyte counts were 12,000 mm^3, ESR of 38 at the end of 1 h, Hb of 14 gm/dl, and seronegative. The patient underwent radiological evaluation and on MRI, was found to have an ill-defined irregular margined enhancing lesion involving the dura of left parietooccipital convexity and left portion of tentorium cerebelli, suggestive of an atypical meningioma, differential diagnosis of metastasis and neoplastic lesion being less likely.

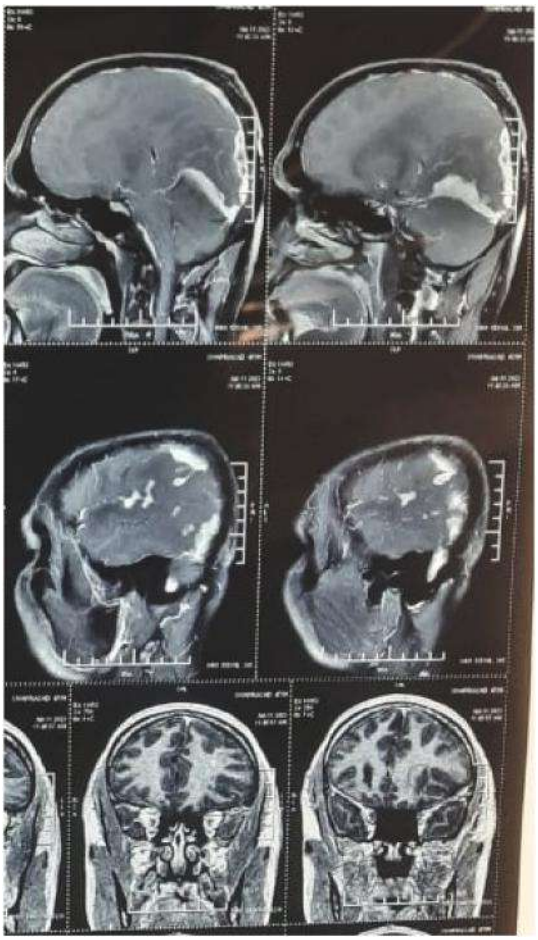


Fig. 4. are the magnetic resonance imaging of the brain showing an irregular ill-defined lesion involving the temporoparietooccipital lesion involving the tentorium cerebelli and dura with significant mass effect and edema.

The patient was prepared for surgery and underwent a left fronto-parietal decompressive craniectomy and a biopsy was taken from the lesion. Along with a histopathology examination, it was also sent for CBNAAT which showed the presence of tuberculosis, sensitive to rifampicin. A histopathology report was awaited and the patient was started on antitubercular drugs. The patient showed a good response to the drug and was discharged after suture removal with advice to follow up.

2.3. Case 3

A 38-year-old male, presented to us with complaints of headache, vomiting, swaying towards his left side, and slurring of speech for 10 days. He was a known case of chronic pancreatitis and was newly diagnosed with diabetes mellitus.

On examination, the patient was conscious and oriented, and vitals were stable with a pulse of 66/minute and blood pressure of 110/70 mm of mercury over the right brachial artery. There were no signs of meningitis or raised intracranial pressure. Cerebellar signs were positive with a wide-based gait and past pointing on the left side. Blood investigations showed a total leucocyte count of 11,500 cm^3, hemoglobin of 12.5 gm %, and ESR of 45 mm at the end of 1-h, and viral markers were negative. Radiological evaluation showed a well-defined lesion in the left posterior fossa with contrast uptake and ring-enhancing lesion.

The patient underwent a craniotomy and excision and the lesion was found to be adherent to the left tentorium cerebelli and was moderately vascular and rubbery. Flakes were present with a centralized area of necrosis. On suspicion of tuberculosis, histopathology and CBNAAT for tuberculosis were sent which came back positive with sensitivity to Rifampicin. The patient was started on antitubercular drugs but unfortunately patient succumbed to postoperative cardiac events.



Fig. 5. are the magnetic resonance imaging of brain showing an irregular ill-defined lesion involving the temporoparietooccipital lesion involving the tentorium cerebelli and dura with significant mass effect and edema.

3. Discussion

Tuberculosis is caused by *Mycobacterium Tuberculosis* and generally affects the lung, extrapulmonary tuberculosis being less common and CNS tuberculosis is even rarer.[11] The Portal of entry of *Mycobacterium tuberculosis* in the central nervous system can be either through direct infection of endothelial cells or by the infected phagocytes followed by the formation of tubercules in either the cortex or the meninges. Tubercules that rupture into the adjacent subarachnoid space cause meningitis whereas the unruptured tubercules progress and enlarge to form tuberculomas.[12] Tuberculomas in the cerebellum in the absence of any pulmonary or disseminated tuberculosis are rare. Solitary lesions are uncommon however multiple tuberculomas may be present. Tuberculomas of the brain show a typical granulomatous reaction consisting of epithelioid cells and giant cells mixed with predominantly lymphocytes around a central area of caseating necrosis. Liquefaction of the central area of necrosis contains clear or straw-colored fluid.[13] Tuberculomas in the brain usually occur in the cerebral hemispheres, especially in the frontoparietal region and basal ganglia. They are usually supratentorial in adults and infratentorial in children.[14,15] Owing to its location, symptoms, signs, and radiological imaging, several other diseases that can produce a similar picture are malignancies like glioma or lymphoma, pyogenic abscess, toxoplasmosis, neurocysticercosis, sarcoidosis, and hydatidosis. [16–18]

Cerebrospinal fluid studies in central nervous system tuberculosis show a moderate lymphocytic pleocytosis, moderately elevated protein levels, and hypoglycorrachia which can be found in many other infectious as well as non-infectious conditions affecting the central nervous system. Some cases have also shown a normal cerebrospinal fluid study.



Fig. 6. are the magnetic resonance imaging of the brain showing a well-defined lesion in the posterior fossa, on the left side with contrast uptake and ring enhancement of the wall.



Fig. 7. are the magnetic resonance imaging of brain showing a well-defined lesion in the posterior fossa, on the left side with contrast uptake and ring enhancement of the wall.

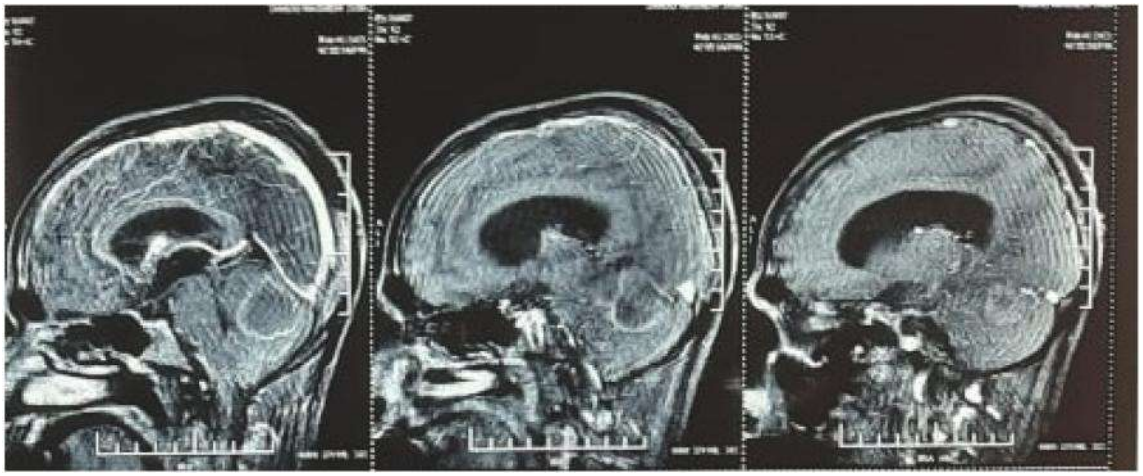


Fig. 8. are the magnetic resonance imaging of the brain showing a well-defined lesion in the posterior fossa, on the left side with contrast uptake and ring enhancement of the wall.

Therefore, cerebrospinal fluid studies cannot be reliably used to rule out the diagnosis of tuberculosis.[19–21]

Radiological examination includes computed tomography and magnetic resonance imaging, both of which do not have any pathognomic features of central nervous system tuberculosis. Tuberculomas are defined as low- or high-density, round or lobulated masses with irregular walls showing homogenous or ring-type contrast enhancement. Occurring as solitary or multiple nodules they are typically found in the frontal and parietal lobes.[22,23]

Molecular and biochemical tests are available which include nucleic acid amplification (NAA), PCR-based studies, antibody detection, antigen detection, or chemical assays such as adenosine deaminase (ADA) and tuberculostearic acid measurement. CBNAAT is cartridge-based nucleic acid amplification test, using either body fluids or tissue samples. Tissue samples are ground with saline and processed which takes approximately 2 h following which the presence of tuberculosis along with sensitivity or resistance to rifampicin can be detected, Rifampicin being the mainstay of the antitubercular regimen.[24] Xpert MTB/RIF is a

qualitative, nested real-time polymerase chain reaction in vitro diagnostic or detection for mycobacterium tuberculosis complex DNA from the prepared tissue sample. The Xpert MTB/RIFAssay also detects rifampicin resistance-associated mutations of the rpoB gene.[25,26] This is an easily available, cost-effective as well and very reliable test, the significance of which cannot be overstated. However, its value as a screening test is limited as the bacilli present in the cerebrospinal fluid is very low as well as the presence of amplification inhibitors in the cerebrospinal fluid.[27]

These things make the diagnosis of central nervous system tuberculosis challenging as there are no specific and non-invasive tests that can be reliably used as there are no pathognomic signs on either radiological or cerebrospinal fluid studies. The low yield in cerebrospinal fluid makes the molecular and biochemical tests difficult for screening central nervous system tuberculosis. Hence the importance of tissue biopsy.[28]

Tuberculosis is rightly called the great mimicker as we can see in the above three cases that the patients were young immunocompetent patients with no history of tuberculosis, exposure to tuberculosis, or evidence of disseminated tuberculosis. Two out of these three cases were of infratentorial tuberculomas, which are a very rare presentation in adults, more so in immunocompetent individuals. The usual site is supratentorial and clinically more meningitic features. Clinical, radiological, and blood investigations were not pinpointing at a diagnosis of central nervous system tuberculosis. However, an intraoperative suspicion of tuberculosis and performing a CBNAAT test for tuberculosis yielded a very benign and easily treatable diagnosis of central nervous tuberculosis which could have been not detected otherwise except for the histopathological diagnosis. Prompt treatment could be started with easily available drugs preventing further comorbidities or complications. Hence in an endemic country like ours, it is pertinent to rule out tuberculosis in even the most unsuspecting cases like the ones we have discussed. CSF studies and other blood investigations could be inconclusive as well as the radiological imaging. The role of CBNAAT cannot be stressed more in the diagnosis and prompt treatment of such a benign yet potentially dangerous disease.

A literature review was done of reported cases of posterior fossa tuberculosis in immunocompetent adults.[29–35] Interesting findings were noted. We found 9 cases in the literature, 6 patients out of the 9 were females. Headache followed by gait disturbance and cerebellar signs were the most common clinical symptoms and signs. Fever was seen in only one patient who also had concomitant pulmonary tuberculosis. In most of the patients, the blood and CSF investigations were normal except in three patients where ESR was elevated, and CSF showed lymphocytosis. Out of these three patients, one had concomitant pulmonary tuberculosis with elevated ESR. Hydrocephalus was seen in three patients. Most of the patients underwent excision with ATT ranging from 8 months duration to 24 months and had good outcomes on immediate as well as long-term neurological follow up. One patient was diagnosed with cerebellar tuberculosis based on nested PCR whereas others were diagnosed based on the biopsy findings.

Headache without fever or any infective symptoms was the most common presentation without any correlation with the presence of hydrocephalus, which could be an important factor to keep in mind while diagnosing cerebellar tuberculosis from other forms of CNS TB where meningitic signs are important giveaway clue. Excision remains the mainstay of treatment for treating as well as diagnostic reasons since CSF, blood investigations failed to give any diagnostic pointers. Ventriculoperitoneal shunt or other CSF diversion procedures were not needed before or after the excision as the excision sufficed for all the patients. Radiological evidence is supportive but not definitive to start the ATT regimen.

A study reported from China by Ning Guo et al[36] discussed posterior fossa tuberculosis in 11 patients. Microscopy for AFB and CSF cultures were negative for all the patients whereas N-PCR for MTB DNA was positive in repeated tests. Surgical intervention is not mentioned however all the patients had ATT and showed good responses to that.

4. Conclusion

Our three cases unfortunately highlight the late presentation of a very rare yet very treatable disease as well as an unusual presentation of central nervous system tuberculosis not to forget the importance of a CBNAAT test of the tissue sample, even in patients with low suspicion of tuberculosis. Hence the diagnosis of tuberculosis should be kept in mind even when dealing with a young immunocompetent patient with no history of contact with tuberculosis or history or symptoms of systemic tuberculosis even when the diagnosis of tumors of other lesions seems more favorable and CBNAAT of the intraoperative sample should be sent for routinely so that a simple diagnosis of tuberculosis should not be missed out.

According to the literature review, almost all the patients showed good outcomes after the treatment reiterating the necessity of an early diagnosis and prompt treatment to prevent any debilitating sequelae of a treatable disease.

Nested PCR for MTB DNA seems like a promising diagnostic tool and needs further studies to affirm its specificity and sensitivity, which should be pursued owing to ease as it requires a CSF sample which is minimally invasive as compared to an excision biopsy.

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Nil.

CRediT authorship contribution statement

Nandita Kujur: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Satheesh Chandra Sugatha Rao:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Bijukrishnan Rajagopalawarrier:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Abbreviations

CNS	central nervous system
MRI	Magnetic resonance imaging
CT	Computed Tomography
CSF	Cerebrospinal fluid
CBNAAT	Cartridge-based nucleic acid amplification testing
NAA	Nucleic Acid Amplification
MTB	Mycobacterium Tuberculosis
Pulm Tb	Pulmonary tuberculosis
Hcp	hydrocephalus
ATT	anti tubercular treatment
ESR	erythrocyte sedimentation rate
NPCR	nested polymerase chain reaction
NA	not available

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THIEME OPEN ACCESS

Retrospective Study on Complications of Abdominal Subcutaneous Bone Flap Preservation among Patients Undergoing Cranioplasty following Decompressive Craniectomy and Literature Review

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Abstract

Background Following decompressive craniectomy (DC), the excised bone flap can be stored either in vivo (subcutaneously in the abdominal wall or thigh) or extracorporeally (cryopreserved). While bone flap preservation techniques and postcranioplasty outcomes have been extensively studied, complications related to abdominal wall bone flap storage remain underreported. A retrospective study was conducted on 92 patients who underwent DC followed by cranioplasty with subcutaneous abdominal wall bone flap preservation.

Results The most common abdominal wall complications included psychological concerns (24%), cosmetic concerns (21.7%), pain at the incision site (19.5%), and abdominal wall heaviness (19.5%). Wound infections occurred in 10% of patients, necessitating bone flap removal in two cases. Other complications included difficulty in squatting (20%), breathing difficulty (2%), and wound hematoma (3%).

Discussion However, abdominal wall complications, including infection, pain, and cosmetic concerns, should be discussed preoperatively with patients and their families. Despite these challenges, abdominal preservation remains an alternative to cryopreservation in neurosurgical centers with limited infrastructure for bone banking.

Conclusion Abdominal subcutaneous bone flap preservation following DC is associated with a range of complications, though most are manageable with conservative measures. Autologous bone flap storage in the abdominal wall remains a viable option, particularly in high-volume and resource-constrained settings, due to its cost-effectiveness, biocompatibility, and reduced risk of bone resorption compared with cryopreservation. Given its efficacy and cost advantages, it remains a relevant choice in select settings.

Keywords
- decompressive craniectomy
- cranioplasty
- bone flap preservation
- abdominal wall complications
- in vivo bone storage

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Introduction

Decompressive craniectomy (DC) is a neurosurgical intervention made specifically to relieve intracranial pressure in patients who suffer from conditions such as severe traumatic brain injury (TBI), malignant middle cerebral artery infarction, and aneurysmal subarachnoid hemorrhage.[1,2] DC allows expansion, and the pressure–volume curve shifts to the right after bone removal.[1,3,4] Bleeding, new or expanded contusion, extracerebral herniation, fever, wound infection, subdural hygroma, infarction, and hydrocephalus are all common neurosurgical complications during and after a DC,[1–3] whereas trephine syndrome and bone resorption are relatively late complications.[1,5,6] After DC, the excised bone flap can be banked for subsequent reimplantation in the form of cranioplasty; this procedure is usually performed for the protection of the brain, hydrodynamic equilibrium, and cosmesis.[4,7,8] Though post-DC complications are under intense research, associated abdominal wall complications are relatively less discussed. In this article, we intend to discuss the abdominal wall complications associated with DC in this study.

Following bone flap removal, it can be stored in vivo in the subcutaneous plane of the anterior abdominal wall or anterior thigh. Even though it needs an additional procedure, the self-proclaimed justification for in vivo bone flap preservation in the abdominal subcutaneous plane includes that the modality of autologous bone flap storage is cost-effective, with no requirements for additional machinery or personnel, which would be challenging in a high-volume center.[4,9] There are few studies suggesting postcranioplasty bone resorption in patients who had their bone cryopreserved.[5,9,10]

Even though cryopreservation is being practiced more often lately, abdominal subcutaneous preservation is still a cost-effective and accessible method, but not without its complications, especially in high-volume or resource-poor settings. This study evaluates the complications of the abdominal wall after the subcutaneous preservation of the bone flaps compared with those that present concerning cryopreservation and other in vivo methods.

Aim of the Study

This study aims to investigate the abdominal wall complications following DC with subcutaneous bone flap preservation and to review the associated literature.

Review of Literature

For centuries, the notion of relieving intracranial pressure by surgical means was known, but advances in neurosurgery, critical care, and neuroimaging paved the way for the modern evolution of DC.[11,12] Though DC can be lifesaving, the long-term outcomes have been the subject of much debate. Most surviving patients succumb to severe disabilities, raising ethical questions regarding the quality of survival.[13] Current research emphasizes better patient selection criteria and improvement in functional outcomes at the time of discharge.[14] Future developments in DC include the introduction of minimally invasive techniques, better biomaterials for skull reconstruction, and improved neuroprotective strategies that eliminate or reduce secondary brain injury after the procedure.

Preservation of the bone flap is important for maintaining the protective and esthetic functions of the skull once the patient's neurological condition becomes stable and intracranial pressure normalizes. Over the years, different techniques for bone flap preservation have been developed and studied, each with its advantages, disadvantages, and potential complications. Autologous bone flap preservation is still the major option for cranioplasty due to its perceived biocompatibility and low cost.[15] Then, in the middle of the 20th century, more controlled procedures emerged for the storage of the bone, including autologous storage and cryopreservation—whose techniques have been perfected over time, with continuing research on the validity of effectiveness in preventing infections, resorptions, and other complications.[4,9]

Today, several approaches to bone flap preservation are employed, each with unique benefits and limitations. These techniques are broadly categorized into autologous preservation methods and extracorporeal preservation methods.

Preservation of Autologous Bone Flap

Subcutaneous Pocket Preservation (Anterior Thigh or Abdominal)

In subcutaneous pocket preservation, the resected bone flap is placed in a subcutaneous pocket, mainly in the abdominal wall. It has several benefits, including a reduced chance of infection as the bone is kept in the patient's own body, and the external contamination risk is reduced. Another benefit is biocompatibility; in most studies, the bone stock retained its biological and structural characteristics after this storage, significantly reducing the possibility of bone resorption upon reimplantation as there is minimal destruction of viable osteoblasts. A study by Movassaghi et al showed that the histology of retrieved bone at the time of cranioplasty showed portions of necrotic bone interspersed with areas of new bone formation. Several studies demonstrate good outcomes with abdominal preservation.[16] A very illustrative study by Schuss et al found less infection and bone flap resorption with this method than with extracorporeal storage methods.[17] However, the abdominal preservation has some potential disadvantages, such as requiring additional surgery to create the subcutaneous pocket, which increases the chance of infection or other complications at the site. Some patients may experience pain or discomfort at the storage site during recovery.

Subgaleal Preservation

In this largely obsolete technique, the bone flap is usually positioned under the galea aponeurotica adjacent to the craniectomy incision over the opposite side of the skull. Subgaleal storage is often argued as less invasive than

abdominal storage.[18] Although no second incision is needed, it is risky compared with abdominal storage because the bone flap is closer to the original surgical site and thus poses more chances of infection and other wound complications. If the patient ends up having wound complications, the clinical outcome will be worse, and it made this technique largely obsolete.

Extracorporeal Bone Flap Preservation

Cryopreservation

Storage of bone flaps at −80°C in a deep-freeze environment is called cryopreservation and maintains the structural integrity of the bone flap till reimplantation.[5,15] The procedure is widely practiced in many neurosurgical centers due to its availability and efficiency. Key advantages include that the bone flaps can be stored for a long time. This is of great value for patients who need a long recovery or rehabilitation period before the cranioplasty since subcutaneously placed bone can have progressive resorption.[19] And the bone flaps preserved by cryopreservation are available and useful for reimplantation without further additional surgical sites, as in the case of autologous methods. It eliminates the need for additional surgery at the time of DC and also cranioplasty. Though rare, when the abdominal wound is opened first to check the condition of the bone flap, cranioplasty may need to be postponed in case the bone flap happens to be unhealthy and results in deferring the cranioplasty. Storage of an extracorporeal flap can save such unwarranted events.

Despite these benefits, cryopreservation also carries the risk of a higher chance of bone flap resorption after reimplantation. There is evidence that postcranioplasty bone resorption is higher compared with autologous storage methods.[5,19] This results in bone fragility and poor cosmetic results after cranioplasty. In addition, improper handling during storage and reimplantation can lead to contamination and infection. In high-volume, low-resource settings, facilities and infrastructure for cryopreservation and bone banks may not be available, and logistical errors can happen.

Finally, alternatives to autologous bone flaps include polymethyl methacrylate, titanium mesh, custom-made titanium molds, or porous polyethylene implants. They have many advantages, such as minimizing the risk of infection and resorption, and they can be custom-shaped with methods such as three-dimensional printing and other advanced techniques for optimal results in cosmetics and protection. They do not, however, offer biological integration as has been known with autologous bone flaps.

Complications and Outcomes

The most common complications associated with bone flap preservation techniques include infection, resorption, and poor cosmetic results. However, they can occur after any preservation technique, each carrying specific risk factors. Each has varied incidence in various studies. A study by Corliss et al showed no significant difference in the infection rate between in vivo-preserved and cryopreserved bone flaps.[4] Bone flap resorption is a significant problem with cryopreserved bone flaps, especially when storage duration exceeds several months. This is due to the absence of nutritive supply to the bone graft such as the in vivo preservation and progressive loss of osteoblastic activity. Young age, longer duration, and fractures are other factors that can increase bone flap resorption.[4,5,19] Cosmetic and functional outcomes have been relatively better for autologous storage methods, especially abdominal preservation because they preserve much of the biological characteristics of the bone tissue postcranioplasty.

Objectives

While complications associated with DC, such as hydrocephalus, wound infections, and bone flap resorption, have been extensively studied, there remains a relative paucity of literature addressing abdominal wall complications arising from in vivo preservation of bone flaps in the subcutaneous plane. In our study, we aim to evaluate and analyze abdominal wall complications following the preservation of bone flaps in the abdominal subcutaneous tissue after DC. This study seeks to shed light on this underexplored area, contributing to a better understanding of the associated risks and outcomes. Our main focus for this research was to assess complications following DC and bone flap preservation in the abdominal wall.

Materials and Methods

This study was conducted in the Department of Neurosurgery, Government Medical College. We studied 92 patients who underwent DC, followed by cranioplasty with the preservation of a bone flap in the abdomen after receiving clearance from the Institutional Review Board and Institutional Ethics Committee. We conducted a record-based retrospective study for 2 years in the Department of Neurosurgery, Government Medical College, Thrissur, from 2022 through 2024.

Data Collection Method and Tools

Data were collected from department records and operative registers in the Department of Neurosurgery, Government Medical College, and with phone interviews if details were insufficient in records. We collected variables such as age, sex, indication for DC, postoperative Glasgow coma scale, side of the surgery, difficulty while squatting, breathing difficulty, heaviness, local pain, psychological problems, wound infection in the abdomen, hematoma, and cosmetic concerns in our study. This is a record-based study; hence, permission was taken from the head of the department and hospital authorities to use details available in the medical records. If the details were not fully available in the available clinical records, details were sought through a phone call, and in such cases, verbal consent was obtained.

Data Analysis

The collected data were inputted on the proforma and later consolidated into the master chart. The results were analyzed using SPSS 22.0. The charted quantitative data and qualitative data were analyzed by descriptive statistics.

Results

During the study period, 92 patients underwent cranioplasty in our department. The mean age of the study population was 44.5 years, with 76% of them being males. TBI was the most common primary pathology for DC (85%), followed by infarct and intraparenchymal hematoma. The mean interval of the cranioplasty period was 3 months (►**Table 1**).

Complications Associated with Abdominal Flap

The data were selected using record reviews and phone interviews with patients awaiting cranioplasty surgery following DC. Eighteen patients had wound site pain in the immediate postoperative period; 9 patients had wound infections in the abdominal flap site out of which 2 bone flaps were removed and were planned for cranioplasty with exogenous implant at a later date; 19 patients had abdominal wall heaviness at the wound site; 20 patients had cosmetic concerns regarding flap site incision; and 19 patients had some psychological issues. Other complications are depicted in ►**Table 2**.

Table 1 Patient characteristics and primary pathology

Demographic details	
Mean age (range)	44.5 (18–72)
Sex: male, n (%)	70 (76)
Primary pathology, *n* (%)	
Trauma	78 (85)
Infarct	8 (9)
Intraparenchymal hematoma	4 (4)
Timing of cranioplasty, *n* (%)	
Mean	5.5 mo
< 6 wk	1 (1)
6 wk–3 mo	18 (20)
3–6 mo	53 (58)
> 6 mo	20 (21)

Table 2 Complications associated with abdominal flap, *n* (%)

Pain	18 (19.5%)
Difficulty in squatting	19 (20%)
Breathing difficulty	2 (2%)
Abdominal wall heaviness	18 (19.5%)
Wound infection	9 (10%)
Psychological concerns	22 (24%)
Cosmetic concerns	20 (21.7%)
Wound hematoma	3 (3%)

Discussion

The removed bone flap after DC is stored in the subcutaneous plane in the anterior abdomen or the thigh, or extracorporeally in the bone biobank. Even though there is a tendency to shift to cryopreservation in recent literature, autologous preservation still has advantages such as biocompatibility, low cost, a perfect match in terms of fit and curvature, and immunological tolerance.[20–24] Even though many studies are comparing different storage techniques on the outcome of cranioplasty in terms of infections, bone flap resorption, etc., there is a relative paucity of literature studying abdominal wall complications following bone flap preservation. In our study, we tried to address this lacuna. In our study group, there were no significant complications except for wound infection in the abdominal site in nine patients. Of which seven patients were treated conservatively. In two patients, the infected bone flap had to be removed, and the wound was closed with a drain. The other complications such as pain are treated successfully with conservative measures. Psychological and cosmetic concerns were managed with counseling and reassurance.

Conclusion

As there were no significant complications following abdominal flap preservation and comparable safety with cryopreservation, it remains a valid choice in high-volume and resource-constrained settings due to its low cost and comparable efficacy. Additional logistical errors and the cost of biobanks for bone preservation can also be avoided.

Even so, the need for an additional procedure and surgical site should be discussed with patients and relatives, and options for biobanking should be offered if available. We need further studies to evaluate the complications and outcomes of in vivo preservation in a larger population. The bone flap resorption and new bone formation are to be studied in subcutaneously preserved bone flaps.

Ethical Approval

The study was approved by the Institutional Review Board and Institutional Ethics Committee (IEC No.: IEC/GMCTSR/2024/087).

Conflict of Interest

None declared.

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OBSTETRICS AND GYNAECOLOGY

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Original Article

Obstetrics and Gynaecology Section

Onset and Progression of Urogenital Symptoms after Surgical Menopause: A Prospective Cohort Study

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ABSTRACT

Introduction: Surgical menopause is the cessation of menstruation resulting from the surgical removal of the uterus and bilateral ovaries, which leads to a sudden decrease in oestrogen levels and its subsequent effects. Urogenital symptoms are chronic and progressive, but only a few women seek medical care for these symptoms, which are often overlooked during routine follow-ups.

Aim: To investigate the onset and progression of various urogenital symptoms after surgical menopause.

Materials and Methods: A prospective cohort study was conducted in the Department of Obstetrics and Gynaecology at Government Medical College, Thrissur, Kerala, India from January 2020 to December 2020. A total of 110 women who underwent Total Abdominal Hysterectomy (TAH) and Bilateral Salpingo-Oophorectomy (BSO) for benign conditions were included in the study. The women were asked about the onset of urogenital symptoms at six weeks and 12 weeks after surgery. They were required to indicate whether they experienced four urogenital symptoms (vaginal dryness, frequent urination, urinary incontinence, and reduced sexual desire) using a menopause rating scale. The severity of symptoms was categorised as none (0), mild (1), moderate (2), severe (3), or very severe (4). The progression of symptom severity from six weeks and 12 weeks of follow-up was analysed using Chi-square tests.

Results: Urogenital symptoms that developed after surgery included vaginal dryness, dyspareunia, bladder symptoms, and reduced sexual desire. At least one of these symptoms developed in 95 (86.4%) women by 12 weeks. Vaginal dryness was reported by 40 subjects (36.4%) at six weeks, with 36 (32.7%) reporting mild symptoms, 4 (3.6%) reporting moderate symptoms, and none reporting severe or very severe symptoms. At 12 weeks, vaginal dryness was reported by 61 subjects (55.5%), with 21 (19.1%) reporting mild symptoms, 18 (16.4%) reporting moderate symptoms, 20 (18.2%) reporting severe symptoms, and 2 (1.8%) reporting very severe symptoms (p-value <0.05). Other symptoms showed a similar pattern of progression.

Conclusion: Urogenital symptoms can start as early as six weeks after surgery and can worsen in severity if left untreated.

Keywords: Dyspareunia, Menopause rating scale, Urinary incontinence, Vaginal dryness

INTRODUCTION

Menopause is defined as the point in time that follows one year after the complete cessation of menstruation [1]. This can occur naturally or be induced by surgery, chemotherapy, or radiation. Although many conservative procedures are available for managing benign conditions of the uterus, hysterectomy remains one of the most commonly performed surgical procedures [2]. Bilateral oophorectomy is often performed concurrently with hysterectomy for benign conditions, even when the ovaries are normal. This procedure can protect women from the risk of developing ovarian cancer later in life. Another reason for performing bilateral oophorectomy is to avoid potential surgeries for benign ovarian pathologies in the future [3].

In natural menopause, there is a period of menopausal transition. Additionally, the postmenopausal ovary remains intact and continues to produce a limited amount of hormones [4,5]. However, surgical menopause results in the complete absence of any steroid production and can cause menopausal symptoms to appear at an earlier age and with greater severity [4,5]. This abrupt decline in oestrogen levels can lead to many short-term and long-term complications. Women experiencing surgical menopause often present with vasomotor and urogenital symptoms that significantly impact their quality of life. The surgical removal of ovaries also eliminates the protective effect of estradiol on bone metabolism and the cardiovascular system. Long-term observational studies have demonstrated that surgical menopause is associated with accelerated cardiovascular changes and increased cardiovascular mortality [6-8].

Urogenital symptoms are common problems faced by women after undergoing surgical menopause. These symptoms are chronic and progressive, worsening if not properly addressed. They encompass a range of physical changes and symptoms associated with oestrogen deficiency, such as vulvovaginal dryness, burning or irritation, dyspareunia, and urinary symptoms including urgency, dysuria, and recurrent urinary tract infections [7,8]. Women who undergo surgical menopause often experience more severe urogenital symptoms compared to those experiencing natural menopause, due to the abrupt and persistent decline in hormone levels and an additional 50% decrease in circulating androgen levels [9].

Despite the abundance of literature on urogenital symptoms and their prevention [9-11], it has been found that only 25% of women seek medical care for these symptoms [12]. This underdiagnosis is primarily due to sexual embarrassment and the sensitive nature of discussing these topics [12]. However, it can have negative effects on partner relationships and self-esteem. This study sheds light on these undisclosed problems, which may later impact the psychosocial well-being of women. The study also emphasises the importance of specifically inquiring about these symptoms using well-phrased questions during early follow-up visits. The majority of women undergoing oophorectomy do not receive necessary information, support, or treatment for sexual consequences [13].

There is the need to educate women undergoing surgical menopause about these symptoms. This study aimed to explore various urogenital

symptoms after surgical menopause, their onset, and the progression of severity over a period of 6 to 12 weeks following surgery.

MATERIALS AND METHODS

A prospective cohort study was conducted among 110 women who underwent TAH and BSO for benign conditions at the Department of Obstetrics and Gynaecology, Government Medical College, Thrissur, Kerala, India during a one-year study period (January 2020 to December 2020). The study protocol was submitted to the Institutional Research Committee and Ethical Committee of Government Medical College, Thrissur, and approval was obtained on 20-12-2019 (Order no.B6-155/2019/MCTCR(16)).

Inclusion criteria: Patients who underwent TAH+BSO for benign conditions (only patients who had not reached natural menopause were included). Patients who provided informed written consent were included in the study.

Exclusion criteria: Patients who were unable to comprehend and respond to the questionnaire, those who received any hormone replacement treatment after surgery, those who had already reached menopause or had urogenital symptoms prior to surgery were excluded from the study.

Sample size: According to Özdemir S et al., hot flushes were observed in 76.5% of women after surgical menopause. Changes in sexual desire were reported by 64.8%, vaginal dryness by 53.1%, and urinary complaints by 48.9% [14]. Vaginal dryness was selected as the major problem to calculate the prevalence. The sample size was calculated using the formula- $N=4pq/d^2$

q=100-p=100-53.1=46.9.

d=allowable error, 20% of p=10.62.

n=4*53.1*46.9/10.62*10.62=88.3.

Considering a 20% potential loss to follow-up.

88.3*20/100=17.66.

Sample size=88.3+17.66=105.96.

Therefore the sample size for this study was rounded to 110.

Data collection and analysis: All patients enrolled in this study received standard care. Awareness regarding the study and its relevance in the present scenario was provided to all participants. Strict confidentiality was maintained, and the investigator alone handled all data containing personal identification details of the patients.

The patients were followed-up and interviewed using a questionnaire at six weeks and 12 weeks after surgery during their routine follow-up visits. They were asked to respond "yes" or "no" to four urogenital symptoms: vaginal dryness, frequent urination, urinary incontinence, and reduced sexual desire at six weeks and 12 weeks. The severity of urogenital symptoms was assessed using the Menopause Rating Scale [15], which consists of 11 questions related to menopausal symptoms, including urogenital symptoms. The respondents marked their personal perception of severity by checking the five possible boxes for each item and recorded their responses in the corresponding columns. The severity was assessed using the Menopause Rating Scale, focusing only on urogenital symptoms.

STATISTICAL ANALYSIS

Chi-square tests were used to analyse the onset and progression of symptoms. Data was entered into Microsoft Excel sheets and analysed using Statistical Package for Social Sciences (SPSS) Statistics Version 20.0.

RESULTS

A total of 110 patients who underwent hysterectomy and BSO for benign conditions were included in the study. Among them, 95 developed at least one urogenital symptom after 12 weeks (86.4%). The mean age of the study population was 45.20±3.881 years. The majority of the study subjects (90 out of 110) underwent hysterectomy for fibroids (81.8%) [Table/Fig-1].

Variable	n (%)
Age group (years)	
30-39	10 (9.1)
40-49	87 (79.1)
>50	13 (11.8)
BMI (kg/m²)	
18.5-22.9	25 (22.7)
23-24.9	56 (50.9)
25-29.9	28 (25.5)
>30	1 (0.9)
Presenting complaints	
Heavy menstrual bleeding	80 (72.7)
Dysmenorrhoea	19 (17.2)
Abdominal distention	15 (13.6)
Abdominal pain	15 (13.6)
Irregular cycle	6 (5.4)
Ovaries in USG	
Normal	67 (60.9)
Abnormal	43 (39.1)
Indication for hysterectomy	
Fibroid	90 (81.8)
Adenomyosis	5 (4.6)
Benign ovarian mass	11 (10)
Endometriosis	4 (3.6)
Indication for oophorectomy	
Elective	60 (54.5)
Benign cyst	46 (41.9)
Adhesions	4 (3.6)
Urological injury during surgery	
Yes	0
No	110 (100)

[Table/Fig-1]: Demographic and perioperative characteristics of the study subjects.

Out of the 95 individuals who developed at least one urogenital symptom after 12 weeks of surgery, 40 (36.4%) reported vaginal dryness at six weeks. Among them, 36 (32.7%) classified it as mild, and 4 (3.6%) had moderate symptoms. None of the patients had severe or very severe symptoms at six weeks. At 12 weeks, 61 subjects (55.5%) experienced vaginal dryness, with 21 (19.1%) reporting it as mild, 18 (16.4%) as moderate, 20 (18.2%) as severe, and 2 (1.8%) as very severe [Table/Fig-2,3].

Symptoms	None	Mild	Moderate	Severe	Very severe
Vaginal dryness	70 (63.6)	36 (32.7)	4 (3.6)	0	0
Frequent urination	91 (82.7)	19 (17.3)	0	0	0
Urinary incontinence	109 (99.1)	1 (0.9)	0	0	0
Reduced sexual desire	73 (66.4)	35 (31.8)	2 (1.8)	0	0

[Table/Fig-2]: Urogenital symptoms after six weeks.

Symptoms	None	Mild	Moderate	Severe	Very severe
Vaginal dryness	49 (44.5)	21 (19.1)	18 (16.4)	20 (18.2)	2 (1.8)
Frequent urination	72 (65.5)	18 (16.4)	19 (17.3)	1 (0.9)	0
Urinary incontinence	108 (98.2)	2 (1.8)	0	0	0
Reduced sexual desire	43 (39.1)	25 (22.7)	18 (16.4)	22 (20)	2 (1.8)

[Table/Fig-3]: Urogenital symptoms after 12 weeks.

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Change in sexual desire at six weeks was reported by 37 women (33.6%), with the majority (35, 31.8%) having only mild symptoms. At 12 weeks, 67 women (60.9%) experienced a change in sexual desire, with 25 (22.7%) having mild symptoms, 18 (16.4%) having moderate symptoms, 22 (20%) having severe symptoms, and 2 (1.8%) having very severe symptoms [Table/Fig-2,3].

There was a significant progression of symptoms of vaginal dryness and reduced sexual desire from six weeks to 12 weeks [Table/Fig-4].

Symptoms	No. of women with symptom at 6 weeks (%)	No. of women with symptom at 12 weeks (%)	p-value
Vaginal dryness	40 (36.4)	61 (55.5)	0.001
Frequent urination	19 (17.3)	38 (34.5)	0.42
Urinary incontinence	1 (0.9)	2 (1.8)	0.11
Reduced sexual desire	37 (33.6)	67 (60.9)	0.001

[Table/Fig-4]: The comparison of onset and progression of symptoms at 6 weeks and 12 weeks.
Chi-square test was used

DISCUSSION

Vaginal physiology is predominantly regulated by oestrogen. During menopause, when oestrogen levels decrease, significant changes occur in the vulvovaginal tissues. Out of 110 cases, 36.4% of the study subjects had vaginal dryness at six weeks, and 55.5% experienced vaginal dryness at 12 weeks. It is noteworthy that the majority had mild symptoms at six weeks but later progressed to moderate, severe, and very severe symptoms at 12 weeks. This indicates a significant change (p-value <0.05). Studies have shown that urogenital symptoms after menopause may progress and worsen if left untreated [16].

The incidence of vaginal dryness has ranged from 53.1% to 80% in various studies [14,17,18]. In a study by Kokcu A et al., it was found that 66% of patients with surgical menopause reported vaginal dryness [17]. Özdemir S et al., in their study, found that 53.1% of women experience vaginal dryness after surgical menopause [14].

Bharadwaj et al., in their study on urogenital problems among menopausal women (both natural and surgical menopause) in Bhopal, found that 80% of them had vaginal dryness [18]. The differences in various studies may be due to socio-demographic changes and women's knowledge about symptoms.

Studies have shown that urinary symptoms such as dysuria, urinary urgency, urethral eversion or prolapse, frequency, and recurrent UTIs can be observed after surgical menopause, which can be attributed to the thinning of the urethral and bladder mucosa [10,19-21]. In this study, 17.3% had urinary symptoms at six weeks, and the severity of these symptoms was found to progress after 12 weeks. Özdemir et al., in their study, found that 48.9% of women experienced urinary complaints after surgical menopause [14].

The impact of surgical menopause on women's psychological well-being and sexuality varies and depends on factors such as their preoperative mental health and sexual function, indication of surgery, and type of surgery performed [22]. It has been found that there is an approximately 50% decline in testosterone levels, which is an important hormone for sexual desire, after ovary removal [23,24]. Kokcu A et al., in their study, found that 85% of patients reported a change in sexual desire [17]. In a study by Castelo-Branco C et al., nearly three out of four women who had undergone surgical menopause were at risk of hypoactive sexual desire syndrome [25]. In this study, 33.6% experienced a change in sexual desire at six weeks, with the majority having only mild symptoms that progressed at 12 weeks (p-value <0.05). This difference may be due to the fact that it was only three months after the surgery, and many may have considered it too early to resume sexual relations. It could also be due to a lack of awareness about sexual symptoms and the social and behavioural taboos associated with them. It has been found that approximately 50% of women experience urogenital symptoms after natural menopause. A study by Topatan S and Yıldız H has shown that the proportion, severity, and duration of urogenital symptoms were much higher in the surgical menopause group than in the natural menopause group [26].

There is a need to initiate hormone therapy as early as six weeks after surgery. Additionally, medical professionals should not overlook inquiring about urogenital symptoms during follow-up visits, as these symptoms can cause continued suffering and poor quality of life for women who may be reluctant to discuss them.

Limitation(s)

The findings of the study cannot be generalised as the follow-up duration was short.

CONCLUSION(S)

The various urogenital symptoms after surgical menopause include vaginal dryness, difficulty in intercourse, increased need to urinate, difficulty in initiating urination, urinary incontinence, and changes in sexual desire. These symptoms can start as early as six weeks after surgery and progress in severity if left untreated. This emphasises the need for our healthcare system to conduct follow-ups with patients and inquire about urogenital symptoms even in the postoperative period, as only a minority seek medical advice on their own.

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Obstetrics and Gynaecology Section

Perinatal Outcome of Twin Pregnancies in Relation to Chorionicity at a Tertiary Care Centre in Central Kerala, India: A Prospective Cohort Study

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BY-NC-ND

ABSTRACT

Introduction: In recent years, there has been a significant increase in the incidence of multiple births due to advanced maternal age at conception and the growing use of infertility treatment. Multiple pregnancies are associated with both maternal and perinatal complications. Maternal complications include anaemia, gestational hypertension, gestational diabetes, preterm labour, operative delivery and postpartum haemorrhage. Preterm birth, growth discordance and complications specific to monochorionic twins predispose these babies to adverse perinatal outcomes.

Aim: To assess the perinatal outcomes of twin pregnancies and compare the outcomes of monochorionic and dichorionic pregnancies.

Materials and Methods: The present prospective cohort study was conducted in the Department of Obstetrics and Gynaecology, Government Medical College (Tertiary care centre), Thrissur, Kerala, India, from September 2019 to August 2020. All twins who delivered at a gestational age of ≥28 weeks during the study period were recruited, totaling 76 twin pregnancies. A structured proforma was used to collect demographic and clinical details, including mode of conception, chorionicity, maternal complications, intrapartum events and neonatal outcomes. Data were analysed using Epi Info software.

Results: The mean maternal age of the study participants was 28.39±6.29 years. The incidence of twin pregnancies delivering at ≥28 weeks at Government Medical College, Thrissur, during the study period was 2.8% (76 twins out of 2709 deliveries). Infertility treatment (ovulation induction alone or Assisted Reproductive Techniques (ART) was associated with dichorionic twinning in 19.7% (15 out of 76 twin pregnancies), with a p-value of 0.008. Maternal complications were similar in both dichorionic and monochorionic twins. Preterm Premature Rupture of Membranes (PPROM) occurred in 23 (28.75%) twin pregnancies, 19 (23.75%) had Gestational Diabetes Mellitus while 13 (16.25%) participants had anaemia. Foetal growth restriction, congenital anomalies, and discordant growth were more prevalent in monochorionic twin pregnancies compared to dichorionic twin pregnancies. Although the proportion of babies requiring Neonatal Intensive Care Unit (NICU) admission was higher in monochorionic twins (64% vs 53.9%), the proportion of neonatal deaths was nearly equal between monochorionic and dichorionic twins (10% vs 9.8%).

Conclusion: In the present study, there was no statistical difference in maternal complications between monochorionic and dichorionic twins. However, monochorionic pregnancies had a poorer perinatal outcome compared to dichorionic pregnancies.

Keywords: Dichorionic, Monochorionic, Multiple pregnancies

INTRODUCTION

Multiple pregnancies are associated with a higher risk of developing adverse maternal and perinatal outcomes. Close and more frequent surveillance is required to ensure favorable results [1]. Factors that contribute to multiple pregnancies include racial factors, heredity, rising maternal and paternal age and infertility treatment. Among these, rising maternal age and infertility treatment are found to be the major contributors [1].

According to the secondary analysis of the World Health Organisation Global Survey (WHOGS) conducted on maternal and perinatal health by Vogel JP et al., wherein twin pregnancies in 23 low and middle-income countries were analysed, the prevalence of maternal death and severe adverse maternal outcomes was significantly higher in twin pregnancies compared to singleton pregnancies [2]. Maternal death was 0.3% in twins compared to 0.1% in singletons, and severe adverse maternal outcomes were 9.6% in twins compared to 3.5% in singletons [2]. According to the secondary analysis of the WHO multicountry survey on maternal and newborn health, conducted by Santana DS et al., there was a threefold increased risk of maternal near miss (1.5% vs 0.5%) and severe maternal outcomes (1.9% vs 0.6%), and a fourfold increased risk of maternal death (0.4% vs 0.1%) in twins compared to singletons [3].

Our understanding of the natural history of multiple pregnancies has greatly improved over the years as there has been a substantial increase in the number of multiple pregnancies. This has helped to improve the management of multiple pregnancies [4]. Monochorionic pregnancies are found to have poorer perinatal outcomes due to the complications specific to these pregnancies, like twin-to-twin transfusion syndrome and selective foetal growth restriction [5]. Therefore, early determination of chorionicity by ultrasound has become the cornerstone of antenatal care of multiple pregnancies [4]. Practices like selective foetal reduction for higher-order multiple pregnancies and twins discordant for structural or chromosomal anomalies have all evolved over time. The American College of Obstetricians and Gynaecologists (ACOG) now recommends counselling women with higher-order pregnancies about foetal reduction to reduce the complications associated with higher-order pregnancies [6].

Literature on the comparison of perinatal outcomes of dichorionic and monochorionic pregnancies is sparse [7]. The present study was aimed to compare the perinatal outcomes of monochorionic and dichorionic twins. This may help us make appropriate and timely interventions in the management of twin pregnancies.

MATERIALS AND METHODS

The present prospective cohort study was conducted in the Department of Obstetrics and Gynaecology, Government Medical College (Tertiary care centre), Thrissur, Kerala, India, from 1st September 2019 to 31st August 2020. Institutional Ethical Committee approval was obtained under Order No.B6-155/2019/MCTCR(07). Written informed consent was obtained from all the participants. All participants in the study were above 18 years, and consent was obtained from them.

Inclusion criteria: All consecutive mothers with twin pregnancies of ≥28 weeks of gestational age, who were admitted and delivered in the hospital during the study period, were included in the study.

Exclusion criteria: Patients with chronic illnesses such as chronic hypertension, overt diabetes, heart disease, renal disease, or systemic lupus erythematosus were excluded from the study.

Sample size calculation: The proportion of perinatal morbidity in twin pregnancies was 21.8% [8].

q is 1-p

Calculation for single proportion-

Absolute precision (%)=5%

Desired confidence level (%)=95%

$$N=\frac{(Z\alpha/2)^2\times pq}{d^2}$$

$$n=\frac{(1.96)^2\times 21\times 79}{5^2}=254$$

Sample size was calculated using Master sample size calculation software produced by the Department of Biostatistics, Christian Medical College, Vellore, Tamil Nadu, India. The sample size calculated for the present study was 254, but this could not be met as there were only 76 women with twin pregnancies of ≥28 weeks of gestational age during the study period, all of whom consented to be part of the study.

Study Procedure

Chorionicity was determined by ultrasound examination in the first trimester between 10 weeks and 14 weeks of gestational age. The chorionicity was confirmed after delivery by placental examination. Gestational age was calculated using the last menstrual period in spontaneous conceptions, as well as, in ovulation induction pregnancies. The date of embryo transfer was used for In-Vitro Fertilisation (IVF) pregnancies. Preterm was defined as gestational age <37 weeks. Appearance, Pulse, Grimace, Activity and Respiration (APGAR) score <7 at 5 minutes is one of the criteria for neonatal near miss and therefore, was included in analysing neonatal outcomes [9]. A structured proforma was used to collect demographic and clinical details of the participants, including mode of conception, chorionicity, maternal complications, intrapartum events, neonatal outcomes and causes of adverse outcomes wherever they could be identified.

Some of the participants had two or more maternal complications. For example, a patient with gestational diabetes also had gestational hypertension. So, the percentages were calculated out of the total number of complications. There were 54 maternal complications in the dichorionic twins and 26 in monochorionic twins. Pregnancies were considered to have foetal growth restriction if the estimated foetal weight was below the 10th centile for the period of gestation. Growth discordance was defined as a birth weight disparity of more than 20% (ACOG) [10]. Foetal growth restriction, growth discordance, and intrauterine foetal demise were considered pregnancy outcomes and the proportions were calculated out of the number of pregnancies, i.e., 76 total twin pregnancies (51 dichorionic and 25 monochorionic).

Birth weight of the babies, NICU admissions, neonatal deaths and live babies at discharge were considered neonatal outcomes. These were calculated out of the total number of babies, i.e., 152 total babies (102 dichorionic babies and 50 monochorionic babies).

STATISTICAL ANALYSIS

The data was coded and entered into Microsoft Excel software and then analysed separately for dichorionic and monochorionic pregnancies using Epi Info software. Quantitative data was analysed using Fisher's-exact test, while qualitative data was analysed using proportions and the Chi-square test. A p-value of ≤0.05 was considered statistically significant.

RESULTS

During the study period, there were a total of 2709 deliveries. 76 twin deliveries met the inclusion and exclusion criteria, making the incidence of twin deliveries 2.8%. Among the 76 twins, 51 (67.1%) were dichorionic diamniotic, 21 (28%) were monochorionic diamniotic, and 4 (5%) were monochorionic monoamniotic. The mean age of the participants was 28.39±6.29 years. Maternal age was higher in women with dichorionic twins (29.14±6.74 years) compared to those with monochorionic twins (26.88±5.06 years) [Table/Fig-1]. A positive family history of multiple pregnancies was observed in 11 out of 76 (14.5%) participants, which was not statistically significant (p-value=1.000). Among those with a family history of twins, 63.6% (7 out of 11) were dichorionic [Table/Fig-1]. Out of 51 dichorionic twins, 11 (21.6%) were conceived through IVF, showing a significant association between ART and dichorionic twinning (p-value=0.008). All monochorionic twin pregnancies were spontaneous conceptions [Table/Fig-1]. The most frequent maternal complication in the study was PPROM, affecting 15 (27.8%) dichorionic twins and 8 (30.7%) of monochorionic twins. Some twin pregnancies had multiple

Variables	DCDA		MCDA+MCMA		p-value
	Number (n)	Percentage# (%)	Number (n)	Percentage$ (%)	
Age (years)					
≤20	3	5.9	2	8	0.488, Fisher's-exact test
21-24	10	19.6	7	28	
25-29	22	43.1	11	44	
30-34	4	7.8	3	12	
≥35	12	23.5	2	8	
Gravidity					
Primigravida	24	47.05	11	44	0.474, Fisher's-exact test
Second gravida	18	35.3	11	44	
Third gravida	6	11.7	1	4	
Fourth gravida	1	1.9	2	8	
Fifth gravida and more	2	3.9	0	0	

Booking status					
Booked in	24	43.1	12	48	0.938, Chi-square test
Referred	27	52.9	13	52	
Family history					
Yes	7	13.7	4	16	1.000, Fisher's-exact test
No	44	86.323	21	84	
Mode of conception					
Spontaneous	36	70.5	25	100	**0.008**, Fisher's-exact test
Ovulation induction	4	7.8	0	0	
IVF	11	21.6	0	0	

[Table/Fig-1]: Maternal characteristics according to chorionicity.
DCDA: Dichorionic diamniotic; MCDA: Monochorionic diamniotic; MCMA: Monochorionic monoamniotic; #calculated out of number of DCDA twin pregnancies; $calculated out of number of MCDA+MCMA twin pregnancies; The p-value in bold font indicates statistically significant values

co-morbid conditions. Gestational diabetes was present in 13 (24%) Dichorionic Diamniotic (DCDA) twins and 6 (23.1%) of monochorionic twins [Table/Fig-2]. In one case, a second gravida with DCDA twin pregnancy developed peripartum cardiomyopathy at 34 weeks, necessitating immediate termination of pregnancy by caesarean section [Table/Fig-2]. Out of 76, 67 (88%) twins were delivered before 37 weeks of gestational age. Only one (4%) monochorionic twin crossed 37 weeks as she did not receive regular antenatal care [Table/Fig-3]. Out of 51, 30 (58.8%) dichorionic and out of 25, 18 (72%) monochorionic twins underwent caesarean section [Table/Fig-3]. There was no significant difference in maternal risk factors between dichorionic and monochorionic pregnancies, and there were no maternal mortalities in the present study.

Maternal complications	DCDA		MCDA+MCMA	
	Number (n)	Percentage# (%)	Number (n)	Percentage$ (%)
Anaemia	9	16.7	4	15.4
Gestational hypertension	5	9.2	3	11.5
Non severe preeclampsia	4	7.4	2	7.7
Severe preeclampsia	2	3.7	0	0
HELLP syndrome (Haemolysis, Elevated Liver Enzymes, Low platelet)	2	3.7	1	3.8
Gestational diabetes	13	24	6	23.1
Preterm Premature Rupture of Membranes (PPROM)	15	27.8	8	30.7
Abruption	1	1.8	0	0
Postpartum haemorrhage	2	3.7	2	7.7
Peripartum cardiomyopathy	1	1.8	0	0

[Table/Fig-2]: Distribution of twins according to chorionicity and maternal complications.
#Calculated out of number of maternal complications in DCDA twin pregnancies; $Calculated out of number of maternal complications in MCDA+MCMA twin pregnancies

Variables	DCDA		MCDA+MCMA		p-value*
	Number (n)	Percentage# (%)	Number (n)	Percentage$ (%)	
Mode of delivery					
LSCS	27	52.9	17	68	0.700
Vaginal	20	39.2	7	28	
Vaginal delivery for first twin/ LSCS for second twin	3	5.9	1	4	
Forceps	1	1.96	0	0	

Gestational age at delivery (weeks)					
>28-30	9	17.6	1	4	0.124
>30-33	7	13.7	6	24	
>33-37	27	52.9	17	68	
>37	8	15.6	1	4	
Foetal growth restriction					
Twin A	2	3.9	2	8	0.805
Twin B	6	1.2	4	16	
Both	6	1.2	2	8	
Discordant twins	8	15.7	6	24	0.530
Intrauterine foetal demise					
Twin A	1	1.96	0	0	1.000
Twin B	4	7.84	2	8	
Both	1	1.96	1	4	

[Table/Fig-3]: Distribution of twin pregnancies according to gestational age at delivery, mode of delivery, foetal growth restriction, discordant twins and intrauterine foetal demise.
*Fisher's-exact test; #Calculated out of number of DCDA twin pregnancies; $calculated out of number of MCDA+MCMA twin pregnancies

The proportion of pregnancies with foetal growth restriction were 8 (32%), out of 25 monochorionic and 14 (27.45%), out of 51 dichorionic twin pregnancies [Table/Fig-3]. Discordant growth was higher among monochorionic pregnancies, with a proportion of 8 (15.7%), out of 51 dichorionic twins compared to 6 (24%), out of 25 monochorionic [Table/Fig-3]. The rate of intrauterine foetal demise of one or both foetuses was similar among dichorionic, 6/51 (11.76%) and monochorionic, 3/25 (12%) pregnancies. Single foetal demise was also similar among dichorionic, 5/51 (9.8%) and monochorionic, 2/25 (8%) twin pregnancies [Table/Fig-3].

Among the 152 babies, 102 were from dichorionic pregnancies, while 50 were from monochorionic pregnancies. Most babies weighed between 2.5 kg and 1.5 kg. Sixty four (62.7%) out of 102 dichorionic babies and 34 (68%) out of 50 monochorionic babies weighed between 2.5 kg and 1.5 kg. Among dichorionic babies, 3/102 (2.94%) had congenital anomalies, While 6/50 (3%) of monochorionic babies had congenital anomalies. The association of chorionicity with congenital anomalies was statistically significant (p-value=0.033) [Table/Fig-4]. The number of babies alive at discharge was consistent between both monochorionic and dichorionic twin pregnancies, with a survival rate of 80% [Table/Fig-4].

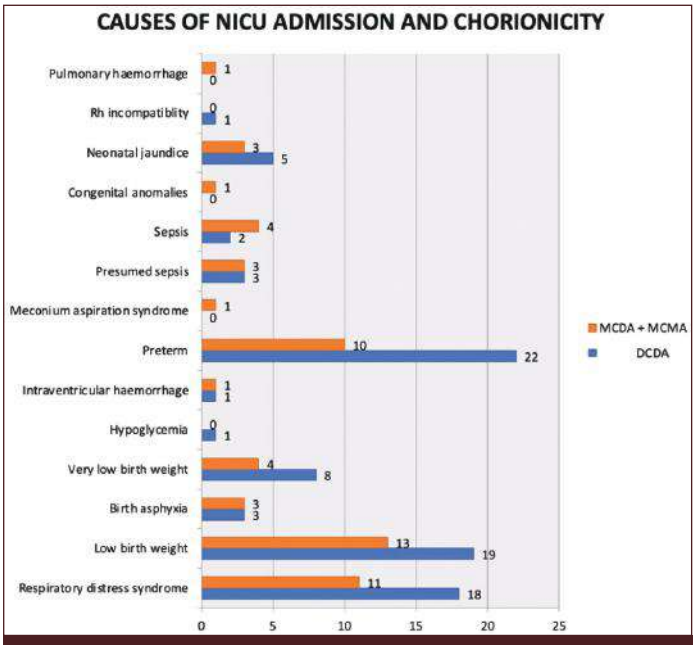
Variables	DCDA		MCDA+MCMA		p-value*
	Number (n)	Percentage# (%)	Number (n)	Percentage$ (%)	
Birth weight (kg)					
>2.5	7	6.9	1	2	1.000
2.5-1.5	64	62.7	34	68	
<1.5	31	30.4	15	30	
Congenital anomalies					
Twin A	1	0.98	0	0	**0.033**
Twin B	0	0	3	6	
Both	1 (=2 babies)	1.96	0	0	

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APGAR score <7 at 5 minutes					
Twin A	1	0.98	2	4	0.591
Twin B	5	4.9	3	6	
Both	10 (=20 babies)	19.6	5 (=10 babies)	20	
NICU admission					
Twin A	3	2.9	3	6	0.740
Twin B	4	3.9	3	6	
Both	24 (=48 babies)	47.05	13 (=26 babies)	52	
Neonatal death					
Twin A	2	1.96	1	2	1.000
Twin B	2	1.96	2	4	
Both	3 (=6 babies)	5.9	1 (=2 babies)	4	
Live baby at discharge					
Both babies live	41	80	20	80	1.000
One baby live	5	9.8	3	12	
No babies live	5	9.8	2	8	

[Table/Fig-4]: Neonatal outcomes according to chorionicity.
*Fisher's-exact test; #Calculated out of number of DCDA babies; $Calculated out of number of MCDA+MCMA babies

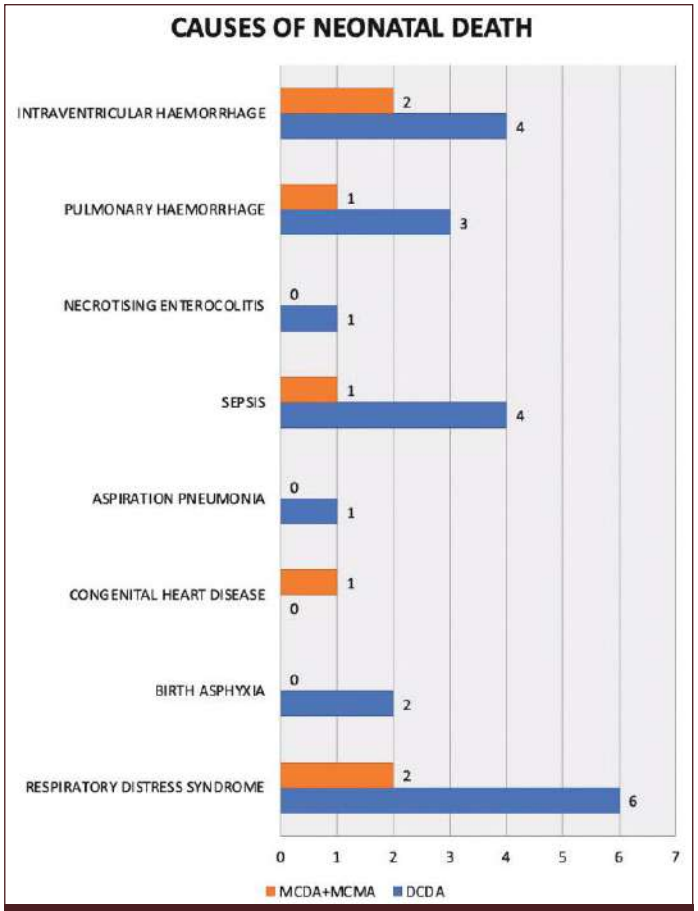
The primary cause for admission to the NICU was prematurity, observed in both dichorionic (22 out of 102) and monochorionic twins (10 out of 50) [Table/Fig-5]. Most twins had multiple complications requiring admission to the NICU. The most common cause of neonatal mortality was respiratory distress syndrome, affecting six dichorionic infants and two monochorionic infants who succumbed during the immediate neonatal period [Table/Fig-6].



[Table/Fig-5]: Causes of Neonatal Intensive Care Unit (NICU) admission.

DISCUSSION

In the present study, the incidence of twin deliveries was 2.8%. All pregnancies conceived following ART in the study were dichorionic, 11/51 (21.6%). There were no monochorionic pregnancies following IVF, likely due to lower survival rates and higher risk of second trimester loss for monochorionic twins conceived after IVF [11]. Participants included in the study were only those who had reached ≥ 28 weeks of pregnancy.



[Table/Fig-6]: Causes of neonatal death.

Among the 76 pairs of twins, 51 (67.10%) were dichorionic diamniotic, 21 (28%) were Monochorionic Diamniotic (MCDA) and 4 (5%) were Monochorionic Monoamniotic (MCMA). This distribution is similar to the findings in the study by Assunção RA et al., where 60% were DCDA, 30.8% were MCDA, and 6.6% were MCMA [12]. Total of 47% of dichorionic pregnancies and 44% of monochorionic pregnancies were primigravidas. The mean maternal age in the present study was 28.39±6.29 years, consistent with other studies [8,12-16].

When maternal complications were analysed, hypertensive disorders accounted for 20% of the complications. A similar incidence of medical complications in twins was reported by Chowdhury S and Hussain MA, with hypertension seen in 22.6% [15]. GDM was present in 23.75% of the participants in the present study, a higher proportion compared to similar studies [15,16]. This could be due to the high prevalence of diabetes in the population and the strict screening protocol for gestational diabetes followed. In a similar study conducted by Alsam S and Rashid Y in Pakistan, a much higher prevalence (36.2%) of diabetes in pregnancy was reported [Table/Fig-7] [8,12-16].

The most common complication found in the present study was PPROM, present in 23 (28.75%) of the study subjects, which is much higher compared to similar studies. In the study by Mercer BM et al., PPROM was found to complicate 7% to 8% of twin pregnancies [17].

In the present study, 67/76 (88%) twins were delivered before 37 weeks of gestational age. Preterm birth among twins was higher compared to other studies [Table/Fig-8] [12-14,18].

The mode of delivery was analysed and was found to be similar to other studies [14,18]. In the present study, 48/76 (63%) participants were delivered by caesarean section, including those done for the second of twins. This comprised 30/51 (58.8%) of dichorionic twins and 18/25 (72%) of monochorionic twins.

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Name of author	Place of study	Number of subjects	Incidence of twins	Mean maternal age	Pregnancy following ART	GDM	HTN	APH	PPH
Present study	Kerala	76	2.8%	28.4	14.5%	23.75%	20%	1.25%	5%
Sarojini et al., [8]	Bengaluru	117	1.1%	25.4	-	-	-	1.3%	5.2%
Assunção RA et al., [12]	Brazil	289	3.4%	29.1	3.8%	-	-	-	-
Upreti P [13]	Nainital	218	1.9%	25.4			17.9%	5.9%	4.1%
Alsam S and Rashid Y [14]	Pakistan	70	0.97%	26.1	-	36.2%	37.8%		
Chowdhury S and Hussain MA [15]	Bangladesh	53	1.4%		-	5.7%	22.6%	5.7%	18.9%
Sultana R et al., [16]	Ujjain	147	1.85%	24.08	-	5.4%	14.3%	6.1%	2.7%

[Table/Fig-7]: Comparison of the present study and similar studies in relation to few of the maternal characteristics and complications [8,12-16].
GDM: Gestational diabetes mellitus; HTN: Hypertension; APH: Antepartum haemorrhage; PPH: Postpartum haemorrhage

Author of study	Place of study	Number of subjects	Preterm birth		CS		Foetal demise		Low birth weight (<2.5 kg)		APGAR <7	
			DC	MC	DC	MC	DC	MC	DC	MC	DC	MC
Assunção RA et al., [12]	Brazil	289	54.3%	83.1%	84.8%		5.1%	24.1%	64.8%	85.5%	3.4%	9.7%
Upreti P [13]	Nainital	218	58.3%	51.2%	11%		-					
Alsam S and Rashid Y, [14]	Lahore	70	30.75%	30.75%	43.6%	45.1%	17.9%	16.13%	-	-	17.9%	16.13%
Domingues AP et al., [18]	Portugal	826	65%	80.2%	56.9%	52.6%	2.2%	3.8%	64%	77.5%	1%	2.6%
Present study	Kerala, India	76	84.3%	96%	58.8%	72%	9.8%	8%	93.1%	98%	25.4%	30%

[Table/Fig-8]: Comparison of the present study with similar studies in relation to preterm birth, CS rate, foetal demise, low birth weight and low APGAR score [12-14,18].

Author of study	Place of study	Number of subjects	Congenital anomalies		NICU admission		Neonatal death	
			DC	MC	DC	MC	DC	MC
Domingues AP et al., [18]	Portugal	826	3.7%	3.7%	38.9%	50%	2.4%	0.6%
Glinianaia SV et al., [20]	United Kingdom	2175	3.43%	6.33%	58.1%	75%	-	-
Present study	Kerala, India	76	2.94%	6%	53.9%	64%	9.8%	10%

[Table/Fig-9]: Comparison of the present study and similar studies in relation to few of the perinatal complications [18,20].

The proportion of pregnancies with foetal growth restriction was higher in monochorionic compared to dichorionic twins, 8 (32%) vs 14 (27.45%). This included pregnancies with either one or both babies with foetal growth restriction. This finding was similar to the study by Fox NS et al., where 27% of women with twin pregnancies delivered at least one twin with a birth weight <5th percentile. In our study, 18% (14 out of 76) of twins had growth discordance whereas in the study by Fox NS et al., 16% of patients had birth-weight discordance of ≥20% [19].

It was found that an APGAR score <7 at 5 minutes was observed in 15/50 (30%) monochorionic twins compared to 26/102 (25.4%) dichorionic twins. Compared to other similar studies, the present study had a larger number of babies with an APGAR score of <7 at five minutes [12,14,18].

A total of 3/102 (2.94%) dichorionic babies had congenital anomalies, while 3/50 (6%) monochorionic babies in the present study had congenital anomalies. The association of monochorionicity with congenital anomalies was found to be statistically significant in the current study (p-value=0.033). This finding was similar to the results of the study by Glinianaia SV et al., [20].

The most common cause for neonatal intensive care admission was prematurity in both dichorionic, 22/102 (21.6%) and monochorionic twins, 13/50 (26%) babies. Respiratory distress syndrome was more common among monochorionic babies (22% vs 17.6%). This is similar to the study by Domingues AP et al., where admission to the NICU was higher among monochorionic babies [18]. Neonatal death occurred in 10/102 (9.8%) babies of dichorionic babies, while 5/50 (10%) babies of monochorionic babies died in the neonatal period. The most important cause of neonatal death was respiratory distress syndrome, similar to the study by Domingues AP et al., [18]. Similar studies related to some perinatal complications have been tabulated in [Table/Fig-9] [18,20].

Limitation(s)

The study duration was only for a one-year period, and the sample size was small. The present study was conducted in a single tertiary centre, which included only women attending a publicly-run healthcare facility. Therefore, the present study cannot be considered representative of twin pregnancies in the general population.

CONCLUSION(S)

Twin pregnancies were associated with a higher risk of PPROM, GDM, and preeclampsia in the present study. Foetal growth restriction, congenital anomalies, and the need for NICU admissions were found to be higher among monochorionic babies. Therefore, twin pregnancies require early diagnosis, determination of chorionicity and focused antenatal care to improve both maternal and perinatal outcomes. Further studies are required to improve foetomaternal outcomes of monochorionic and dichorionic pregnancies.

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Perinatal Outcome in Growth Restricted Fetuses of Normotensive Pregnant Women at a Tertiary Referral Centre in Kerala, India: A Cross Sectional Study

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Abstract: ***Introduction:*** Foetal growth restriction (FGR), is a condition that occurs due to various reasons.It is an important cause of foetal and neonatal morbidity and mortality. It has been defined as a rate of foetal growth that is less than the growth potential of that specific infantor as having birth weight less than two standard deviations below the mean or less than the 10th percentile of a population-specific birth weight for specific gestational age. It has been found to be associated with a variety of adverse perinatal outcomes.These infants have many acute neonatal problems that include perinatal asphyxia, hypothermia, hypoglycaemia, polycythaemiaetc. The likely long-term complications that are prone to develop when FGR infants grow up includes growth retardation, major and subtle neurodevelopmental handicaps etc. ***Methods:*** This cross-sectional study included all growth restricted babies born in the department of Obstetrics and Gynecology at Government Medical College, IMCH Kozhikodeduring the study period and their mothers. Multiple pregnancy with growth restriction were excluded from the study. Babies born outside IMCH but being referred to IMCH were also excluded. Socio –demographic and fetomaternal characteristics were collected after getting consent. Maternal data regarding socio-demographic variables including age, domicile (rural/ urban), socio-economic status, data regarding gestational age, nature of ANC, past obstetric history including parity. ***Results:*** Perinatal mortality rate was 64.2/1000 in growth restricted babies born to normotensive mother group. The stillbirth rate was 36.6/1000 in growth restricted babies born to normotensive mother group. Fetal growthrestriction occurred more in rural womencompared to urban women. Women below poverty line had more fetal growth restriction compared to the women above poverty line and the difference was statistically significant. Early neonatal mortality rate was 28/1000 live IUGR babies in normotensive group. ***Conclusion:*** Mothers belonging to low socio-economic status have high risk of delivering babies with growth restriction. This is because of inadequate dietary intake, increased physical activity, passive smoking, increased rate of infections and low educational levels leading to decreased awareness regarding health care facilities.

Keywords: Fetal growthrestriction,Normotensive,Stillbirth, Stillbirth rate, Perinatal outcome, Perinatal morbidity, perinatal mortality, pregnancy, neonatal death

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OBJECTIVES

1) To estimate the perinatal mortality and morbidity among growth restricted fetuses of normotensive pregnant women, who are delivered at IMCH Kozhikodeat or after 34 weeks.
2)To analyze the socio- economic, health and demographic factors associated with fetal growth restriction

MATERIALS AND METHODS

This cross-sectional study was conducted in the Dept of OBG, Government Medical College, Kozhikode (IMCH), a tertiary care center of North Kerala, India from first November 2008 to 30th April 2009.

All growth restricted babies born in IMCH during the study period and their mothers were included in the study.

Institutional ethics committee approval was obtained. Written informed consent was obtained from the subjects after explaining the motive of the study and they were ensured that the information collected, shall be kept confidential. A total of 109 IUGR babies born to normotensive mothers and 167 IUGR babies born to hypertensive mothers, who fulfilled the inclusion criteria were included in the study.

Inclusion criteria

All singleton growth restricted fetuses detected by clinical examination and confirmed by USG, of pregnant woman who are delivering at or after 34 weeks in IMCH Kozhikode.

The mothers of these babies were also included in the study. They were grouped as normotensives and hypertensives.

Exclusion criteria

Hypertensive mothers with other illness were excluded from the study.

Multiple pregnancy with growth restriction were also excluded from the study. Babies born outside IMCH but being referred to IMCH were also excluded.

Study procedure

The investigator collected data from subjects using proforma, by personal interview and using maternal and baby case sheets. Maternal data regarding socio-demographic variables including age, domicile (rural/ urban), socio-economic status [7], data regarding gestational age, nature of ANC, past obstetric history including parity.Past history of any medical or surgical illness, antenatal and intrapartum complications, mode of delivery, birth weight of baby, APGAR score and other baby details were collected.Everyday data was collected and each subject was followed up in the postnatal ward. Babies who were admitted in neonatal ICU were followed up for 7 days and data regarding neonatal mortality and morbidity were collected.

OPERATIONAL DEFINITIONS [8,9]

Registered gravida: Four or more antenatal visits

Stillbirth: Birth of a baby with no signs of life Preterm stillbirth: Stillbirth occurring before 37 weeks

Post-term stillbirth: Stillbirth occurring after 41 weeks

Antepartum stillbirth: Intrauterine fetal demise occurred before the onset of labor

Intrapartum stillbirth: Intrauterine fetal demise occurred duringlabor.

Perinatal death: Death of babies occurring either during pregnancy or labor or within first week of neonatal period.

Perinatal morbidity: Any illness occurring in the baby Fetal during the first 7 days of life.

Fetal growth restriction: Fetus with estimated weight (using USG morphometric parameters HC, AC, BPD, FL) less than 10th percentilefor the GA.

Normotensive - Blood pressure never > 140/90 mm Hg.

Hypertensive - BP> 140/90 mmHg on at least 2 occasions 6 hours apart.

Statistical analysis

Performed using SPSS 16.0. Pearson's chi-square test and Fischer's exact test. Statistical significance was assumed at a p value of < 0.05.

RESULTS

There were 109 growth restricted babies born to normotensive mothers and 167 growth restricted babies born to hypertensive mothers, who fulfilled the criteria during the study period.

Parameter	Hypertensive	Normotensive
Age		
18-20 yrs	24	15
21-30 yrs	119	78
31-35 yrs	19	13
>35yrs	5	3
Birth weight		
1-1.49	32	21
1.5- 2.5	135	88

[Table/Fig-1]: Distribution of maternal age and baby weight

In both normotensive and hypertensive groups, majority of mothers were in the age group of 21-30 years. A systematic review had shown that older mothers have increased risk for fetal growth restriction, but majority of mothers with fetal growth restriction in present study were in the 20-30 years group [10]. High prevalence of early completion of family before 35 years in Indian culture can explain the higher number of births and stillbirths among this age group [11].

Socio demographic and feto maternal characteristics among normotensives with fetal growth restriction

Characteristics	Normotensive	Hypertensive	P value
Domicile			
Urban Rural	24 85	43 124	P=0.049
Economic status			
BPL	89(81.7)	150	P= 0.06
APL	20(18.3)	17	
Booking status			
Referral	19(17.4)	28	0.332
Booked	90(82.6)	139	
Parity			
Multi	39(35.8)	70	0.585
Primi	70(64.2)	97	
Baby sex			
Male	50(45.9)	88 (52.7%)	0.249
Female	59(54.1)	79(46.1%)	

Characteristics	Normotensive	P value
Domicile		
Urban Rural	24 85	P=0.05
Economic status		
BPL	89(81.7)	P= 0.04
APL	20(18.3)	
Booking status		
Referral	19(17.4)	P=0.332
Booked	90(82.6)	
Parity		
Multi	39(35.8)	P=0.585
Primi	70(64.2)	
Baby sex		
Male	50(45.9)	P=0.249
Female	59(54.1)	

[Table/Fig-2]: Socio-demographic and foetomaternal characteristics of normotensive mothers

BPL: Below poverty line; APL: Above poverty line

Fetal growth restriction occurred more in rural women compared to urban women and women below poverty line had more fetal growth restriction compared to the women above poverty line and the difference was statistically significant.All women with fetal growth restriction gave history of attending antenatal clinics during the current pregnancy. A total of 19(17.4%) women were referred from periphery and 90 (82.6%) women were booked with this Institution among normotensive group. There were 39 (35.8%) multies and 70 (64.2%) primis. Fetal growth restriction was more in Primiscompared to multiparas, but the difference was not significant (p=0.585). A total of 50(45.9%) babies were male and 59 (54.1%) were female babies and the difference in gender was notfound to be significant (p=0.249)

MATERNAL MEDICAL CONDITIONS AMONG NORMOTENSIVE MOTHERS

Heart disease	4
Recurrent UTI	4
PGDM	2
Epilepsy	2
Bronchial asthma	1
Fibroid complicating pregnancy	1
Psychiatric illness	1
Hyperthyroidism	2
Hypothyroidism	1
SLE	2
HIV	1
Rheumatic fever	1
APLA positive	1

[Table/Fig-3]: Distribution of maternal medical condition

Among the 4 mothers with heart disease, 2 had rheumatic heart disease, 2 had congenital heart disease. (1 ASD, 1 VSD). One baby had ASD same as that of mother.Babies of both PGDM mothers had hypoglycemia, one baby had cleft lip and cleft palate and other had polycythemia. Both babies were admitted in ICU. Among two mothers with epilepsy, one had a baby with spina bifida occulta and the baby had hypoglycemia and was admitted in NICU. Among two mothers with SLE, none of the babies had congenital heart block. Among 2 mothers with hyperthyroidism, one of the babies had birth asphyxia.

MODE OF DELIVERY AND FGR

		Mode of delivery					
		Vaginal Delivery	LSCS	VE	forceps	assisted Breech	Total
Normotensive	Number %	69 63.3%	34 31.2%	2 1.8%	2 1.8%	2 1.8%	109
Hypertensive	Number %	104 62.3%	47 28.1%	9 5.4%	4 2.4%	3 1.8%	167
Total	Number %	173 62.7%	81 29.3%	11 4.0%	6 2.2%	5 1.8%	276

[Table/Fig-4]: Mode of delivery and FGR

In this study labor was induced in 60.8% normotensive mothers and 64.2% hypertensive mothers. Perinatal outcome of FGR babies born after induced delivery did not differ from those with spontaneous delivery.

Vaginal delivery was the commonest mode of delivery in both groups. P=0.661.

Mode of delivery and APGAR

There were 16 cases of birth asphyxia (23.5%) among the FGR babies delivered vaginally and 4 cases of birth asphyxia (11.8%) among those delivered by caesarean section. Hence babies delivered by caesarean section had a better APGAR than those delivered vaginally. p=0.001. Among 8 babies with breech presentation, 2 had assisted breech delivery and both had APGAR< 1'7 and babies delivered by caesarean section had APGAR >1'7. p=0.894.

SEX OF BABY and FGR

		male	Female	total
NORMOTENSIVE	Number %	50 45.9	59 54.1	109
HYPERTENSIVE	Number %	88 52.7	79 46.1	167
TOTAL	Number %	138 50	138 49.3	276

[Table/Fig-5]:SEX OF BABY and FGR

Even though female babies slightly outnumbered male babies in normotensive group, there was no statistically significant difference between normotensive and hypertensive group when sex of baby was considered, p=0.249.

Birth weight and perinatal outcome

	Birth weight 1-1.5 kg	Neonatal death	Still birth
normotensive	21	2	3
Hypertensive	32	4	6

[Table/Fig-6]:Birth weight and perinatal outcome.

There were 21 (19.3%) babies in normotensive group and 32(19.2%) babies in hypertensive group with birth weight between 1-1.5 kg. There were 3 neonatal deaths in normotensive group, 2 were with birth weight between 1-1.5 kg. 4 out of 8 neonatal deaths in hypertensive group were also with birth weight between 1-1.5 kg. There were 13 stillbirths, 4 among normotensive and 9 among hypertensive group.2 out of 4 stillbirths in normotensive and 5 out of 9 still births in hypertensive group were with birth weight between 1-1.5 kg. it is seen that low-birth-weight babies had high mortality compared to babies with birth weight more than 1.5 kg. Thus, it can be seen that birth weight is a powerful indicator of perinatal mortality and morbidity among growth restricted babies.

Perinatal morbidity and FGR

Morbidity	Normotensive	hypertensive
Birth asphyxia	18(16.5%)	24(14.3%)
hypoglycemia	2 (1.8%)	2(1.19%)
Meconium aspiration syndrome	1(0.91%)	8(4.97%)
hypoglycemia	8(7.3%)	16 (9.58%)
hyperbilirubinemia	4 (3.6%)	15(8.98%)
hypocalcemia	1(0.91%)	2(1.197%)
septicemia	0(0.0%)	5 (2.29%)
Intraventricular hemorrhage	0(0.0%)	1(0.598%)
Necrotisingentero colitis	0(0.0%)	1(0.598%)
Transient tachypnoea of newborn	1 (0.91%)	3 (1.796%)

[Table/Fig-7]:Perinatal morbidity and FGR

45.1% ofbabies of hypertensive group had some type of neonatal morbiditybut only 32.9% babies of normotensive group had neonatal morbidity, p=0.04. The most common perinatal complication was birth asphyxia in both groups, followed by hypoglycemia and hyperbilirubinemia.

Neonatal mortality

There were 3 neonatal deaths in normotensive and 8 neonatal deaths in hypertensive groups. p=0.38

Cause of death	normotensive	hypertensive
Birth asphyxia	2(1.86%)	4(2.30%)
Congenital anomaly	1(0.59%)	0(0.0%)
septicemia	0(0.0%)	2(1.18%)
hyperbilirubinemia	0(0.0%)	1(0.58%)
hypoglycemia	0(0.0%)	1(0.58%)

[Table/Fig-8]: Neonatal mortality and FGR

When cause of neonatal mortality was considered, difference was not statistically significant, p=0.597. Most common cause of death was birth asphyxia in both groups. Other causes were congenital anomaly, septicemia, hyperbilirubinemia, hypoglycemia.There were 3 NND in normotensive groupaccounting to 2.45% of live babies and 8 NND in hypertensive group accounting to 4.64% of live babies.

Analysis of stillbirth

There were 13 stillbirths, 4 among normotensive and 9 among hypertensives.

	Alive	stillborn	Total
Normotensive	105(96.3%)	4(3.7%)	109
hypertensive	158 (94.6%))	9(5.4%)	167
total	263(95.3%)	13(4.7%)	276

When stillbirth was compared between normotensive and hypertensive groups, the difference was not statistically significant, p=0.510

50% of stillborn babies of normotensive group had weight t< 1.5 kg and 11.1% stillborn babies of hypertensive group had weight <1.5 kg. p= 0.125.25% of stillborn babies in normotensive and 55.6% of stillborn babies of hypertensive group were born to mothers with inadequate nutrition. 25% stillborn babies in normotensive group and 22.2% stillborn babies in hypertensive group were born to mothers, who were exposed to passive smoking, as their husbands were chain smokers, p= 0.532. 3/4normotensive and 6/9 hypertensive stillbirths were associated with maternal anemia, this cannot be considered significant because majority of mothers had only mild anemia.

The stillbirth rate was 36.6/1000 IUGR babies in normotensive mother group and 53.8/1000 IUGR babies in hypertensive group.

SBR in India varies from 13 to 26.48/1000 births and this wide interstate variation may be due to differences in population characteristics and the risk factors [12,13].

Perinatal mortality rate was 64.2/1000 IUGR babies in normotensive group and 101/1000 IUGR babies in hypertensive group.

Early neonatal mortality includes early neonatal deaths, within first 7 days of life. Early neonatal mortality rate was 28/1000 live IUGR babies in normotensive group and 50.6/1000 live IUGR babies in hypertensive group. There were 3 neonatal deaths in normotensive group and 8 neonatal deaths in hypertensive group. P=0.38.

DISCUSSION

Systematic review had shown that older mothers have increased risk but majority of mothers with poor perinatal outcome in present study were in the 20-30 yrs group [10]. High prevalence of early completion of family before 35 years in our culture can explain the higher number of births and stillbirths among this age group [11]. Lack of awareness in young women about pregnancy complications may contribute to the less favorable outcomes of pregnancy.

The stillbirth rate was 36.6/1000 IUGR babies in normotensive mother group and 53.8/1000 IUGR babies in hypertensive group.

SBR in India varies from 13 to 26.48/1000 births and this wide interstate variation may be due to differences in population characteristics and the risk factors [12,13].

Perinatal mortality rate was 64.2/1000 IUGR babies in normotensive group and 101/1000 IUGR babies in hypertensive group. The reason for high perinatal mortality rate in our study was due to referral of all high-risk cases from periphery and even from neighboring districts to our hospital which is a referral tertiary care center

Analysis revealed that obstetric score had no influence on stillbirth as there was no significant difference between primies and multies in the present study and similar result was shown in a study from Hyderabad [14] But another study reported an increased risk of stillborn in first and after fifth pregnancy [15]

The study revealed that most of mothers were from rural areas. This is in concurrence to a study from Bihar state [15]. Higher rate of SBs among rural population indicates the need of improved obstetric care and emergency services in the villages. Results revealed that most of the mothers with FGR were below poverty line. Socioeconomic status influences the health seeking behavior of women in accessing emergency obstetric care [16]. Many national programs are there to improve maternal care but worst outcomes are more in women from rural areas suggesting the need for improving the quality of obstetric care in rural settings.

There were 16 cases of birth asphyxia (23.5%) among the FGR babies delivered vaginally and 4 cases of birth asphyxia (11.8%) among those delivered by caesarean section. Hence babies delivered by caesarean section had a better APGAR than those delivered vaginally. p=0.001. [17] Among 8 babies with breech presentation, 2 had assisted breech delivery and both had APGAR< 1'7 and babies delivered by caesarean section had APGAR >1'7. p=0.894. Similar results were seen in a study from Nepal.[18]

Intrapartum stillbirths drop by 1.6/1000 births with every percentage rise in caesarean section rates from 0-8% in low middle income countries [19]. Antepartum stillbirths indicate the need for improving the quality of antenatal care. Early detection of high-risk pregnancies and need based termination should be ensured [20]. Prompt diagnosis of hypertensive disorder in pregnancy, universal screening for detection of gestational diabetes mellitus, multidisciplinary management for diabetes mellitus, early pick up of fetal growth restriction and follow up with Doppler studies are can prevent many fetomaternal complications [10]. But there are limitations in peripheral health services system in terms of man power and facilities. Expertise is needed for Doppler studies which is a hurdle in peripheral health centers. Antenatal care by skilled health care professionals and early diagnosis with prompt effective management is very important in improving the obstetric outcomes [21].

Early detection and timely intervention of high-risk cases appears very crucial for better fetomaternal outcome in such conditions [22].

CONCLUSION

Mothers belonging to low socio-economic status have high risk of delivering babies with growth restriction. This is because of inadequate dietary intake, increased physical activity, passive smoking, increased rate of infections and low educational levels leading to decreased awareness regarding health care facilities. Primis have increased risk of having growth restricted babies. Male babies are found to have higher rates of perinatal mortality and morbidity. But exact reason for this is not understood. Perinatal morbidity and mortality were high in babies of hypertensive mothers. NICU admissions were high in babies of hypertensive mothers. The major cause of perinatal mortality and morbidity was birth asphyxia in growth restricted babies of both normotensive and hypertensive groups.

Even though all cases were registered for ante natal care, a major proportion of cases were antepartum stillbirths indicating the need for improving the quality of antenatal care in peripheries and importance of timely referral of high-risk cases. More awareness should be generated among young women regarding the need for early detection and management of medical co morbidities like hypertension and diabetes in pregnancy. Third trimester growth scan will help in picking up the cases with fetal growth restriction.

The study stress on the importance of regular antepartum and intrapartum surveillance, regular growth monitoring by USG and plotting on customized growth charts. Early detection of FGR and delivery at appropriate time and place having appropriate neonatal facilities help to reduce perinatal morbidity and mortality.

The study highlights the importance of institutional deliveries of women combined with effective antenatal care. Hence health education and awareness among the people and primary health workers regarding this health issue is necessary in bringing down the maternal and neonatal morbidity and mortality.

STRENGTHS AND LIMITATIONS

The present study was done in a single institute. Relatively smaller sample size was a limitation. However, multicentric studies with larger sample size would have better results. The Study provided insight on the perinatal outcome of growth restricted babies and causes which are important in planning the preventive strategies.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Ethical issues: NIL (The study was approved by the Institutional Ethics Committee)

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Authors' contributions

All authors have made substantial contributions to conception, design and data acquisition of this study. All co-authors revised it critically for important intellectual content. All authors read and approved the final manuscript.

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Research Article

Identification Of Factors Leading to Stillbirth with Recode System (Relevant Condition at Death System) In A Tertiary Care Centre in Kerala

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Abstract: **Background**: Stillbirths constitute a major part of perinatal deaths. It is influenced by a wide range of maternal social and circumstantial factors. The study was done to find out the various factors associated with stillbirth in our hospital with the help of the existing ReCoDe System. **Materials And Methods**: A cross-sectional observational study was conducted at the Department of Obstetrics and Gynaecology, Government Medical College, Thrissur by collecting data from all pregnant women who had during the study period of 12 months, i.e., from 1st January 2022.Data was then collected using a semi-structured interview after obtaining informed and signed consent. The questionnaire included general information, detailed clinical history. The relevant investigations, ultrasonography (growth parameters, liquor, biophysical profile, doppler parameters) were noted. After delivery, the stillborn baby Placenta, Umbilical cord and Amniotic fluid examined for any abnormalities. **Results**: Out of the134 cases of stillbirths during the study period of 12 months majority (52, 38.8%) were in the age group of 20 – 25 years, and 25 patients were included in the high-risk group in which 10 (7.5%) were below 20 years and 15 (11.2%) were above 35 years. Among the study participants, 51 (38.1%) were overweight and 27 (20.1%) were obese, 10 (7.5%) women had a Bad Obstetric History. There were 58 (43.3%) primigravida women. There were 4 (3.0%) women who were unbooked, while 20(14.9%) women had irregular antenatal care. 15 of the participants had maternal infection in the antenatal period of which 5 (3.7%) had viral and 10 (7.5%) had bacterial infection. 47(35.1%) patients had anemia in our study. A significant number of pregnant women (60, 44.8%) had gestational hypertension which was the most common cause leading to intra uterine fetal death. Gestational diabetes accounted for 49 (36.6%) of stillbirth in our study, 47 (35.1%) had hypothyroidism. IUGR was present in 51 (38.1%) of the study participants, and this was the second most common cause identified, resulting in stillbirth. **Conclusion**: Hypertensive Disorders of pregnancy was seen as the most common cause associated with intra uterine foetal demise. Intra uterine growth restriction and Gestational diabetes were the other important associated factors identified that led to stillbirth.

Keywords: Stillbirth, Gestational Diabetes, Gestational hypertension, IUGR, ReCoDe

INTRODUCTION

Stillbirth is defined as dead fetus of 1000 g or more at birth, or after 28 completed weeks of gestation, or attainment of at least 35 cm crown-heel length according to WHO.(1) The Perinatal Mortality Surveillance Report (CEMACH)3 defined stillbirth as 'a baby delivered with no signs of life known to have died after 24 completed weeks of pregnancy (RCOG).(2)Stillbirths constitute a major part of perinatal deaths, yet they largely remain invisible.(3) Every stillbirth is a tragedy and a potential life lost. There are, in addition, many psychosocial consequences for parents, including anxiety, long term depression, posttraumatic stress disorder and stigmatisation.(4)Sadly, woman who have experienced a stillbirth are more likely to experience this again in subsequent pregnancies than those who have not.(5)

According to a study by Jacob P. Koshy et al, the incidence of stillbirth in 1995 was 3.3 million and this decreased to 2.6 million in 2009.(6) Thus from 1995 to 2009, the stillbirth rate had declined by 14%. Therefore, the stillbirth rate had reduced by 1.1% per year (according to world stillbirth rate). At least 2.65 million cases of annual stillbirths were calculated worldwide in 2008, with 1.2 million of these fetal deaths occurring intrapartum. Because of developments in diagnostic and therapeutic modalities in the last few decades, there has been a marked reduction in stillbirth in developing countries, including India. In spite of this, our stillbirth rate is still much higher than that of the developed countries.

This is a complex situation too, as a probable cause and contributing factors involved are to be identified and a suitable method of termination of pregnancy has to be suggested. Data suggests that most of these deaths could have been prevented.If these factors are identified early implementation of effective and timely interventions could prevent the preventable stillbirths, thus improving maternal and perinatal outcomes.

There are only a few studies in India which have studied

these aspects of stillbirths. We therefore, wanted to find out the various factors associated with stillbirth among patients admitted in our hospitalusing the existing ReCoDe system of classification.

MATERIALS AND METHOD

This is Cross sectional observational study conducted at the Department of Obstetrics and Gynaecology, Government Medical College, Thrissur. Data was collected from antenatal women who were admitted with Intrauterine foetal demise in labour room/ ward of Obstetrics and Gynaecology Department or who were admitted for other conditions and had Intrauterine foetal demise during their stay in the ward of Obstetrics and Gynaecology Department at Government Medical College Thrissurduring the study period of 12 months, i.e., from 1stJanuary 2022 to 31st December 2022. All the study subjects were evaluated for inclusion and exclusion criteria. Data was then collected using a semi-structured interview after obtaining informed and signed consent from the study subjects. The questionnaire included detailed clinical history regarding age, socioeconomic status, parity, body mass index, regularity of ANC, presence of other risk factors, past and present medical and surgical history, any relevant drug intake, gestational age at diagnosis of IUFD (Intra Uterine Fetal Death) and if gestational age was not known all stillbirths weighing more than 500gms were included). The relevant investigations, ultrasonography (growth parameters, liquor, biophysical profile, doppler parameters) were noted.

After delivery, the stillborn baby was examined for foetal weight, morphology, skin staining, maceration, colour and other details were recorded. Placenta was weighed and examined for blood clots, meconium staining, infarcts, oedema, hydropic changes, structural abnormalities like circumvallate placentae or accessory lobes. Umbilical cord was examined for entanglement, knots (true or false), hematomas, strictures, assessment of Wharton's jelly, number of vessels and insertion abnormalities. Amniotic fluid was noted for volume colour and odour.

Data was coded and entered in Microsoft excel spreadsheet and analysed using SPSS Version 25. Qualitative variables were expressed as proportions and quantitative variables was depicted as mean and median values with its standard deviation and interquartile range respectively.

RESULT

A total of 134 study subjects had stillbirthduring the study period of 12 months. These women with intrauterine fetal death were studied to assess the risk factors that may have been associated with stillbirth. Majority of the study participants were in the age group of 20 – 25 years (52, 38.8%), and 25 patients were included in the high-risk group in which 10 (7.5%) were below 20 years and 15 (11.2%) were above 35 years. 76.1% of the study participants were unemployed, while 53% were educated up to or below high school level. Out of the 134 study participants 61.9% belonged to BPL (below poverty line) socioeconomic class and 10.4% were tribal women, with a large majority hailing from rural areas. Among the study participants, 51 (38.1%) were overweight and 27 (20.1%) were obese. (Table no.1)

Table No 1General details of the study participants

AGE GROUP (in years)	**FREQUENCY**	**PERCENTAGE**
<20	10	7.5
20-25	**52**	**38.8**
26-30	42	31.3
31-35	15	11.2
>35	15	11.2
EDUCATION		
Illiterate	28	20.9
Up to 10	71	53.0
Plus Two	28	20.9
Graduate	7	5.2
OCCUPATION		
Unemployed	102	76.1
Employed	32	23.9
INCOME		
APL	37	27.6
BPL	83	61.9
Tribal	14	10.4
BMI		
<18.5	11	8.2
18.5-24.99	40	29.9
25 -29.99	51	38.1
30-39.99	27	20.1
≥40	5	3.7

TOTAL	134	100

There were 58 (43.3%) primigravida women and majority were in the gestational age 31-37 weeks (72, 53.7 %).10 (7.5%) women had a Bad Obstetric History.Majority of the patients 90 (67.2%) were referred from other peripheral centres. There were 4 (3.0%) women who were unbooked, while 20(14.9%) women had irregular antenatal care. 21.6 % of the study subjects with still birth had history of infertility treatment. 25 (18.7 %) had previous history of abortion and out of 76 participants who were multigravida, 43 (56.6%) participants had a previous vaginal delivery while 33 (43.4%) were delivered by caesarean section in their previous pregnancy.10 (7.5 %) study subjects had Bad obstetric history and Previous history of IUD. (Table No.2)

Table No.2 Distribution of study subjects based on maternal factors

PARITY	**FREQUENCY**	**PERCENTAGE**
One	58	43.3
Two	47	35.1
Three	24	17.9
More than 3	5	3.7
GESTATIONAL AGE(In weeks)		
24-30	45	33.6
31-37	72	53.7
>37	15	11.2
Past Date	2	1.5
ANTENATAL CARE		
Booked	20	14.9
Unbooked	4	3.0
Referred	90	67.2
Irregular ANC	20	14.9
H/O INFERTILITY RX		
Yes	29	21.6
No	105	78.4
PREVIOUS H/O ABORTION		
Yes	25	18.7
No	109	81.3
PREVIOUS DELIVERY		
Vaginal Delivery	43	56.6
Caesarean	33	43.4
BOH (Bad Obstetric History**)**		
Yes	10	7.5
No	124	92.5
PREVIOUS H/O IUD		
Yes	10	7.5
No	124	92.5
MODE OF DELIVERY (current pregnancy**)**		
Vaginal Delivery	117	87.3
Caesarean	17	12.7

In our study, 60 (44.8%) participants had hypertensionwhile 49 (36.6%) of the women had gestational diabetes and 47 (35.1%) study subjects had hypothyroidism. 15 of the participants had maternal infection in the antenatal period of which 5 (3.7%) had viral and 10 (7.5%) had bacterial infection. 47(35.1%) patients had anemia in our study. 11 (8.2%) participants had taken drugs which included antiepileptics, immunosuppressants, 5 (3.7%) had viral maternal infection during pregnancy, 10 (7.5%) had bacterial infection including urinary tract infection, vulvovaginal infections etc. 4 (3.0%) of the study participants were diagnose to have bicornuate congenital uterine anomalies while 9 (6.7%) had cervical incompetence.

The congenital anomalies seen in the foetus included 6 (4.5%) fetuses showed syndromic anomalies, 2 (1.5%) had facial anomalies, 1 (0.7%) had limb anomalies, 4 (3.0%) had gastrointestinal tract anomalies and 4 (3.0%) had neural tube. In our study, out of 134 participants, 2 (1.5%) had birth asphyxia and 1 (0.7%) had birth trauma. MSAF grade I was seen in 3 (22.2%) participants, grade II in 3 (2.2%) and grade III in 6 (4.5%). There was no unidentified cause. (Table No.3)

Table No.3 Distribution of study subjects based on risk factors

RISK FACTOR	**FREQUENCY**	**PERCENTAGE**
Hypertension	60	44.8
GDM	49	36.6
Anemia	47	35.1
Hypothyroidism	47	35.1

Heart Disease	14	10.4
Chronic Maternal disease (CKD, CLD)	1	0.7
Seizure Disorder	10	7.5
Bronchial Asthma	11	8.2
Thrombocytopenia	1	0.7
Psychiatric Illness	1	0.7
MATERNAL INFECTIONS		
Viral	5	3.7
Bacterial	10	7.5
MATERNAL DRUG INTAKE		
Yes	11	8.2
No	123	91.8
CONGENITAL UTERINE ANOMALIES (BICORNUATE)	4	3.0
CERVICAL INCOMPETENCE		
Yes	9	6.7
No	125	93.3
USS		
IUGR Normal Doppler	20	14.9
IUGR Abnormal Doppler	31	23.1
Macrosomia	14	10.4
CONGENITAL ANOMALIES OF FOETUS		
Syndromic	6	4.5
Facial Anomalies	2	1.5
Limb Anomalies	1	0.7
Git Anomalies	4	3.0
Neural Tube	4	3.0
Uterine Rupture	2	1.5
INTRAPARTUM COMPLICATIONS		
Birth Asphyxia	2	1.5
Birth Trauma	1	0.7
MSAF		
Grade I	3	2.2
Grade II	3	2.2
Grade III	6	4.5
UNIDENTIFIED CAUSE	0	0

Out of 134 study subjects 29 (21.6%) of the women had oligohydramnios, while in 15 (11.2%) polyhydramnios was present. Out of 134 study participants, 31 (23.1%) had experienced placental abruption and 3 (2.2%) had placenta previa. There were 22 (16.4%) foetuses who had cord around neck and meconium-stained liquor was noticed in 12 (8.9%) cases. Among the fetuses majority of the fetus were between 1 – 1.5kg (38, 28.4%) and most of them were male fetuses (73, 54.5%) and macerated stillborn (76, 56.7 %). (Table No.4)

Table No.4 Distribution of study subjects based on characteristics of placenta, amniotic fluid, umbilical cord and foetus

PLACENTA	**FREQUENCY**	**PERCENTAGE**
Abruption	31	23.1
Previa	3	2.2
Normal	100	74.6
AMNIOTIC FLUID		
PPROM/Chorioamnionitis	15	11.2
Oligamnios	29	21.6
Polyhydramnios	15	11.2
UMBILICAL CORD		
Cord Around Neck	22	16.4
True Knot	2	1.5
Cord Presentation	1	0.7
Cord Prolapse	2	1.5
SEX OF FETUS		
Male	73	54.5
Female	59	44.0

Unidentified	2	1.5
TYPE OF IUD (Intrauterine death)		
FSB (Fresh stillborn)	58	43.3
MSB (Macerated stillborn)	76	56.7
BIRTH WEIGHT(in Kg)		
Up to 1	36	26.9
1 - 1.49	38	28.4
1.5 - 1.99	19	14.2
2 - 2.49	17	12.7
2.5 - 2.99	14	10.4
3 - 3.49	4	3.0
3.5 - 3.99	2	1.5
≥ 4	4	3.0

Table No. 5 Frequency and Percentage distribution according to ReCoDe.

ONDITIONS	REQUENCY (N=134)	ERCENTAGE
roup A: Foetus		
UGR		.1
ongenital Anomaly		.7
fection		.2
roup B: Umbilical Cord		
olapse		5
onstricting loop		.7
roup C: Placental		
ruption		.1
evia		2
roup D: Amniotic Fluid		
norioamniotics		.2
olyhydramnios		.2
igohydramnios		.6
roup E: Uterus		
upture		2
roup F: Mother		
ypertensive disorders		.8
iabetes Mellitus		.6
undice		0
hyroid disease		.1
roup G: Intrapartum		
sphyxia		5
roup H: Trauma		
rth Trauma		7
roup I: Unclassified		
nidentified	1	1

IUGR was present in 51 (38.1%) of the study participants, and this was the second most common cause identified, resulting in stillbirth. (Table No.5)

DISCUSSION

There were a total of 2877 live births and 139 stillbirths during the study period of one year from January 1st 2022 to December 31st2022 at Government Medical College Thrissur. Being a tertiary referral centre, most (67.2%) of the participants were referred to our hospital after confirming stillbirth from other peripheral centres.

Age Of the Patient

Out of 134 women recruited in the study majority 52 patients (38.8%) were between the age group of 20 – 25 years. 18.7% of the women belonged to the high-risk group. This included 10 women below 20 years and 15 women above 35 years. This was similar to the finding of Murali Paul Kannan in their study conducted at JIPMER Pondicherry, which found that stillbirth rate was higher when maternal age was less than 20 years.(7) In a study conducted by Das Lucy et al, it was found that the largest number of fetal deaths occurred when the maternal age was more than 35 years.(8)There is a felt need for improving family welfare measures to delay the age at first pregnancy, thereby reducing the multiple complications that may occur in the young mother and her new-born baby.

Educational Status

Educated mothers assume greater responsibilities in planning their families and also availing timely and good maternal services. In our study, stillbirths were seen most

among women who were not educated beyond high school level (53%). Those who were illiterate constituted 20.9% of the study population. In a study conducted by Auger N etal in NCBI edition about relation between education and stillbirth, found that low levels of education was associated with stillbirth.(9) This study also found that education beyond high school reduced the risk of perinatal mortality by 20% among the white population.Countries or regions with high female literacy rates have lower birth rates and mortality rates. According to NFHS survey – 3 female literacy rates in Kerala was 93.91% compared with the whole of India (74.04%). Stillbirth rate is less in Kerala compared to the rest of India.(10)

Socioeconomic Status

In our study, 83% of the participants were below poverty line (BPL) as per the ration card issued by the state government of Kerala. Similar findings were reported by Erdem et al in his study from Turkey which showed that stillbirths and neonatal deaths were high among those who had a poor socioeconomic status.(11)In our study, 10.4 % were tribal women. In a study conducted by Sophie L P et al, socioeconomic inequalities in neonatal mortality in eastern India remained high and PVTGs (previously known as Primitive tribal group) are most severely affected.(1)

BMI

Out of 134 study participants, 51 (38.7%) were overweight and 27 (20.1%) were obese. Similar observations were found by Vickflendy et al.(12) They found that overweight and obesity were the leading factors for gestational hypertension and diabetes which if not well controlled, finally led to stillbirth and other maternal complications.

BOH (Bad Obstetric history)

BOH is said to be present in those with a history of at least one stillbirth or more than 2 abortions or at least one perinatal mortality. In our study out of 134 study participants, 10 (7.5%) women had BOH. In a study by Beegum SFs et al they found that in those with a history of previous stillbirth or abortions, gestational diabetes and obstructed labour the most important contributory factors resulting in adverse perinatal outcomes.(13)

OBSTETRIC HISTORY

Out of 134 study participants, 58 (43.3%) were nullipara, 47 (35.1%) were parity two, 24 (17.9%) were parity three while 5 (3.7%) women had a parity of more than 3. Similar observations were found in a study done by Nazia Hashim.(14)Other observations included a previous history of stillbirth was present in 7.5% of the study population, previous history of abortion was seen in 19%, while 43% had a previous history of caesarean section. Previous mode of delivery has been shown to influence fetal outcome. Caesarean delivery in a first pregnancy has been associated with an increased risk of stillbirth in the second pregnancy.(15)Previous history of still birth has been seen to be a risk factor for another stillbirth.(16)

GESTATIONAL AGE

Out of 134 study participants, majority 72 (53.7%) were between 31 and 37 weeks of gestational age. According to a study conducted by Melissa G Rosenstein, the risk of stillbirth after 32 weeks of gestation increases with gestational age, and half of the late fetal deaths occurred at term.(17)

Antenatal Visit Status

Proper antenatal care is essential for a favourable fetal outcome. Antenatal care is reflected by the number of antenatal visits. At least 3 visits are recommended by the National child survival and Safe Motherhood Programme, for the enhancement and expansion of MCH Programme of Govt of India. Majority of the patients in our study had undertaken regular antenatal check-up with a minimum of 3 visits. 90 (67.2%) were referred from other centres while 20 (14.9%) were booked at our institution. 20 (14.9%) participants had irregular ANC. According to a study conducted by Trhas Tadesse Berhe et al in Ethiopia, having a good quality of ANC significantly reduced antepartum stillbirth.(18)

Maternal Infections

Maternal infections like respiratory tract infection, urinary tract infection and other infections associated with fever can contribute to stillbirth. There were 15 (11.1%) women who had fever during their antenatal period among the study subjects. Similar observations were found in a study conducted by Robert et al.(19) In a study conducted by Indu Lata et al, the incidence of poor pregnancy outcome was higher in bacterial vaginosis, with UTI (urinary tract infection).(20)

Anemia In Pregnancy

Anemia is one of the major public health problems globally. Anaemia can be associated with an increased incidence of stillbirths, perinatal deaths, low birth weight babies and prematurity. There were 47 (35.07%) patients who had anemia in our study, which is similar to a study conducted by Pretty P et alat Baroda where they confirmed that anaemic mothers were more prone for preterm delivery and IUGR.(21)

Gestational Hypertension

Out of the 134 study subjects 44.8% had gestational hypertension. Das Lucy et al in their study from Orissa on perinatal mortality reported that gestational hypertension accounted for 21.9% of perinatal mortality.(22)Similar outcomes have been observed in other studies on women with medical complications in pregnancy. In a WHO antenatal care trial analysis of 39615 pregnancies it was found that fetal deaths were higher in pre-eclampsia (2.2%) in comparison to gestational hypertension (1.4%).(16) In a study conducted by Indu Verma et al Preeclampsia-eclampsia was associated with increased risk of adverse perinatal outcomes as compared to Gestational and Chronic Hypertension, necessitating screening, vigilant antenatal care, timely intervention, and referral.(23)

Gestational Diabetes

Diabetes was present in 36.6% of stillbirth which contributed to the third most common cause of stillbirth in our study. According to Johnston et al gestational diabetes with elevated glucose levels is at high risk of unexplained stillbirth. Earlier studies have shown the rate of stillbirths to be 1.5% in diabetic pregnancies. This is five times that

of a non-diabetic pregnant population.(24)

Thyroid Disease

Pregnant women with thyroid disease generally have poor obstetric outcome, if the metabolic control is poor. According to Davis et al there is increased incidence of preterm delivery, IUGR and stillbirth associated with thyroid disorders in pregnancy. In our study hypothyroidism was present in 35.1 % of the study participants.(25)

Iugr And Low Birth Weight

In our study, 38.1 % women had babies with IUGR which was significant, contributing to the second most common cause of stillbirth. 28.4% babies had a birth weight between 1 kg and 1.5kg, while 26.9% babies weighed below 1 kg. Birth weight is one of the most significant factors for adverse fetal outcome. Stillbirth is strongly associated with fetal growth restriction. The risk factors and potential causes of stillbirth and fetal growth restriction mostly overlap. Other studies have shown a strong relationship between stillbirth and growth retardation with half the stillborn being less than 10 percentiles for weight.Data from Brimingham COGS project 2009 reported that stillbirth rate is 7 times higher when fetus have intrauterine growth restriction. In our study 26.9% babies weighed less than 1 kg.(26)

Cord Around Neck

16.4% of stillborn babies had cord around neck in the present study and tight cord around neck can affect the outcome of delivery. A study on perinatal mortality conducted by V Bangal et al found that some of the umbilical cord accidents can be prevented by identifying risk factors like malpresentation, cephalopelvic disproportion, polyhydramnios and multiple pregnancy during the antenatal visits.(27)

Antepartum Hemorrhage (Aph)

In our study, APH occurred in 23.1% of mothers who delivered stillborn babies. Bhandari S et al in their study reported that pregnancies complicated by APH of unknown origin are at a greater risk of stillbirth and adverse maternal outcome. Abruptio placentae was associated with adverse perinatal outcomes too.There were 3 cases of placenta previa and 2 cases of uterine rupture, all being women with previous caesarean section in our study.(28)

Meconium-Stained Liquor

Meconium-stained liquor was seen in 9% of the stillbirths in our study. Erum et al reported, in their study that meconium-stained liquor is associated with fetal mortality as it is a sign of hypoxia.(29)

Sex Of Baby

There were 54.4% male babies compared to 44% females in the presentstudy. In a study conducted by Debapriya Mondal et al, risk of stillbirth in males is elevated by about 10%.(30) There were 2 cases where the sex of the stillborn babies could not be unidentified. Gender was not a significant risk factor for stillbirth according to a study conducted by Sonal et al.(31)

Congenital Anomalies

Congenital anomalies were present in 12.7% of the stillborn babies in our study. Among them 4.5% babies had syndromic congenital malformations. 3% of the stillborn babies had both neural tube defects as well gastro intestinal tract anomalies. A very high percentage (25%) of stillbirths were attributed to congenital malformations.(16)

Liquor Abnormalities

In our study 21.6% (29 women) patients had oligohydramnios where as 11.2 % (15 women) participants had polyhydramnios. 11.2 % patients had PPROM out of which 3 women had features of chorioamnionitis.

ReCoDeSYSTEM

The ReCoDe system is an important step towards understanding the causes of still births. In our study, hypertensive disorder accounted for the commonest (44.8%) cause for stillbirth followed by IUGR (38.1%) and diabetes complicating pregnancy (36.6%). In our study we can identify the cause of stillbirth in almost 100% of cases and the factor which contributes maximum was taken into consideration.

In a study by Jason Gardosi et al in 2003 by the conventional Wigglesworth classification 66.2%of the stillbirths were unexplained. The proportion of stillbirths that were unexplained was high regardless of whether a post-mortem examination was carried out or not. By the ReCoDe classification, the most common condition was fetal growth restriction (43%) and only 15.2% remained unexplained. ReCoDe identified 57.7% of Wigglesworth unexplained stillbirths as growth restricted. The size of the category for intrapartum asphyxia was reduced from 11.7% (Wigglesworth) to 3.4%.(32)

In a study conducted by Ajini et al in 2017 which studied 177 cases of stillbirth, the SBR was 38.56 per 1000 live births and this study could explain the cause of stillbirths in 87.58% of cases by using ReCoDe system. In this study, they found that Intrauterine Growth Restriction (41.8%) was the commonest cause for stillbirth. It was followed by hypertensive disorders (27.68%), oligohydramnios (23.16%), congenital anomalies (12.42%), diabetes (14.68%) as the other causes.(16)

CONCLUSION

The new ReCoDe (Relevant Condition at Death) system is currently the only classification system specifically developed for classification of causes of stillbirths. With the help of new ReCoDe system we can identify the factors leading to stillbirth in our institution. It was seen that the factors leading to stillbirth included socio demographic factors like age of the patient, education, income, occupation, obstetric factors like parity, BMI, maternal medical disorders like gestational hypertension, gestational diabetes, maternal infections and fetal factors like IUGR, Oligamnios, and congenital anomalies of the fetus.

In our study 44.8% stillbirths were associated with hypertensive disorders contributing to the largest number stillbirths. Therefore Preeclampsia-eclampsia has been associated with increased risk of adverse perinatal

outcomes, necessitating screening, vigilant antenatal care, timely intervention, and referral. IUGR fetuses were associated with a high stillbirth rate. Prenatal recognition of IUGR will improve pregnancy outcomes by allowing close monitoring and timely delivery. The third most common cause of stillbirth was diabetes and it is recognized to be a major risk factor for stillbirth beyond 32 weeks, where timely intervention could reduce the stillbirth rate. Stillbirth was high in women who had lower levels of education, had a low socioeconomic status and when there were maternal factors like overweight and obesity. Other factors involved were cord around neck, antepartum haemorrhage, prolonged labour and meconium-stained amniotic fluid.

Thus,maternal and child death reviews, tracking of all deaths in the hospitals and simultaneously expanding it to the community in which most births occur will help in sharper understanding of the preventable causes and their management. So, to conclude, for improved perinatal outcomes it is imperative that the strategies should aim to improve quality of antenatal and intrapartum care with timely referral wherever necessary.

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Original Research Article

A cross-sectional study of corneal topography and ocular parameters in patients with myopia

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ABSTRACT

Background: Myopia is a leading cause of visual impairment. This study aims at determining the changes in corneal asphericity, central corneal radius of curvature, anterior chamber depth, lens thickness, vitreous chamber depth, and axial length with increasing myopia.

Materials and Methods: Spherical equivalent refractive error of each myopic eye was determined and grouped into three, according to increasing powers of myopia. Corneal asphericity (Q value) and central corneal radius of curvature were determined using corneal topography. Anterior chamber depth, lens thickness, vitreous chamber depth, and axial length were determined using Ascan. Changes with increasing myopia was assessed.

Result: Among 80 myopic eyes of age group 6 to 40 years, more patients were between 21 to 30 years. 60% of them were males. 60% were low myopes (<-3D), 32% were moderate myopes (-3D to -6D) and 8% were high myopes (>-6D). Mean Q values were -0.49±0.09, -0.39±0.04 and -0.28 ±0.04 for low, moderate and high myopes respectively. Mean values of apical radius of curvature of cornea were 7.66±0.07, 7.53±0.08 and 7.35±0.07 for low, moderate and high myopes respectively. Mean values of anterior chamber depth were 3.19±0.09, 3.32±0.09, 3.88±0.08; vitreous chamber depth were 19.82±0.67, 21.66±0.24, 22.66±0.45 and axial length were 23.01±0.76, 24.98±0.32,26.54±0.51 for low, moderate and high myopes respectively. A statistically significant positive correlation of increasing degrees of myopia was observed with Q value, anterior chamber depth, vitreous chamber depth and axial length; and a statistically significant negative correlation with the apical radius of curvature.

Conclusion: In myopic eyes, a statistically significant relation exists between corneal asphericity and spherical equivalent refractive error such that, there is a tendency for the cornea to flatten less rapidly in the periphery with increasing myopia and eyes with higher levels of myopia have steeper central corneal curvature, with deep anterior and vitreous chamber and greater axial length.

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1. Introduction

Myopia is a refractive error in which the light rays that enter parallel to the optical axis are brought into focus in front of the retina with accommodation being at rest. It can be due to the eyeball being elongated in the anteroposterior axis, or by an excessive corneal curvature or in the presence of lens with an increased optical power.[1] The image of the object which is projected anterior to the retina requires corrective lenses to displace the image posteriorly, thus producing a clear retinal image.[2] Refractive errors are the leading cause of moderate to severe visual impairment throughout the world, as many a times it goes undiagnosed and uncorrected. It is also the second most common cause of avoidable

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blindness.[3] The prevalence rate of myopia has increased throughout the world, and according to WHO, it is seen to increase from 22% in 2000 to 52% by 2050.[4] Myopia paves the way to ocular morbidity especially in school-going children and in young adults.[5] Myopia is caused by a wide variety of factors, ranging from genetic to environmental factors. Environmental factors are considered to be the major causative and most modifiable factors for myopia, especially in school going children, while genetic factors are responsible for a small proportion. Increased amount of time spent outdoors is found to be protective against the development and progression of incident myopia.[6] Single nucleotide polymorphisms (SNP)-based heritability estimation showed a heritability range from 25% to 35% 2050. It is more prevalent in developed and industrial areas and can affect individuals belonging to all age groups.[7] High myopia-associated genes were collagen type I, alpha 1 (COL1A1), transforming growth factor beta 1 (TGFB1), transforming growth beta-induced factor (TGIF), lumican (LUM), hepatocyte growth factor (HGF), myocilin (MYOC), paired box 6 (PAX6), and uromodulin-like 1 (UMODL1).[8]

At birth, most infants are born hypermetropic, but when the eyes grow they gradually become less hypermetropic and by the age of 5-8 years the eyes are emmetropic. The process of emmetropization refers to the adjustment in the length of the optical axis to the optical characteristics of the lens and cornea after the end of the second year of life. The development of myopia occurs when there is an overshooting of the process of emmetropization. The major structural change that takes place in myopic eyes is axial elongation, due to which alterations occur in the scleral extracellular matrix (ECM), which results in various changes in the shape of the sclera.[9]

Mild myopia is up to −1.5 D, moderate up to −6.0 D, and high myopia is −6.0 D or more. Pathological myopia occurs with greater than −8.0 D.[10] Complications of high myopia are open angle glaucoma, nuclear, cortical and posterior sub capsular types of cataract, retinal tears which may lead to a retinal detachment, myopic maculopathy which includes lacquer cracks, Foster Fuchs spot, choroidal neovascularization, chorioretinal atrophy and posterior staphyloma.[11]

Myopia is considered to be a public health problem causing visual loss and is a risk factor for various other ocular conditions.[12] Comparing the quality of life of those with low and moderate myopia, patients with a high degree of myopia suffer an impaired quality of life.[13] Hence it is important to diagnose as well as correct myopia at earlier years of life.

Correction of myopia include both non-surgical and surgical measures.[14] Non surgical measures consists of optical devices like spectacles and contact lenses.[15] Now a days surgical options for correction of myopia has gained popularity especially the refractive surgery.

Refractive surgical procedures includes radial keratotomy,[16] Excimer laser refractive surgery and intraocular surgery. Excimer laser assisted refractive surgery consists of laser-assisted sub epithelial keratectomy (LASEK) and laser-assisted in-situ keratomileusis (LASIK).[17] Both these procedures utilize laser to change the shape of the corneal tissue in order to correct the underlying refractive error by creating flaps prior to laser treatment of corneal stromal tissue. The flap in LASEK is more superficial and epithelial, whereas in LASIK it is thicker as it includes some stromal tissue from the anterior portion. The invention of femtosecond laser technique has helped to promote microkeratome free refractive surgeries. Both femtosecond laser-assisted laser in situ keratomileusis (FS-LASIK) and small incision lenticule extraction (SMILE)[18] have become the preferred surgical choice for many patients and the surgeons who perform refractive surgeries. Intraocular options include phakic intraocular lenses (pIOLs) which is another remedial method for the surgical correction of high myopia and in those with thinner corneas. Three types of lenses can be used for this purpose : anterior chamber angle-supported, anterior chamber iris-fixated, and posterior chamber phakic IOLs.[19] Therapeutic measures for slowing or halting the progression of myopia include progressive additional lenses,[20] peripheral defocusing lenses, contact lenses, overnight orthokeratology (Ortho-K),[21] multifocal soft contact lenses, outdoor activities,[22] and pharmaceutical agents like 0.01% Atropine.[23]

Assessment of the shape of the cornea is important for both cataract and refractive surgery, to screen the candidates and for analyzing its postoperative outcomes.[24] Advances in corneal mapping technology in the form of computer-aided corneal topography, or videokeratoscopes, has lead to the complete and accurate descriptions of the corneal shape prior to any procedure. The corneal topography provides clinicians and researchers with a wide range of graphical and numerical representations of the human corneal shape.[25] The cornea which is the major refractive component of the human eye, contributes to roughly about 70% of the total refractive power of the eye. The human cornea is a quadric surface with surface asphericity. The Q value, which is a quantified indicator of the aspherical degree, is defined as the radial change that occurs from centre to periphery of a quadric surface.[26] Corneal asphericity refers to the rate of change of curvature along the corneal surface from apex to periphery.

The typical shape of the human cornea is that of a prolate ellipse- which suggests that the cornea flattens from apex to periphery, and that the light rays that enters the centre of cornea tend to converge on a point in front of the peripheral rays to produce a negative spherical aberration. Normal cornea has a Q value of -0.26. Understanding asphericity

is important in adaptation following any refractive surgery. The modification of spherical aberration caused by contact lenses and corneal warpage induced by rigid lenses also have been studied.[27] It is predicted that the postoperative outcome in terms of corneal shape in all myopic corneas after excimer laser surgery would be increased oblateness.[28] Newer strategies are there to control asphericity in order to keep the spherical aberration to the minimum. There is a strong correlation between the change in corneal shape and the introduction of higher-order aberrations (HOAs) which in turn leads to poor night vision, glare, halo and poor quality of visual acuity thereby causing a long term negative effect on the patient.[29] The shape of cornea which can be determined roughly by the corneal asphericity is also important for prescribing an orthokeratology lens which is used to decrease the progression of myopia.[30]

Not many studies regarding asphericity and degree of myopia has been reported from Kerala and since refractive surgeries like SMILE and LASEK are on the rise, the preoperative assessment of corneal asphericity helps to predict postoperative outcomes and can give better results. This study aims at determining the corneal asphericity for myopic patients and assessing the change in the value of corneal asphericity with increasing degrees of myopia. This study highlights on the importance of assessing the corneal asphericity value for myopic patients since it has an implication in contact lens wear and refractive surgery. The main aim of this study is to analyse the change in corneal asphericity.

The second objective is to assess the changes of ocular parameters like central corneal radius of curvature, lens thickness, axial length, anterior and vitreous chamber depth with increasing degrees of myopia.

2. Materials and Methods

A cross-sectional study was conducted for a period of one year from 3/6/2020 to 2/6/2021 with the IEC number B6-155/2019/MCTCR(1) at Ophthalmology out patient department, at Government medical college Thrissur, Kerala among patients diagnosed with myopia.

The study included patients > 6years up to 40 years with myopic spherical equivalent refractive error ranging from -0.5D up to -10D and with corneal cylindrical power ⩽ -1.50D. Whereas, the study excluded those not giving consent for the study and those not cooperating for measurements. Specifically, the study excluded patients with dry eyes, irregular astigmatism, corneal lesions and lens defects, uveitis and infections of the eye, anomalies of the face & orbit, open angle glaucoma, keratoconus, pseudophakia, aphakia, vitreous hemorrhage.

According to a study conducted by Leo G. Carney et al.,[31] the proportion of patients having corneal asphericity was 95%.

Sample size - Z2 pq/d2 (d- 5% of p)

= 1.96 x 1.96 x 95 x 5/ 22.56

Sample size: 80 eyes

A written informed consent was taken from all patients who participated in this study. Preliminary examination of visual acuity for distance was done with Snellen's chart and a pinhole improvement was also noted.[32] Manifest refraction was performed for all patients with tropicamide (0.8%) with phenylephrine hydrochloride (5%) eye drops, and for those less than the 18 years of age, a cyclopegic like homatropine hypobromide (2%) eye drops was used. Further, post mydriatic refractive correction test was done for these patients. Subjects were divided into three groups:

Low myopes (SE <-3D), Moderate myopes (SE -3D to -6D), High myopes (SE> -6D).[33]

Corneal asphericity (Q value) and central corneal radius of curvature were determined using placido disk based corneal topography with a computerised videokeratoscope.

A scan (Amplitude scan) was done to determine lens thickness, axial length, anterior chamber and vitreous chamber depth. Changes in each parameter was studied with increasing degrees of myopia.[34]

3. Results

Statistical analysis was performed using SPSS software. The mean and standard deviation was calculated in different levels of refractive errors and assessed using ANOVA and Post Hoc test. Correlations were examined using Pearson correlation test. Values of $p<0.05$ were considered statistically significant in all the tests.

In this study a total of 80 eyes were studied, and the following were my observations.

Table 1: Distribution of age

Age	Frequency	Percentage
6-12	20	25
13-20	21	26
21-30	22	28
31-40	17	21

Table 2: Distribution of gender

Gender	Frequency	Percentage
Male	48	60
Female	32	40

Table 3: Distribution of grades of myopia

Myopia Grade	Frequency	Percentage
Low myope	48	60
Moderate myope	26	32
High myope	6	8
Total	80	100

Table 4: Mean values of Q value (Corneal asphericity) and other ocular parameters such as apical ROC (apical radius of curvature in mm), ACD (Anterior chamber depth in mm), Lens thickness in mm, VCD (Vitreous chamber depth in mm) and Axial length in mm with increasing degrees of myopia

Variables	Degrees of myopia					
	Low myope		Moderate myope		High myope	
	Mean	SD	Mean	SD	Mean	SD
Q value	-0.49	0.09	-0.36	0.04	-0.28	0.04
Apical ROC	7.66	0.07	7.53	0.08	7.35	0.07
ACD	3.19	0.09	3.32	0.09	3.88	0.08
Lens Thickness	3.45	0.25	3.47	0.25	3.56	0.27
VCD	19.82	0.67	21.66	0.24	22.66	0.45
Axial length	23.01	0.76	24.98	0.32	26.54	0.51

4. Results of statistical analysis

One way Anova test showed statistically significant differences in the following parameters between the three grades of myopia.

Table 5: One way Anova test was applied to obtain P-values

Ocular parameters	P value
Q value	<0.001
Apical radius of curvature	<0.001
Anterior Chamber Depth (ACD)	<0.001
Vitreous Chamber Depth (VCD)	<0.001
Axial Length	<0.001
Lens thickness	0.300

P-values of Q value (corneal asphericity), Apical radius of curvature, Anterior Chamber Depth, Vitreous Chamber Depth and Axial Length were <0.001 and P-value of Lens Thickness was 0.300

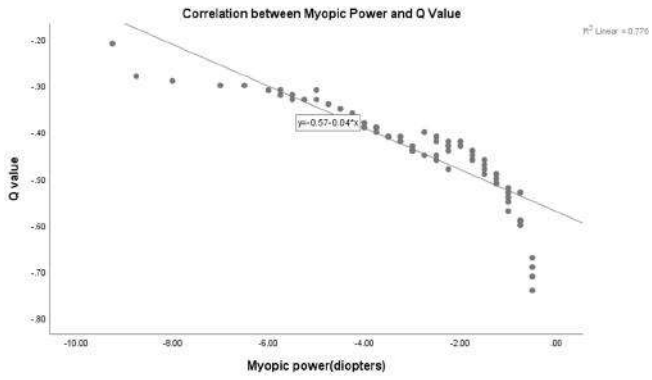


Figure 1: Scatter diagram depicting correlation of increasing degrees in myopia with Q-value

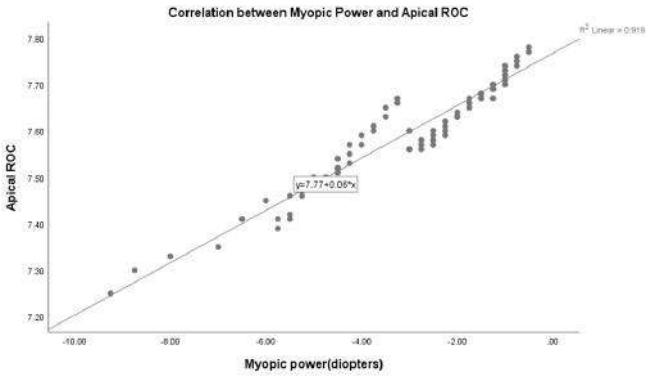


Figure 2: Scatter diagram depicting correlation of increasing degrees in myopia with Apical radius of curvature (ROC)

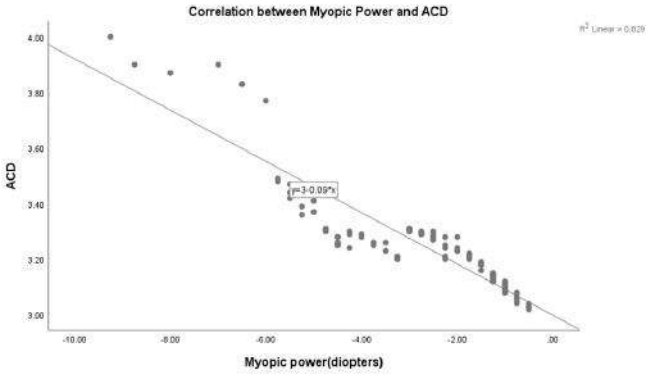


Figure 3: Scatter diagram depicting correlation of increasing degrees in myopia with Anterior chamber depth (ACD)

5. Discussion

This study was conducted among 80 myopic eyes of age group ranging from 6 to 40 years with more patients belonging to the age group 21 to 30 years. The percentage of males and females were 60% and 40% respectively. 60% of the patients were low myopes with refractive error of <-3D. 32% were moderate myopes with a refractive error in between -3D to -6D. 8% were high myopes with a refractive error of >-6D. Mean Q values were -0.49±0.09, -0.39±0.04 and -0.28 ±0.04 for low, moderate and high myopes respectively. Thus, the mean Q value increased with increasing degrees of myopia, which was similar to the result obtained in the studies conducted by D G Horner et al[35] and Zhengwei Zhang et al.[36] Mean values of apical radius of curvature of cornea were 7.66±0.07, 7.53±0.08 and 7.35±0.07 for low, moderate and

Table 6: Correlation coefficients of increasing degrees of myopia with Q value and other ocular parameters like apical radius of curvature, axial length, lens thickness, anterior chamber depth (ACD) and Vitreous chamber depth (VCD)

Parameters	Pearson Correlation coefficient	Type of correlation
Myopia vs Q value	0.881	High positive
Myopia vs Apical ROC	-0.958	Very high negative
Myopia vs ACD	0.910	Very high positive
Myopia vs VCD	0.960	Very high positive
Myopia vs Axial length	0.974	Very high positive
Myopia vs lens thickness	0.117	Negligible correlation

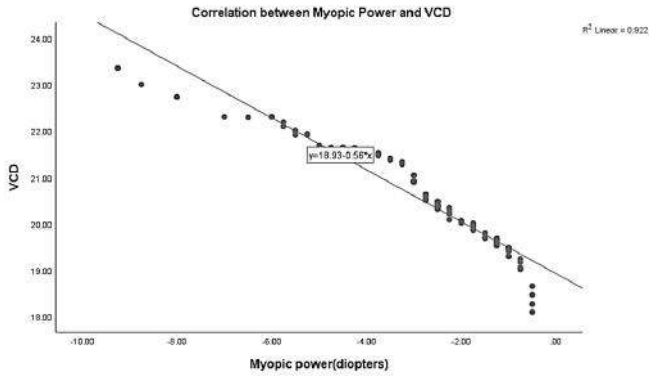


Figure 4: Scatter diagram depicting correlation of increasing degrees in myopia with Vitreous chamber depth (VCD)

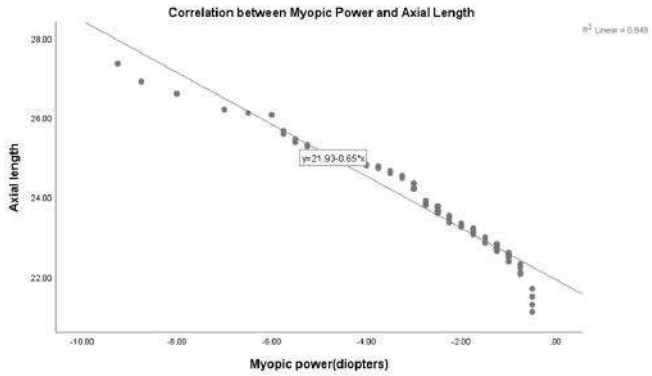


Figure 5: Scatter diagram depicting correlation of increasing degrees in myopia with Axial length

high myopes respectively indicating that apical radius of curvature decreased with increasing degrees of myopia. Whereas the mean values of anterior chamber depth were 3.19±0.09, 3.32±0.09, 3.88±0.08; vitreous chamber depth were 19.82±0.67, 21.66±0.24, 22.66±0.45 and axial length were 23.01±0.76, 24.98±0.32,26.54±0.51 for low, moderate and high myopes respectively, therefore showing an increase with increasing degrees of myopia. This study also showed a statistically significant positive correlation of increasing degrees of myopia with Q value, axial length, anterior chamber and vitreous chamber depth and statistically a significant negative correlation of increasing

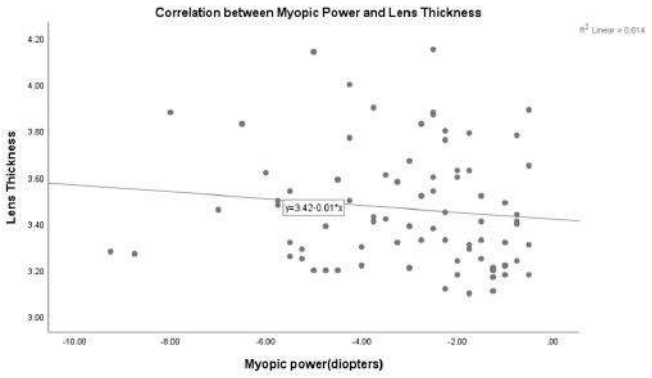


Figure 6: Scatter diagram depicting correlation of increasing degrees in myopia with lens thickness

degrees of myopia with apical radius of curvature, and all these with p<0.05. The lens thickness showed negligible correlation with increasing degrees of myopia.

This study determined a statistically significant positive correlation between corneal asphericity (Q value) and myopic spherical equivalent refractive error (ρ=0.881, p<0.001), which was in accordance with the study conducted by Carney L G et al.[31] A study conducted by W.R Davis et al[25] found that corneal asphericity was less prolate among myopes which also was similar to our study. Koray Budak et al[37] found that higher the degree of myopia, the negative asphericity increased, and the corneal radius of curvature decreased, as in our study. This study also determined that axial length, anterior chamber and vitreous chamber depth were positively correlated with myopia and significantly increased as myopia increased, that is (ρ=-0.910, p<0.001), (ρ=0.96, p<0.001) and (ρ=-0.974, p<0.001) respectively, which was similar to the studies conducted by Carney L G et al[31] and Wadhwa et al.[38] The positive correlation of vitreous chamber depth with increase in degrees of myopia was similar to that obtained in the study conducted by Ruozhong Xie et al.[39] A Study done by Majumder C, Tan YC[40] determined a statistically significant increase in axial length and corneal curvature similar to this study, but there was no significant difference noted in anterior chamber depth with increase in degrees of myopia, which was contradictory to this study.

In the recent years, the number of corneal refractive surgical procedures performed worldwide has been increasing at steady pace.

The renowned interest in the analysis of human corneal topography has accompanied this rise in the number of such refractive surgical procedures, which in turn helps to determine the postoperative outcome in regard to the corneal shape and the resulting visual performance. Knowledge of the shape of the normal human cornea and the extent of variation in corneal topography between individuals is also vital for designing contact lenses, schematic eye modelling, and ocular aberration analysis.[41]

In this study, the corneal asphericity (Q value) and apical radius of curvature of the cornea was obtained using placido disc based corneal topography, however, newer machines like Orbscan and Pentacam gives more accurate results. The ocular biometric values were obtained using Ascan ultrasonography in this study; but more accurate results are obtained with immersion technique or the optical technique.

6. Conclusion

The study has shown that in myopic eyes, a statistically significant relation exists between corneal asphericity and myopic spherical equivalent refractive error indicating that, there is a tendency for the cornea to flatten less rapidly in the periphery with increasing degrees in myopia. The study also confirmed that eyes with higher levels of myopia have increased central corneal curvature, deeper anterior and vitreous chamber and greater axial length.

7. Source of Funding

None.

8. Conflict of Interest

None.

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Original Research Article

The Ocular Manifestations of Systemic Tuberculosis –A Hospital Based Observational Study

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ABSTRACT

Aim
To determine the prevalence and factors associated with ocular manifestations of tuberculosis in a population of persons with tuberculosis in central Kerala

Methods
A cross sectional study of persons with tuberculosis referred to the ophthalmology department by the RNTCP program with a confirmed diagnosis of tuberculosis. All patients underwent a detailed ophthalmology assessment including visual acuity, colour vision, and anterior and posterior segment assessments. A Fishers exact test was used to explore for associations with ocular tuberculosis in a bivariate analysis.

Results
The study included 143 patients and eleven patients (7.69%, 95% CI: 4.35, 13.25) had ocular manifestations of tuberculosis. One hundred and six patients (74.13%) were diagnosed as pulmonary tuberculosis and 21 (14.69%) had extrapulmonary tuberculosis. Posterior uveitis was seen in 5 (3.50%) patients and optic nerve involvement in 3 (2.10%) patients. The distribution of ocular TB was not associated with age, gender, site of TB, and other diagnostic test results in the study population.

Conclusion
The results of our study suggest that a targeted screening for ocular TB only in a subgroup of persons with tuberculosis may not be a feasible strategy. The presumptive diagnosis, difficulty in confirmation of the diagnosis and the possibility of vision loss due to posterior uveitis that

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involves the macula or optic nerve involvement makes it imperative that every person with tuberculosis is screened for ocular manifestations.

Key Words: Tuberculosis, Ocular tuberculosis, Posterior Uveitis, Optic Neuritis.

INTRODUCTION

The World Health Organization estimates that approximately 2 billion people worldwide have tuberculosis (TB) that includes 10% with symptoms and 90% with latent infection.[1] The incidence of tuberculosis is increasing worldwide due to multidrug-resistant TB, human immunodeficiency virus (HIV), and global migration.[2-4] Approximately 40% of the Indian population is affected with Mycobacterium tuberculosis with most of the infection latent in nature. The incidence of TB in Kerala is 67/100000, which is only half the national rate of 138/100000 as per RNTCP. Ocular TB is defined as a mycobacterium tuberculosis infection in the eye, around the eye, or on its surface that is usually not associated with clinical evidence of pulmonary TB, as up to 60% of extrapulmonary TB patients may not have pulmonary TB.[5,6] Ocular TB can be primary when the eye is the primary port of entry of the mycobacterium into the body, or secondary when ocular manifestations are a result of seeding by hematogenous spread from a distant site. Inflammation of the uveal tract is the most common eye manifestation of the disease due to its high blood supply and oxygen tension.[7,8] The prevalence of tuberculosis as a cause of uveitis ranges from 0.5% in the USA to 6.9% in Japan, 9.86% in north India, 10.5% in Saudi Arabia, and 11.4% in Iraq.[9-13] We designed a cross sectional study to determine the prevalence of ocular morbidity in systemic tuberculosis, and factors associated with ocular manifestations in a population of persons with tuberculosis attending the ophthalmology unit of a tertiary care teaching hospital in central Kerala.

MATERIALS & METHODS

The study protocol that utilized a cross sectional study design was approved by the institutional ethics committee. Informed consent was obtained from all participants before enrolment in the study. The study included consecutive patients with tuberculosis who were referred to the ophthalmology department of the study institute as part of the RNTCP protocol from February 2019 to February 2020. The study excluded patients with exclusive ocular tuberculosis and those already diagnosed with mimicking conditions like Sarcoidosis and Brucellosis. The sample size for the study was estimated based on an anticipated prevalence of 15% and a d of 5 and using the formula $N= 4PQ/d^2$.

A detailed history including age, sex, drug history, co morbid conditions, medical history, date of diagnosis, date of initiation of antitubercular therapy was collected from the case records of each participant. Each participant underwent a detailed ophthalmic examination that included best corrected visual acuity, near vision, colour vision, anterior segment assessments using slit lamp biomicroscopy and posterior segments assessments with direct and indirect ophthalmoscopy. A fundus fluorescein angiography was done if the posterior segment assessment indicated retinal or choroidal involvement. Details of additional investigations including Sputum AFB, Mantoux test, chest x-ray PA views, ESR, serum calcium/ACE levels, routine blood test, random blood sugar and HIV/ELISA tests were documented.

Statistical Analysis

The data collected was entered into an anonymized MS Excel spreadsheet and subsequently exported to the statistical software SPSS v 20.0 for further analysis. The distribution of ocular manifestations of TB were expressed as a proportion. Bivariate analysis was performed using a Fishers Exact test to explore for associations of various factors with ocular TB. A p value <0.05 was considered as statistically significant.

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RESULTS

The study included 143 patients who were examined at the ophthalmology department of the study institute after referral from the RNTCP program. Eleven of the 143 patients (7.69%, 95% CI: 4.35, 13.25) had ocular manifestations of tuberculosis. Most of the study participants were aged >50 years (n=67, 46.83%) and 91 (63.64%) were males. The baseline characteristics of the study population are presented in Table-1. One hundred and six patients (74.13%) were diagnosed as pulmonary tuberculosis and 21 (14.69%) as extrapulmonary tuberculosis. Disseminated TB was found in 4 patients, CNS involvement in 2 and TB in other locations in 8 patients. Two patients were considered as a relapse/failed primary therapy. One hundred and thirty-two (92.31%) patients did not have any ocular manifestations of TB. Posterior uveitis was seen in 5 (3.50%) patients and included fresh choroiditis patches in 2 patients, old choroiditis patches in 2 patients and early vasculitis in 1 patient. Optic nerve involvement was seen in 3 (2.10%) patients and included disc pallor after antitubercular therapy in 2 patients. The cornea, anterior segment, and conjunctiva was involved in 1 patient each. The distribution of ocular TB was not associated age, gender, site of TB, and other diagnostic test results in the study population (see Table-2).

Characteristics	Number of patients (percentage)
Age < 20 years	8 (5.59%)
Age 20-40 years	39 (27.27%)
Age 40-50 years	27 (19.15%)
Age >50 years	67 (46.83%)
Males	91 (63.64%)
Sputum Positive	46 (32.17%)
CBNAAT Positive	54 (37.76%)
ESR >50	68 (47.55%)
HIV Positive	1 (0.70%)
Random Blood Sugar >160	31 (21.68%)
Colour Vision Normal	117 (81.82%)
Visual Acuity better than 6/18	105 (73.43%)
Visual Acuity worse than 6/60	11 (7.69%)

Table-1: Baseline characteristics of the study population

Factor	P- Value (Fishers Exact Test)
Age	0.94
Sex	0.26
Sputum Positivity	0.70
CBNAAT Positivity	0.08
ESR	0.84
Random Blood Sugar	0.50
Location of TB	0.41

Table-2: Clinical and demographic associations with ocular Tuberculosis in the study population

DISCUSSION

The prevalence of ocular manifestations in this study (7.69%) is consistent with a previous study from North India that reported a prevalence of 9.86%.[11] The prevalence of posterior uveitis (45.45%) in the study population is also consistent with a previous study from India that reported a prevalence of 42% for posterior uveitis.[14] The diagnosis of ocular TB is often

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problematic due to a wide spectrum of presentations and the difficulty to have a definitive histopathological diagnosis and hence the diagnosis of ocular TB is presumptive in most cases.[8.15] Tuberculous uveitis mimics various other causes of uveitis and can be considered in the differential diagnosis of any type of intraocular inflammation especially in areas where TB is endemic. The management of tuberculous uveitis is affected by the uncertainty whether the ocular manifestations result from a direct mycobacterium infection or hypersensitivity reaction. The presence of choroidal nodules may suggest direct hematogenous infection, but immune hypersensitivity is a more likely cause for vasculitis and choroiditis.[16,17]

We did not find an association of pulmonary TB with ocular manifestations of tuberculosis in this study. These results are consistent with previous studies that have reported that most patients with ocular involvement have no history of pulmonary or other systemic forms.[18] Ocular TB can be present even in the absence of clinically evident pulmonary TB as nearly 60% of patients with extrapulmonary TB have no evidence of pulmonary TB and chest X-rays are normal in cases of latent TB.[19,20]

The lack of associations and the presumptive diagnosis are important considerations in the management of uveitis that may presumably be due to TB. Several studies have reported a favourable response when systemic corticosteroids are administered simultaneous with antitubercular therapy.[14,21,22] Use of ATT in these patients may help by killing the intraocular microorganisms and eliminating the antigen load, the recurrences, and the resultant hypersensitivity inflammation.[15] In eyes with presumed TB uveitis, it might be better to add systemic steroids only when lesions are involving or threatening the macula or to reduce macular scarring.[15] The difficulty in establishing a diagnosis and the lack of associations with ocular manifestations of TB can lead to diagnostic and clinical management challenges. The lack of association in our study can be a true lack of association or possibly can be due to the small number of patients with ocular TB in our study. Our study coincided with the implementation of lockdown for the COVID-19 pandemic and hence had to be stopped.

Newer diagnostic modalities may help reduce the clinical management difficulties. Interferon gamma release assay (IGRA) is based on gamma interferon production by T cells sensitized to specific antigens that are specific to mycobacteria TB and are not influenced by BCG and most nontuberculous bacteria. The IGRA test is more sensitive and specific compared to the tuberculin skin test to detect active pulmonary infections but are less sensitive to detect latent infections.[15] The accuracy of diagnosing TB uveitis increases when IGRA and Tuberculin skin testing are used in combination with suggestive clinical signs.[23] Polymerase chain reaction (PCR) tests are increasingly used based on skin, conjunctiva, aqueous, vitreous, choroidal tissue, epiretinal membrane. A case control study in tuberculous uveitis showed 77.2% sensitivity and 92.1% specificity for PCR[24] but several studies have reported a low sensitivity as many ocular manifestations may represent a delayed hypersensitivity reaction making the analysis of a fluid sample from the eye less sensitive.[8,25]

The results of our study suggest that a targeted screening for ocular TB only in a subgroup of persons with tuberculosis may not be a feasible strategy. The presumptive diagnosis, difficulty in confirmation of the diagnosis and the possibility of vision loss due to posterior uveitis that involves the macula or optic nerve involvement makes it imperative that every person with tuberculosis is screened for ocular manifestations. The screening becomes important when medications like Ethambutol are considered for the management. Further studies on a larger population of patients with ocular TB will help to understand possible associations with the onset and progress of ocular TB.

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CONCLUSION

Our study suggests that targeted screening for ocular TB in select TB patients may not be effective due to diagnostic challenges and potential vision loss. Therefore, all TB patients should be screened for ocular manifestations at the initial time of diagnosis of the disease itself.

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Original Article

Ophthalmology Section

Effect of Corneal Collagen Crosslinking with Riboflavin in Patients of Progressive Keratoconus: A Prospective Cohort Study

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ABSTRACT

Introduction: Keratoconus is a non inflammatory disease characterised by progressive corneal thinning that results in a cone-like ectasia, irregular astigmatism, and decreased vision. Advanced disease can result in corneal scarring and blindness, necessitating penetrating keratoplasty. The only treatment believed to have the ability to stop or decrease the progression of keratoconus is Collagen Cross-Linking (CXL).

Aim: To evaluate the efficacy of corneal collagen cross-linking with riboflavin (C3R) in patients with keratoconus by studying the outcomes in terms of Uncorrected Visual Acuity (UCVA), Best Corrected Visual Acuity (BCVA), manifest refraction, and corneal topography.

Materials and Methods: A hospital-based prospective cohort study was conducted at the Regional Institute of Ophthalmology, Government Medical College, Thiruvananthapuram, Kerala, India from June 2017 to June 2018. Fifteen eyes of 12 patients who underwent corneal collagen cross-linking for progressive keratoconus were included. Routine ophthalmological examinations was done for all patients. Patients under the age of 35 years with progressive keratoconus, an average K value not exceeding 60 D, and who had not undergone any other surgical modalities of treatment were included in the study. Patients with scarred cornea or hydrops, active ocular infection, or pachymetry <400 µm were excluded. Detailed informed consent was obtained from all patients before surgery. Preoperative UCVA, BCVA cylinder, Spherical Equivalent (SE), and topography values were obtained. All patients were followed-up at three and six months postoperative period to look for changes in UCVA, BCVA, manifest refraction, and corneal topography. Data were expressed as the mean±Standard Deviation (SD) pre- and postoperatively and analysed statistically using the paired t-test, with $p<0.05$ considered statistically significant. Analysis was conducted using Statistical Package for Social Sciences (SPSS) version 16.0.

Results: On follow-up at six months post-treatment, UCVA (log MAR) improved from 0.87±0.40 to 0.65±0.35 (p-value=0.001), and BCVA (log MAR) changed from 0.37±0.21 to 0.17±0.22 (p-value=0.001). K max decreased from 54.90±6.05 to 52.67±5.02 (p-value=0.001), and K min decreased from 48.14±4.24 to 45.93±4.07 (p-value=0.001). Astigmatism and SE also showed statistically significant improvement post-procedure (p-value 0.001 and 0.002, respectively). Astigmatism reduced from -3.50±1.58 to -2.90±1.37. SE reduced from -4.93±3.92 to -4.28±3.48. No significant complications were noted in any of the patients.

Conclusion: The CXL is an effective procedure for stabilising the progression of keratoconus, thus reducing the burden of preventable blindness and the need for keratoplasty.

Keywords: Best corrected visual acuity, Corneal ectasia, Corneal topography

INTRODUCTION

Keratoconus is a bilateral, non inflammatory corneal ectasia characterised by progressive corneal thinning and protrusion leading to progressive myopia, irregular astigmatism, and corneal scarring [1]. Several modalities such as hard contact lenses, intracorneal stromal ring implantation, and penetrating keratoplasty are used to treat keratoconus [1]. Spectacles and contact lenses are the usual treatment modalities in the early stages of keratoconus. As the disease advances, severe corneal astigmatism and stromal opacities develop to the point where contact lenses can no longer provide useful vision, and penetrating keratoplasty becomes necessary to restore visual function [2]. Penetrating keratoplasty is the most commonly performed surgical procedure for keratoconus, but is associated with complications, including graft rejection [3], and is also limited by the availability of donor corneas in developing countries. Additionally, all these techniques only correct the refractive error of the cornea with no effect on the progression of keratoconus [4]. The only treatment believed to have the ability to stop or decrease the progression of keratoconus is CXL [5]. CXL changes the biomechanical, thermomechanical, and morphological properties of the cornea [6]. This procedure, utilising riboflavin and ultraviolet-A light, significantly increases the biomechanical strength of the cornea by photochemical cross-linking of individual collagen fibers [4]. Riboflavin (Vitamin B2) has a dual function of acting as a photosensitiser for the production of oxygen free radicals, which induce physical CXL, and it provides a shielding effect by absorbing 90% of the UV-A irradiation, thereby preventing damage to deeper ocular structures. UV-A light of 370 nm wavelength at 3 mW/cm^2 allows approximately 95% of the UV light to be absorbed into the cornea; thus, there is no risk of damage to the lens and retina [2,7]. It increases the stiffness and rigidity of the anterior corneal stroma and enhances corneal resistance to proteolytic enzymes by inducing photochemical cross-linking and covalent bonding between individual collagen fibers [5], thus preventing the progression of corneal ectasia in keratoconus and stabilising the vision. CXL halts the progression of keratoconus with a failure rate of approximately 3% and a complication rate of ≤1% [8]. Since corneal CXL alters the corneal shape and structure, it would be helpful to assess resulting changes in quantitative descriptors of the cornea, which can affect the clinical outcome of this procedure. Studies by Bamdad S et al., and Greenstein SA et al., have shown that CXL improves visual acuity, average keratometry values, and definable measures of corneal topography regularity [9,10].

Though it has been extensively studied in other parts of the world, there are limited studies regarding the same in India. The current study aims to evaluate the efficacy of C3R in preventing the progression of keratoconus and stabilising the vision by studying the outcome in terms of UCVA, BCVA, manifest refraction, and

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corneal topography in South Indian patients. The study also had an objective to note the side-effects of CXL, if any.

MATERIALS AND METHODS

This hospital-based prospective cohort study was conducted at the Regional Institute of Ophthalmology, Government Medical College, Thiruvananthapuram, Kerala, India from June 2017 to June 2018. Ethical clearance was obtained from the Institutional Ethics Committee (IEC No.068/HEC/RIOTVPM dated 35/02/2017). Informed consent was obtained from all the patients.

Inclusion criteria: Patients aged <35 years with progressive keratoconus who were not improving with spectacles or contact lenses and with an average k value not exceeding 60D were included in the study.

Exclusion criteria: Patients who had undergone any other surgical modalities of treatment for keratoconus were excluded. Pregnant or lactating women, patients with active ocular inflammation, chronic ocular surface disease, autoimmune diseases, and a past history of herpetic disease were also excluded from the study. Patients with a scarred cornea, central corneal thickness <400 μm, and vision at presentation <2/60 were also excluded from the study.

Sample size: The sample size was calculated from preoperative and postoperative UCVA in the reference study by Arbelaez MC et al., based on the formula [2].

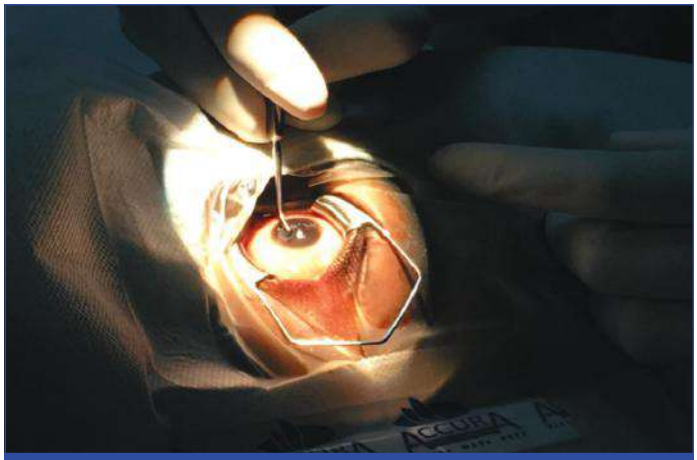
$N=(z_{\alpha/2}+z_{1-\beta})^2\ (\sigma_1^2+\sigma_2^2)/(\mu1+\mu_2)^2$ Where $(z_{\alpha/2}+z_{1-\beta})^2=7.9$ for $\alpha=0.05$ and $\beta=0.2$

In the reference study, the mean preoperative UCVA was found to be 1.18±0.69 and the mean six months postoperative UCVA was 0.63±0.32. So the calculated sample size was 15.

A history was taken using a proforma, routine ophthalmological examination, and measurement of the following parameters before and after C3R: UCVA, BCVA, cylinder value, and SE. UCVA and BCVA were measured using a log MAR chart. Corneal topography and central corneal thickness were measured with an ultrasonic Pachymeter (Quantel medical- compact touch). Corneal curvature was measured with an auto refractometer/keratometer and corneal topography (Topcon corneal topographer-KR-1W). Refraction was measured with an auto refractometer and subjective refraction. SE was calculated as the spherical refractive error plus 0.5×cylindrical refractive error [11]. For example, if the refraction is +2.50 DS -0.50DC at 90°, the SE is calculated as SE=+2.50+(-0.50/2)=+2.25 DS.

Study Procedure

Initial assessment included history taking using a proforma, and routine ophthalmological examination was done. The procedure was performed in the operating room under sterile conditions. Topical proparacaine hydrochloride (0.5%) eye drops were instilled before the procedure. The central 8 mm corneal epithelium was removed by mechanical debridement to allow better penetration of riboflavin [Table/Fig-1]. This was followed by the application of the photosensitiser riboflavin (0.1% solution) to the de-epithelised cornea every two minutes for a period of approximately 30 minutes. Exposure to UV-A light was initiated after ensuring that adequate penetration of riboflavin had occurred, as indicated by the presence of yellow flare in the anterior chamber [Table/Fig-2]. The cornea was then subjected to UV-A radiation (370 nm) in a dose of 3 mW/cm^2 by an irradiating source placed at a distance of 5 cm from the center of the cornea. To complete photosensitisation and to provide photoprotection by a barrier effect, riboflavin drops were again instilled every two minutes during the irradiation treatment. On completion of the procedure, antibiotic drops were instilled, following which a sterile Bandage contact lens was applied for three days or until there was re-epithelialisation of the cornea. Patients were instructed to use antibiotic and steroid eye drops four times a day for a week following the procedure. The steroid drops were gradually tapered over one month.



[Table/Fig-1]: Mechanical debridement of epithelium in C3R.



[Table/Fig-2]: Exposure to UVA after application of riboflavin.

STATISTICAL ANALYSIS

The data was entered in MS Excel and analysed using SPSS version 16.0. All parameters were analysed pre and postoperatively using the paired t-test for each parameter. The data was expressed as the mean±SD pre and postoperatively. A p-value of <0.05 was considered to be statistically significant.

RESULTS

Fifteen eyes of 12 patients who underwent corneal C3R with riboflavin for progressive keratoconus were studied. Demographic details are shown in [Table/Fig-3].

Patient characteristics	n (%)
Sex	
Males	10 (83.3)
Females	2 (16.7)
Age (years)	
15-20	7 (58.3)
21-26	5 (41.7)
Laterality	
Unilateral	9 (75)
Bilateral	3 (25)

[Table/Fig-3]: Patient characteristics.

Changes in Uncorrected Visual Acuity (UCVA): The mean preoperative UCVA was 0.87±0.40 (log MAR), which improved to 0.75±0.39, three months post-treatment and was found to be statistically significant (p-value=0.001). The UCVA further improved to 0.65±0.35 at six months follow-up (p-value=0.001) [Table/Fig-4].

Changes in Best Corrected Visual Acuity (BCVA): The mean preoperative BCVA was 0.37±0.21 (log MAR), which improved to 0.25±0.27, three months postoperatively, which was found to be statistically significant (p-value=0.001). At six months follow-up,

there was further improvement to 0.17±0.22 (p-value=0.0001) [Table/Fig-5].

Examination time	UCVA (logMAR) Mean±SD	p-value	t value
Preoperative	0.87±0.40	-	-
3 months	0.75±0.39	0.001	4.999
6 months	0.65±0.35	0.001	7.837

[Table/Fig-4]: Mean UCVA before and after surgery.
*analysed with paired t-test, p-value=0.001

Examination time	BCVA (logMAR) SD±mean	p-value	t value
Preoperative	0.37±0.21	-	-
3 months	0.25±0.27	0.001	4.210
6 months	0.17±0.22	0.0001	8.756

[Table/Fig-5]: Mean BCVA before and after surgery.
*analysed with paired t-test, p-value=0.001

Changes in Keratometry

Changes in Kmax

The mean preoperative Kmax was 54.90±6.05. Three months after the procedure, it decreased to 53.67±5.32 and was found to be statistically significant (p-value=0.001). At six months follow-up, it further decreased to 52.67±5.02 (p-value=0.001) [Table/Fig-6].

Examination time	Kmax (dioptres) Mean±SD	p-value	t value
Baseline	54.90±6.05	-	-
3 months	53.67±5.32	0.001	5.212
6 months	52.67±5.02	0.001	5.492

[Table/Fig-6]: Mean kmax before and after C3R.
*analysed with paired t-test, p-value=0.001

Changes in K min

The mean baseline Kmin in dioptres was 48.14±4.24 (mean±SD), which decreased to 46.88±3.89 three months after the procedure (p-value=0.001). At six months follow-up, it further reduced to 45.93±4.07 (p-value=0.001) [Table/Fig-7].

Examination time	Kmin (diopters) Mean±SD	p-value	t-value
Baseline	48.14±4.24	-	-
3 months	46.88±3.89	0.001	4.940
6 months	45.93±4.07	0.001	4.839

[Table/Fig-7]: Mean Kmin before and after C3R.
*analysed with paired t-test, p-value-0.001

Changes in cylinder value: The mean preoperative cylinder value was -3.50±1.58, which decreased to -3.35±1.54 (p-value 0.03) at three months follow-up and -2.90±1.37 at six months follow-up. Both changes were found to be statistically significant (p-value=0.01) [Table/Fig-8].

Examination time	Cylinder value(D) Mean±SD	p-value	t value
Baseline	-3.50±1.58	-	-
3 months	-3.35±1.54	0.03	2.358
6 months	-2.90±1.37	0.001	4.664

[Table/Fig-8]: Mean cylinder value before and after surgery.
*analysed with paired t-test, p-value=0.001

Changes in Spherical Equivalent (SE): The mean preoperative SE was -4.93±3.92, which decreased to -4.69±3.76, three months after the procedure (p-value=0.032). At six-month follow-up, it further decreased to -4.28±3.48 (p-value=0.002) [Table/Fig-9].

In the current study, out of the 15 eyes studied, 14 of the eyes showed improvement in visual acuity, gradual reduction in keratometry values, and gradual flattening of the cornea, reducing the astigmatism post-surgery. Only one patient showed mild worsening of corneal topography and manifest refraction, but he maintained his preoperative UCVA and BCVA with glasses. The patient had chronic allergic conjunctivitis with constant eye rubbing, which probably resulted in further progression of keratoconus.

Examination time	Spherical Equivalent (SE) Mean±SD (dioptres)	p-value	t-value
Baseline	-4.93±3.92	-	-
3 months	-4.69±3.76	0.032	2.377
6 months	-4.28±3.48	0.002	3.912

[Table/Fig-9]: Mean Spherical Equivalent (SE) before and after surgery.
*analysed with paired t-test, p-value=0.002

DISCUSSION

Corneal collagen cross-linking with riboflavin and UVA (CXL) is a new technique of corneal tissue strengthening that combines the use of riboflavin and UVA irradiation. Riboflavin works as a photosensitiser for the induction of cross-links between collagen fibrils and at the same time acts as a shield from the penetration of UVA into the underlying tissues [2]. It was first introduced by Wollensak G et al., as a promising technique to slow or stop the progression of keratoconus. He included 23 eyes with moderate or advanced progressive keratoconus and showed that CXL was effective in halting the progression of keratoconus over a period of four years. In all treated eyes, the progression of keratoconus was at least stopped. In 16 eyes (70%), regression with a reduction of the maximal keratometry readings by 2.01 diopters was noted [4], whereas in the current study, Kmax decreased by 2.23 D.

CXL treatment has an arresting effect on the progression of keratoconus. Due to an increased number of cross-linking sites within the collagen molecule after CXL, stiffer fibrils and lamellae are likely generated. This process produces a rearrangement of corneal lamellae and the consequent relocation of the surrounding matrix, which, in turn, results in the reduction of the central corneal curvature. A small regression occurring may be explained as an effect of the rearrangement of corneal lamellae and the surrounding matrix [12]. Various studies have proved the efficacy of the procedure in reducing the corneal curvature, SE refraction, and astigmatism in keratoconus eyes after the application of CXL [4,9,12-15]. Kymionis GD et al., demonstrated that there was no discrepancy in terms of endothelial cell density between treated and untreated eyes, thus proving the safety of the method [16].

In the present study, 15 eyes of 12 patients with progressive keratoconus who underwent corneal collagen cross-linking were included. In the study done by Nasrollahi K et al., 140 eyes of 110 patients were studied [17]. In a study done by Raiskup-Wolf F et al., 480 eyes of 272 patients were included [18]. Other similar studies with a relatively small sample size include that done by Arbelaez MC et al., where 20 eyes of 19 patients were studied [2]. The minimum age of the patients in the present study was 15, and the maximum age was 26. The mean age of the patients was 19.62±3.52 years. A study done by Fatima T et al., found that in India, keratoconus presents at an early age compared to the Western population [19]. In the study done by Arbelaez MC et al., the mean age of the patients was found to be 24.4 years. Patients ranging from 18-44 years of age were studied by them [2]. Meanwhile, the current study did not include patients aged over 35 years. In a study done by Koller T et al., it was found that restricting patient age to younger than 35 years may reduce the complication rate to 1% [8].

In the study done by Caporossi A et al., patients were divided into three groups based on age: paediatric patients (age ≤18 years), an intermediate group (19-26 years), and adults (≥27 years). The study found that corneal collagen cross-linking was more effective in the paediatric and intermediate age groups on long-term follow-up [20]. The male-to-female ratio in the present study was 5:1. This can be attributed to the fact that the majority of the patients who presented

to the OPD of the institute at the time of the study were males. In a study from North India [21] and one from Western India [22], keratoconus was noted more often in males, while the Central India study found a higher prevalence in women [23].

All the patients were followed-up for a period of six months to look for changes in UCVA, BCVA, corneal topography, and manifest refraction. In the current study, UCVA improved by 0.22 (from 0.87±0.40 to 0.65±0.35) at the final follow-up after six months post-surgery, which was found to be statistically significant (p-value=0.001). In the study done by Arbelaez MC et al., UCVA improved by 0.55 at six months follow-up [2]. In a similar study done by Saffarian L et al., UCVA improved by 0.3D one year after the procedure [14]. BCVA showed an improvement of 0.2 (from 0.37±0.21 to 0.17±0.22) at six months follow-up, which was also found to be statistically significant (p-value=0.001). In the study by Arbelaez MC et al., BCVA improved by 0.16 at six months follow-up [2]. Similar studies done by Bamdad S et al., and Peyman A et al., have found statistically significant improvement in BCVA following the procedure [9,24]. A study done in India on paediatric patients by Arora R et al., has demonstrated statistically significant improvement in both uncorrected and BCVA following the procedure [25]. Thus, most of the studies have demonstrated an improvement in visual acuity following corneal collagen cross-linking irrespective of the population demographic.

In the present study, Kmax and Kmin showed a gradual flattening in comparison with the preoperative values at all postoperative visits in a statistically significant manner. Kmax decreased by 2.23D (from 54.90±6.05 to 52.67±5.02) and Kmin decreased by 2.21D (from 48.14±4.24 to 45.93±4.07) at the final follow-up after six months. Keratometry values showed a reducing trend in all patients except one in the current study. The patient had a history of allergic conjunctivitis with constant eye rubbing, and slight worsening of keratometry values were noted on follow-up.

In the first in-vivo controlled clinical study by Wollensak G et al., which included 23 eyes with moderate or advanced progressive keratoconus, max K decreased by 2.01 D post-procedure [4]. Another study by Jankov II MR et al., found that progression of keratoconus stopped in all patients in which it was actively progressing six months prior to treatment. Max K decreased by more than 2D [12].

Agrawal VB in his study found similar results among an Indian population of 37 eyes after one year of follow-up. The K value of the apex decreased by a mean of 2.73 D in 66% of eyes, and the maximum K value decreased by a mean of 2.47D in 54% of eyes [26]. Wittig-Silva C et al., and Hersh PS et al., observed a reduction in the value of Kmax at the end of their one-year study [13,27]. Kankariya VP et al., noticed transient worsening of the topographic indices in the early postoperative period, but these indices stabilised on subsequent visits without any intervention [28].

The cylinder value decreased by 0.6D at six months in the current study (from -3.50±1.58 to -2.90±1.37). In similar studies done by Bamdad S et al., and Jankov II MR et al., the cylinder value decreased by 0.6D and 0.5 D, respectively [9,12]. In the study done by Saffarian L et al., the mean cylinder value decreased by 0.78D at one-year follow-up [14]. These changes might be indicative of gradual corneal flattening post-corneal collagen cross-linking. In the current study, SE was found to be decreasing in all postoperative visits. It decreased by 0.65 Dioptres at six months follow-up (from -4.93±3.92 to -4.28±3.48). In the study done by Vinciguerra P et al., mean SE refraction showed a significant decrease of 1.57 dioptres 24 months after the procedure [15]. No significant complications were noted in any of the patients post-procedure.

Corneal collagen cross-linking with riboflavin is a promising treatment in arresting the progression of keratoconus. With the patients being diagnosed and treated early, late complications like acute hydrops and corneal scarring can be avoided. It could also reduce the need for keratoplasty. Given the low cost and simplicity of the procedure, it can be widely done in developing countries, compared to other modalities like intracorneal ring segments. Collagen cross-linking is now also being evaluated in the treatment of other conditions like post-LASIK ectasia, keratitis, and corneal oedema [29].

Limitation(s)

Limitations of the present study include a shorter follow-up period. Since the patients were followed-up for only six months, it is not known whether the disease has progressed at a later stage or not.

CONCLUSION(S)

Corneal collagen cross-linking with riboflavin is a safe, simple, and effective procedure for arresting the progression of keratoconus, with the majority of patients obtaining an improvement in visual acuity. It is a simple, safe, and effective procedure that could help to reduce the burden of preventable blindness. Long-term results are necessary to evaluate the duration of the stiffening effect and to exclude long-term side effects.

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Commentary on: Nonpenetrating deep sclerectomy in advanced open-angle glaucoma

This retrospective review is probably one of the very few Indian studies available on the safety and efficacy of nonpenetrating deep sclerectomy (NPDS) with Mitomycin-C (MMC) in advanced glaucoma. This is because only very few centers in South India are performing NPDS. I congratulate the authors for their analyses. The follow-up period was limited to 1 year. They had an intraocular pressure (IOP) reduction of 52.1% from baseline and a decrease in the number of anti-glaucoma medications (AGMs) by 45% at the end of the first year. 55.6% required additional bleb needling for IOP control. They concluded that NPDS with MMC with or without phacoemulsification was a safe surgery for management of advanced glaucoma.

Maheshwari *et al*.[1] also had a similar IOP reduction in advanced glaucoma, but only 35% patients needed an additional procedure for control of IOP. However, as compared to advanced glaucoma, NPDS in childhood glaucoma has shown a higher success rate with respect to reduction in IOP and complications as compared to trabeculectomy.[2,3] Al-Obeidan *et al*.[2] showed that the probability to survive was 74.6% after the 12th month with the mean IOP decreasing to 11.5 ± 3.0 mmHg compared to 31.9 mmHg preoperatively. Yet, a Brazilian study found that NPDS effectiveness did not differ among different glaucoma stages.[4]

Studies have shown that advanced glaucoma requires IOP in the range of 8–12 mm Hg or lower to prevent the progression of the disease, more so in patients with normal tension glaucoma.[5,6] Since these values approach the clinical definition of hypotony, a thin line exists between the very low IOP needed to achieve control of glaucoma and the devastating complication of hypotony. To walk this tightrope, surgeries such as NPDS provide a barrier in the form of the Trabeculo-Descemet's membrane, which keeps the anterior chamber (AC) deep with lesser inflammation, which in the long run decreases the chances of cataract formation.

Although IOP reduction targets for clinical studies can be achieved using the standard definitions of complete and qualified success, the need for a very low target IOP should be incorporated in studies where advanced glaucoma is considered. Most of our surgeries did not achieve this goal. The present results are also more in tune with targets for mild-to-moderate glaucoma where the advent of minimally invasive glaucoma surgery (MIGS) has completely revolutionized the scene.

Studies with the XEN stent combined with phacoemulsification were as effective and safe as phaco with NPDS at 9 months; however, NPDS alone may be more effective than the XEN gel stent in reducing IOP in patients with OAG, with longer surgical success.[7,8] The former had a 25.6% mean drop in IOP in the NPDS group as compared to the 18.9% drop in the Xen group. Suture gonioscopy-assisted transluminal trabeculotomy (GATT), a form of MIGS, has also provided similar efficacy and a better safety profile as compared to trabeculectomy.[9] Both NPDS and Ex-PRESS produce an IOP-lowering effect of approximately 25%. Success rates are similar after both procedures, and both seem to lead to a stabilization of visual loss.[10] Studies have also indicated that the 3-year success rate for IOP control for trabeculectomy with MMC was 68–79%[4,5]

NPDS has a steeper learning curve as compared to the so-called gold standard trabeculectomy. The peeling of the juxtacanalicular trabecular meshwork with the capsulorrhexis forceps is an important step in this surgery. The creation of the deep flap is a challenge, and for that, the superficial flap must be thin, which itself is a challenge. Furthermore, the accidental perforation of the Trabeculo-Descemet's membrane may require conversion to trabeculectomy, thereby abandoning NPDS. Since a bleb is formed in NPDS too, all the complications associated with it and its management will be present as in a trabeculectomy. Therefore, controversy exists regarding the safety and efficacy of this procedure as compared to trabeculectomy, more so in

the patients with advanced glaucoma. The long-term safety profile of NPDS must be taken into consideration. The concern for transconjunctival oozing is high.[11]

Finally, the efficacy and safety of a surgical procedure for glaucoma can also be indirectly determined by its acceptance by the glaucoma surgeons. More than 25 years down the line, acceptance of NPDS appears to be on the decline, especially for cases of advanced glaucoma, the increasing numbers of which are becoming more and more apparent.[12]

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PAEDIATRICS

Clinical and Epidemiological Characteristics and Rotavirus Vaccination Status in Children Aged Under 2 Years Hospitalized with Intussusception in Kerala, India, 2019–2022: A Multicenter Observational Study

Abstract

Objectives

Some rotavirus vaccines (RVV) have been associated with an increased risk of intussusception (IS). RVV was introduced in Kerala on September 6, 2019 through Universal Immunization Program (UIP). Aim of this study was to describe clinical and epidemiological characteristics and oral pentavalent rotavirus vaccination status in children hospitalized with IS in Kerala.

Methods

This descriptive cross-sectional study was conducted at six tertiary-care hospitals in Kerala between September 2019 and December 2022. Children aged under 2 y admitted with intussusception were enrolled consecutively and data collected through caregiver interviews, ultrasonography records, procedure notes, and vaccination cards.

Results

Among 727 children, males were 62.7%; median (IQR) age at presentation was 9 (6–16) mo. Seasonal peaks occurred from January to March in 2020–2021 and April to June in 2022. Vomiting (67.7%) was the predominant presenting symptom and ileocolic (91.6%) was the most frequent anatomical site. Hydrostatic reduction (676, 93%) was the primary successful treatment modality. Surgery was performed in 51 (7%) children of whom 14 (1.9%) underwent intestinal resection and anastomosis. First, second, and third doses of RVV were received by 554, 540, and 471 children respectively. A statistically significant difference ($p = 0.001$) was found between median (IQR) ages (in months) at onset of intussusception of vaccinated [8 (6–14), $n = 554$] and unvaccinated [14 (8–19), $n = 173$] groups. Sixty (10.8%) out of 554 vaccinated children had onset of IS between 1 and 21 d of preceding RVV.

Conclusions

Intussusception has a seasonal occurrence in Kerala. Surveillance of intussusception should continue in parallel with UIP specifically focusing on the risk window period between 1 and 21 d following RVV.

CASE REPORT

ROWELL SYNDROME WITH BASAL GANGLIA CALCIFICATION IN A CHILD WITH NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS

***Ananda Kesavan TM**
****Deepa Anirudhan**
****Deepthi R**

Abstract: *In patients diagnosed with systemic lupus erythematosus, any acute neurological symptom, even subtle, warrants thorough evaluation for neuropsychiatric systemic lupus erythematosus. Immunosuppressive therapy can be life-saving in cases of lupus with severe systemic symptoms. Features such as early age of onset/presentation, history of consanguinity in parents, negative anti-ds DNA antibody status and predominant neurological manifestations should prompt suspicion of complement deficiency-associated systemic lupus erythematosus.*

Here, we report a complex case of an eight-year-old girl presenting with cutaneous manifestations consistent with Rowell syndrome, progressive neuropsychiatric involvement refractory to initial therapy, and imaging findings of basal ganglia calcifications, highlighting the diagnostic and therapeutic challenges encountered. This case underscores the importance of early aggressive immunosuppression and consideration of complement deficiency in pediatric lupus with prominent neurological symptoms.

Keywords: *Systemic Lupus erythematosus, Erythema multiforme, Basal ganglia calcification.*

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Impact of Wasting on the Severity of Rotavirus and Non-rotavirus Diarrhea in Children Aged Under 5 Years Hospitalized with Acute Gastroenteritis in Kerala, India

- Rose Xavier,
- Aparna Namboodiripad,
- Madona Devassikutty Fiji,
- Vellani Thamunni Ajithkumar,
- Shermin Nasreen Abdul Jaleel,
- Priya Sreenivasan,
- Ragavi Lin

- # Abstract
- ## Objectives
- This analysis assessed the relationship between wasting and severity of rotavirus and non-rotavirus diarrhea among children hospitalized with acute gastroenteritis in Kerala.
- ## Methods
- Children aged under 5 y admitted to sentinel hospitals in North, Central, and South Kerala with acute gastroenteritis between November 2020 and December 2023 were prospectively enrolled. Sociodemographic, anthropometric, and clinical data were collected using a case report form, and stool samples were tested for rotavirus using an enzyme-linked immunosorbent assay. Anthropometry was performed according to World Health Organization guidelines.
- ## Results
- Of the 1,142 children aged under 5 y admitted to the sentinel hospitals with acute gastroenteritis during the study period, 666 were enrolled in the study. Of the 643 children with stool samples tested for rotavirus, 115 (17.7%) were positive for rotavirus. Compared with children with wasting, children without wasting were (significantly more likely to have received ≥ 1 dose of rotavirus vaccine (69.5% vs. 60.2%; $p = 0.022$). In a subgroup analysis of children with wasting, compared with rotavirus-negative children, rotavirus-positive children were significantly more likely to develop severe to very severe disease (odds ratio: 5.31, 95% confidence interval: 2.28–12.34; $p = 0.001$).
- ## Conclusions
- In children with wasting, rotavirus diarrhea was more severe than non-rotavirus diarrhea. Strategies to prevent and treat diarrhea should target children with wasting, who are at greater risk of severe disease. Maintaining high rotavirus vaccination coverage and measures to reduce the incidence of wasting are necessary to reduce incidence of severe diarrhea.

Epidemiology and Clinical Profile of Rotavirus Diarrhea in Children Aged Under 5 Years in Kerala, India After the Introduction of Rotavirus Vaccination: A Surveillance Study

- Vellani Thamunni Ajithkumar,
- Madona Devassikutty Fiji,
- Shermin Nasreen Abdul Jaleel,
- Aparna Namboodiripad,
- Priya Sreenivasan,
- Rose Xavier,
- Varsha Sudhir Chaudhary,

Abstract

Objectives

ROTASIIL®, an indigenous oral pentavalent rotavirus vaccine, was included in the Universal Immunization Program of Kerala in September 2019. This study aimed to describe the epidemiology and clinical profile of rotavirus diarrhea among children aged under 5 y in Kerala in the postvaccination period.

Methods

This prospective observational study was conducted at three tertiary-care hospitals in Kerala from November 2020 to December 2023. Children aged under 5 y who were hospitalized with acute diarrhea were enrolled. Stool samples were collected from participants and tested for rotavirus using an enzyme-linked immunosorbent assay. Rotavirus-positive samples were genotyped.

Results

Of the 666 children enrolled, 643 had a stool sample tested for rotavirus, of which 17.9% tested positive. Rotavirus diarrhea occurred throughout the year, with a small peak between December and February. Most children with acute rotavirus diarrhea (56.5%) were aged 24–59 mo. The incidence of rotavirus-positive and rotavirus-negative acute diarrhea was higher among boys than among girls (male-to-female ratio of 1.3:1 and 1.5:1, respectively). The prevalence of rotavirus positivity was lower in children who had received three doses of oral rotavirus vaccine, ROTASIIL® than in unvaccinated children (13.9% vs. 26.4%). G3P[8] was the dominant rotavirus genotype throughout the study period. No fatal cases of rotavirus diarrhea were reported.

Conclusions

In children hospitalized with acute diarrhea, the prevalence of rotavirus was lesser among vaccinated than unvaccinated children. Monitoring of age shift, breakthrough infections in vaccinated children, and genotypic surveillance of emerging rotavirus genotypes are required to inform the development of next-generation vaccines.

Genotyping of Rotavirus Gastroenteritis in Kerala, India, in the Postvaccination Period (2020–2023)

Original Article

Published: 03 October 2025

Abstract

Objectives

To evaluate rotavirus (RV) genotypes after the addition of the oral pentavalent rotavirus vaccine (RVV), ROTASIIL, in the Universal Immunization Program (UIP) of Kerala.

Methods

This prospective, multicenter, observational study was conducted between November 2020 and December 2023 across three major referral hospitals in Kerala, India. Children aged < 5 y admitted to the hospitals with acute gastroenteritis (AGE) were enrolled, and their stool samples were tested for RV using an enzyme immunoassay (EIA). Positive samples were then genotyped using polymerase chain reaction.

Results

In total, 666 patients were enrolled during the 3-y study period. Adequate stool samples were collected from 643 patients; of these samples, 115 were EIA-positive—an RV positivity rate of 17.9%. Genotyping was performed for 109 samples; of these samples, 53 (48.6%) were from unvaccinated children and 56 (51.4%) were from children who had received at least one dose of the RVV (ROTASIIL). G3P[8] was the most common strain isolated in children hospitalized for AGE in Kerala in the period following vaccine introduction, whereas the prevalence of G2P[4] varied throughout the study period.

Conclusions

Less than one-fifth of the samples tested were positive for RV. The findings indicate a need to closely monitor RV strains during the postvaccine introduction period to evaluate potential changes and understand the effectiveness of vaccines against different genotypes.

CASE REPORT

A CASE OF GATA2 MUTATION PRESENTING AS AUTOIMMUNE HEMOLYTIC ANEMIA

***Deepthi R**
****Deepa Anirudhan**
****Ananda Kesavan TM**
*****Ajithkumar VT**

Abstract: *Inborn errors of immunity are one of the important causes of immune cytopenias. In patients with immune cytopenias genetic mutations are being recognized more often in recent times with the advent of molecular testing laboratory facilities. Identification of these genetic mutations plays an important role in the management and prognostication in these diseases. GATA 2 mutation is one such mutation associated with lymphopenia and immunodeficiency which presented as autoimmune hemolytic anemia in one of our patients.*

Keywords: *Autoimmune hemolytic anemia, GATA2 mutation.*

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Curative hematopoietic stem cell transplantation in a child with specific granule deficiency due to a homozygous SMARCD2 variant

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ABSTRACT

Background: Children with recurrent, severe infections that respond poorly to treatment are likely to have an underlying inborn error of immunity.

Case Report: A three-year-old male child of non-consanguineous parentage presented with recurrent severe infections from the neonatal period, including abscesses, pneumonia, diarrhea, meningitis, cystitis, and pyelonephritis. The child had subtle dysmorphic features. The dihydro rhodamine assay was abnormal, and the peripheral smear showed hypogranular, hypolobated neutrophils. Clinical exome sequencing revealed a homozygous variant in the SMARCD2 gene, confirming the diagnosis of specific granule deficiency 2. The child underwent a haploidentical hematopoietic transplant and is asymptomatic five months post-transplant. Conditioning chemotherapy included rabbit anti-thymocyte globulin/treosulphan/thiotepa/fludarabine. The CD34 dose infused was 15 x 10^6/kilogram recipient body weight. The infused product was TCR alpha/beta and CD19 depleted with preserved TCR gamma/delta cells.

Conclusion: This case demonstrates that although ultra-rare inborn errors of immunity are often diagnosed by next-generation sequencing, simple hematological and immunological tests provide valuable clues. Timely hematopoietic stem cell transplantation is curative.

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1. Introduction

Phagocytes are the predominant first responders at sites of infection. Phagocytic defects are often misdiagnosed due to the limited availability of investigative modalities and poor awareness among clinicians. Children usually present early in life with recurrent pyogenic and fungal infections. Common phagocytic defects are associated either with low absolute neutrophil counts or with functional defects that affect migration, adhesion, ingestion, degranulation, or oxidative metabolism [1].

We present a three-year-old male child with phenotypic features of chronic granulomatous disease (CGD), later diagnosed as specific granule deficiency 2 (SGD2) with a variant on the *SMARCD2* (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily D, member 2) gene on exome sequencing [2,3]. To our knowledge, this is the first report from India.

2. Case

A male baby born at term to non-consanguineous parents had early-onset neonatal sepsis, hypoglycemia, and hypocalcemia. There was no history of delayed separation of the umbilical stump. He had a bulbous nose, long philtrum, thin upper lip, micrognathia, low set ears, brachydactyly, and hypertelorism (Fig. 1). Multiplex Ligation-dependent Probe Amplification (MLPA) for 22q11.2 deletion was negative.

At 5 months of age, he had a mandibular abscess, pneumonia, and pyogenic meningitis, necessitating mechanical ventilation. Blood culture yielded *Staphylococcus aureus*. Three months later, he had an axillary abscess and moderate hepatosplenomegaly. *Pseudomonas aeruginosa* was grown from pus. The Immunoglobulin profile was unremarkable. Prophylaxis with cotrimoxazole and itraconazole was started. He had recurrent diarrhea and bilateral pyelonephritis with cystitis at two years of age. All infections were severe, necessitating prolonged hospitalization. He underwent surgery for a unilateral cataract at two years of age. Complete blood count revealed moderate anemia.

Peripheral smear showed anisopoikilocytosis, tear drop cells, pseudo-Pelgher-Huet cells, and hypolobated hypogranular neutrophils with a shift to the left (Fig. 2). The nitroblue tetrazolium (NBT) test was normal, but the dihydrorhodamine (DHR) assay was abnormal (Figs. 3 and 4), suggesting neutrophil granular defect.

The assay showed an abnormal pattern with a single peak with no shift to the right, suggesting an absent oxidative burst.

A homozygous nonsense variation in exon 2 of the SMARCD2 gene was found on exome sequencing that results in a stop codon and premature truncation of the protein at codon 131 (p.Gln131Ter)

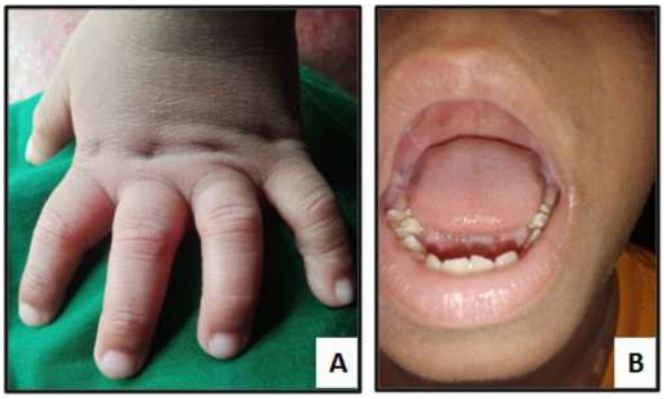


Fig. 1. Brachydactyly (A) and misaligned teeth (B).

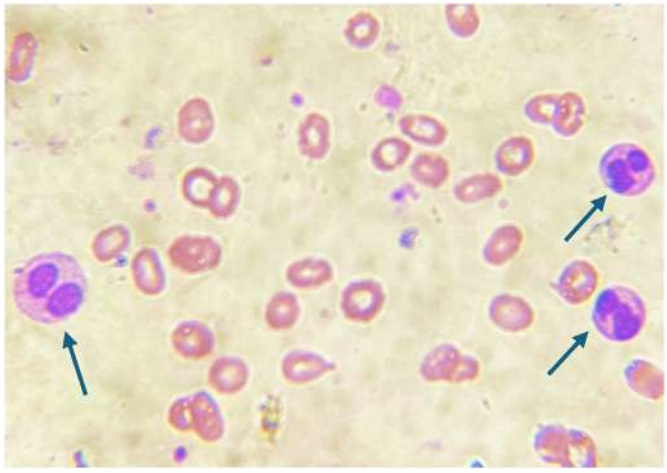


Fig. 2. Peripheral blood smear showing anisopoikilocytosis, tear drop cells, pseudo-Pelgher-Huet cells, and hypolobated hypogranular neutrophils (Leishman stain; X 100).

and was reported as 'likely pathogenic.'

Since the child did not have a fully matched donor, a haploidentical hemopoietic stem cell transplantation (HSCT) was performed with the father as the donor. The donor-specific antibody test was negative.

For pre-transplant immunosuppression, one cycle of fludarabine at 40 mg/m^2/day intravenously and dexamethasone at 25 mg/m^2/day, spanning over five days, was administered. One week later, the child had a viral respiratory infection and pancytopenia. After he had recovered, he was admitted for HSCT. The conditioning regimen consisted of rabbit anti-thymocyte globulin 1.5 mg/kg/day for 3 days, thiotepa 5 mg/kg bd for one day, fludarabine for 4 days at 40 mg/m^2/day, and treosulfan at 14 gm/m^2/day for 3 days.

A total of 15 million peripheral blood stem cells per kg of TCR alpha/beta and CD19-depleted stem cells with preserved TCR gamma/delta cells mobilized from the father were infused. T-depleted product collected was documented to have 13.53 x 10^5/kg recipient body weight of CD34 cells. CD19 and TCR alpha/beta cells were 0; TCR gamma/delta cells were 21.84 x 10^6/kg recipient body weight.

The child developed grade 3 cytokine release syndrome and grade 3 mucositis. He engrafted on day 10 and was discharged on prophylactic antibiotics. The graft-versus-host disease (GVHD) prophylaxis included cyclosporine and steroids. Cyclosporine was given for 9 months, tapered, and stopped. Prednisolone at 1 mg/kg/day in two divided doses was tapered and stopped after 2 months. Topical steroids were also used.

Complete donor chimerism was documented on 15, 30, 60, 90 days, and 5 months post-HSCT. He had cytomegalovirus reactivation, which required ganciclovir and grade 2 skin GVHD, which settled with steroids. Follow-up immune reconstitution revealed that T- and B-lymphocytes gradually improved by day +100. The child remains well 5 months post-HSCT off immunoglobulin support and immunosuppressants and free of infections with 100 % donor chimerism with absolute CD4 counts of 540 cells/mm^3 and absolute CD19 counts of 356 cells/mm^3.

3. Discussion

An inborn error of immunity was suspected in the index case given neonatal sepsis and frequent severe infections since early childhood. DiGeorge syndrome was excluded by MLPA.

The next diagnostic possibility was chronic granulomatous

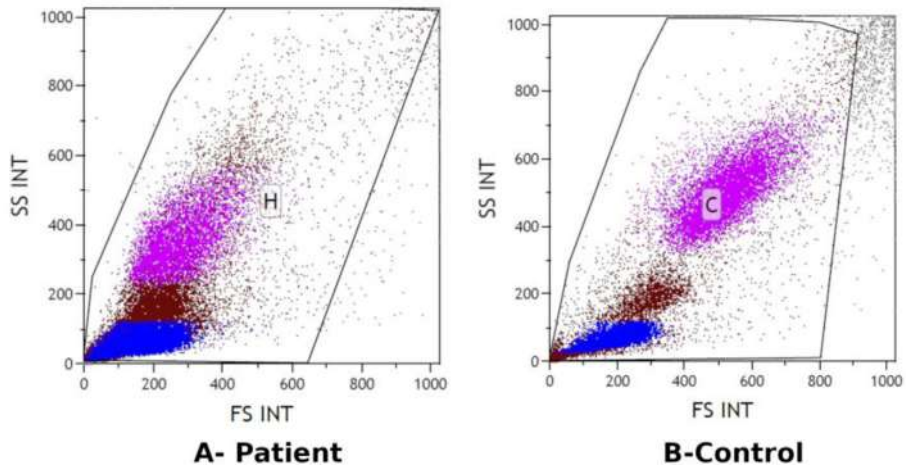


Fig. 3. Dihydrorhodamine test. The forward scatter side scatterplot of the patient (A) revealed hypogranular neutrophils, which were not easily separable from the lymphocyte population. Forward scatter side scatter plot of control (B) showed distinct, easily separable populations of neutrophils and lymphocytes.

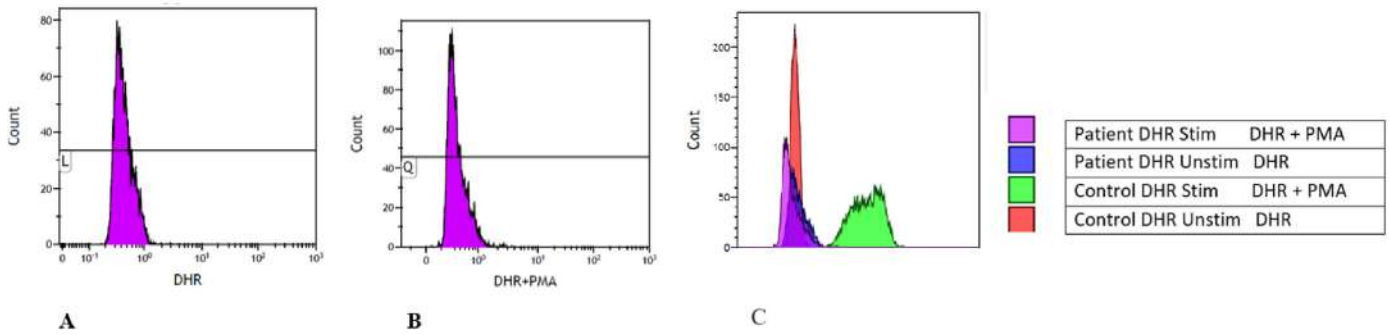


Fig. 4. Dihydrorhodamine assay: Unstimulated (A), stimulated (B), and overlay plots (C).

disease due to the early onset of recurrent abscesses, pneumonia, organ involvement, need for prolonged parenteral antibiotics, and abnormal DHR results. Infections due to *S. aureus and P. aeruginosa* were consistent with CGD [1]. Features of leukocyte adhesion defects included umbilical sepsis and delayed fall of the umbilical stump. Exome sequencing revealed an ultra-rare phagocytic defect, SGD2, due to a nonsense variant in the SMARCD2 gene (17q23.3).

SGD is a rare autosomal recessive condition where neutrophils lack the ability to express granule proteins, leading to impaired chemotaxis and bactericidal activity [2]. Patients present with recurrent pyogenic infections and may have dysmorphic facies, developmental delay, dental defects, and skeletal anomalies [3]. Pyogenic infections may result in deep organ abscesses or superficial, indolent skin infections [4].

SGD type 1 (SGD1) is caused by a defect in a myeloid-specific transcription factor, CCAAT/enhancer-binding protein epsilon (CEBPE) [5]. In SGD2, SMARCD2, a pivotal player in myeloid cell differentiation, is deficient [3,6]. SMARCD2 is also crucial for interacting with distinct transcription factors-associated expression of genes related to neutrophil function. Certain features not usually seen in CGD, including misaligned teeth, brachydactyly, facial dysmorphism, dental abnormalities, cataracts, and motor developmental delay, were observed [6–8].

The peripheral smear re-examined following the exome sequencing report, showed bilobed nuclei and pseudo-Pelgher-Huet cells. An abnormal DHR on stimulation with phorbol myristate (PMA) has been described in SGD due to loss of granularity of neutrophils and difficulty in separation from lymphocytes [9]. Detection of neutrophil granules by flow cytometry has been suggested as a rapid screening test [4].

The patient exhibited a homozygous nonsense variation in the SMARCD2 gene, the stop-gained variant c.391C > T (p.Gln131Ter). This mutation leads to a truncated SMARCD2 protein and impaired neutrophil function. Congenital neutropenia has been described in some patients with SGD [10–13].

SGD2 has been reported to be associated with myelodysplasia, and HSCT is the recommended treatment. Pre-transplant immunosuppression was employed to decrease the risk of graft rejection. The patient achieved 100 % donor chimerism 5 months post-HSCT, with successful infection management and immunological support. Good outcomes with HSCT have been reported with myeloablative conditioning [8,10,12,13]. Several studies have documented the role of TCR alpha/beta-depleted HSCT in CGD [14,15]. Neutropenia in SGD may not respond optimally to G-CSF like other severe congenital neutropenia syndromes. The efficacy of the thrombopoietin receptor antagonist, romiplostim, in combination with G-CSF has been reported [11].

To conclude, it is imperative to confirm the genomic diagnosis of a child with features of CGD since an abnormal DHR is not specific. Peripheral smear yields invaluable clues to this rare disorder and will enable life-saving antibacterial and antifungal prophylaxis even before a genomic diagnosis is made. Subtle clinical features, including mild facial dysmorphism, dental abnormalities, peripheral skeletal defects, and developmental delay, are additional pointers to the underlying diagnosis.

Patient's/Guardian's consent

Written informed consent for publication of case details, including figures depicting investigations performed, was obtained from the child's parents.

Ethical clearance

Not applicable.

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Declaration of competing interests

None.

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Children with Differences in Sex Development

Taking a Multidisciplinary Management Approach

- Textbook
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Accessibility Information

Overview

Editors:

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About this book

This manual covers all possible aspects of managing a child with differences in sex development, an entity easily missed by the unsuspecting clinician. Managing such children is challenging due to various processes (genetic, hormonal, environmental, chromosomal, and environmental) involved in developing gonads and brain imprinting. The entity of Gender dysphoria adds further to this complexity. With a global uproar caused by the cropping up of medicolegal issues concerning sex allotment and sex of rearing, a need is felt to know about the line of approach to address the problems of management of these children, which does not stop at medical and surgical treatment. Whereas many social and legal organizations are relentlessly working for the cause of such children, there is a lack of comprehensive literature on the round management of such children, which makes the book more of an essential addition to the existing reading material. Esteemed writers give all these aspects and explain lucidly with the help of tables, figures, and diagrams.

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Case Report

Intestinal hypomagnesemia-two cases of recurrent seizures: a diagnostic odyssey

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ABSTRACT

Familial hypomagnesemia with secondary hypocalcemia (FHSH) is a rare autosomal recessive disorder that is manifested as severe hypomagnesemia and moderate to severe hypocalcemia. Affected children present with refractory seizures in infancy. It results from mutations in the gene encoding transient receptor potential cation channel member 6 (TRPM6) on chromosome 9q22. The primary defect is impaired intestinal absorption of magnesium with secondary defect in the renal conservation of magnesium. We report two infants who presented with refractory seizures beginning in the first three months of life, the clinical phenotype of both these children was normal. Both were diagnosed to have hypocalcemic seizures. The children were managed with intravenous calcium and magnesium during their hospital stay, however were discharged on calcium supplementation alone. As they continued to have seizures inspite of good compliance to medications and in view of persistently low magnesium levels, hypomagnesemia as a cause of seizures was considered. Genetic evaluation revealed variants in the TRPM6 gene in both the cases The seizures were brought under control once the magnesium levels were normalized. A possibility of hypomagnesemia with secondary hypocalcemia should be thought of in any case of refractory hypocalcemia and inappropriately low levels of parathyroid hormone (PTH) The purpose of this series is to highlight the importance of systematically working up children with inherited hypomagnesemia.

Keywords: Hypomagnesemia, Seizures, Infancy

INTRODUCTION

Hypomagnesemia is a common dyselectrolytemia with significant clinical implications. Magnesium constitutes one of the major intracellular cations and is absorbed via two distinct transport pathways - through both the small and large intestine and the kidneys. In the kidneys 60-70% of magnesium is reabsorbed via the thick ascending limb of Henle.[1] Magnesium plays a vital role in the functioning of several enzymes, regulation of ion channels and the stabilization of negatively charged molecules. The magnesium homeostasis is influenced by the balance between the gastrointestinal absorption and the excretion of magnesium through the kidneys.[2]

Hypomagnesemia is an uncommon cause of seizures and it can sometimes be overlooked when a child presents with a seizure in the emergency or the out- patient setting. In children with known causes of hypomagnesemia, the prevalence of seizures is noted to be 16%.[3] If a child with seizures is found to have low serum calcium and magnesium levels, its cause should be thoroughly investigated. This includes evaluating renal function, performing a renal ultrasound to exclude medullary nephrocalcinosis, and exploring endocrine causes, such as, inadequate levels of PTH or vitamin D or resistance to these hormones. The underlying cause of hypomagnesemia could be genetic or acquired. A few

common genetic causes include poor gastrointestinal absorption or excessive renal wasting.[4,5]

The aim of this case series is to emphasize the importance of systematic evaluation in children experiencing seizures and hypocalcaemia, with a particular focus on identifying hypomagnesemia. We present two cases of genetically confirmed hypomagnesemia, who presented with refractory hypocalcemia accompanied by low parathormone levels.

CASE REPORTS

Case 1

Clinical description

A 3-month-old male infant presented with complaints of abnormal movements of the eyes followed by tonic posturing of both the upper and lower limbs which lasted for 10 minutes and had developed bluish discoloration of the lips. The infant had another episode which lasted for 5 minutes on the day of presentation. There was no associated history of fever, ear discharge, vomiting, polyuria, lethargy or refusal to feed. There was no history of fall, trauma or bleeding. There was no history of abnormal movements in the past, no history of loose stools, vomiting, passing excessive urine or difficulty in dressing up the infant noted by the mother. He was exclusively breastfed and gaining weight well according to the mother.

The baby was born at term, first child born of a non-consanguineously married couple following an uncomplicated pregnancy with no adverse perinatal events and had a birth weight of 3.3 kg. There was no history of abortion. He had developed neck control, attained social smile and responded to sound. The mother had not noted abnormal eye movements. The paternal uncle and the maternal aunt had history of febrile seizures. He was immunized upto age.

The infant's weight, length and head circumference were 7 kg (50th-85th centile), length-66 cm (85th-97th centile) and head circumference 44 cm (+2SD). On examination, he was alert and active with a HR of 124/min, RR of 62/min, BP of 86/60 mm Hg, afebrile and capillary refill time was less than 2 seconds. He had no pallor, icterus cyanosis or edema. There was no evidence of dysmorphism. The anterior fontanelle was level, and the head appeared large. There was no frontal bossing, widening of wrist or Harrison's sulcus. There were no neurocutaneous markers. Detailed developmental assessment showed minimal head lag when pulled to sit up. He had social smile and was cooing. On neurological examination. his tone and power were normal in all four limbs. The deep tendon reflexes were normal and plantar reflex was flexor. Other systemic examinations were within normal limits.

Based on the history and the examination findings, uneventful antenatal and postnatal period in a well thriving infant and absence of a systemic illness we considered the possibility of a structural anomaly of the brain or a metabolic disorder.

Management and outcome

He had recurrent seizures following admission requiring multiple anti- epileptics like phenytoin and levetiracetam. His initial routine investigations showed a hemoglobin of 10.9 g/dl, total leucocyte count of 16,500 cells/mm^3 (neutrophil 48%, lymphocytes 45%) and platelet count of 5.5 lakh/mm^3, C-reactive protein levels was 6.2 mg/dl, serum creatinine 0.3 mg/dl, total protein of 6.2 g/dl, serum albumin of 4.5 mg/dl, ALT 34 IU/l, AST 32 IU/l, serum sodium 136 mEq/l, serum potassium 5 mEq/l and RBS was 92 mg/dl. CSF examination revealed a total count of 5 cells/mm^3, sugar was 64 mg/dl and a protein of 44 mg/dl. As we wanted to rule out metabolic causes we got a serum calcium level which revealed hypocalcemia 7.2 mg/dl (8.5-10.2 mg/dl), ionized calcium 4 mg/dl (4.65-5.25 mg/dl), serum phosphorus was 4.1 mg/dl, 25 OH vitamin D was 18 ng/dl, and alkaline phosphatase level 239 U/l. It was striking to note that PTH was only 30 pg/ml (8.5-10.2) despite the hypocalcemia. Magnesium levels were done in view of the recurrent seizure episodes inspite of starting on intravenous calcium and was found to be low (1.2 mg/dl). Neurosonogram done in view of the increase in head circumference showed asymmetric size of the frontal horn of the lateral ventricle (L>R- 7.2 mm >4.1 mm). The electroencephalogram (EEG) was normal and magnetic resonance imaging (MRI) brain showed benign enlargement of subarachnoid spaces. The child was treated with intravenous calcium and magnesium but was discharged only on oral calcium (150 mg/kg/day), vitamin D supplementation (2000 IU/day) and levetiracetam 40 mg/kg/day. the child was treated with intravenous calcium and magnesium but was discharged only on oral calcium (150 mg/kg/day), vitamin D supplementation (2000 IU/day) and levetiracetam 40 mg/kg/day, with a diagnosis of unprovoked seizures and was decided to follow up the child. The serum calcium was 10.9 mg/dl, serum phosphorus 5.1 mg/dl, ALP- 240 U/l and magnesium levels were not rechecked.

He was followed up closely, he had attained complete neck control by 5.5 months, started sitting without support by 10 months of age and at one year his developmental age was 8 months. The child had further episodes of seizures at 1 year and 1.5 years. At 1 year he was treated at a local hospital and the dose of levetiracetam was hiked up and when ionized calcium was checked on review it was 4.8 mg/dl. At 1.5 years again his serum calcium was 11.2 mg/dl, ionized calcium 5.4 mg/dl, serum phosphorus level was 4.9 mg/dl and 25 OH vitamin D level was 58 ng/dl; however, these were not done during the acute episode of seizure and the dose of levetiracetam was further hiked up. His seizures typically lasted for 5-10 minutes and were generalized tonic-clonic type.

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At 3 years 5 months he was brought with seizures associated with fever. Physical examination revealed normal growth patterns: weight was 14.6 kg (+ 0.15 SD), height was 97 cm (+ 0.25 SD) and head circumference was 50 cm (50th centile). He had speech delay, but had caught up on the motor milestones. Neurological examination at the time of presentation was essentially normal. It was noted that hypocalcemia persisted even while he was on calcium supplementation. His urine calcium creatinine ratio was normal (0.09) which ruled out hypercalciuria; Absence of nephrocalcinosis on ultrasonography also supported this. PTH level was not elevated (17 pg/ml; normal 5.7-34 pg/ml) despite of hypocalcemia 8.2 mg/dl (8.5-10.2 mg/dl)). Venous blood gas analysis and serum electrolytes were normal.

The fractional excretion of magnesium done after correction of magnesium levels was elevated at >10% (normal: 2-4%) which indicated renal magnesium wasting.[6]

The persisting low magnesium levels during all these years was striking. Gastrointestinal causes of hypomagnesemia were unlikely in the absence of loose stools and vomiting. Prolonged intake of proton pump inhibitors and diuretics could lead to hypomagnesemia but the child was not any medications. Barter syndrome or Gitelman syndrome could lead to urinary magnesium wasting. Absence of polyuria, failure to thrive, hypokalemia and metabolic alkalosis made Barter syndrome unlikely. Gitelman syndrome was also ruled out as there was no concomitant metabolic alkalosis or hypokalemia. Hence, we considered the possibility of familial hypomagnesemia with secondary hypocalcemia and proceeded with genetic evaluation.

Clinical exome sequencing was done which revealed an autosomal recessive, homozygous mutation of *TRPM6* gene at intron 18 a variant of c.2392-3T>G which could lead to intestinal hypomagnesemia type 1. Parental sanger sequencing done revealed a heterozygous mutation involving intron 18 of *TRPM6* gene in both the parents confirming our diagnosis.

He was started on oral magnesium oxide (tablet Magmaxx 400 mg) (30 mg/kg/day of elemental Mg), oral calcium was continued (70 mg/kg/day) and currently he is 4-year-old, levetiracetam is being tapered. On follow up the child showed improvement in motor milestones, speech delay and has had no further seizures. The magnesium dosage was titrated on follow up to 60mg/kg/day based on serum magnesium levels.

Case 2

Clinical description

A 14-day-old baby boy, the first child of non-consanguineous parents, was born to a 19-year-old mother with a history of one abortion. He was exclusively breastfed. However, on day 10 of life, he began experiencing multiple episodes of abnormal movements. The abnormal movements were generalized tonic clonic movements involving both the upper and lower limbs. He had up-rolling of eyes and frothing from the mouth. The seizures were unprovoked, he had no history of fever, ear discharge, loose stools or trauma. He was born at term with a birth weight of 2.77 kg. There was no history of hypoxia or adverse perinatal events.

His weight on admission was 2.9 kg. The family history was unremarkable. HR was 180/min, RR was 56/min, capillary refill time <3 seconds. He was irritable but sucking well and the anterior fontanelle was level. On neurological examination his tone and reflexes were normal. Other systemic examination was also normal.

Management and outcome

His hemogram, C-reactive protein, renal function test, liver function test, thyroid function test and venous blood gas analysis were normal. Investigations revealed severe hypocalcemia, ionized Ca 0.8 mmol/l (normal range 1.16-1.31 mmol/l), hyperphosphatemia 8.1 mg/dl (normal range 3.8- 6.5 mg/dl) and hypomagnesemia 1.4 mg/dl (normal range 1.7-2.4 mg/dl). Serum parathormone level was found to be 26 pg/ml which was inadequate for the level of hypocalcemia. Maternal vitamin D was 2.25 ng/dl, urine calcium creatinine ratio was 0.06 and ultrasonography of the kidneys showed no nephrocalcinosis. Investigation results are shown in Table 1. MRI brain revealed altered signal intensities in bilateral caudate nuclei and thalamus suggesting calcification (Figure 1). EEG was abnormal and showed multiple spike and wave discharges. The child was discharged on post-natal day 25 with calcium (200 mg/kg/day), magnesium (20 mg/kg/day), vitamin D3 800 IU/day and calcitriol 0.25 mcg thrice a day. At 2 months the baby was brought for follow up. He had no further seizures and his serum calcium and Vitamin D levels were normal. The magnesium levels were not done. Calcitriol and Mg were discontinued and the child was sent home on oral calcium supplements (150 mg/kg/day). The child presented again with refractory seizures at 6 months and required admission to the pediatric intensive care unit. On examination, he had hypotonia and delayed milestones; serum calcium-6.1 mg/dl, P-4.9 mg/dl, serum magnesium-0.8 mg/dl and PTH-5.9 pg/ml. His seizures subsided only after magnesium sulphate (50%) was given at 0.1 ml/kg (50 mg/kg/dose) intravenous infusion over 1 hour and the dose was repeated every 6 hours for 3 doses. Rapid intravenous infusion needs to be avoided as that may lead to arrhythmias. Clinical exome sequencing in this case also revealed an autosomal recessive, homozygous mutation of *TRPM6* gene at intron 18 a variant of c.2392-3T>G (3' splice site) suggestive of intestinal hypomagnesemia -1. The parents Sanger sequencing could not be done due to financial constraints.

The child was discharged on levetiracetam 40 mg/kg/day, calcium 60 mg/kg/day, magnesium 20 mg/kg/day and

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calcitriol 0.25 mcg/day. Calcitriol was later stopped on follow up. The child is now 1 year 4-month-old with no further seizures and age-appropriate milestones. Hearing evaluation was found to be normal. Repeat values of Ca and Mg are 9.6 mg/dl and 2.1 mg/dl respectively.

Table 1: Summary of investigations done in both the cases.

Parameters	Case 1 (at 3 months of age)	Case 1 (on discharge)	Case 1 (at 3 years 5 months)	Case 2 (14 days)	Case 2 (1 year 4 month)
Serum calcium (8.5-10.2 mg/dl)	7.2	10.1	8.2	5.6	9.6
Ionized calcium (4.65-5.25 mg/dl)	4		4.57	3.21	
Serum phosphorus (3.8-6.5 mg/dl)	4.1	5.1	6.5 (high phosphorus could be secondary to hypoparathyroi-dism)	8.1	
PTH (10-65 pg/ml)	30.2		17	26	
25 OH vitamin D (15-40 ng/ml)	18		55	11.16	
ALP (203-553 U/l)	239	240		210	
Serum creatinine (0.2-0.4 mg/dl)	0.4		0.4	0.3	
Serum Na/K (135-145; 3.5-5.3)	136/3.8			141/4.2	
CRP	6.2			4	
Serum magnesium (1.7-2.2 mg/dl)	1.2		0.8	1.4	2.1
Urine calcium creatinine ratio	0.09		0.03	0.06	
Maternal vitamin D				2.25	
CSF examination	Normal			Normal	
TMS	Normal			Not done	

DISCUSSION

Hypomagnesemia can occur in children due to inadequate intake of magnesium, abnormal gastrointestinal absorption, impaired renal reabsorption or the redistribution of magnesium from the intracellular space to the extracellular space.

Decreased intake could occur due to inadequate dietary consumption or starvation. The gastrointestinal causes of hypomagnesemia include diarrhoea, vomiting, nasogastric suction, malabsorption or small bowel surgeries. Excessive and prolonged use of proton pump inhibitors has also been noted to cause hypomagnesemia.[7] Renal causes include defects in the magnesium excretory pathways, which may be inherited or acquired. Bartter syndrome, Gitelman syndrome and familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) are a few autosomal recessive inherited disorders which may result in urinary magnesium wasting. Gitelman and Bartter syndromes are unlikely if the blood gas, serum and urine electrolytes, blood gas, serum and urine elcetrolytes are normal and there is no hypocalciuria and hypermagnesuria.[8]

Hypomagnesemia resulting due to shift of magnesium from extracellular to intracellular compartments could be due to refeeding syndrome, hungry bone syndrome, treatment of diabetic ketoacidosis and acute pancreatitis. In refeeding syndrome, already existing hypomagnesemia is worsened by intracellular movement of magnesium with intake of carbohydrates.[9] The increased uptake of magnesium by the regenerating bone after parathyroidectomy or thyroidectomy in hungry bone syndrome causes hypomagnesemia. Hypomagnesemia also occurs in diabetic ketoacidosis as magnesium is driven into the cells following insulin therapy. Saponification of magnesium into the necrotic fat results in hypomagnesemia in acute pancreatitis.[10] Additionally, certain drugs such as aminoglycosides, proton pump inhibitors, digoxin, diuretics and osmotic agents can lead to hypomagnesemia.[11]

Familial hypomagnesemia with secondary hypocalcemia (FHSH) is a rare autosomal recessive disorder caused by transient receptor potential melastatin 6 (*TRPM6*) gene mutations which result in a defect in the magnesium permeable ion channel.[12] Only about 100 cases have been reported in the literature to date, with both sexes equally affected. *TRPM6* gene is expressed in the intestine and the kidney on the apical membrane of the distal convoluted tubules (DCT) but the defect primarily affects the intestine which leads to hypomagnesemia. No racial or familial association has been noted but parental consanguinity is usually present. The affected individuals can have low or normal magnesium excretion; the renal magnesium leak becomes apparent only when the serum magnesium concentration increases. This indicates a low renal magnesium threshold. The increase in fractional excretion of magnesium after correcting the serum magnesium levels is a valuable test to aid diagnosis. The diagnosis is sometimes delayed as renal magnesium wasting is not detectable during periods of profound hypomagnesemia.[13]

Convulsions that are refractory to anti-convulsant treatment, muscle spasm or tetany in the first months of life are common presentations. Laboratory evaluation at

initial presentation can demonstrate a magnesium level as low as 0.2 mmol/l.

Symptoms of hypomagnesemia might be absent until the magnesium levels are as low as 0.5 mmol/l. Clinical manifestations include hyperexcitability, tremors, tetany, convulsions and coma. Hypocalcemia secondary to hypomagnesemia can lead to atrial and ventricular arrhythmias.[14] Untreated hypomagnesemia over a prolonged period could lead to failure to thrive, delayed attainment of developmental milestones, intellectual disability and severe cardiomyopathy.[13] Hypomagnesemia is accompanied by hypoparathyroidism and hypocalcemia secondary to inhibition of the secretion of PTH. Magnesium is essential for the functioning of adenylate cyclase, which in turn produces cyclic adenosine monophosphate (cAMP). Since cAMP mediates both the end organ effects of PTH and its secretion, a magnesium deficit that results in adenylate cyclase function impairs PTH levels.[12]

Treatment of acute symptoms includes intravenous magnesium supplementation which helps in alleviating the symptoms. Lifelong administration of high dose of oral magnesium is needed. In patients with FHSH, the substitution of high oral doses of Mg^{2+} achieves at least subnormal serum Mg^{2+} levels.

Physiological studies in the intestine show that two distinct magnesium transport systems function in parallel: an active transcellular pathway and a passive paracellular pathway. *TRPM6* represents a molecular component of active transcellular Mg^{2+} transport. An increased intraluminal Mg^{2+} concentration (by increased oral intake) enables compensation for the defect in active transcellular transport by increasing absorption via the passive paracellular pathway.[14] Flatulence and abdominal discomfort are reported as an occasional side effect of oral Mg. A few other cases of intestinal hypomagnesemia reported across India are summarized in Table 2.

Table 2: Review of literature showing case reports of intestinal hypomagnesemia.

Authors	Age at presentation (months), sex	Place	Family history	Clinical presentation	Genetic mutation	Outcome
Joshi et al, 2012[15]	9 month/ male	Mumbai, Maharashtra	Consanguineously married couple	Multiple episodes of generalized tonic clonic convulsions since 8 months of age	*TRPM6* gene-missense mutation at p.T2L at exon 1	Treated with intramuscular magnesium initially and then with oral magnesium carbonate at 40 mg/kg/day normalized
Kamate et al, 2014[8]	13 month/male	Belgaum, Karnataka	Second degree consanguineously married couple, 2 sibling death at 2 and 8 months of age	Recurrent generalized clonic seizures	Genetic study for the mutation could not be done	Intravenous magnesium along with intravenous calcium for 3 days, child became seizure free. Antiepileptics withdrawn and discharged on parental magnesium sulphate given orally
Kekatpure et al, 2016[16]	7 month/ female	Bangalore, Karnataka	Non consanguineous parents, no family history	Recurrent multifocal clonic and myoclonic seizures	Homozygous mutation in exon 19 of TRPPM 6 gene [Chr9: 77407598; C > T; c. 2480G>A] resulting in stop codon	Oral magnesium 0.5 g/kg/day
Lal et al, 2018[17]	17 month/ male	New Delhi	Non consanguineous couple	Recurrent multifocal seizures since day 28 of life	Novel homozygous frame shift mutation, p.Leu1476Cysfs*75 that leads to a truncated *TRPM6* protein.	He was treated with intravenous magnesium (up to 12 g/day) and calcium. He was discharged on oral magnesium (8.5 gm/kg/day) and calcium supplements.

Continued.

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Authors	Age at presentation (months), sex	Place	Family history	Clinical presentation	Genetic mutation	Outcome
Geethalakshmi et al, 2021[18]	Case series of three children - 1: 6-year-old/ male, 2: elder female sibling of case 1, who had died at 6 months of age, and 3: 1 year/female	Cochin, Kerala	Consanguinity not mentioned; Death of an elder female sibling with intractable seizures since 1 month of age who died at 6 months of age. Consanguinity not mentioned	Refractory seizures since 1 month of age. Recurrent seizures from 5 months of age	Novel homozygous mutation of TRPM 6 in intron 18 (c.2392 -3 T>G) with parents heterozygous for the same mutation. Genetic test sent and results awaited	High dose magnesium supplements with which hypocalcemia resolved and he was seizure free off AED. Seizure free on magnesium supplements

CONCLUSION

These two cases are presented here to spread awareness about this treatable condition causing refractory seizures and developmental delay. The diagnosis should be suspected in children presenting with recurrent seizures, refractory hypocalcemia and hypomagnesemia. Early detection by genetic studies and specific treatment of FHSH with high dose magnesium can help to prevent severe neurological consequences.

Recommendations

The possibility of hypomagnesemia with secondary hypocalcemia should be considered in any child with refractory hypocalcemia and inappropriately low PTH levels. Early diagnosis and appropriate treatment are crucial to prevent seizures and developmental delay. A precise genetic diagnosis of FHSH has treatment implications and can help in optimal clinical management as well as prenatal counselling.

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CORRESPONDENCE

Profile of Aeroallergen Sensitization in Childhood Asthmatics Aged 4–14 y at a Tertiary Care Hospital

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To the Editor: Allergen sensitization is a criterion of the modified asthma predictive index [1, 2]. Sensitized children have severe asthma and severe exacerbations [3, 4]. Skin prick testing (SPT) results help in environmental control, keeping medication doses to a minimum, and considering allergen-specific immunotherapy to treat and prevent IgE-mediated allergy [4]. This cross-sectional study of one-year duration aimed to determine the aeroallergen sensitization profile in childhood asthmatics aged 4–14 y attending the asthma clinic of a tertiary care hospital in South India. Excluding children with systemic illnesses, severe asthma, severe eczema, and anaphylaxis, data was collected using a proforma from consecutive 60 patients after taking IEC approval, informed consent from parents, children or oral assent as appropriate. SPT was done using negative and positive controls and indoor allergen extracts [Allcure 1:10 w/v in glycerinated buffered saline (50%)]. Results were analyzed.

The predominant age of symptom onset was 4–6 y (26.7%); most had moderate persistent asthma category of severity (58.3%). Of the 39 sensitized children, 29 (74.3%) had moderate persistent asthma ($\chi^2 = 0.713$, df = 2, p-value = 0.70). Thirty-nine children out of 60 (63%) were either mono- or poly-sensitized. Considering the positive history of allergens exposure, 21 out of 28 cockroaches-exposed children were sensitized (68.2%), 21 out of 23 house dust mites (HDM)- exposed (91%) were sensitized, while less sensitization was noted in Alternaria (2.5%), and cats exposed (12.5%). Moderate persistent asthma was noted in 24 (79.4%) of the 31 cockroach-sensitized children ($\chi^2 = 9.973$, df = 2, p-value = 0.007) and in 24 (82.75%) of the 29 HDM sensitized children ($\chi^2 = 13.777$, df = 2, p-value = 0.001). The maximum wheal size with pseudopodia was for HDM (20 × 16 mm). Borderline wheal sizes need follow-up testing for progression.

To conclude, aeroallergen sensitization to HDM and cockroaches could be a marker for increased severity of asthma in children.

Declarations

Conflict of Interest None.

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CORRESPONDENCE

Response to Pyridostigmine in Congenital Myasthenia with LRP4 Mutation

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To the Editor: A baby boy, small for gestation, delivered at term, with hypotonia, poor suck and feeding difficulty with no tongue fibrillations was suspected to have a myopathy in neonatal period. The whole exome sequencing revealed LRP4 (lipoprotein related protein 4) mutation, a pathogenic variant described in congenital myasthenia syndromes. The baby showed dramatic improvement with increased movements of limbs, resolution of ptosis and elicitable reflexes on a trial of pyridostigmine at 1 mg/kg/dose 6 hourly.

With 32 mutations described till date, congenital myasthenia syndromes are genotypically and phenotypically heterogenous group of neuromuscular disorders where there is an impaired neuromuscular transmission [1]. LRP4 is the gene which encodes for a protein which function as receptor for nerve-derived proteoglycan agrin [2]. Agrin binding to LRP4 leads to activation of muscle-specific kinase receptor (MuSK), a transmembrane component of post synaptic neuromuscular junction. Activated MuSK leads to clustering of acetylcholine receptors (AChRs), it also anchors acetylcholine esterase to the neuromuscular junction and thus aids in neuromuscular transmission [3].

COLQ^{-}, LAMB2^{-}, DOK7 and MuSK mutations are known to worsen clinically with pyridostigmine. Salbutamol or ephedrine can be used to treat myaesthenic synfdrome caused by DOK7 and COLQ variants; fluoxetine, quinidine, or quinine may be used to treat slow channel syndrome [4].

There is no definite recommendation of pyridostigmine use in LRP4 mutation. Pyridostigmine being an inhibitor of acetyl cholinesterase acting at post synaptic transmission, could probably explain the response of the patient to the medication. Very few cases of LRP4 mutation are described worldwide; first reported case showed poor response to acetylcholine esterase inhibitor (AChEI) [1]. The treatment option with AChEI may still offer positive hopes in lives of children with LRP4 mutation. We recommend initiation of the drug in this mutation, thus contributing to data pool regarding the condition.

Declarations

Conflict of Interest None.

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PATHOLOGY

CASE REPORT

Primary leiomyosarcoma of pulmonary artery causing sudden death in a young female: An autopsy case report

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Abstract

Even though a cardiovascular aetiology is the most common finding in a sudden death scenario, malignancy is quite a rare contributor. Sarcomas of pulmonary artery are very uncommon malignancies which can cause sudden death. This rare and unique case of a primary leiomyosarcoma of pulmonary artery in a 38-year-old lady who died suddenly, was revealed during autopsy, and subsequently confirmed by histopathology and immunohistochemistry.

Key words: Pulmonary, Sarcoma, Smooth muscle, Sudden, Young, Death

Introduction

A natural, unexpected death that occurs within 24 hours of the onset of final symptoms in an apparently healthy individual is called sudden death by World Health Organization[1]. About 88% of all sudden deaths are of cardiac etiology[2]. However, about 40% of sudden death cases are unwitnessed, which makes it difficult to obtain relevant evidence and information. In such cases, medicolegal autopsy is usually performed, which is also required to gain any information[2].

Malignancies, in particular, sarcomas are quite unusual findings in cases of sudden death[2]. Sarcomas per se are less common than carcinomas. Cardiac involvement by sarcomas resulting in sudden death is still uncommon. Sarcomas of the pulmonary artery are rare tumors that can result in sudden death or unusual clinical scenarios[2-3]. They comprise of only 0.5% of all lung malignancies. Cases with primary sites of sarcoma in vital organs are more vulnerable to sudden death, and are less likely to be diagnosed antemortem[2]. These tumors appear to arise from multipotential mesenchymal cells of the arterial intima, classifying them as intimal sarcomas owing to their distinct features and different morphological subtypes have been described[4]. Among primary pulmonary artery sarcomas (PPAS), primary pulmonary artery leiomyosarcoma (PPAL) is an aggressive subtype with smooth muscle differentiation and carries a poor prognosis. PPAL grows and fills the pulmonary artery lumen, with the obstruction causing dyspnea, pulmonary hypertension, and elevation of right ventricular pressure and it can cause death by bilateral pulmonary artery occlusion[3].

Case Report

A 37-year-old female was brought dead to the casualty of a peripheral hospital. Four days prior to the death, there was a history of fever, giddiness, and flu like symptoms, for which she sought treatment from a primary health center and the symptoms were relieved. Subsequently, she was taken to the peripheral hospital following a fainting episode in the early morning, where she was declared as brought dead. There was neither any clinical history of significant organ or functional disease, such as epilepsy, that could have caused sudden death nor there was any family history of heart disease/sudden cardiac death. Notably, she was on antihypertensive medications.

During medicolegal autopsy conducted at our institution, the general appearance was that of a moderately built and nourished adult female of length 159cms and weight 55kg. Conjunctivae were congested, corneas hazy and pupils mid-dilated. No traumatic injury was found. Brain, trachea, bronchi, and lungs were congested. Pleural cavities, mediastinum and esophagus were normal. Right atrial and right ventricular chambers were dilated. Pulmonary trunk at its beginning was fully occluded by a protruding, whitish, firm, and friable mass, attached to the pulmonary valves and to its intima. Right ventricular chamber and pulmonary trunk showed blood clots. Left atrium and left ventricle were normal. Coronary arteries were

patent. Whole dissected heart, bits from lung, liver, kidney, and spleen were sent for histopathological evaluation.

On gross examination, the heart weighed 300 g. Thickness of right ventricle and left ventricle was 0.5cm and 1.2cm respectively. Chambers, coronaries, valves, and myocardium were within normal limits except for blood clots within right ventricle. Pulmonary trunk showed a nodular, friable occlusive mass measuring 6x5.5x3.4cm. Cut section was grey white and fleshy with areas of spotty necrosis, haemorrhage and focal myxoid change (Fig.1a, b). Other organs were congested, without major findings.

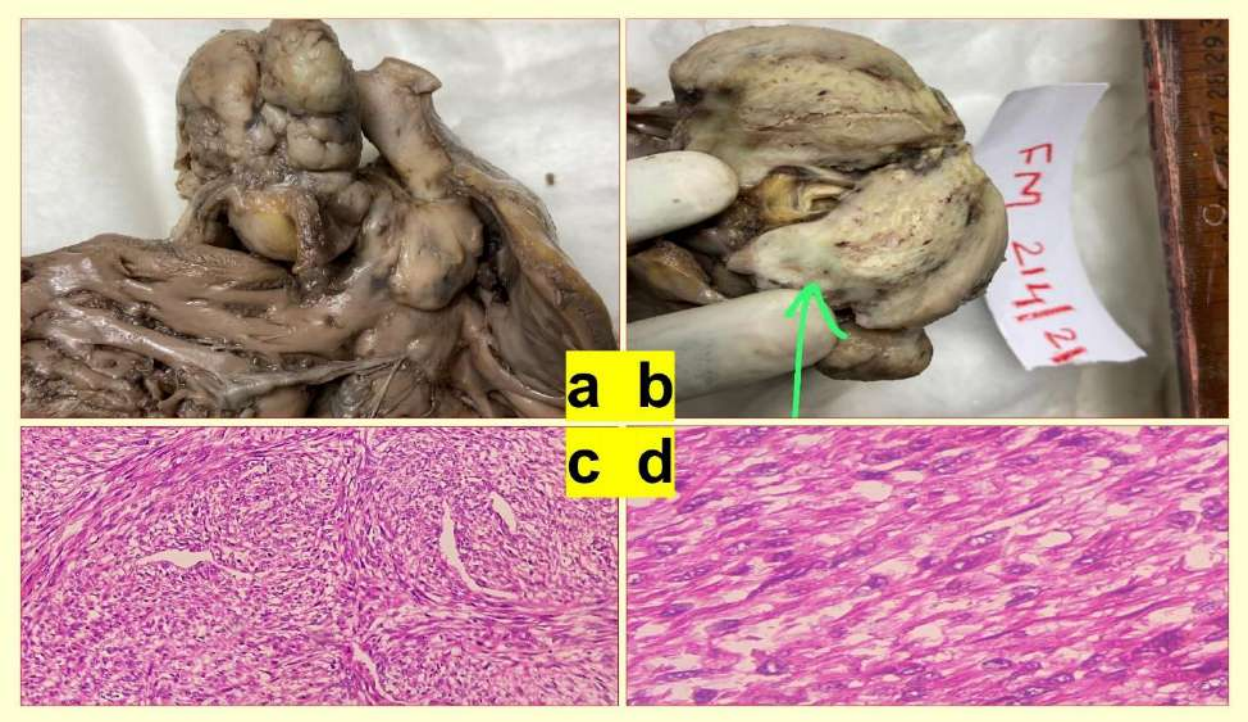


Figure 1: a. nodular, friable mass occluding the pulmonary trunk b. cut surface of the mass with grey white, fleshy look and areas of spotty necrosis, myxoid change and hemorrhage c. (H&Ex100) infiltrative tumor with cells in interlacing fascicles and thin blood vessels within d. (H&Ex400) pleomorphic spindle cells with vesicular nuclei, moderate eosinophilic cytoplasm, and occasional prominent nucleoli.

Microscopically, bits from liver, lungs, spleen, fallopian tubes, and ovaries showed congestion. Endometrium was haemorrhagic. Kidney showed congestion and features of calculous nephropathy. Sections from the nodular mass revealed an infiltrating tumour with cells arranged in interlacing bundles and fascicles in a loose myxoid stroma. Individual cells were pleomorphic, spindle to ovoid cells having variable amount of eosinophilic cytoplasm, vesicular nuclei with blunt ends and prominent nucleoli in some. 4-5 mitotic figures were noted/10 high power fields. Atypical mitoses, multinucleate giant cells and extensive areas of necrosis were noted. Tumour was seen infiltrating into the underlying muscle.

Immunohistochemically, tumour cells strongly expressed smooth muscle actin. Desmin showed strong patchy expression. Cytokeratin was reactive in focal areas of tumour. Ki-67 proliferation index was about 15%. Tumour cells were negative for CD34 (with positive internal control) and S100 (Fig.2). With these findings, a final diagnosis of primary pulmonary artery leiomyosarcoma was offered.

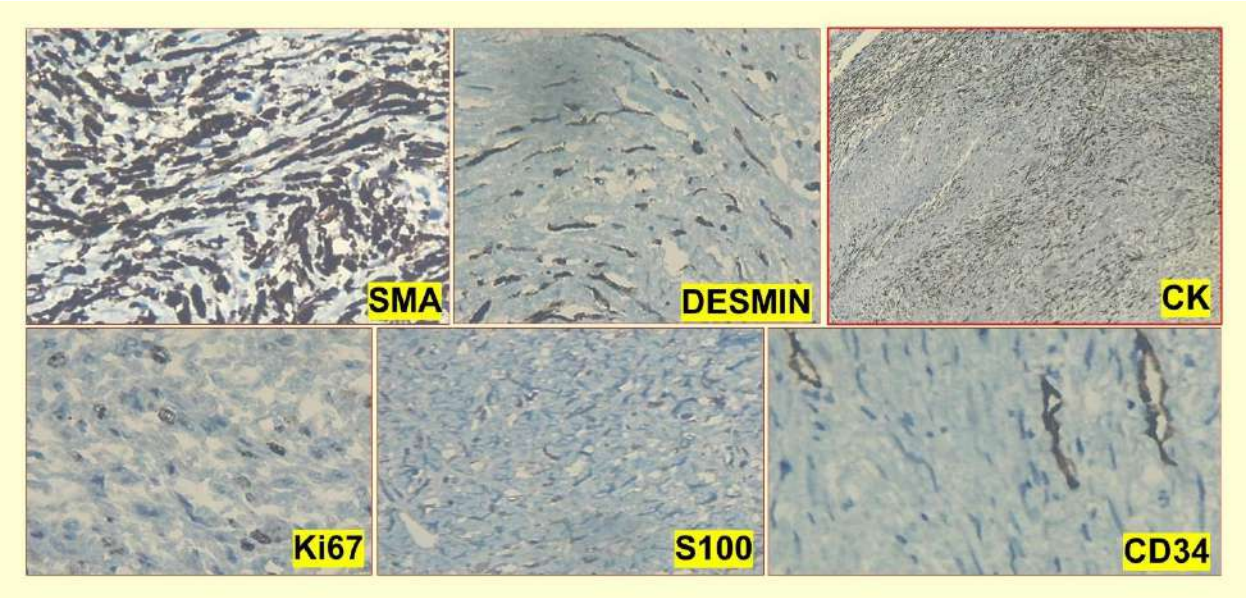


Figure 2: Tumor cells showing strong, diffuse SMA positivity, patchy strong desmin positivity, focal CK positivity, Ki-67 expression in about 15% cells, CD34 and S100 negativity. (CD34 shows vascular channels as positive internal control)

Discussions

The first published case of PPAS was from an autopsy in 1923 by Mandelstamm[3]. It has a very low incidence and only a total of 400 cases have been reported in the literature[3]. Sarcomas of pulmonary artery can result in a clinical syndrome that may be mistakenly recognized as pulmonary embolism or right heart failure. The differential diagnoses include pulmonary artery sarcoma, thromboembolism, and lung cancer. Various histologic subtypes of intrathoracic sarcoma are described, including angiosarcoma, leiomyosarcoma, fibrosarcoma, hemangiopericytoma, and rhabdomyosarcoma[5]. Cox et al. have reported undifferentiated sarcoma as the most common subtype of PPAS[6] However, Bandyopadhyay et al. found leiomyosarcoma as the most common histological type of PPAS (20%) followed by spindle cell sarcoma; in their literature review[7]. Pulmonary artery leiomyosarcomas present with a mean age of 50 years at diagnosis, and with equal frequency in men and women[5]. PPAL almost always originates from the pulmonary trunk with attachment to the wall, grows intraluminally, and may extend into one or both pulmonary arteries or to the pulmonary valve and right ventricular outflow tract. Histologically, atypical spindle cells with

coarse chromatin arranged as bundles in loose myxoid stroma with foci of necrosis are seen. Aberrant cytokeratin expression is described in leiomyosarcoma, as in our case[8].

The tumor can spread transmurally Into adjacent lung parenchyma, bronchi, or lymph nodes and may extend to the myocardium and mediastinum. Systemic metastases can be found in about 20% of cases[9]. Survival was said to be poor in patients with tumor size more than 5 cm and in high grade tumors because of higher frequency of local invasion and distant metastasis[10].

Conclusion

Histomorphology of autopsy specimens helps in detection of unexpected and unknown pathologies which can help to formulate better management strategies for living patients with similar clinical background.

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Endocardial fibroelastosis causing sudden death in an infant: Autopsy case report of an unusual lesion

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ABSTRACT

Endocardial fibroelastosis is characterized by proliferation of both elastic and collagenous fibers within the endocardium, causing diffuse or localized thickening. A four-and-a-half-month-old baby was admitted to a local hospital, with a history of seizures for one day. Baby developed features of heart failure and died within one week after admission. At the post-mortem examination, heart was found to be enlarged with dilated ventricles. The endocardium of left ventricle was markedly thickened with a whitish appearance. Histopathology showed a thick layer of collagenous fibrous tissue in the endocardium, which was confirmed by Masson trichrome stain. The cause of death was offered as dilated cardiomyopathy due to endocardial fibroelastosis. The underlying mechanisms of myocardial fibrosis remain unclear. It is hypothesized that genetic, infectious, inflammatory, and nutritional processes are involved in this condition. This case highlights the importance of gross specimen examination and special staining methods to support histopathology after postmortem examination, for ascertaining the cause of death.

KEY WORDS: Cardiac, endocardial, fibroelastosis, infant, postmortem

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INTRODUCTION

The term endocardial fibroelastosis was introduced by Weinberg and Himmelfarb in 1943, in children who presented with unexplained heart failure previously known as "fetal endocarditis."[1] Endocardial fibroelastosis (EFE) is an uncommon heart disease characterized by focal or diffuse fibroelastic thickening usually involving the left ventricular endocardium.[2] EFE results in the formation of a subendocardial fibrotic tissue layer around the myocardium impeding its growth, which can eventually lead on to cardiac enlargement and presents as unexplained heart failure. The exact etiology of EFE is obscure, and the diffuse endocardial involvement may be responsible for rapid and progressive cardiac decompensation and death. EFE is included under pediatric cardiomyopathies (both dilated and restrictive type) by some authors.[3] It is most common in infants and young children and is accompanied by aortic valve obstruction or other congenital cardiac anomalies like hypoplastic left heart syndrome, in about one third of cases.[2,3] We hereby report the case of a 4.5-month-old female baby diagnosed with endocardial fibroelastosis at autopsy and subsequent histopathological examination, following development of heart failure.

CASE REPORT

A 4.5-month-old female baby was admitted to their nearby hospital with a history of an episode of seizures and adverse events following immunization. Pentavalent vaccine was administered one week back. History of COVID infection was there within the family. No known allergies were present, and no known family history of sudden, unexpected death or autoimmune diseases were present, whereas on treatment, the baby developed features of heart failure. Echocardiography showed a significantly dilated and hardly contracting heart. Clinical differential possibilities of (1) multisystem inflammatory syndrome with multiorgan dysfunction syndrome,

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(2) dilated cardiomyopathy with acute heart failure and ischemia related multiorgan failure, and (3) acute myocarditis, were considered. Irrespective of intensive care treatment, the child succumbed to death.

Autopsy presentation

A medicolegal postmortem examination was conducted at our institution. General examination findings revealed a moderately built, well-nourished female baby of length 62 cm and weight 7.5 kg. Conjunctivae were normal, corneas hazy and fingernails were blue. All natural orifices and external genitalia were normal. Apart from few tiny abrasions over the ventral aspect of chest and side of neck and few needles puncture marks over ventral aspect of elbows, dorsal aspect of hands, right thigh, and right side of neck and over each groin, there were no apparent antemortem injuries. Rigor mortis was not established, and postmortem hypostasis was fixed over the dorsal trunk.

Skull, ribs and chest wall, diaphragm, mediastinum, esophagus, trachea, and bronchi were normal. Heart weighed 50 grams, flabby, with dilated ventricles and whitish appearance of the endocardium. Brain, liver, and spleen were congested. Lungs and kidneys were edematous. Chest cavity contained 200 ml of straw-colored fluid. Peritoneal cavity also contained 300 ml of similar fluid. Other organs were normal. Whole heart (after dissection by inflow outflow method), bits of lungs, brain, kidney, pancreas, and adrenals were sent for histopathological evaluation.

Gross examination showed an enlarged, globular heart weighing 50 grams [Figure 1a]. Right and left ventricle thickness was 0.2 cm and 0.6 cm, respectively. Left ventricle chamber was dilated, and wall was hypertrophic. Endocardium of left ventricle was thickened with a glistening white appearance [Figure 1b]. Both coronaries were patent and originated from the aortic root. Pancreas appeared normal. All other organs were congested.

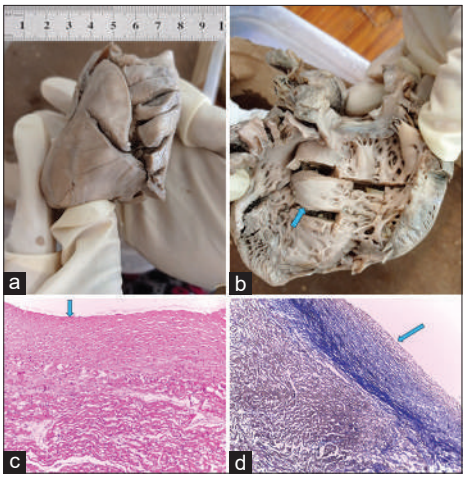


Figure 1: (a) Gross specimen of dissected, dilated heart weighing 50 gms. (b) Left ventricle showing hypertrophy with glistening white, thickened and fibrotic endocardium. (c) Photomicrograph showing thick layer of collagenous fibrous tissue in the sub endocardium of left ventricle (H&E × 100). (d) Photomicrograph showing Masson trichrome stain confirming the presence of collagen (blue color) in the sub endocardium (MT × 100)

Microscopy showed a thick layer of collagenous fibrous tissue and elastic fibers in the endocardium of left ventricle [Figure 1c], confirmed by Masson trichrome stain [Figure 1d]. Myocardium showed focal hypertrophic fibers and focal disarray with wavy, attenuated fibers along with small, scattered foci of lymphocytic infiltration and focal edema in the interstitium. There was no evidence of fibrosis or necrosis in the myocardium.

Pancreas was within normal limits. All other organs showed evidence of congestion.

With these findings, a final diagnosis of dilated type, primary endocardial fibroelastosis was offered. The resultant poor contractility of the significantly dilated heart leading to decompensated heart failure was considered as the most probable cause of death.

DISCUSSION

Endocardial fibroelastosis, also known as endocardial sclerosis, refers to a unique form of fibrosis causing diffuse thickening of the ventricular endocardium by excessive proliferation of fibrous and elastic tissues. Pediatric cardiomyopathy is a broad entity that includes EFE with an overall incidence of approximately 1 in 100,000 children.[3] Enough data about the incidence or prevalence of this lesion are not available in the literature due to its rarity.[3] Majority of cases of EFE reported in the literature are of small children, usually in the first year of life.[3-5]

EFE can be primary (dilated form) or secondary (contracted form).[4] Primary lesions arise de novo and are not combined with other congenital heart diseases, while secondary lesions are often combined with other cardiovascular malformations, such as coarctation of the aorta, aortic valve stenosis, atresia, abnormal origin of the coronary artery, left ventricular dysplasia syndrome, and incomplete myocardial densification.[6,7] EFE has been linked to both dilated and restrictive type of cardiomyopathies by some authors.[3,8]

Few studies have suggested a genetic component for primary EFE, which includes mutations of tafazzin protein encoded by the gene TAZ (also known as EFE2) located on chromosome Xq28.[6] Some authors have pointed out a role of viral etiology for EFE.[6] Xu X *et al*.[9] have demonstrated that fibrogenic cells within EFE tissue originate from endocardial endothelial cells via aberrant endothelial to mesenchymal transition caused by dysregulated transforming growth factor beta/bone morphogenetic proteins signaling.

Some authors have suggested infectious and viral etiologies, along with the possible autoimmune role of anti-Ro and anti-La antibodies.[3,10,11] Complete regression of EFE in the fetus after corticosteroids to mothers with Sjogren's syndrome supports this concept.[12]

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The endocardium is a transparent thin layer approximately ten micrometers in thickness consisting of only five layers. In EFE, there is thickening of all five layers, and an increase in elastin and collagen fibers deposition. Neustein *et al.* suggested that light smooth muscle cells, along with leiomyoid cells, are the culprit in the production of excessive collagen and elastin in the endocardium.[13] Rare disorders like fibroplastic parietal endocarditis, cardiovascular collagenosis, and endomyocardial fibrosis should be included in differential diagnoses.[6]

EFE most commonly presents with signs and symptoms of left heart failure following a recent respiratory infection.[3] Other less common presentations reported in the literature are hydrops fetalis, congestive heart failure, myocardial infarction, congenital heart block, pulmonary embolism, mural thrombi, and sudden cardiac death.[3,14] Prognosis is relatively worse in infants who present with acutely decompensated heart failure.

Echocardiography and magnetic resonance imaging (MRI) using perfusion and myocardial delayed enhancement can be useful in establishing the diagnosis of EFE.[3,15] Xiao W *et al.* have shown that the characteristic morphological changes of the heart could be displayed accurately using cardiac MRI than echocardiography and that the parameters assessed by MRI correlated more with the clinical cardiac function scores.[3,16] Medical therapy for heart failure is the mainstay of treatment. Transplantation may be recommended for those with end stage disease.[3]

Hartung B. *et al.* have found an unusual combination of two biparental MYBPC3 gene mutations in association with EFE and highlight the role of post-mortem molecular testing (molecular autopsy). It is important to be aware of the role of molecular autopsy and genetic testing, which can bring consequences for the relatives of the deceased child and impacts on further family planning, in EFE.[17]

In our case, the baby developed heart failure. Upon autopsy and gross examination, heart was enlarged, dilated, and globular, and the left ventricular cavity was out of proportion. The left ventricular mural endocardium was markedly thickened with glistening white, opaque appearance with marked thickening by elastic fibers and collagen, and the left ventricular myocardium was focally hypertrophied with wavy fibers and small foci of lymphocytic infiltrate. With these features and the absence of significant structural cardiac anomalies, we believe that the baby met the diagnostic criteria for primary dilated type of EFE, which had caused the decedent's death.

CONCLUSION

Endocardial fibroelastosis is a rare cardiac condition associated with high morbidity and mortality. Parents with a history of a child with EFE should undergo genetic counseling and prenatal assessment in subsequent pregnancies.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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HISTOPATHOLOGICAL STUDY OF LUNG CHANGES IN COVID -19 CASES: AUTOPSY STUDY

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Abstract

A novel coronavirus-severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) hit the world towards the end of 2019. This has caused deaths worldwide. Lungs being the primary site for COVID-19 pathology. We attempt a retrospective histopathology study of the lung changes due to SARS–CoV-2 infection of all the medicolegal autopsies done for covid patients for two years (June 2020 to May 2022). Postmortem lung samples of persons who died due to Covid 19 infection were collected in 10% formalin. A total of 71 cases were studied. Representative bits from the lungs were processed. Histopathology sections were stained with hematoxylin and eosin (H & E) stain and special stains were used as and when required. The gross and microscopic findings were studied. Of these 53 were males (74.64 %) & 18 females (25.35%). The age group of the study population ranged from 23 days to 92 years. The major histopathological findings noted were pulmonary edema, pneumonia, intrapulmonary hemorrhage, chronic phase of diffuse alveolar damage, acute phase of diffuse alveolar damage, subacute phase of diffuse alveolar damage, microthrombi, pneumonia with abscess formation. Acute pneumonia with consolidation was seen in 20 cases (28.1%), intrapulmonary hemorrhage in 15 cases (21.1%), chronic phase of diffuse alveolar damage in 9 cases (12.6%), acute phase of DAD was seen in 7 cases (9.8%), subacute phase in 6 cases (8.4%).

Downloads

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Section: Pathology

Original Research Article

SERUM HEPCIDIN LEVELS IN FEMALE BREAST CARCINOMA PATIENTS AND ITS RELATIONSHIP WITH ANEMIA: A CROSS-SECTIONAL STUDY

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ABSTRACT

Background: Breast cancer, comprising 24% of female cancers, is the leading cause of female cancer death globally and the second most common cancer overall. Anemia is prevalent but often undiagnosed in breast cancer patients. Hepcidin, a hepatic peptide hormone, plays a key role in breast carcinoma-related anemia. Considering its pivotal role in iron metabolism, hepcidin-targeting drugs under research may offer novel treatments, potentially improving the quality of life for those with breast carcinoma and anemia. The objectives of this study are to compare serum hepcidin levels in breast carcinoma patients with those having benign breast diseases and to assess serum hepcidin levels in breast carcinoma patients with anemia and those without anemia.

Materials and Methods: The present study is a comparative cross-sectional investigation conducted at the Department of Pathology and Biochemistry, Government Medical College, Thrissur, spanning from January 1, 2020, to December 31, 2021. Two groups were selected for the study population: the first group comprised 30 cases of breast carcinoma patients, while the second group comprised 30 cases of benign breast diseases.

Results: The mean age for breast carcinoma patients was 51.1 years, compared to 35.8 years for those with benign breast disease. In Group 1, serum hepcidin levels were 45.05 ng/ml, significantly higher than 22.08 ng/ml in Group 2 ($p < 0.001$). Group 1 further divided into anemic (mean hepcidin: 53.28 ng/ml) and non-anemic (mean hepcidin: 28.6 ng/ml) subgroups, showing significant differences ($p < 0.001$). Serum hepcidin correlated negatively with RBC indices in both carcinoma (hemoglobin r= -0.830, hematocrit r= -0.813, RBC count r= -0.833) and benign (hemoglobin r= -0.825, hematocrit r= -0.735, RBC count r= -0.633) groups. In the benign group, a weak negative correlation was observed with MCHC (r= -0.385, p= 0.036), and a positive moderate correlation with RDW in the carcinoma group (r= 0.407, p= 0.026).

Conclusion: The study identified elevated serum hepcidin levels in breast carcinoma patients, particularly in those with anemia, as opposed to benign cases.

Keywords: Serum hepcidin, Breast carcinoma, Anemia.

INTRODUCTION

Breast cancer in females has taken the forefront as the most commonly diagnosed cancer, surpassing lung cancer and has secured the fifth position among the leading causes of cancer death worldwide.[1] Breast cancer has held the top position among Indian females, with an age-adjusted rate as

high as 25.8 per 100,000 women and a mortality rate of 12.7 per 100,000 women.[2]

Anemia is frequent in breast cancer patients but often remains undiagnosed and untreated.[3]Hepcidin, a hepatic peptide hormone, plays a pivotal role in the development of anemia in breast carcinoma by closely regulating iron metabolism. Its increased levels have been noted in neoplastic diseases, inflammation, and sepsis, emphasizing its significance.[4,5]Hepcidin, a key regulator of iron metabolism, influences iron release from cells such as enterocytes, macrophages, and hepatocytes. Its interaction with ferroportin inhibits iron release by inducing ferroportin internalization and degradation. Hepcidin expression, responsive to iron, erythropoietic demand, hypoxia, and inflammation, plays a pivotal role in maintaining iron homeostasis but can lead to iron deficiency in chronic inflammatory states, contributing to conditions like the anemia of chronic disease observed in malignancies.[6,7]

The objectives of this study are to compare serum hepcidin levels in breast carcinoma patients with benign breast diseases and to assess serum hepcidin levels in breast carcinoma patients with anemia compared to those without anemia.

MATERIAL AND METHODS

This study was conducted at the Department of Pathology and Biochemistry, Government Medical College, Thrissur, a tertiary care institution in Kerala. The study utilized a comparative cross-sectional design involving two distinct groups of participants. Group 1 was comprised of female breast carcinoma patients undergoing mastectomy in the General Surgery department of Government Medical College, Thrissur. Group 2 included female patients undergoing excision biopsy for benign breast swellings in the same department. The study spanned from January 1, 2020, to December 31, 2021, lasting for 24 months. Inclusion criteria for both groups encompassed females above 18 years, while exclusion criteria involved patients diagnosed with other malignancies, breast carcinoma patients with chronic liver disease, those with bone metastasis and individuals unwilling to provide consent for the study. The targeted sample size for each group was 30 cases: carcinoma breast (Group 1) and benign disease of the breast (Group 2).

Overnight fasting blood samples were collected from patients using EDTA vials for complete blood count and peripheral smear and clot activator vials for hepcidin estimation. Measurements of hemoglobin, hematocrit, MCV, MCH, MCHC, RDW, and RBC count were conducted from EDTA tube blood using a Sysmex XT-1800i 5-part auto analyzer. A manual peripheral smear was prepared from EDTA tube blood stained with Leishman's stain. The serum was separated and stored at -20 °C, and hepcidin values were determined using a 96-well Human Hepc25 (Hepcidin 25) ELISA Kit from Elabscience Biotechnology Inc.

The collected data were coded and entered into an Excel sheet, then analyzed using IBM SPSS Statistics, Version 20.0, a statistical software package. Continuous measurement results are presented as Mean ± SD, while categorical measurements are expressed in numbers and percentages. Significance was assessed at a 5% level. Independent T-tests were conducted to identify statistically significant differences in serum hepcidin levels (ng/ml) between breast carcinoma and benign breast disease groups. Additionally, the tests were performed to compare serum hepcidin levels between anemic and non-anemic groups of breast carcinoma patients, with a significance threshold set at $p < 0.05$. Bivariate Pearson correlations were conducted to identify statistically significant correlations between serum hepcidin levels and hemoglobin, hematocrit, MCV, MCH, MCHC, RBC count, and RDW among patients with breast carcinoma and benign breast diseases. For determining the optimal cutoff of serum hepcidin levels in benign and breast carcinoma patients, receiver operating characteristic (ROC) curve analysis was conducted. The obtained cutoff value categorized serum hepcidin levels into two groups. A Chi-square test was then performed to identify statistically significant differences between benign breast disease and breast carcinoma groups using the optimal cutoff level of serum hepcidin.

RESULTS

In the current study, the first group comprised 30 patients with breast carcinoma, while the second group consisted of 30 patients with benign breast diseases. Among the 30 cases of benign breast diseases in the second group, 21 were diagnosed as fibroadenoma, 4 as fibrocystic disease of the breast, 2 as benign adenomyoepithelioma, 2 as benign phyllodestumor, and a breast lipoma. Group 1 was subdivided into two subgroups. The first subgroup comprised patients with anemia and breast carcinoma(n=20), while the second subgroup included patients without anemia(n=10).

The age of patients in the breast carcinoma group ranged from 30 to 67 years, while the age of patients in the benign breast disease group ranged from 18 to 64 years. The mean age of patients in the breast carcinoma group is 55.1 years, while the mean age of patients with benign breast disease is 35.8 years. A comparison of various parameters between the two study groups is shown in Table 1. The serum hepcidin level in the breast carcinoma group is 45.05ng/ml (SD-14.61), whereas in the benign breast disease group, it is 22.08ng/ml (SD-3.51). Among breast cancer patients, the mean serum hepcidin levels are 53.28 ng/ml (SD=8.82) for anemia patients and 28.6 ng/ml (SD=8.5) for non-anemia patients. [Table 2]

ROC curve analysis was conducted to determine serum hepcidin's sensitivity, specificity, and optimal cut off value. The ROC curve yielded an area under the curve (AUC) of 0.903, with a 95% confidence interval of 0.817-0.990 and a p-value less than 0.001. The serum hepcidin value of 24.5ng/ml was identified as the most accurate cut off point, above which a patient can be categorized as belonging to the breast carcinoma group. This cut off demonstrated a sensitivity of 83.3% and a specificity of 76.7%. The positive likelihood ratio was also calculated to be 3.58, while the negative likelihood ratio was determined to be 0.22. The comparison between breast carcinoma and benign breast disease groups is presented in Table 3, categorized according to serum hepcidin cut off values. The distribution of peripheral smear pictures among the two groups is illustrated in Figure 1. The various presentations included are dimorphic anemia, microcytic hypochromic anemia, normocytic normochromic anemia, normocytic normochromic anemia with macrocytes and normocytic normochromic blood picture. The association between serum hepcidin and age was assessed using linear regression for both the breast carcinoma group (Figure 2) and the benign breast disease group. [Figure 3]

Strong negative correlations were observed between serum hepcidin and hemoglobin in both the carcinoma group ($r = -0.830$, $p < 0.001$) and the benign group ($r = -0.825$, $p < 0.001$). Similarly, strong negative correlations were found between serum hepcidin and hematocrit in the carcinoma group ($r = -0.813$, $p < 0.001$) and the benign group ($r = -0.735$, $p < 0.001$). The benign group had a weak negative correlation with MCHC ($r = -0.385$, $p = 0.036$). Additionally, strong negative correlations were observed between serum hepcidin and RBC count in both the carcinoma group ($r = -0.833$, $p < 0.001$) and the benign group ($r = -0.633$, $p < 0.001$). Furthermore, a positive moderate correlation was noted between serum hepcidin and RDW in the carcinoma group ($r = 0.407$, $p = 0.026$). [Table 4]

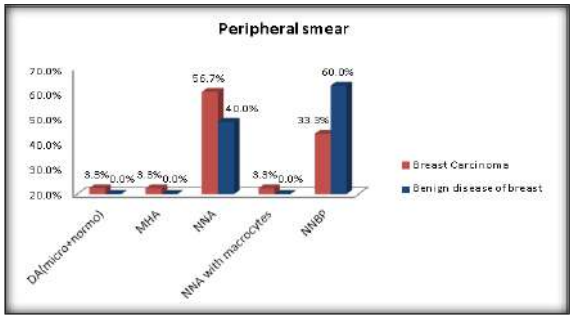


Figure 1: Peripheral smear distribution among two groups

[DA- Dimorphic anemia, MHA- Microcytic hypochromic anemia, NNA- Normocytic normochromic anemia, NNBP- Normocytic normochromic blood picture]

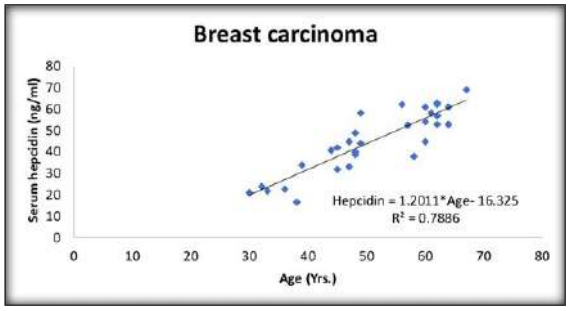


Figure 2: Linear regression to measure the association of serum hepcidin with age among breast carcinoma group

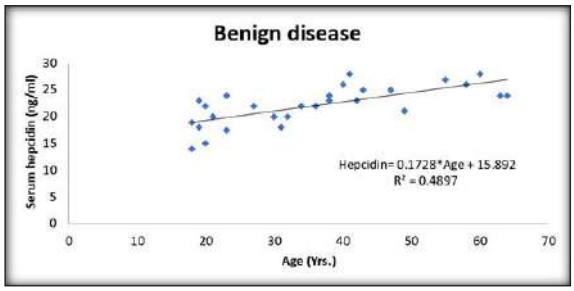


Figure 3: Linear regression to measure the association of serum hepcidin with age among benign disease of breast group

Table 1: Comparison of various parameters between the two study groups

	Breast Carcinoma (N=30)		Benign disease of breast (N=30)		
Parameters	**Mean**	**Std. Deviation**	**Mean**	**Std. Deviation**	**p-value**
Hemoglobin (g/dl)	11.16	1.49	12.25	1.06	0.010
Hematocrit %	33.49	4.32	35.76	3.01	0.022
MCV (fl)	86.38	3.69	85.97	3.93	0.679
MCH (pg)	28.75	1.36	29.04	1.82	0.486
MCHC (g/dl)	33.31	1.25	33.78	1.22	0.151
RBC count(x10^6/mm3)	3.89	0.56	4.17	0.4	0.036
RDW (fl)	46.08	4.34	44.81	3.73	0.23
Serum hepcidin (ng/ml)	45.05	14.61	22.08	3.51	<0.001

Table 2: Mean serum hepcidin levels among anemia and non- anemia patients in breast carcinoma group

Parameter	Anaemia(N=20) (Mean±SD)	Non-Anaemia(N=10) (Mean±SD)	Pvalue
Serum hepcidin level(ng/ml)	53.28±8.82	28.6±8.5	<0.001

Table 3: Comparison of breast carcinoma and benign disease of breast groups based on serum hepcidin cut off values

Groups	Serum hepcidin(ng/ml)		Total	p value
	>=24.5	<24.5		
Breastcarcinoma	25 (78.1%)	5 (17.9%)	30	<0.001
Benigndiseaseof breast	7 (21.9%)	23 (82.1%)	30 (50%)	

Table 4: The correlation between serum hepcidin levels and RBC indices in the two study groups

Variables	Breast Carcinoma(N=30)	Benign diseaseof breast(N=30)
	r value,p value	r value,p value
Hemoglobin(g/dl)	-0.830, p<0.001	-0.825,p<0.001
Hematocrit%	-0.813, p<0.001	-0.735,p<0.001
MCV (fl)	0.319, p=0.086	-0.026,p=890
MCH(pg)	0.192, p=0.310	-0.250,p=0.184
MCHC(g/dl)	-0.119,p=0.531	-0.385,p=0.036
RBCcount(x10^6/mm3)	-0.833, p<0.001	-0.633,p<0.001
RDW(fl)	0.407, p=0.026	0.281, p=0.133

DISCUSSION

Globally, breast cancer is the most frequently diagnosed cancer among women. In India, the incidence of breast cancer is rapidly increasing, and it has become the most common cancer affecting Indian women. There is compelling evidence linking anemia to unfavourable outcomes in individuals diagnosed with breast cancer. Unfortunately, anemia is frequently underestimated, adversely impacting both the quality of life for patients and diminishing their overall survival. Hepcidin, a peptide hormone primarily synthesized by the liver and released into the bloodstream, is crucial in regulating iron absorption and its distribution within tissues.[7,8]

In a study by Shao X et al., the incidence of anemia significantly differed among breast cancer patients with bone metastasis, breast cancer patients without bone metastasis, and those with breast hyperplasia.[9]The hepcidin levels followed this order: metastatic breast cancer (86.37±16.30) > non-metastatic breast cancer (47.21±18.48) > breast hyperplasia (34.31±16.79) - which is comparable to our study. In a study conducted by Pan X et al, the mean serum hepcidin was 8.18 ± 3.75µg/L in breast carcinoma patients with anemia and 4.53 ± 2.07µg/L in those without anemia, indicating a statistically significant difference (t=3.7090, p< 0.01). Moreover, there was a negative correlation between serum hepcidin and hemoglobin levels (r = −0.502, p < 0.01).[10] These results align with the observations made in the current study. In a study conducted by Ciniselli et al., elevated hepcidin levels were observed in malignant breast tumours as opposed to benign ones.[11]

In the current study, it is evident that hepcidin levels are increased in breast cancer and in association with anemia. Reduction of Serum hepcidin may prove beneficial in restraining growth of tumour cells. Besides, correcting anemia in a patient with breast carcinoma through iron therapy alone may prove inadequate, given the persistently elevated serum hepcidin levels. Consequently, iron-restrictive anemia in these cases might respond well to therapy involving hepcidin antagonists.

CONCLUSION

Our study revealed increased serum hepcidin levels in patients with breast carcinoma, as compared to cases of benign breast disease. We analyzed serum hepcidin levels in both anemic and non-anemic patients within the breast carcinoma group, finding higher levels in breast carcinoma patients with anemia. The correlation between elevated hepcidin levels and lower hemoglobin, hematocrit, and RBC count was observed in both groups. These findings provide valuable insight into the relationship between serum hepcidin and anemia across different breast disease categories.

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Original Article

Varied presentations of primary cutaneous lymphoma: A case series from a tertiary care center in South India

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Abstract

Background: Recent studies indicate an upsurge of primary cutaneous lymphoma (PCL) in the Indian population. Of late, we too have come across varied presentations of PCL in relatively younger individuals. Hence, we decided to study the clinical and immunohistological profile of patients with PCL in our department.

Methods: All cases diagnosed as PCL from October 2016 to October 2019 were included. Clinical details, complete blood count, peripheral smear, imaging, histopathology, and immunohistochemistry of skin specimens were analyzed. Lymph node biopsy and bone marrow studies were done in most cases. Human T lymphotropic virus-1 (HTLV1) serology was done in 10 cases.

Results: Of the 24 patients with PCL, 12 were below 50 years of age. Twenty-three patients (95.8%) had T-cell lymphoma and only one had B-cell PCL. Mycosis fungoides (MF) (n = 17; 71%) was the most common type of PCL. There were two (8.3%) cases each of adult T-cell lymphoma/leukemia (ATLL) and Sezary syndrome. MF had varied clinical morphology at presentation and variable clinical outcomes. Both cases of ATLL had features of immunosuppression in the form of infective dermatoses.

Conclusion: We observed an increased proportion of T-cell type of PCL, with the age of onset being relatively early. HTLV-1 positivity was noted in three out of the 10 cases tested. More studies are needed to determine the factors responsible for the younger age of onset of PCL and the role of HTLV-1 infection in the development of PCL.

Keywords:
Adult T-cell Lymphoma/Leukemia, HTLV-1, mycosis fungoides, mycosis fungoides with large cell transformation, primary cutaneous lymphoma

Introduction

Primary cutaneous lymphoma (PCL) is a group of extranodal non-Hodgkins lymphoma (NHL) characterized by clonal proliferation of atypical T or B lymphocytes and less commonly of natural killer cells or plasmacytoid dendritic cells.[1] They do not show evidence of non-dermatologic origin at the time of diagnosis.[2] They form the second most common group of extranodal NHL, the first being gastric lymphomas. The 2018 World Health Organization (WHO)–European Organization of Research and Treatment of Cancer (EORTC) classification of cutaneous lymphomas broadly classifies them into T-cell and B-cell types. PCL has

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also been classified based on clinical, pathological, immunopathological, molecular, and cytogenetic findings. Unlike other extranodal lymphomas, T-cell lymphomas form the majority of PCL. Mycosis fungoides (MF), the most common type of primary cutaneous T-cell lymphoma (CTCL), is characterized by distinct clinicopathologic features, but is closely related to other subtypes of CTCL, like Sezary syndrome (SS) and adult T-cell lymphoma/leukemia (ATLL).

Various studies have shown that the site of origin, rather than the tumor morphology of extranodal lymphoma, determines their clinical behavior, prognosis, and appropriate therapeutic approach. The WHO–EORTC classification is based on the site of origin. We report a 3-year retrospective case series of PCL from a tertiary care center in South India. This retrospective study aims to analyze the clinical and immunopathological profile of these cases.

Methods

After obtaining ethical clearance, clinical records of all cases diagnosed as PCL between October 2016 and October 2019 were scrutinized. Clinical details such as age at the time of diagnosis, gender, duration of illness, presence of pruritus or any other symptom, family history of any malignancy, morphological type and distribution of cutaneous lesions, and the presence of lymphadenopathy and hepatosplenomegaly were collected for all cases. Details of treatment and outcome, if available, were collected. Histopathologic examination (HPE) and immunohistochemical (IHC) examination of skin specimens, hemogram, peripheral blood smear, renal and liver function tests, urinalysis, chest X-ray, ultrasonogram of abdomen, and estimation of serum calcium and lactate dehydrogenase (LDH) levels were done in all patients. Bone marrow studies and fine needle aspiration cytology (FNAC) and histopathology of lymph node were done in relevant cases. Due to financial constraints, human T lymphotropic virus-1 (HTLV-1) testing by enzyme-linked immunosorbent assay (ELISA) method was done in 10 cases only. Based on the clinical features and investigations, patients were categorized into an appropriate type of lymphoma according to the WHO-EORTC classification. MF was diagnosed based on the diagnostic algorithm proposed by the International Society for Cutaneous Lymphoma (ISCL).[3] Patients with erythroderma, peripheral lymphadenopathy, and atypical mononuclear cells (Sezary cells) more than 20% of the total lymphocyte count or a total Sezary count of more than 1000 × 10^9/L were diagnosed with SS. Those patients presenting with nodular skin lesions without any extracutaneous involvement and immunohistopathology demonstrating majority of the infiltrate as CD30+ tumor cells were diagnosed as primary cutaneous CD30+ anaplastic large cell lymphoma (ALCL). Patients with diffuse atypical lymphocytic infiltrate restricted to and extending throughout the subcutis without epidermotropism were classified as subcutaneous panniculitis-like T-cell lymphoma (SPTCL). Patients with MF-like presentation and immunohistochemical (IHC) demonstrating CD25+ cells with positive HTLV-1 infection were diagnosed as ATLL. MF and SS were staged based on ISCL/EORTC revision to the classification of MF/SS.[4] PCLs other than MF/SS were staged according to the ISCL/EORTC proposal on tumors, nodes and metastases (TNM) classification of non-MF/SS PCL.[5]

Results

There were 24 patients diagnosed with PCL. Twenty-three (95.8%) had T-cell PCL. There was only one case of B-cell PCL in our series. MF was the most common type of PCL (n = 17; 71%). There were two (8.3%) cases each of ATLL and SS. We also had one (4.2%) case each of CD30+ALCL, SPTCL, and diffuse large B-cell lymphoma-leg type (DLBCL-LT).

Age of the patients ranged from 18 to 82 years [Table 1]. Twelve (50%) patients were aged less than 50 years. They included nine cases of MF, two cases of ATLL, and one case of SPTCL. Majority (58.3%) of the PCL cases were men (M:F = 1.4:1) [Table 2]. MF was more (58.8%) among men.

Mycosis fungoides

Majority (53%) of the cases of MF presented before 50 years of age. The youngest patient was a 19-year-old man with hypopigmented MF

Table 1: Age distribution of patients (n=24) with primary cutaneous lymphoma

Age (years)	MF	ATLL	SS	CD30+ALCL	SPTCL	DLBCL	Total
<30	1	-	-	-	-	-	1
31-40	4	2	-	-	1	-	7
41-50	4	-	-	-	-	-	4
51-60	2	-	-	1	-	-	3
61-70	6	-	-	-	-	-	6
71-80	-	-	1	-	-	-	1
>80	-	-	1	-	-	1	2
Total	17	2	2	1	1	1	24

ALCL=anaplastic large cell lymphoma, ATLL=adult T-cell lymphoma/leukemia, DLBCL=diffuse large B-cell lymphoma, MF=mycosis fungoides, SPTCL=subcutaneous panniculitis-like T-cell lymphoma, SS=Sezary syndrome

and the oldest was aged 69 years presented with erythematous plaques on the face. Twelve (70.6%) patients had a single type of skin lesion. Psoriasiform MF was the most common (n = 10; 58.8%) type in our series [Table 3]. The other morphological types observed were hypopigmented MF (n = 4; 23.5%), erythrodermic MF (n = 2; 11.8%), and poikilodermatous MF (n = 1; 5.9%) [Figure 1a–c].

Table 2: Gender distribution of patients (n=24) with primary cutaneous lymphoma

	Men	Women
Total (24)	14	10
MF (n=17)	10	7
ATLL (n=2)	1	1
SS (n=2)	2	-
CD30+ALCL	1	-
SPTCL (n=1)	-	1
DLBCL (n=1)	-	1

ALCL=anaplastic large cell lymphoma, ATLL=adult T-cell lymphoma/leukemia, DLBCL=diffuse large B-cell lymphoma, MF=mycosis fungoides, SPTCL=subcutaneous panniculitis-like T-cell lymphoma, SS=Sezary syndrome

The patient with poikilodermatous MF developed large cell transformation later and expired within 6 months. Trunk was the most common site involved in MF. One patient with hypopigmented MF developed epidermodysplasia verruciformis-like lesions and palmar warts. She was later found to be positive for HTLV-1, but had no other features of ATLL.

The most common histopathologic findings in MF were hyperkeratosis (n = 16; 94.1%) and acanthosis (n = 16; 94.1%) [Table 4]. Majority showed epidermotropism (n = 13; 76.5%). Pautrier microabscess was seen in seven (41.2%) cases [Figure 1d]. The seven (41.2%) patients had atypical T-cell infiltrates in both papillary and reticular dermis. The infiltrate was perivascular in seven (41.2%) and periappendageal in four (23.5%) patients.

All cases of MF showed CD3 positivity [Figure 1e]. CD4 positivity was seen in 12 (70.6%) cases [Table 5]. All four cases of hypopigmented MF showed CD8 positivity, and a case of MF with

Table 3: Morphological features in different types of cutaneous lymphomas

Morphological features	MF (n=17)	ATLL (n=2)	SS (n=2)	CD30+ALCL (n=1)	SPTCL (n=1)	DLBCL (n=1)	Total
Macules only	4	-	-	-	-	-	4
Papules only	-	1	-	-	-	-	1
Plaques only	5	-	-	-	-	-	5
Macules and plaques	4	-	-	-	-	-	4
Plaques and nodules	-	1	-	-	1	1	3
Plaques or nodules with ulceration	2	-	-	1	-	-	3
Erythroderma	2	-	2	-	-	-	4

ALCL=anaplastic large cell lymphoma, ATLL=adult T-cell lymphoma/leukemia, DLBCL=diffuse large B-cell lymphoma, MF=mycosis fungoides, SPTCL=subcutaneous panniculitis-like T-cell lymphoma, SS=Sezary syndrome

Table 4: Histopathologic features of primary cutaneous lymphomas

Histopathologic features	MF (n=17)	ATLL (n=2)	SS (n=2)	CD30+ALCL (n=1)	SPTCL (n=1)	DLBCL (n=1)
Hyperkeratosis	16	1	2	1	-	-
Parakeratosis	12	1	2	1	-	-
Acanthosis	16	-	1	1	-	-
Epidermotropism	13	2	2	-	-	-
Pautrier microabscess	7	1	-	-	-	-
Infiltrate						
Diffuse	3	2	2	1	1	1
Nodular	3	-	-	-	-	-
Perivascular	7	-	-	-	1	-
Periappendageal	4	-	-	-	-	-
Extent of infiltrate						
Papillary dermis only	5	-	2	-	-	-
Papillary and reticular dermis	7	2	-	1	-	-
Reticular dermis and subcutaneous	2	-	-	-	-	-
Papillary and reticular dermis and subcutaneous	1		-	-	1	1

ALCL=anaplastic large cell lymphoma, ATLL=adult T-cell lymphoma/leukemia, DLBCL=diffuse large B-cell lymphoma, MF=mycosis fungoides, SPTCL=subcutaneous panniculitis-like T-cell lymphoma, SS=Sezary syndrome

large cell transformation showed CD30 positivity. The mean LDH was 526.1 units/L (normal = 140–280). All patients with hypopigmented MF had normal LDH levels.

Majority (10 out of 17) of the patients with MF came under Stage I. Of these, three were included in Stage IA and seven in Stage IB. There were three patients with Stage IIA MF and two patients with Stage IIB MF. The two patients with erythrodermic MF who did not meet the criteria for SS were classified as Stage IIIA.

Patients with MF (n = 10) with limited skin involvement were treated with narrowband-ultraviolet B radiation (NB-UVB) phototherapy (n = 8) and Psoralen plus ultraviolet A radiation (PUVA) therapy (n = 2) along with topical steroids. All four patients with hypopigmented MF were treated with NB-UVB phototherapy and showed very good response to it. The two patients with erythrodermic MF were managed with total skin electron beam therapy and phototherapy along with systemic chemotherapeutic agents like methotrexate and gemcitabine. The case with large cell transformation had undergone chemotherapy followed by bone marrow transplantation, but relapsed and succumbed to illness within 6 months of bone marrow transplantation.



Figure 1: (a) Erythematous plaque on the face of an elderly man with MF. (b) Large hypopigmented patch with the center showing erythema and scaling on the back of a young man with hypopigmented MF. (c) MF presenting as an ulcerated plaque on the lower limb. (d) Epidermotropism with Pautrier microabscess (H and E, ×400). (e) IHC of MF with atypical lymphocytes expressing CD3 positivity (×200). H and E = hematoxylin and eosin, IHC = immunohistochemical, MF = mycosis fungoides

Sezary syndrome

The two cases of SS were men aged 80 and 82 years. Both of them presented as erythroderma

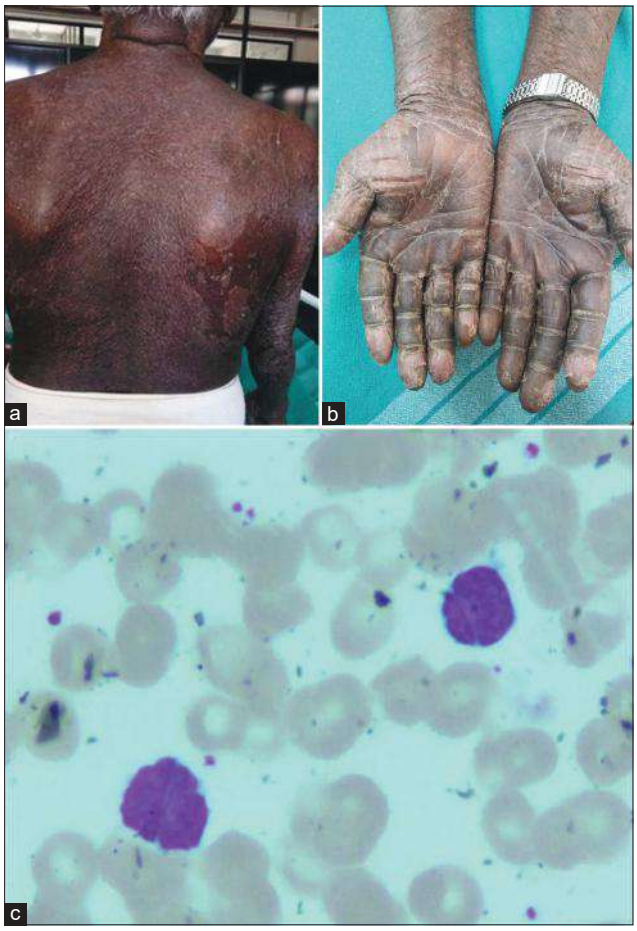


Figure 2: (a) Erythroderma with generalized pruritus and scaling in an elderly man with Sezary syndrome. (b) Painful fissured keratoderma of palms in the same patient. (c) Sezary cells in peripheral smear (H and E, ×100). H and E = hematoxylin and eosin

Table 5: Immunohistochemical features of primary cutaneous lymphoma

Immunohistochemical features	CD3	CD4	CD7	CD8	CD20	CD25	CD30	CD56
MF (n=17)	17	12	-	9	-	-	1	-
ATLL (n=2)	2	2	-	-	-	2	-	1
SS (n=2)	2			-	-	-	-	-
CD30+ALCL (n=1)	-	1	-	-	-	-	1	-
SPTCL (n=1)	1	-	-	1	-	-	-	-
DLBCL (n=1)	-	-	-	-	1	-	-	-

ALCL=CD30+anaplastic large cell lymphoma, ATLL=adult T-cell lymphoma/leukemia, DLBCL=diffuse large B-cell lymphoma, MF=mycosis fungoides, SPTCL=subcutaneous panniculitis-like T-cell lymphoma, SS=Sezary syndrome

and had severe pruritus [Figure 2a]. One of them had depigmented macules, generalized hyperpigmentation, and also extensive dermatophytosis during presentation. Both patients had painful and fissured palmoplantar keratoderma [Figure 2b]. HPE showed atypical cells in a band-like arrangement at a dermo-epidermal junction with no significant epidermotropism. IHC was positive for CD3 and negative for CD20. Serum LDH was markedly elevated (>1000 units/L). Peripheral smear showed Sezary cells and eosinophilia [Figure 2c]. Both cases had significant generalized lymphadenopathy without any visceral organ involvement, and hence were classified under Stage IVA1. One patient was treated initially with daunorubicin, vincristine, and cytarabine. While on maintenance chemotherapy with 6-mercaptopurine and methotrexate, he had a relapse of disease with nodules on the face and was later treated with gemcitabine and oxaliplatin (GEMOX) regimen and went into remission. The other patient died soon after diagnosis, though the exact cause of death could not be ascertained.

Adult T-cell lymphoma/leukemia

There were two cases of ATLL: a 32-year-old man had chronic ATLL and a 30-year-old woman had acute ATLL. The latter had infiltrated papules and plaques on extremities and upper back. She also had extensive tinea corporis and recalcitrant genital warts. The man presented with pruritic papules, nodules, and plaques predominantly involving photo-exposed sites for 3 years and later progressed to acute ATLL [Figure 3a]. He had generalized lymphadenopathy, extensive dermatophytosis, and scabies [Figure 3b and c]. Histopathology of both cases was similar to MF with hyperkeratosis, parakeratosis, epidermotropism, and Pautrier microabscess. CD3, CD4, and CD25 were positive on IHC. One patient had CD56 positivity also [Table 5]. Mean LDH was 1228 units/L (±622.3). Anti-HTLV-1 antibody was positive and peripheral smear showed atypical lymphocytes with flower cell nuclear morphology in both patients [Figure 3d]. Both patients had an advanced stage of disease ($T_{3b}N_2M_1$ and $T_{3b}N_3M_1$, respectively) and succumbed to their disease within 1 year of diagnosis, in spite of receiving chemotherapy.



Figure 3: (a) Multiple erythematous and skin-colored infiltrated papules on the face in a man with ATLL. (b) Extensive tinea corporis in the same patient. (c) Scabies in the same patient. (d) Flower cells in peripheral smear in ATLL (H and E, ×100). ATLL = adult T-cell lymphoma/leukemia, H and E = hematoxylin and eosin

CD30+ ALCL

A 55-year-old man who presented with recurrent ulcerated nodules on the trunk of 2-years duration had CD30+ ALCL. HPE showed large, atypical lymphocytes, which expressed mainly CD30 and were negative for anaplastic lymphoma kinase (ALK). His treatment details could not be obtained as he was lost to follow-up.

Subcutaneous panniculitis-like T-cell lymphoma

A 33-year-old woman who was diagnosed with SPTCL presented with multiple indurated plaques on the face, scalp, chest, abdomen, and arms, mimicking lupus panniculitis [Figure 4a]. HPE showed lobular panniculitis with infiltration by atypical

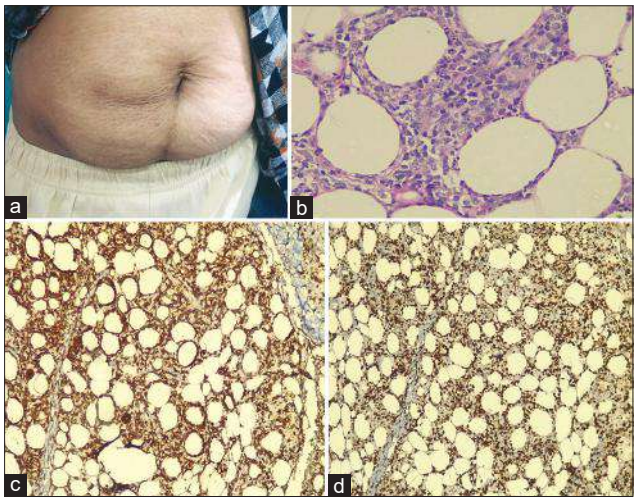


Figure 4: (a) Depressed plaque on the right side of abdomen with peau d'orange appearance in a patient with SPTCL. (b) Atypical lymphocytes in the subcutaneous tissue rimming individual adipocytes (H and E, ×400). (c) IHC of SPTCL showing CD4 positivity (×200). (d) IHC of lymphoma cells showing high Ki67 index (×200). H and E = hematoxylin and eosin, IHC = immunohistochemical, SPTCL = subcutaneous panniculitis-like T-cell lymphoma

lymphocytes surrounding adipocytes [Figure 4b]. The neoplastic cells were CD4 positive with high Ki67 [Figure 4c and d]. She was having an early disease stage ($T_{2b}N_0M_0$) and responded well to six cycles of chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) and was in remission.

Diffuse large B-cell lymphoma

The patient with diffuse large B-cell lymphoma (DLBL) was an 82-year-old woman who presented with erythematous nodules on the lower limbs. We could not get any evidence of extracutaneous disease even after 6 months of initial diagnosis, and it was classified as $T_{2a}N_0M_0$ stage. HPE showed a dense infiltrate of large, atypical lymphocytes with enlarged nuclei and prominent nucleoli in the lower dermis and subcutaneous tissue. IHC revealed positivity for CD20 and Bcl-2. Hence, we made a diagnosis of DLBL-LT. She was treated with Rituximab-CHOP (R-CHOP).

Discussion

Majority (95.8%) of cutaneous lymphomas in our series were of T-cell type. This is similar to several previous hospital-based reports from India.[1,6,7] The low frequency of primary cutaneous B-cell lymphoma in our series was in concordance with studies from other Asian countries like China and Iran.[8,9] But some other reports from Japan, Korea, USA, and certain western countries show the prevalence of B-cell lymphoma to be higher (20%-30%), though it is less common than T-cell lymphoma.[10-12]

There was a bimodal age peak in our series: the first between 31 and 40 years and the second between 61 and 70 years. Half of the patients were less than 50 years of age. A similar trend was reported in some recent studies from India, Korea, and Iran.[1,8,13] In our study, 9/17 (52.9%) cases of MF and all cases of ATLL and SPTCL were below 50 years of age. In 2009, Bradford *et al.*[10] from the USA reported that CTCL showed an exponential increase with age, with a peak around 80 years. A younger age peak in our series could reflect a changing epidemiology of the disease, favoring younger persons, or could be due to earlier diagnosis due to advances in investigation methods. As in previous studies, preponderance of men was noted in our study as well.[1,6] MF was seen more among men, similar to previous reports from India.[1,6] SS was observed exclusively in older men.

In our study, MF was the most common type of PCL (71%). Though 8.3% of patients each had SS and ATLL, it may be premature to conclude that these conditions are more frequent in our population, as this was a short case series. Interestingly, Khader *et al.*[1] from Calicut, which is only about 100 km away from our center, had reported a frequency of 17.1% (6/35) of ATLL in their case series. One woman patient with hypopigmented MF in our study had developed epidermodysplasia verruciformis-like presentation while on phototherapy, with the development of palmar warts and tinea versicolor-like lesions. On further evaluation, she was found to be HTLV-1 positive, but had no other features of ATLL. Though provisionally placed in the group of MF, she is being followed up for possible evolution to ATLL.

Similar to a few other studies from Asia, our series had a relatively high frequency of hypopigmented MF (24%).[1,8,9] Patients with hypopigmented MF were comparatively young.[1,14] The frequency of hypopigmented MF in Caucasian studies is less compared to ours. Some studies report a mixed clinical pattern with areas of erythema within hypopigmented patches.[13] All cases of hypopigmented MF had a very good prognosis in our series. All of them achieved complete remission with NB-UVB phototherapy alone, with no history of relapse till date. In a study on hypopigmented MF by Kanokrungsee *et al.*,[15] 7/11 patients had complete remission with NB-UVB twice weekly and 4/11 had partial remission. Three of them had relapsed after a mean of 10 months. Wongpraparut *et al.*[16] reported that 4/6 patients with hypopigmented MF treated with NB-UVB relapsed within 2 months to 6 years. A study in Egyptian patients with hypopigmented MF showed 86.7% response with phototherapy, 66.7% response with NB-UVB, and 80% response with PUVA.[17]

Another patient with MF later developed large cell transformation with CD30 positivity. This can occur in 20%–50% of advanced MF.[18] MF with CD30+ large cell transformation should be differentiated from other CD30+ lymphoproliferative disorders like primary cutaneous CD30+ ALCL, lymphomatoid papulosis (LyP), and borderline cases, as the treatment outcome varies a lot among them. Primary cutaneous CD30+ ALCL and LyP usually have an excellent outcome. One of our patients with MF deteriorated fast and succumbed to the disease after she developed large cell transformation. Previous studies have shown that MF with CD30+ large cell transformation has a poor prognosis, with a 5-year survival of 28.6%–44.4%.[19,20] MF with coexisting LyP is found in 3% of MF patients and these patients have a favorable prognosis.[21-25] Early large cell transformation in MF (<2 years from the diagnosis of MF), more advanced disease at the time of transformation (Stage IIB–IV), older age (≥60 years), and extracutaneous spread were associated with poor outcomes.[20,26]

Clinicopathologic features of ATLL are often similar to those of MF. Hence, the demonstration of flower cells on peripheral smear and HTLV-1 positivity are mandatory to diagnose ATLL. Mean LDH values were higher in ATLL group than the MF group in our study. Patients with ATLL in our series had a relatively poor prognosis compared to those with MF. HTLV-1 infection is endemic in Japan, the West Indies, and Central Africa. There are some studies showing presence of HTLV-1 infection in India too.[1,27,28] Routine screening for HTLV-1 may be warranted in all cases of suspected cutaneous lymphoma.

We had a relatively higher frequency of SS cases (8%) than that reported in a recent study from South India (5%).[1] Elderly patients with erythroderma should always be evaluated for SS, as many such cases can be missed and managed as primary erythroderma or atopic dermatitis. Repeated cutaneous biopsies and peripheral smear examination should be performed in those cases.

We had just one case of CD30+ ALCL during our study period, which was much lower when compared to previous studies from Asia.[29] A lower frequency of CD30+ALCL was seen in a recent study from India.[1] In our study, the frequency of SPTCL was similar to what is reported in several Asian studies.[29-31] The frequency of SPTCL reported from western countries is less than ours.[13,32,33] SPTCL primarily involves subcutaneous fat tissue with infiltrate composed of CD8+ and cytotoxic T cells with high Ki67 index.

The relatively small number of cases and the inability to do serological testing for HTLV, complete panel of lymphocyte markers, and gene rearrangement studies in all cases due to financial constraints are some limitations of this study. Also, it is difficult to make definite conclusion on the trends about the disease in the general population as the study was conducted in a tertiary care hospital. However, our study indicates an increased frequency of T-cell type of PCL in younger age group. We also noticed several patients with HTLV-1 positivity in our series. More population-based studies with larger sample size are needed to determine the factors responsible for younger age of onset of PCL and the role of HTLV-1 infection in the development of PCL among our population.

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Conflicts of interest
There are no conflicts of interest.

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Original Article

Pathology Section

Clinicopathological Study of Mucormycosis in COVID-19: A Cross-sectional Study from a Tertiary Care Centre in North Kerala, India

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ABSTRACT

Introduction: Mucormycosis is an angioinvasive disease associated with high morbidity and mortality caused by fungi of the order Mucorales. The rise in the incidence of mucormycosis, along with the surge of Coronavirus Disease-2019 (COVID-19), justifies reassessment of associated risk factors and the susceptible population. The present study aims to highlight the specific clinicopathological features and risk factors of mucormycosis in COVID-19 patients.

Aim: To investigate the histopathological features, key clinical findings in mucormycosis, and the predisposing factors associated with mucormycosis in post-COVID-19 patients.

Materials and Methods: This descriptive cross-sectional study was conducted at the Department of Pathology, Government Medical College, Manjeri, Malappuram, Kerala, India, in the Department of Pathology. It included all histopathologically proven Mucormycosis specimens from confirmed COVID-19 positive and post-COVID-19 cases in this Medical College from January 1, 2021, to December 31, 2021, amounting to a total of 30 cases. The type of tissue reaction, fungal hyphae, angioinvasion, necrosis, and fungal co-infections were assessed. Histopathologic analysis was performed using routine Haematoxylin and Eosin (H&E) slides, followed by special stains such as Periodic Acid Schiff (PAS) and Grocott Methenamine Silver (GMS). Data was collected using a proforma, and the clinical details were obtained from the request form received along with the biopsy specimen and case sheets. Age, gender, site of involvement, and risk factors were assessed and subjected to descriptive tabulation and analysis.

Results: The mean age was 49.5 years with a male-to-female ratio of 1.30:1. The major risk factors observed in the present study were Diabetes Mellitus (DM) and steroid therapy, 30 all cases (100%), along with others such as chronic kidney disease 2 cases (6.67%) immune disorders, and renal transplantation 1 case each (3.33%). The most commonly involved site was sinuses 27 cases (90.00%). Multiple sinuses were affected in 22 cases (73.33%), with the ethmoid sinus being the most common site 24 cases (80.00%), followed by the maxillary sinus 21 cases (70.00%). The most common reaction pattern observed was acute inflammation 15 cases (50.00%). Angioinvasion was noticed in 19 cases (63.33%) and necrosis was present in 28 cases (93.33%). Co-infection with fungal pathogens was observed in 8 cases (26.67%), with aspergillus being the most common co-infection in all except one of the eight cases. Fungal hyphae were visible on H&E slides in 28 cases (93.33%), while the remaining cases were identified only through special stains (PAS and GMS).

Conclusion: Mucormycosis infection is strongly associated with DM and steroid therapy. A more even distribution between males and females was noted, deviating from the male predominance described in most studies. The histopathological appearance of angioinvasion was less frequent compared to most studies, consistent with previous studies on the Indian population. Higher rates of co-infection and the presence of granulomatous inflammation were observed. Further studies are needed to explore the relationship between host immunity, morphological patterns, and their influence on prognosis.

Keywords: Angioinvasion, Coronavirus disease-2019, Diabetes mellitus, Histopathological features, Risk factors

INTRODUCTION

As COVID-19 cases have surged, there has been a dramatic rise in mucormycosis infections among patients infected with or recovered from COVID-19. Mucormycosis is an angioinvasive disease associated with high morbidity and mortality. It is caused by fungi of the order Mucorales, which includes Rhizopus, Mucor, Rhizomucor, Cunninghamella, and Absidia. Rhizopus oryzae is the most common type and responsible for nearly 60% of mucormycosis cases in humans, accounting for 90% of the Rhino-Orbital-Cerebral-Mucormycosis (ROCM) form. The mode of contamination occurs through the inhalation of fungal spores [1].

The prevalence of mucormycosis in India is approximately 0.14 cases per 1000 population, which is about 80 times higher than the prevalence in developed countries [1]. In a prospective multicentre study conducted by Patel A et al., from January 1, 2016, to September 30, 2017, at 12 tertiary care centres across India [2], Rhino-Orbital Mucormycosis (ROM) was reported as the most common presentation of mucormycosis. Diabetes mellitus was identified as the most common predisposing factor. The study also reported that disseminated mucormycosis and ROM with cerebral extension, shorter duration of symptoms, shorter duration of antifungal therapy, and treatment with amphotericin B deoxycholate (as opposed to liposomal) were independent risk factors for mortality. The changing epidemiology of mucormycosis due to the increased incidence during COVID-19 necessitates a reassessment of associated risk factors and susceptible populations. The principal risk factors for mucormycosis include diabetes mellitus with or without ketoacidosis, haematological malignancies, organ transplant, chronic kidney or liver disease, immunological disorders, prolonged corticosteroid therapy, deferoxamine therapy, and trauma [3,4]. Limited published studies from a pathologist's perspective in this part of South India are available [5,6]. Therefore, the present study aims to highlight the specific clinicopathological features and risk factors of mucormycosis in COVID-19 patients.

Mucormycosis has been classically described as an aggressive opportunistic infection occurring in immune-compromised patients. Fungal co-infections associated with the global COVID-19 pandemic, based on a retrospective analysis by Song G et al., [7],

have been reported. They presented the epidemiology of fungal co-infections in COVID-19 patients based on a Worldwide Web search and suggested the possibility of neglected fungal co-infections in COVID-19 patients, drawing ideas from Severe Acute Respiratory Syndrome (SARS) and influenza worldwide data. Sen M et al., reported six cases of ROM with a mean age of 60.5 years [8]. The major risk factors reported were uncontrolled type 2 diabetes with systemic corticosteroids for COVID-19 in all patients. Mehta S and Pandey A, Mekonnen ZK et al., and Werthman-Ehrenreich A each presented a case of concurrent COVID-19 infection with invasive ROM [9-11].

Different pathophysiological models have been proposed on the pathogenesis of mucormycosis in COVID-19. In a SARS-CoV-2 infected individual, numerous factors have been shown to be involved in the pathogenesis of COVID-19 Associated Mucormycosis (CAM). Mucorales invades vessels through its spore coat protein (CotH3) with Glucose-regulated 78 KDA Protein (GRP78) on the human endothelial cells acting as a receptor for vascular invasion. Hyperglycaemia, diabetic ketoacidosis, and the presence of iron are the key factors promoting this interaction. SARS-CoV-2 directly increases GRP78 expression, precipitating diabetic ketoacidosis, and might alter innate immune cell functions [12]. Glucocorticoids used in the treatment can worsen the scenario by causing hyperglycaemia and immunosuppression. An increase in mucormycosis in the Indian context has been linked to a triad of diabetes, widespread use of corticosteroids, and COVID-19, mainly through cytokine storm, lymphopaenia, and endothelial damage [13].

Sree Lakshmi I et al., reported that histopathological features of mucormycosis, such as angioinvasion, perineural invasion, severe fungal load, and large areas of necrosis, were directly proportional to the mortality rate [6]. Diabetes and a history of corticosteroid intake for the treatment of COVID-19 were identified as the two most common predisposing factors for the development of mucormycosis.

Hence, the present study aimed to study the histopathological features of mucormycosis and the associated risk factors of mucormycosis in patients with COVID-19.

MATERIALS AND METHODS

The present descriptive cross-sectional study was conducted in the Department of Pathology, Government Medical College, Manjeri, Malappuram, Kerala, India. All histopathology-proven Mucormycosis specimens in confirmed RT-PCR COVID-19 positive and post-COVID-19 cases at the study institution from January 1, 2021, to December 31, 2021, were included after obtaining approval from the Institutional Ethics Committee (IEC number-IEC/GMCM/93).

Inclusion criteria: All histopathology-proven Mucormycosis specimens in confirmed RT-PCR COVID-19 positive and post-COVID-19 cases were included.

Exclusion criteria: COVID-19 cases diagnosed with positivity in the rapid antigen test and autopsy cases of COVID-19 were excluded.

Study Procedure

Data were collected using a proforma. The clinical details were obtained from the request forms received along with the biopsy specimen, including age, gender, site of involvement, and risk factors such as diabetes mellitus, steroid therapy, immunological disorders, organ transplant, etc. Histopathologic analysis of routine H&E slides, PAS, and GMS stained slides of Mucormycosis specimens in COVID-19 and post-COVID-19 cases was performed. Assessment included the type of tissue reaction, presence of fungal hyphae, angioinvasion, necrosis, and fungal co-infections on H&E stained slides, followed by special stain studies including PAS and GMS.

STATISTICAL ANALYSIS

The data, which included age, sex, risk factors, site, interval between COVID-19 and mucor presentation, histopathological findings, and co-infections, was entered into an excel sheet and subjected to descriptive tabulation and analysis.

RESULTS

In the present study, a total of 30 cases were included. The subjects had an age range from 23 to 76 years. Most of the subjects (10 out of 30, 33.33%) belonged to the age group of 51 to 60 years. Of all the thirty study subjects, 17 (56.67%) were males and 13 (43.33%) were females. The mean age in the present study was 49.5 years with a male-to-female ratio of 1.30:1. The age and sex distribution of cases in the present study are given in [Table/Fig-1].

Age (in years)	Number of cases
21-30	1
31-40	2
41-50	3
51-60	10
61-70	9
71-80	5

[Table/Fig-1]: Age distribution of cases.

The major risk factors observed in the present study were diabetes mellitus and steroid therapy in all the cases (100%), followed by chronic kidney disease in 2 cases (6.67%), immune disorder, and renal transplantation in 1 case each (3.33%) [Table/Fig-2].

Risk factors involved	No. of cases (n)
Diabetes mellitus	30
Steroid therapy	30
Chronic kidney disorder	2
Immune disorder	1
Renal transplant	1

[Table/Fig-2]: Risk factors associated with COVID-19 Associated Mucormycosis (CAM) (N=30).

Most of the patients presented in the second week (7-13 days) after commencement of COVID-19 treatment 12 cases (40%), followed by the first week (0-6 days, 11 cases (36.67%) [Table/Fig-3].

Interval between COVID-19 treatment commencent and presentation of mucor symptoms	No. of cases (n)	Percentage (%)
0-6 days (First Week)	11	36.7
7-13 days (Second week)	12	40
14-20 days (Third week)	6	20
21-27 days (Fourth week)	1	3.33

[Table/Fig-3]: Interval between COVID-19 treatment commencent and presentation of mucor symptoms.

The sites involved were sinuses in 27 cases (90.00%), followed by the nasal cavity 17 cases (56.67%), orbit 5 cases (16.67%), pterygopalatine fossa 4 cases (13.33%), and brain in 1 case (3.33%) [Table/Fig-4]. Multiple sinuses were involved in 22 out of 30 cases in the present study (73.33%). The most common sinus involved was the ethmoid sinus 24 cases (80.00%), followed by the maxillary sinus 21 cases (70.00%), sphenoid sinus in 18 cases (60.00%), and frontal in 6 cases (20.00%). All the sinuses were involved in 6 cases (20.00%).

Microscopic examination showed various histopathological reactions [Table/Fig-5]. The most common reaction pattern observed was acute inflammation, which was seen in 15 cases (50.00%), followed by chronic inflammation in 8 cases (26.67%), granulomatous reaction in four cases (13.33%), foreign body reaction in 2 cases (6.67%), and eosinophilic reaction in 1 case (3.33%). Angioinvasion was noticed

in 19 cases (63.33%) and was absent in the remaining 11 cases (36.67%). Necrosis was present in 28 cases (93.33%) and absent in 2 cases (6.67%). The presence of co-infection was observed in 8 cases (26.67%), out of which seven were Aspergillus. Co-infection with the bacteria Actinomycosis was seen in one case [Table/Fig-6].

Sites	No. of cases (n)
Nasal cavity	17
Ethmoid sinus	24
Maxillary sinus	21
Sphenoid sinus	18
Frontal sinus	6
Orbit	5
Pterygopalatine fossa	4
Brain	1

[Table/Fig-4]: Sites involved and distribution among sinuses (N=30).

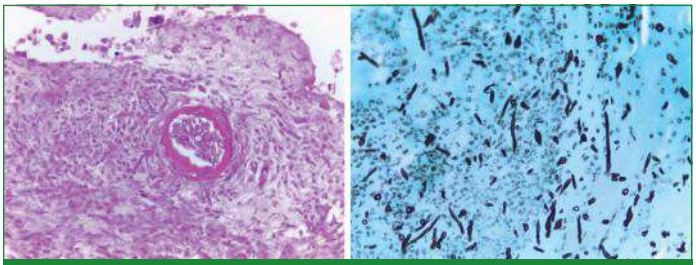
Histopathological features	No. of cases (n)
Acute inflammation	15
Chronic inflammation	8
Granulomatous reaction	4
Eosinophilic reaction	1
Foreign body reaction	2
Presence of angioinvasion	19
Presence of necrosis	28

[Table/Fig-5]: Histopathological Features noted in cases of COVID-19 Associated Mucormycosis (CAM) (N=30).

Co-infection	No. of cases
Aspergillus	7
Actinomycosis	1
Absent	22

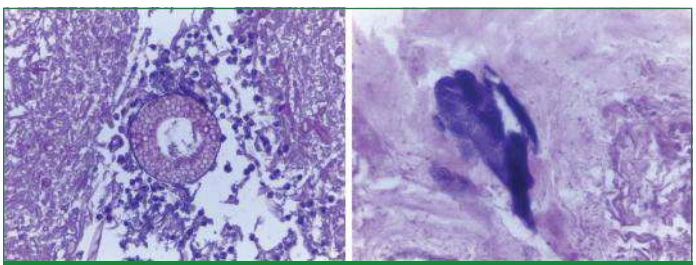
[Table/Fig-6]: Presence of co-infection and organisms involved (N=30).

The authors were able to identify the fungal hyphae on H&E slides in 28 cases (93.3%) [Table/Fig-7], and in the remaining 2 cases (6.67%), hyphae were identified only on special stains (PAS and GMS) [Table/Fig-8].



[Table/Fig-7]: Fungal hyphae with angioinvasion, 40x, H&E.
[Table/Fig-8]: GMS stain highlighting hyphae, 40x. (Images from left to right)

Nine out of the 30 patients (30%) died during the period of the present study. Co-infection with actinomycosis and aspergillosis was present [Table/Fig-9,10]. The clinical presentation of mucormycosis cases can be seen in [Table/Fig-11-13].



[Table/Fig-9]: Aspergillus fruiting body co-infection with mucor, 40x, H&E.
[Table/Fig-10]: Actinomycosis- co-infection with mucor, 40x, H&E. (Images from left to right)



[Table/Fig-11]: Case presented with supra-orbital and infra-orbital swelling.



[Table/Fig-12]: Case of Rhino-Orbital-Cerebral Mucormycosis (ROCM).
[Table/Fig-13]: Case presenting as orbital cellulitis diagnosed as mucormycosis on biopsy. (Images from left to right)

DISCUSSION

The study included a total of 30 cases during the study period. RT-PCR positivity was considered as the operational definition of a case. Most of the cases in the present study belonged to the age group of 51 to 60 years (33.33%). The youngest person was 23 years old, and the oldest was 76 years old. Out of the thirty study subjects, 17 (56.67%) were males, and 13 (43.33%) were females. In comparison to the present study, a much stronger male predominance has been noted in most studies. In a multicentre observational study of mucormycosis in India, conducted by Patel A et al., on a total of 287 individuals, 74.6% were men, and only 25.4% were women [14]. Mucormycosis was more common in males (73.60%) with a mean age of 46.8 years in a study by Jain K et al., among patients in a rural tertiary setting in central India [15]. The mean age of the entire study population was 53.4 years in the study by Patel A et al., [14]. In comparison, the mean age in the present study is 49.5 years. According to a systematic review of COVID-19 cases from 18 countries by Hoenigl M et al., 78% of CAM cases reported were males [16].

The rhino-orbital (ROM) area was the most common site involved in the present study. All the cases studied (100%) involved this area. The common sites involved were sinuses in 27 cases (90.00%), followed by the nasal cavity 17 cases (56.67%) and the orbit 5 cases (16.67%). Hoenigl M et al., reported that rhino-orbital cerebral infection was the most frequent presentation of the disease (74%) [16]. This study noted that ROCM infection was particularly common in patients from India, where 41 out of 42 patients (98%) had rhino-orbital cerebral infection, compared with 18 out of 38 patients (47.37%) from outside India. The results from our study are in line with this finding.

A systematic review on CAM by Muthu V et al., reported that ROM and ROCM accounted for 89% of cases in India, while globally, they accounted for only 64% [12]. Proof of cerebral involvement was found in 11 (27%) of these 41 patients in the study mentioned above by Hoenigl M et al., whereas authors only had one case involving the brain in the present study. Multiple sinuses were involved in 22 out of 30 cases in the present study (73.33%), with the most common sinus involved being the ethmoid sinus 24 cases (80.00%), followed by the maxillary sinus 21 cases (70.00%), the

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sphenoid sinus in 18 cases (60%), and the frontal sinus in 6 cases (20.00%). A prospective observational study conducted by Lakshmi I et al., also showed the ethmoid sinus to be the most common site, followed by the maxillary sinus [6]. Authors did not have any cases involving the lung in the present study. The study by Muthu V et al., also pointed out that pulmonary, disseminated, and other sites were less frequently reported from India [12]. Several explanations for the observed preponderance of rhino-orbital cerebral infection in India have been put forward, the most important being the difference in the distribution of species, with Rhizopus arrhizus being the most common species in India, compared to Cunninghamella spp. being the most common species in countries like Spain [16]. Pulmonary disease almost exclusively occurred in the Intensive Care Unit (ICU) setting and was present in 50% of patients reported from outside India, with most of the cases being from Europe and the USA, as per the study by Hoenigl M et al., [16].

As observed in most studies, DM and corticosteroid therapy were the most common risk factors in the present study as well. All cases (100%) were diabetic and had received steroid therapy. A systematic review of 101 cases reported worldwide by Singh AK et al., found that pre-existing DM was present in 80% of cases [13]. Diabetes was the most prevalent condition overall in Hoenigl M et al., review of cases, reported in 66 (83%) of 80 cases overall [16]. However, the same study also noted the almost ubiquitous presence of Diabetes CAM in cases from India (present in 95%) and reported a higher prevalence of diabetes as a risk factor in Indian patients compared to patients from other countries (40 of 42 patients in India (95%) vs 26 of 38 (68%) from outside). The present study also reported that ROCM was mostly seen in patients with diabetes. According to this study, 93% of patients with rhino-orbital cerebral disease were diabetic, compared to pulmonary cases which showed a weaker association (55%). Authors did not have any pulmonary cases in the present study for a similar comparison.

The mainstay of treatment offered in the present hospital was steroids, liposomal amphotericin B, oxygen, and supportive therapy. Corticosteroid intake for the treatment of COVID-19 was reported in 76.3% of cases in India, as reported by Singh AK et al., in a systematic review of cases reported worldwide and in India. The review also reported an association with the intake of remdesivir (20.6%) and tocilizumab (4.1%) as therapy [13]. However, none of the patients received remdesivir or tocilizumab.

Among the patients, 2 had chronic kidney disease (6.67%). This is comparable to Hoenigl M et al., study, which reported chronic kidney disease in 6% of cases [16]. One case in the present study had a history of organ transplantation (3.33%). Muthu V et al., reported solid organ transplant in five out of the 233 Indian cases they studied (2.14%) [12]. Regarding other well-studied risk factors, the authors did not have any cases with haematologic malignancy developing CAM. Muthu V et al., reported 2 cases among 233 cases from India (0.9%), while the association was stronger in patients outside India (four out of 42 cases, 9.52%). Hoenigl M et al., study reported 5 cases out of 80 CAM cases (6.25%) having a haematological malignancy [16].

Most of the patients in the present study presented in the second week (7-13 days) after commencing COVID-19 treatment, accounting for 12 cases (40%) in our study. Mucormycosis was diagnosed at a median of 10 days (range: 0-90 days) after the diagnosis of COVID-19 in the study conducted by Hoenigl M et al., [16]. In another multicentre observational study conducted by Patel A et al., [14], the number of days between the diagnosis of COVID-19 and CAM was 18.

Out of the 30 patients in the present study, 9 (30%) died during the study period. In the study by Hoenigl M et al., [16], all-cause mortality occurred in 39 (49%) out of 80 patients. The mortality rate reported in the present study, however, was 37% in patients with Rhino-Orbital-Cerebral Mucormycosis (ROCM), which was comparable to the present study where all cases were Rhino-Orbital in nature. The fatality rate of cases reported from India (36.5%) was lower than the globally reported cases (61.9%), probably due to the predominance of Rhino-Orbital-Mucormycosis (ROM) as per a multivariate analysis of 275 cases of CAM, of which 233 were reported from India and 42 from the rest of the world by Muthu V et al., [12]. A lower value of 16% mortality was reported in the study by Sree Lakshmi I et al., [6].

Among the histopathological findings in the present study, an inflammatory background consisting of neutrophils, lymphocytes, and plasma cells was observed in 50% of the cases, whereas the presence of a granulomatous response (13%), eosinophilic response (3%), and foreign body reaction pattern (5%) was less frequent. In the present study, granulomas did not show necrosis in the centre in any of the cases. Frater JL et al., [17] have described inflammation in mucormycosis, where a neutrophilic response was seen in 50% of the cases, pyogranulomatous response in 25%, only granulomatous response in 5%, and no inflammation in 20% of the cases. The presence of granulomatous response is consistent with other studies in the Indian population, such as those by Ganesan N and Sivanandam S and Sree Lakshmi I et al., which reported granulomatous inflammation at 23% and 11%, respectively [5,6]. Angioinvasion was noted in 63% of the cases in the present study, which was lower than in many of the previous studies, and necrosis was observed in 95% of the cases. Frater JL et al., [17] identified angioinvasion in 100% of the cases, while studies in the Indian population by Ganesan N and Sivanandam S, found it in 71.67% of the samples, which is closer to the present findings [5]. Angioinvasion was present in only 24% of the patients in the study by Sree Lakshmi I et al., [6].

In the present study, authors found 8 cases (26.67%) of co-infection. Out of these cases, seven were Aspergillus and one was Actinomycosis. The study by Ganesan N and Sivanandam S, identified Aspergillus in 20% of the cases and Candida in 13.33% [5]. One of the cases in the present study had a fungal ball of Aspergillus. Co-infection with Actinomycosis was not described in the mucor-related articles that authors could find in the published literature. The histomorphology of these cases was confirmed by special stains and culture.

Limitation(s)

The limitations of the present study were that we could not obtain all the clinical information, such as the mode of presentation and follow-up after the study period. Additionally, the study sample size was small. Another limitation was the inability to include culture confirmation in all cases due to its unavailability.

CONCLUSION(S)

Mucormycosis infection was found to be overwhelmingly associated with DM and steroid therapy. The association was much stronger than what was identified in previous studies, especially in study populations outside India. Male preponderance was much lower in our study compared to most available studies. The histopathological appearance of angioinvasion was less frequent compared to most studies, although it is consistent with previous studies conducted on the Indian population. The unexpected findings were higher rates of co-infection and a higher incidence of the granulomatous type of inflammation. Further studies need to be conducted to investigate the relationship between host immunity and morphological patterns, and how it influences the prognosis.

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Case Series

Pathology Section

Cytological Diagnosis of Malignant Pleural Effusion caused by Metastatic Squamous Cell Carcinoma: A Series of Four Cases

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ABSTRACT

The majority of malignant pleural effusions are caused by adenocarcinomas, with the most common primary sites being the lung and breast in men and women, respectively. Metastatic squamous cell carcinoma in serous effusions is rare, accounting for less than 3% of all malignant effusions. The most common primary site of origin for metastatic squamous cell carcinoma involving serous effusions is the lung, followed by the head and neck, oesophagus, and cervix. Well-differentiated squamous cell carcinoma in pleural effusion, characterised by keratinised cells with hyperchromatic nuclei, tadpole cells, and fiber cells, is exceedingly rare. Poorly differentiated squamous cell carcinomas often present a diagnostic challenge and can be mistaken for poorly differentiated adenocarcinoma, malignant mesothelioma, or reactive mesothelial hyperplasia. Immunohistochemistry is often required for a definitive diagnosis. Making an accurate diagnosis is crucial for providing optimal treatment to the patient. In this series, four cases (56 years old male,69 years old male, 60 years old female and 81 years old male) of malignant pleural effusion caused by metastatic squamous cell carcinoma arising from the lung, oropharynx, cervix, and oesophagus were examined. While one of the cases involved a well-differentiated squamous cell carcinoma with characteristic cellular morphology that allowed for a straightforward diagnosis, the other three cases were poorly differentiated squamous cell carcinomas that required cell block preparation and immunohistochemistry for confirmation.

Keywords: Immunohistochemistry, Keratinized cells, Neoplasm metastasis

INTRODUCTION

Malignant effusions are most often caused by metastatic adenocarcinoma. Serous effusions due to metastatic squamous cell carcinoma are rare, accounting for only 0.5-2.7% of all malignant effusions [1]. Well-differentiated squamous cell carcinoma cells exhibit characteristic cytologic features, enabling a reliable morphological diagnosis. Poorly differentiated squamous cell carcinoma in effusions, due to its rarity and lack of cytomorphological differentiation, may be misdiagnosed as poorly differentiated adenocarcinoma or sometimes as malignant mesothelioma [2]. Squamous cell carcinoma, in comparison to adenocarcinoma, has a poorer prognosis. It has a lower diagnostic yield in pleural fluid cytology as its cells are shed less into effusions due to their tight intercellular junctions and robust anchors to the basement membrane [3].

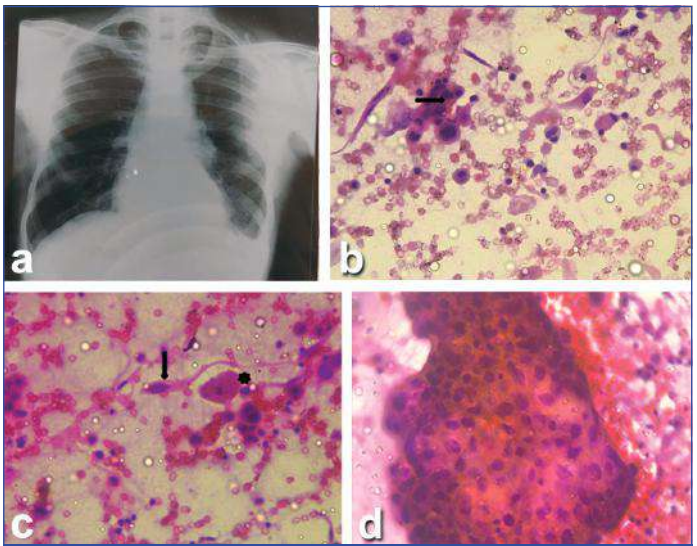
This study describes four cases of malignant pleural effusion caused by metastatic squamous cell carcinoma. Two cases had no prior history of malignancy, and pleural effusion was the initial manifestation. The diagnosis of squamous cell carcinoma was made from pleural fluid cytology smears. Radiological investigations revealed a primary lung malignancy. Two patients with a history of squamous cell carcinoma of the cervix and oropharynx, respectively, were treated with chemoradiation and later presented with pleural effusion.

Case 1

A 56-year-old male patient presented with complaints of cough and dyspnoea lasting for two weeks. The patient was a smoker and had no history of tuberculosis or any other significant past medical conditions. Upon examination, the patient was afebrile, with a pulse rate of 90/min and a respiratory rate of 26/min. Dullness on percussion and decreased breath sounds were observed in the left 6th, 7th, and 8th intercostal spaces. A chest X-ray [Table/Fig-1a] revealed a left hilar mass and left-sided pleural effusion. The provisional diagnosis was lung carcinoma with malignant pleural effusion, with a differential diagnosis of TB lung with effusion. Pleural tapping was performed, and 5 mL of red-coloured fluid was sent for cytological study.

The pleural fluid cytology smear showed dispersed cells, both singly and in occasional clusters. The cells exhibited moderate to abundant dense eosinophilic to orangeophilic cytoplasm, well-defined cell borders, and pleomorphic hyperchromatic nuclei. Fiber cells and tadpole cells were also observed [Table/Fig-1b-d].

A diagnosis of well-differentiated squamous cell carcinoma in pleural effusion was made. The final diagnosis was primary lung squamous cell carcinoma with metastasis to the pleural cavity. Unfortunately, the patient passed away after one cycle of chemotherapy.



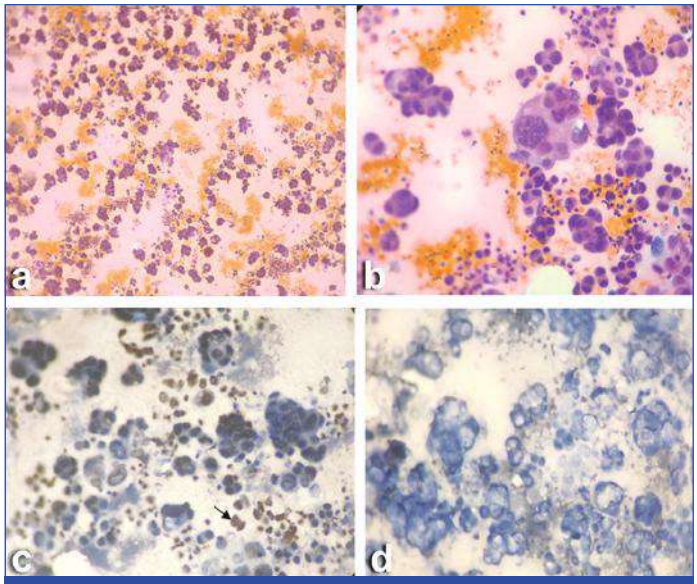
[Table/Fig-1]: a) Chest X-ray showing a left hilar mass lesion; b) Cytology smear showing fiber cells (indicated by arrow, pap stain x400); c) tadpole cell indicated by arrow, keratinised cells with pyknotic nuclei indicated by asterisk (pap stain x 400); d) large cluster of cells with orangeophilic cytoplasm and pleomorphic hyperchromatic nuclei (pap stain x400).

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Case 2

A 69-year-old male patient presented with a cough, dyspnoea, and right-sided pleuritic chest pain lasting for three weeks. He was a non-smoker and non-alcoholic. The patient had a past history of oropharyngeal squamous cell carcinoma, for which he underwent radiotherapy one year ago. Upon examination, his vitals were stable, and breath sounds were diminished on the right-side of the chest. A chest X-ray revealed right-sided pleural effusion. A Computerised Tomography scan of the thorax showed a soft tissue density nodule with spiculated borders, measuring 15.3×15 mm in the apex of the right lung. The provisional diagnosis was lung and pleural metastasis from primary oropharyngeal squamous cell carcinoma, with a differential diagnosis of primary lung carcinoma with metastasis to the pleural cavity. A 5 mL red-coloured pleural fluid sample was sent for cytological study.

The pleural fluid cytology smears showed cells arranged in spherical clusters and dispersed singly [Table/Fig-2a]. The cells exhibited a moderate amount of cytoplasm, a high nuclear to cytoplasmic ratio, pleomorphic hyperchromatic nuclei with coarsely granular chromatin [Table/Fig-2b]. Occasional bizarre cells were observed. A cytological diagnosis of poorly differentiated carcinoma was made. Immunohistochemistry study was conducted on the cytology smears, revealing strong nuclear positivity for p63 [Table/Fig-2c], which confirmed their squamous origin, and Thyroid Transcription Factor (TTF-1 negativity [Table/Fig-2d], which ruled out the possibility of a non-squamous lung carcinoma.



[Table/Fig-2]: a) Cytology smear showing cells arranged in small clusters and singly (pap stain x100); b) Large pleomorphic cells with hyperchromatic nuclei are seen (pap stain x400); c) Neoplastic cells show nuclear positivity for p63 (indicated by arrow, x400); d) Neoplastic cells are negative for TTF-1(x400).

A diagnosis of poorly differentiated squamous cell carcinoma in pleural effusion was made. The final diagnosis was primary oropharyngeal squamous cell carcinoma with metastasis to the lung and pleural cavity. The patient is currently undergoing chemotherapy.

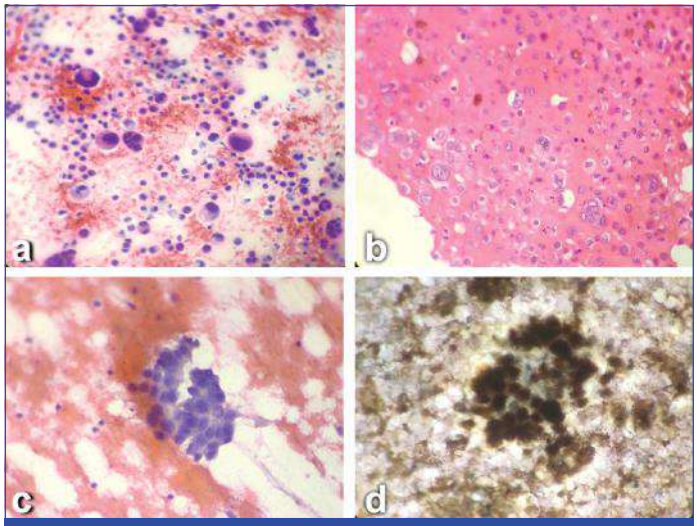
Case 3

A 60-year-old female patient presented with breathlessness lasting for two weeks. She had a history of squamous cell carcinoma of the cervix, for which she underwent chemoradiation one year ago. Upon examination, she was afebrile, had tachypnea (respiratory rate-32/min), diminished breath sounds on the left-side of the chest, and an enlarged, single, hard left supraclavicular lymph node measuring 2×2 cm. A chest X-ray revealed a left-sided massive pleural effusion. One litre of red-coloured pleural fluid was sent for cytological study.

The pleural fluid cytology showed a cellular smear with cells dispersed singly and arranged in small clusters [Table/Fig-3a]. The cells had sharp cell borders, moderate to abundant cytoplasm, and pleomorphic hyperchromatic nuclei. Bizarre cells and multinucleated tumour cells were observed. Mesothelial cells were also seen in a background of blood.

The cell block preparation exhibited cells dispersed singly, with a moderate amount of cytoplasm and nuclei displaying irregular contours and coarse granular chromatin [Table/Fig-3b].

The fine needle aspiration cytology smears of the left supraclavicular lymph node showed atypical cells in clusters. These cells had a moderate amount of dense eosinophilic cytoplasm and pleomorphic hyperchromatic nuclei [Table/Fig-3c]. The background displayed lymphocytes and blood. A cytological diagnosis of metastatic poorly differentiated carcinoma, possibly of squamous origin, was made for the pleural fluid and lymph node aspirate smears. Immunohistochemistry using p63 was performed on the lymph node aspirate smear, revealing diffuse strong nuclear positivity [Table/Fig-3d], confirming squamous differentiation.



[Table/Fig-3]: a) Pleural fluid cytology smear showssingly dispersed pleomorphic cells with hyperchromatic nuclei (pap stain x400); b) Cell block preparation of pleural fluid shows dispersed cells with marked nuclear atypia (H&E stain x400); c) Left supraclavicular lymph node FNAC smear shows a cluster of atypical cells (pap stain x400) d) Neoplastic cells show strong nuclear positivity for p63 on lymph node aspirate smears (x400).

The final diagnosis was primary squamous cell carcinoma of the cervix with metastasis to the pleural cavity and supraclavicular lymph node. Unfortunately, the patient passed away one week after initiation chemotherapy.

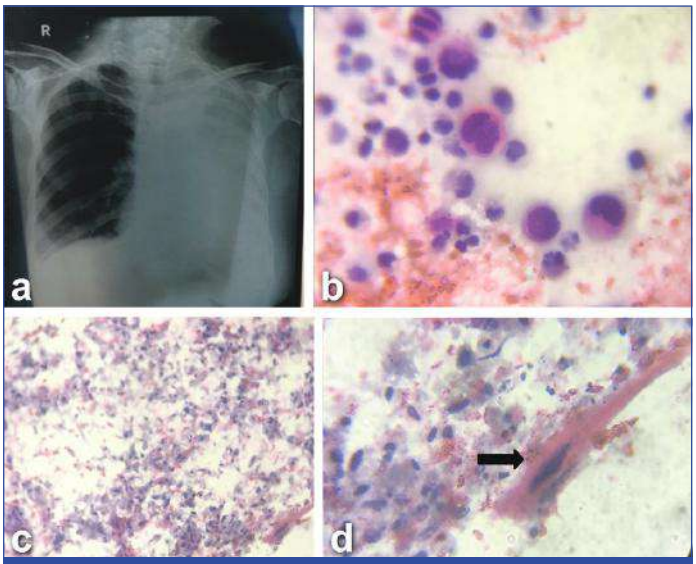
Case 4

An 81-year-old female patient presented with dysphagia and weight loss lasting for one month, and dyspnoea lasting for two weeks. Upon examination, she appeared emaciated, had tachypnea (respiratory rate-34/min), and an 8×8 cm hard swelling over the sternum. Diminished breath sounds were observed on the left-side of the chest. A chest X-ray revealed a left-sided massive pleural effusion [Table/Fig-4a]. Endoscopic examination revealed an ulceroproliferative growth measuring 5 cm in the distal 7 cm of the oesophagus. Yellow-coloured pleural fluid, with a volume of one litre, was sent for cytological study.

The pleural fluid cytology smear showed cells dispersed singly and arranged in small clusters. The cells had a moderate to abundant cytoplasm, well-defined cell borders, and pleomorphic hyperchromatic nuclei [Table/Fig-4b]. The background displayed mesothelial cells.

Fine Needle Aspiration Cytology (FNAC) of the sternal swelling was performed. The smears showed cells dispersed singly, with a moderate amount of dense eosinophilic to orangeophilic cytoplasm and hyperchromatic pyknotic nuclei [Table/Fig-4c,d]. The background showed necrotic debris. The oesophageal biopsy revealed a poorly differentiated squamous cell carcinoma.

The final diagnosis was squamous cell carcinoma of the oesophagus with metastasis to the sternum and pleural cavity. All cases have been summarised in [Table/Fig-5].



[Table/Fig-4]: a) Chest X-ray PA view shows left-sided massive pleural effusion; b) Pleural fluid cytology smear shows singly dispersed pleomorphic cells with hyperchromatic nuclei (pap stain x400); c) FNAC smear from sternal swelling shows cells in a necrotic background (pap stain x100); d) FNAC smear from sternal swelling-cell showing squamous differentiation (indicated by arrow) (pap stain x400).

S. No.	Age	Sex	Effusion cytology diagnosis	Primary site of malignancy	Secondary sites
1	56	M	Well differentiated squamous cell carcinoma	Lung	Pleural cavity
2	69	M	Poorly differentiated squamous cell carcinoma	Oropharynx	Lung, pleural cavity
3	60	F	Poorly differentiated squamous cell carcinoma	Cervix	Lymphnode, pleural cavity
4	81	F	Poorly differentiated squamous cell carcinoma	Oesophagus	Sternum, pleural cavity

[Table/Fig-5]: Shows age and sex of patients, cytological diagnosis, primary site of malignancy and secondary site of metastasis.

DISCUSSION

Serous fluid cytology is an essential diagnostic test for detection and categorising malignancies based on their morphological characteristics. Metastatic adenocarcinoma accounts for the majority of malignant effusions in adults. Although squamous cell carcinoma is a common malignancy, it is rarely encountered in serous effusions. The pleural cavity is the most commonly involved body cavity, followed by the peritoneal and pericardial cavities [1]. The lung, larynx, and cervix are the most common primary sites for squamous cell carcinoma metastasising to body cavities [2]. In this case series, the primary sites of squamous cell carcinoma metastasising to the pleural cavity were the lung, oropharynx, cervix, and oesophagus.

The largest published series includes a study of 46 cases of metastatic squamous cell carcinoma collected from 9,297 effusions over a span of 33 years. Squamous cell carcinoma of the lung was the most common origin in the study, accounting for 13 out of 34 pleural fluid samples, 2 out of 4 pericardial fluid samples, and 1 out of 8 peritoneal samples. Other primary sites included the female genital tract and larynx [3].

In another study of 277 cases of non-small cell lung carcinoma with malignant pleural effusion, 29 were squamous cell carcinomas and 248 were adenocarcinomas. Pleural fluid cytology had a low diagnostic yield in cases of squamous cell carcinoma with malignant effusion, and these patients had reduced survival compared to those with adenocarcinoma [4]. Squamous cell carcinoma cells have tight intercellular junctions and are firmly anchored to the basement membrane, resulting in reduced shedding of squamous cells in effusions compared to adenocarcinomas [5].

The diagnosis is straightforward when serous effusions are involved in metastatic, well-differentiated squamous cell carcinoma. It typically exhibits a predominantly single-cell pattern with occasional small clusters. The cells have well-defined cell borders, dense eosinophilic to orangeophilic cytoplasm, and pleomorphic hyperchromatic nuclei. Tadpole cells, fiber cells, anucleated cells, keratinous debris, and squamous pearls may also be observed [1]. Serous effusions involved in other malignancies may show small degenerated/necrotic orangeophilic tumour cells that mimic keratinising cells of squamous cell carcinoma [6].

Making a diagnosis of poorly differentiated squamous cell carcinoma in serous effusions is challenging as its cytological features overlap with those of poorly differentiated adenocarcinoma, malignant mesothelioma, and reactive mesothelial hyperplasia [7]. However, certain features such as a single-cell presentation, the presence of many bizarre nuclear forms, coarse chromatin, and cells with sharp cytoplasmic outlines can indicate a squamous cell carcinoma, especially in the context of a known clinical history of a primary squamous cell carcinoma [1]. It is crucial to make an accurate diagnosis as squamous cell carcinoma requires a different treatment protocol compared to adenocarcinomas. Immunohistochemistry can aid in confirming the diagnosis. Squamous cell carcinoma cells will test positive for p63, p40, and Cytokeratin5/6 [8].

Metastatic adenocarcinoma reacts positively to Carcinoembryonic Antigen (CEA), Ber-EP4, and MOC-31 [9]. Thyroid transcription factor-1 and Napsin A have high specificity for lung adenocarcinomas [4]. Malignant mesothelioma cells will show positivity for mesothelial markers (Wilm's tumour gene 1, calretinin) and Epithelial Membrane Antigen (EMA), while reactive mesothelial cells will show positivity for mesothelial markers (WT 1, calretinin) and desmin [10]. Published literature suggests that the pleural cavity is the most commonly involved secondary cavity [Table/Fig-6] [4,11-16].

S. No.	Authors	No. of SCC cases with malignant effusion	Body cavity involved	Primary sites of SCC
1	Dorry M et al., [4], 2021	29	Pleural cavity	Lung
2	Llanos N and Vera Roman JM [11], 1999	1	Pleural cavity	Urinary bladder
3	Joglekar K et al., [12], 2016	1	Pleural cavity	Skin
4	Paul P et al., [13], 2023	1	Pleural cavity	Oral cavity
5	Ishikawa H et al., [14], 1999	1	Pleural cavity	Gingiva
6	Gamez RG et al., [15], 2009	1	Pleural cavity	Cervix
7	Erra S et al., [16], 2016	1	Pleural cavity	Vulva

[Table/Fig-6]: Shows primary site of squamous cell carcinoma and secondary site of metastasis in various published studies [4,11-16].

CONCLUSION(S)

Metastatic squamous cell carcinoma involving serous effusions is rare, and well-differentiated squamous cell carcinoma causing malignant pleural effusion is exceedingly rare. Morphological mimickers of poorly differentiated squamous cell carcinoma in effusions include poorly differentiated adenocarcinoma, malignant mesothelioma, and reactive mesothelial hyperplasia. It is imperative to make a definitive diagnosis of squamous cell carcinoma as it has a worse prognosis and a different management protocol compared to adenocarcinoma. The clinical history of a primary squamous cell carcinoma and/or effusion fluid showing a predominance of a single cell population, numerous bizarre nuclear forms, and cells with a sharp cytoplasmic outline should raise the possibility of metastatic squamous cell carcinoma. Immunohistochemistry helps to confirm the diagnosis.

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ORIGINAL ARTICLE

Correlation between Ki-67 labeling index and mitotic index in Head and neck squamous cell carcinoma

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ABSTRACT

Background: Proliferative activity of any tissue or neoplasm can be determined by its growth rate by mitotic count or by using antibodies directed against specific antigens like Ki-67. The usefulness of Ki-67 in head and neck cancers has been debated for the past 20 years; however, no study has definitively resolved this controversy. **Aim:** Assess the correlation between Ki-67 expression and mitotic index in head and neck squamous cell carcinoma. **Materials and Methods:** This cross-sectional study was performed in 66 histologically proven cases of Head and Neck Squamous cell carcinoma (SCC) received in a histopathology laboratory and satisfied the specified criteria. Tumor was graded. Mitotic and Ki67 labeling index was calculated. Statistical analysis was performed using appropriate techniques to determine the correlation coefficient. **Results:** A statistically significant difference in the Ki67 labeling index (LI) between the grades of the tumor proper was noted ($P = 0.040$). An increase in the mean mitotic index with histological grade was noted, which was statistically significant in the proliferating margin ($P = 0.037$). A statistically significant positive correlation was noted between Ki67 LI and mitotic index in tumor proper ($r = 0.263$, $P = 0.033$) and proliferative margin ($r = 0.364$, $P = 0.003$). **Conclusion:** Mitotic index, a rapid and affordable tool for assessing cellular proliferation, becomes more relevant and practically effective when used in conjunction with Ki-67. Combined analysis of the two indices can be useful in the early diagnosis of possibly malignant lesions and in predicting tumor behavior.

KEY WORDS: Head and neck squamous cell carcinoma, Ki67 labeling index, mitotic index

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INTRODUCTION

Head and neck cancers represent the seventh most common cancer worldwide. According to the GLOBOCAN 2018 report, worldwide head and neck cancer statistics indicate that there are 834,860 cases of Head and neck cancer (HNC) per year, resulting in approximately 431,131 deaths per year.[1] More than 90% of head and neck malignancies are squamous cell carcinomas, which develop from the mucosal surfaces of the oral cavity, oropharynx, and larynx.[2] Over the past 20 years, there has been an increase in the incidence of oropharyngeal squamous cell carcinoma, which is attributed to a rise in the frequency of associations with high-risk subtypes of the human papillomavirus.[2] The prevalence of HNCs has significantly increased in India. One of the most crucial mechanisms in oncogenesis is thought to be cell proliferation. Neoplasia and malignant transformation may be indicated by any abnormal proliferative alterations in the epithelium.[3] The rate of cell proliferation and differentiation characterizes the behavior of squamous cell carcinoma. The mitotic figure is the most obvious histological indicator of the cell cycle stage. Cellular alterations in epithelial dysplasia include increased nucleoli numbers and mitotic figures. The characteristic appearance of the chromosome sets during the various M-phase subphases can be used to identify cells in the mitotic phase. Mitotic counting has been based on this.[4,5] The earliest method of evaluating proliferation is the counting of mitotic figures. The ease with which mitosis may be identified without additional equipment aside from a reasonable microscope and a well-stained section has contributed to the growing popularity of counting mitotic figures, even if many other methods of evaluating proliferation have emerged.[6] By identifying unique protein markers, immunohistochemistry now aids in

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histopathological diagnosis. Since both internal and external factors have minimal effect on Ki-67, it has become a very reliable marker and is considered as the standard to determine cell proliferation. The nuclear expression of Ki-67 during a particular time in the cycle demonstrates that it is advantageous to use this marker to assess mitotic activity.[7]

Numerous studies have been performed using Ki-67 as a diagnostic and prognostic marker in various neoplasms with mixed results. This study aims to determine the role of ki67 as a tumor proliferation marker in head and neck squamous cell carcinomas and to analyze the relationship between the mitotic index and Ki- 67 expression in head and neck squamous cell carcinomas. Also to evaluate the expression of the protein Ki-67 and mitotic index in normal epithelium, adjacent hyperplastic epithelium, tumor proper and proliferating margin, which has implications in prognostication.

OBJECTIVES

To assess the correlation between Ki-67 expression and mitotic index in head and neck squamous cell carcinoma, evaluate the relationship of Ki-67 LI and mitotic index with various degree of differentiation in head and neck squamous cell carcinoma and study the expression of Ki-67 protein and mitotic index in normal epithelium, adjacent hyperplastic epithelium, tumor proper and proliferating margin.

MATERIALS AND METHODS

This cross-sectional study was performed in 66 histologically proven cases of head and neck squamous cell carcinoma received in the histopathology laboratory. Samples insufficient for immunohistochemical evaluation, received chemoradiotherapy, and samples where adjacent hyperplastic epithelium and proliferating margins not included were excluded.

Study procedure

Specimens were fixed using 10% formalin. Gross features were recorded. Tissue paraffin blocks are made, and sections of 4-5 μm have been cut and stained with hematoxylin and eosin. Slides were then examined under light microscope. Tumor was graded in accordance with the histopathological classification recommended by the World Health Organization. Mitotic index was calculated in H and E stained sections using 40 X objective, evaluating 1000 tumor cells for the presence of mitoses. The mitotic index (MI) was calculated by dividing the mitotic count determined in 10 consecutive high-power fields by the total number of cells in these fields and expressed as the number of mitotic figures per 1000 cells.

The sections from the tumor tissue were subjected to immunostaining for Ki-67 expression. Then slides were examined, and four different areas were noted under ×400 magnification, namely, normal epithelium (NE), hyperplastic epithelium (HE), tumor proper (TP) or center of tumor, and proliferating margin (PM) of tumor. The invasive front or PM is defined as the region centered on the border separating the host tissue from the malignant nests, with an extent of 1 mm. Central tumor corresponds to all the tissue inside the invasive margin.[8] Nuclear staining was evaluated.

Ki-67 labeling index (LI) was calculated as number of positive epithelial cells/total number of epithelial cells ×100. Basal cell immunopositivity was excluded from Ki-67 LI. The Ki-67 LI was noted in each of these four zones. MI was calculated in TP and PM only. Intensity of Ki-67 immunopositivity was graded as weak, moderate, or strong depending on the appearance of nuclei as faint brown, brown, and dark brown, respectively.

Ki-67 LI was graded as similar to Buch *et al.* [Table 1].[3]

Statistical analysis

The collected data was coded and entered in excel sheet. Statistical analysis was performed using IBM SPSS version 26. Quantitative variables were reported as mean and standard deviation. Qualitative variables were expressed as frequency or percentage. Correlations were performed using bivariate Spearman correlations since the data was not normally distributed. One-way analysis of variance (ANOVA)/Kruskal–Wallis one-way ANOVA non-parametric tests were conducted based on the distributions of the data to explore the statistically significant differences of variables between the grades. *Post hoc* test (Independent samples Kruskal–Wallis test) with Bonferroni correction for multiple tests was performed.

Ethics committee approval obtained on 28/4/21.

RESULTS

A total of 66 cases were evaluated. The age of patients ranges from 31-90 years. The most frequent age group in this study was 51-60 years (37.9%). 88% (58) cases were males. Females were just 12% (8 cases). In the present study, the oral cavity, accounting for 51% of all the cases, was the most frequently involved anatomical site, followed by the larynx (29%). Hypopharynx and oropharynx were the least affected. In the oral cavity, the most commonly involved site was tongue followed by buccal mucosa. Most of the patients presented with ulceroproliferative lesions. maximum number of cases were well-differentiated squamous cell carcinomas (70%). Only a few cases (5%) were poorly differentiated. All cases in the study showed grade 1 positivity in normal and HE. Ki-67 positive cells were sprinkled within its basal and parabasal layers only. TP and PM mostly had grade 2 positivity. The mean values of the parameters studied are shown in Table 2.

Correlations between MI and Ki67 were performed using bivariate Spearman correlations since the data was not

Table 1: Grading of Ki67 labeling index

Ki 67 labeling index	*0%*	*1-25%*	*26-50%*	*51-75%*	*>75%*
Grade	0	1	2	3	4

normally distributed. There was a negligible positive correlation between MI and Ki67 LI in TP (r = 0.263, *P* = 0.033) and a low positive correlation between MI and Ki67 LI in PM (r = 0.364, *P* = 0.003) [Table 3].

Bivariate Spearman correlations were carried out to find any significant correlations between MI and Ki-67 LI in TP with various grades, and the result showed that there was a moderate positive correlation in moderately differentiated carcinoma. (r = 0.494, *P* = 0.044) [Table 4].

Bivariate Spearman correlations were carried out to find any significant correlations between MI and Ki-67 LI in PM with various grades, and the result showed that there were low positive correlations in well-differentiated carcinoma (r = 0.357, *P* = 0.015) and moderate positive correlation in moderately differentiated carcinoma (r = 0.624, *P* = 0.007) [Table 5].

One-way ANOVA/Kruskal–Wallis one-way ANOVA non-parametric tests were conducted based on the distributions of the data to explore the statistically significant differences of MI between the grades in TP and PM. Results showed that there was a statistically significant difference in MI-PM between the grades, as the *P* values were 0.037. No significant result was obtained in the case of MI-TP. Same test was performed to explore the statistically significant differences in Ki67 LI between the grades, and the results showed that there were statistically significant differences in Ki 67 LI-TP between the grades as the *P* value was 0.040. No significant result was obtained in the case of Ki67-PM.

Post hoc test (independent samples Kruskal–Wallis test) with Bonferroni correction for multiple tests also confirmed that there were significant differences between moderately differentiated and poorly differentiated grades in MI of PM (*P* = 0.031). Statistically significant differences were also noted between well-differentiated and moderately differentiated grades in Ki-67 LI of TP (*P* = 0.029).

Table 2: Mean distribution of study variables

Parameters (n=66)	*Mean*	*Standard deviation*	*Minimum*	*Maximum*
MI–TP	6.58	3.487	2	16
MI-PM	7.18	3.637	2	18
Ki 67 LI-NE	3.92	1.834	1	10
Ki 67 LI-HE	7.92	4.074	2	18
Ki 67 LI-TP	44.86	18.545	10	78
Ki 67 LI-PM	50.11	18.238	16	90

MI=mitotic index, LI=labeling index, TP=tumor proper, PM=proliferating margin, NE=normal epithelium, HE=hyperplastic epithelium

Table 3: Correlation between Ki67 LI and mitotic index

Parameters (n=66)	*Correlation Coefficient (r)*	*P*
MI tumor proper Vs. Ki-67 LI tumor proper	0.263	0.033
MI proliferating margin Vs. Ki-67 LI proliferating margin	0.364	0.003

Table 4: Correlation between Ki67 and mitotic index with various grades in tumor proper

Parameters (n=66)	*Grades*	*Correlation Coefficient (r)*	*P*
MI tumor proper Vs. Ki-67 LI tumor proper	Well-differentiated	0.247	0.098
	Moderately differentiated	0.494	0.044
	Poorly differentiated	0.500	0.667

Table 5: Correlation between Ki67 and mitotic index in Proliferating Margin with grades

Parameters (n=66)	*Grades*	*Correlation Coefficient (r)*	*P*
MI proliferating margin Vs. Ki-67 LI proliferating margin	Well-differentiated	0.357	0.015
	Moderately differentiated	0.624	0.007
	Poorly differentiated	-0.500	0.667

DISCUSSION

This study entitled "Correlation between Ki-67 LI and MI in head and neck squamous Cell Carcinoma" was performed on 66 cases of head and neck squamous cell carcinoma diagnosed on histopathology. Patients with head and neck squamous cell carcinoma in the current study ranged in age from 31 to 90 years, with a mean age between 51 and 60. Head and neck cancer is more prevalent in the fourth to sixth decades of life, according to Chauhan *et al.* and many other investigators.[9,10] This is in concordance with the present study. Males accounted for the majority of cases (88%), while females constituted just 12% in this study, which is consistent with findings from numerous other research.[1,11] This is because of heavier indulgence in tobacco and alcohol habits.

In the present study, oral cavity, accounting for 51% of all the cases, was the most frequently involved anatomical site, followed by larynx (29%). It was observed that hypopharynx and oropharynx were the least affected. In the oral cavity, the most commonly involved site was the tongue followed by buccal mucosa, whereas in the oropharynx the posterior wall of the pharynx was found to be involved more frequently. Supraglottis and pyriform fossa were found to be more affected in the larynx and hypopharynx, respectively. Most of the patients presented with ulceroproliferative lesions in the present study. Maximum number of cases were well-differentiated squamous cell carcinomas (70%). Only few cases (5%) were poorly differentiated. Study conducted by Sharma *et al.* in oral SCC had maximum cases of moderately differentiated carcinoma followed by well-differentiated carcinoma.[12]

All cases in the study showed grade 1 positivity in normal and HE. Ki-67 positive cells were sprinkled within its basal and parabasal layers only. TP and PM mostly had grade 2 positivity. These findings are in agreement with the study of Buch *et al.*[3] Majority of cases in this study showed strong Ki-67 immunostaining in TP (90.9%).

Correlation between Ki-67 expression and MI

HE showed higher Ki67 compared to NE. Mean Ki67 index was more in PM compared to TP. This finding is consistent with the findings of Dissanayake *et al.*[13] which states that more oral SCC cells in the invasive tumor front are in the proliferative stage than in the tumor center.

In NE, poorly differentiated carcinoma has the highest mean LI. In the TP and proliferative margin, well-differentiated carcinoma had the lowest mean Ki67 LI. Meanwhile, poorly and moderately differentiated carcinomas have the highest mean LI in PM and TP, respectively. These findings are similar to those reported by Buch *et al.* and Mittal *et al.* in oral SCC.[3,14]

The current investigation demonstrates a statistically significant difference in Ki67 LI between the grades of the TP, but this difference with grades in PM did not reach statistical significance, which may be due to the difficulty in obtaining invasive front in small biopsy samples and extensive tumors. This was discordant from a study by Buch *et al.*[3] It was observed that in TP, there were statistically significant differences in LIs between well-differentiated and moderately differentiated grades ($P = 0.029$). A study by Sharma *et al.*[12] found that comparing Ki-67 expression to histological grading revealed a statistically significant correlation. (Pvalue = 0. 0121). Rakheja Mahima *et al.*[15] in 105 cases revealed results that were remarkably similar. Statistical research revealed a significant connection ($P < 0.001$) between the expression of Ki-67 and oral SCC grades. Premalatha and Uma[16] and Pity IS and Jalal[17] also had similar findings. This makes it evident that the rate of cell proliferation in SCC increases as the degree of tumor differentiation decreases. This obvious variation in Ki-67 levels across different tumor grades has demonstrated the validity of the proliferative index and is therefore seen to be a useful tool for assessing prognosis. But, studies by Omer and Rashid[18] and Vukelic *et al.*[19] found no association between the immunoexpression of Ki67 and age, sex of the patient, site of the tumor, or grade of the tumor. Numerous research have discussed how the Ki-67 growth fraction affects prognosis. To support this, Bu *et al.*, Wangsa *et al.*, and Maheshwari *et al.* demonstrated that a higher Ki67 LI could be associated with poor prognosis.[20-22] High LI levels were found by Lipsa Bhuyan *et al.*[23] to be predictive of metastasis.

Usually, as SCC grades increase, so does the Ki-67 reactivity. The proliferative activity in well-differentiated SCC is confined to the edges of the tumoral fronds. The tumor nests lack Ki-67 expression and develop into numerous squamous pearls in the center [Figure 1]. The Ki-67 positive cells sporadically start to populate more centrally in case of moderately differentiated SCC, much as they do at the edges of tumor nests. In poorly differentiated SCC, the relatively undifferentiated cancer cells have a more diffuse staining pattern.[24,25] The report that is being described was no different either.

MI has been employed to assess a tumor's proliferative potential since a long time and ultimately, it is a measure of tumor growth. Rapidly growing tumors usually behave aggressively.[26] An increase in mean MI with histological grade was noted, which was statistically significant in PM. There were significant differences between moderately differentiated and poorly differentiated grades in MI of PM ($P = 0.031$).

Since both Ki67 LI and the MI are indicators of cellular proliferation, we looked at their relationships in TP and proliferating margins. A statistically significant positive correlation was noted between Ki67 LI and MI in TP ($r = 0.263$, $P = 0.033$) and proliferative margin ($r = 0.364$, $P = 0.003$). However, this correlation was negligible positive in case of TP. On finding the difference in various grades, a moderate positive correlation was found in moderately differentiated carcinoma in case of TP, and a significant correlation in well-differentiated grade and moderately differentiated grades was noted in PM. These findings are comparable to that of Buch *et al.*[3] Figures 2 and 3 show MI and Ki67 staining in PM, respectively.

The hypopharynx had the highest mean Ki67 LI. For site differences in Ki67, no statistically significant values were found in this study.

Ki 67 shows a positive correlation with the MI, in addition to being a prognostic and predictive marker for the evaluation of

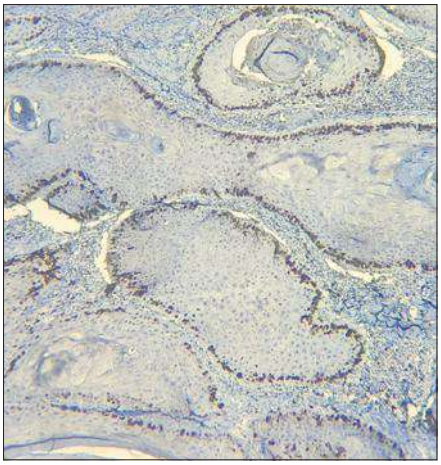


Figure 1: Squamous cell carcinoma—well-differentiated tumor proper (Ki67 immunostaining, 20x)

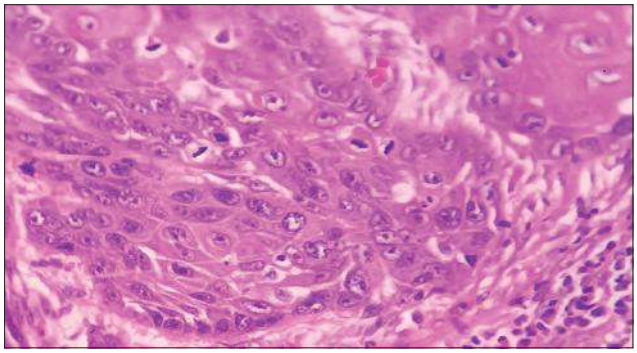


Figure 2: Squamous cell carcinoma—mitotic figures in proliferating margin (H&E stain, 40x)

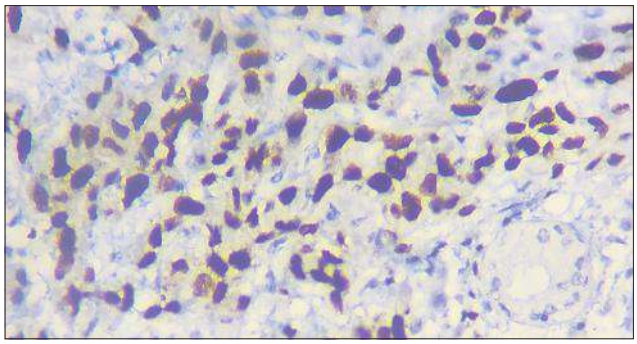


Figure 3: Squamous cell carcinoma—proliferating margin (Ki67 immunostaining, 40x)

head and neck SCC. The rapid division of cells in tumor margin leads to a higher number of tumor cells in the mitosis phase, and this could have been the reason for higher MI in these areas. Additionally, it is positively correlated with the histopathological grade of malignancy in TP. When used in conjunction with Ki-67, the MI—a quick and inexpensive method for evaluating cellular proliferation becomes more relevant and practically useful.

Limitations

Interobserver variability can arise in field selection while assessing MI and Ki 67 LI. Expression in dysplastic epithelium has not been studied. The sample size had a limited number of poorly differentiated carcinoma cases. It was often difficult to distinguish the invasive margin from TP in small biopsy samples. Due to a lack of follow-up time, a correlation between Ki67 growth fraction and survival has not been investigated.

CONCLUSION

Ki67 is a reliable proliferation marker in head and neck squamous cell carcinoma. In conjunction with Ki-67, the MI—a quick and inexpensive method for evaluating cellular proliferation has become more relevant and practically useful. Additionally, combined analysis of the two indices can be useful in early diagnosis of possibly malignant lesions, predicting tumor progression and appropriate therapy could be initiated.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Pathology Section

Determining the Oestrogen and Progesterone Receptor Expression in Cases of Endometrial Carcinoma: A Cross-sectional Study

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ABSTRACT

Introduction: Endometrial carcinoma is the second most common female genital tract malignancy in India with a incidence rising globally. Hormone receptors are positive in 35-90% of endometrial carcinomas. Hormone therapy can be given to patients with hormone receptor positive tumours.

Aim: To determine whether Progesterone and Oestrogen Receptors (PR and ER) are most often expressed in endometrial cancer cases, and to correlate this expression with histopathologic features in these cases.

Materials and Methods: A cross-sectional study was conducted in the Department of Pathology, Government Medical College, Thrissur, Kerala, India, on 37 cases of endometrial carcinoma. ER and PR expression were assessed and correlated with histopathologic parameters in carcinoma endometrium.

Results: 75.6% of the patients were in the 51-70 age range. Grade I endometrioid cancer accounted for 24 (77.42%) of the 31 cases, grade II for 5 (16.13%) and grade III for 2 (6.45%). 19 (51.4%) of cases had ER positivity and 21 (56.8%) had PR positivity. While all grade III tumours were PR and ER negative, grade I tumours had 70.83% and 79.17% ER and PR positivity, respectively. While ER expression did not correlate negatively with grade (p-value=0.076), PR expression did (p-value=0.043). In 29.73% of patients, lymphocytic infiltrates were seen, and they had a strong correlation with the expression of ER and PR. All cases of papillary serous carcinomas (100%), mucinous carcinomas (100%), and clear cell carcinomas (100%), showed ER negative. Hormone receptor status did not significantly correlate with FIGO (The International Federation of Gynecology and Obstetrics) stage, lymphovascular emboli, or myometrial invasion.

Conclusion: Most of the endometrioid endometrial carcinomas showed ER and PR positivity, while all of the non endometrioid endometrial carcinomas were negative for both ER and PR. ER and PR were positive in most of the grade I tumours, whereas in the high-grade tumours, they were often negative. Immunoreactivity for PR had a stronger association with tumour grade, when compared to ER.

Keywords: Endometrial neoplasms, Hormone therapy, Uterine neoplasms

INTRODUCTION

Endometrial carcinoma is the most common malignancy of the female genital system in developed countries. In India, mainly in Kerala, it ranks as the second most common genital malignancy among women [1,2]. Bokhman JV, categorised endometrial carcinoma into two major types: type I (endometrioid) and type II (non endometrioid), based on endocrine and metabolic factors [3]. Subsequent studies have revealed distinct molecular genetic differences between these types [4]. Endometrioid carcinoma often arises from prolonged oestrogen exposure and is typically preceded by a premalignant lesion known as Endometrial Intraepithelial Neoplasia (EIN) or atypical endometrial hyperplasia [5]. Potischman N et al., found elevated serum oestrogen levels in patients with endometrioid carcinoma [6]. This type generally occurs in women aged 40-60 years and has a favourable prognosis postsurgery [7]. In contrast, type II endometrial carcinoma typically occurs in older women, without prior hyperestrogenism or EIN precursor. These tumours are usually poorly differentiated and have a poorer prognosis [8,9]. Serous Endometrial Intraepithelial Carcinoma (serous EIC) is a rare precursor to non endometrioid adenocarcinomas, like serous carcinoma [10,11]. Endometrioid carcinoma is the most common form of endometrial carcinoma, accounting for 80% of cases [12]. They are termed endometrioid due to their similarity to proliferative endometrium, while non endometrioid carcinomas include subtypes like serous, mucinous, clear cell, neuroendocrine, mixed, undifferentiated, and dedifferentiated carcinomas.

Similar to breast carcinomas, endometrioid carcinomas express hormone receptors. These receptors are positive in 35-90% of cases, with their absence potentially indicating advanced disease [13]. Oestrogen regulates endometrial carcinogenesis, countered by progesterone's differentiating effects via PR, promoting apoptosis and inhibiting invasion. Loss of ER-alpha and PR positivity correlates with decreased survival in endometrial carcinoma patients [3].

A subset of patients with advanced or recurrent endometrial cancer often does not respond to standard therapies, which are associated with significant side-effects. Many of these patients are elderly with co-morbidities, complicating treatment and increasing morbidity and mortality. There is significant potential to improve treatment outcomes by using prognostic and predictive markers to individualise therapy. Reliable biomarkers could help identify patients who might benefit from aggressive treatment versus those who could avoid toxic therapies, like approaches in breast cancer treatment [3].

This study aims to assess the histomorphological types of endometrial carcinoma, evaluate ERR and PR expression in these cases, and correlate ER and PR expression with histopathologic parameters.

MATERIALS AND METHODS

The present cross-sectional study was conducted in the Department of Pathology at Government Medical College, Thrissur, Kerala, India on 37 cases. The study period spanned 18 months, from February 1, 2014, to July 31, 2015. The study was approved by Institutional Ethics Committee (IEC). All procedures followed were in accordance with the ethical standards of the responsible committee. The study population consisted of all hysterectomy specimens of carcinoma endometrium received in the Department of Pathology during the study period.

Inclusion criteria: All hysterectomy specimens of carcinoma endometrium were included in the study.

Exclusion criteria: Endometrial curetting samples of carcinoma endometrium and hysterectomy specimens with other pathological conditions were excluded from the study.

Study Procedure

Gross examination of the hysterectomy specimens of endometrial carcinoma was performed, and the findings were documented. Tissue samples were taken and routinely fixed, processed, and embedded in paraffin. Four-micron thick sections were cut and stained with Haematoxylin and Eosin (H&E) for microscopic assessment. Histological grading, myometrial and lymphovascular invasion, and prominent lymphocytic infiltrates were evaluated. The FIGO grading [14] system for endometrial cancer was the classification scheme utilised for grading in this study. Immunohistochemical analysis was performed on serial sections using an immunoenzymatic soluble complex method. The antibodies used were Monoclonal Mouse Antihuman ER Alpha (Clone 1D5, Ready to Use, Dako Autostainer/ Autostainer Plus) and Monoclonal Mouse Antihuman PR (Clone PgR 636, Ready to Use, Dako Autostainer/Autostainer Plus). The immunostaining of ER and PR was determined by calculating the positivity index (PI), representing the percentage of positive cells per 1000 cells counted on a 40× power field.

Cases with more than 10% of neoplastic cells showing nuclear positivity were considered positive. The results were scored accordingly. The expression of ER and PR and their association with histopathologic parameters, such as tumour type, histologic grade, mitosis, prominent lymphocytic infiltrate, lymphovascular emboli, myometrial invasion, and FIGO stage, were analysed. Several clinical and pathological features were evaluated, such as the tumour's grade, age distribution, myometrial invasion, lymphovascular invasion, and FIGO staging. The study included immunohistochemical analysis with antibodies against PR and ER. The staining intensity was categorised using the ER and PR expression grading system.

Scoring of ER, PR Expression [15]

Score 0: Negative ≤10% of neoplastic cells show nuclear positivity

Score 1: 11-25% of neoplastic cells show nuclear positivity

Score 2: 26-50% of neoplastic cells show nuclear positivity

Score 3: 51-75% of neoplastic cells show nuclear positivity

Score 4: >75% of neoplastic cells show nuclear positivity

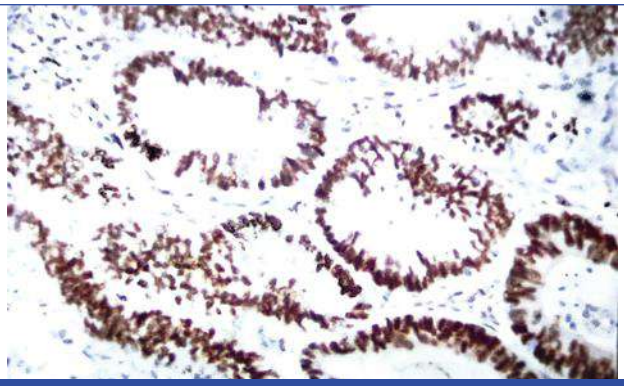
STATISTICAL ANALYSIS

Data were collected and entered a Microsoft Office Excel 2007 sheet. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software, version 16.0 The tests used included the Chi-square test, Kendall's tau-b correlation coefficient, and Spearman's correlation coefficient.

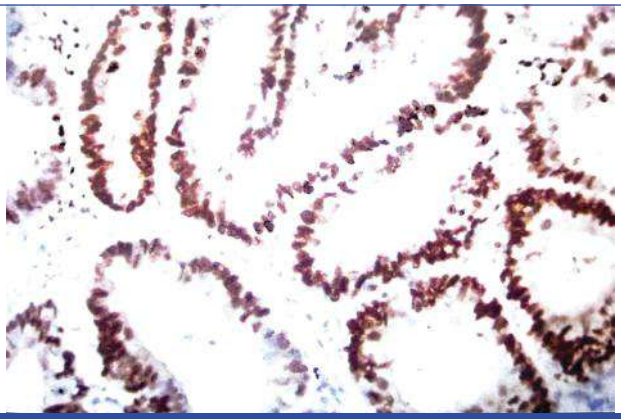
RESULTS

The patients' ages ranged from 38 to 85 years, with a mean age of 56.65 for endometrioid carcinomas and 59.17 for non endometrioid carcinomas. Immunohistochemical staining of the tissue sections revealed Endometrioid EC grade 1 ER and PR positivity (score 4) [Table/Fig-1,2]; grade 3 ER and PR negativity (score 0) [Table/Fig-3,4]. In clear cell carcinoma endometrium the IHC staining was seen to be negative for both ER and PR (score 0) [Table/Fig-5,6].

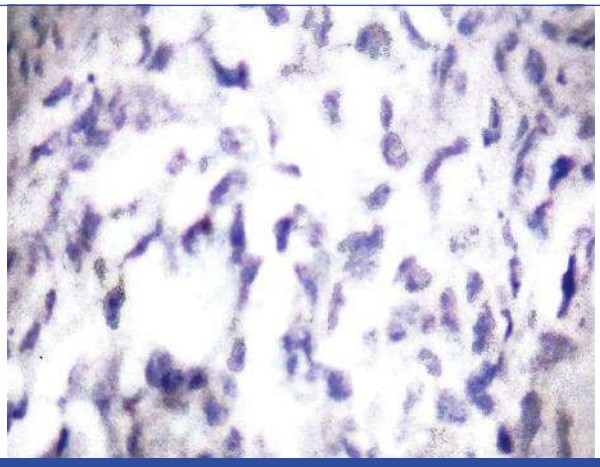
Most patients (75.6%) were in the 51-70 age group [Table/Fig-7]. Among the 31 cases of endometrioid carcinomas, 24 (77.42%) were grade I tumours, 5 (16.13%) were grade II tumours, and 2 (6.45%) were grade III tumours. Lymphocytic infiltrates, lymph vascular emboli and myometrial invasion are shown in [Table/Fig-8]. The pattern of ER and PR staining in 37 cases of endometrial cancer is shown in [Table/Fig-9]. Out of the 37 cases, the distribution of score (0-4) for ER and PR is shown in [Table/Fig-10]. The distribution of ER staining across various tumour types in 37 endometrial cancer



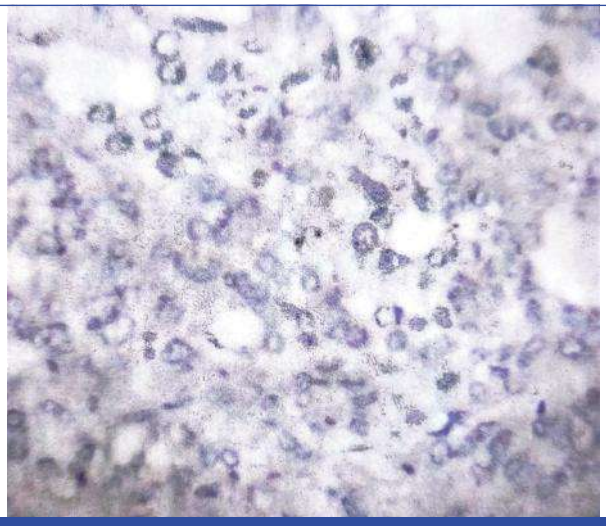
[Table/Fig-1]: Endometrioid endometrial carcinoma grade 1 showing ER positivity, score 4 (400x).



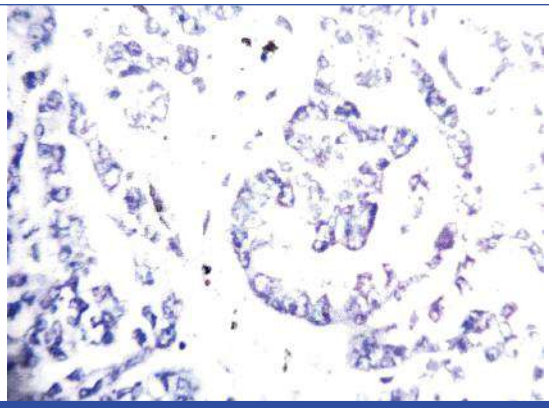
[Table/Fig-2]: Endometrioid endometrial carcinoma grade 1 showing PR positivity, score 4 (400x).



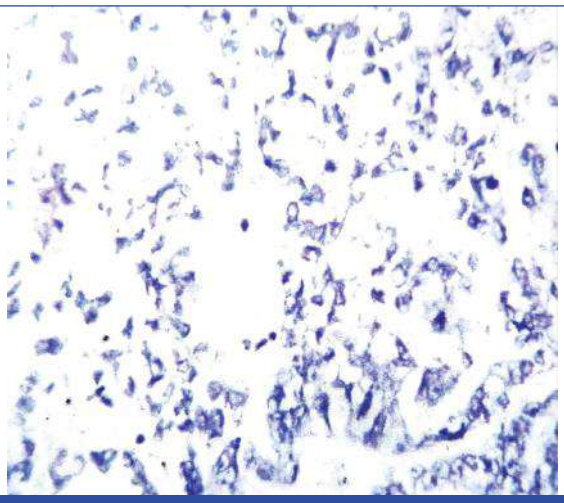
[Table/Fig-3]: Endometrioid endometrial carcinoma grade 3 showing ER negativity, score 0 (400x).



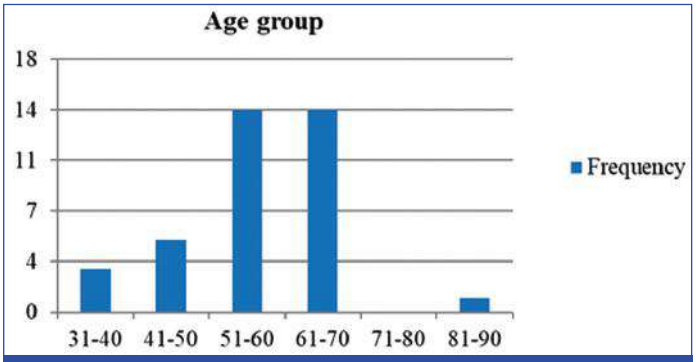
[Table/Fig-4]: Endometrioid endometrial carcinoma grade 3 showing PR negativity, score 0 (400x).



[Table/Fig-5]: Clear cell carcinoma endometrium (IHC; (400x) showing ER negativity.



[Table/Fig-6]: Clear cell carcinoma endometrium (IHC; (400x) showing PR negativity.



[Table/Fig-7]: Age distribution of the cases in the study (total n=37).

Parameters	n (%)
Grade I tumours	24 (77.42)
Grade II tumours	5 (16.13)
Grade III tumours	2 (6.45)
Lymphocytic infiltrates	11 (29.73)
Lymphovascular emboli	4 (10.8)
Myometrial invasion	
• Less than half of myometrium	19 (51.4)
• More than half of myometrium	18 (48.6)

[Table/Fig-8]: Summary of findings in endometrioid carcinomas analysis.

Parameters	ER staining n (%)	PR staining n (%)
Negative	18 (48.6)	16 (43.2)
Positive	19 (51.4)	21 (56.8)

[Table/Fig-9]: Comparison of ER and PR staining in endometrioid carcinomas.

cases is shown in [Table/Fig-11]. Twelve instances (38.7%) of the endometrioid carcinomas were ER negative, whereas nineteen cases (61.3%) were ER positive. Interestingly, ER negative was present in

Score	ER frequency n (%)	PR frequency n (%)
0	18 (48.7)	16 (43.2)
1	3 (8.1)	3 (8.1)
2	4 (10.8)	2 (5.4)
3	1 (2.7)	4 (10.8)
4	11 (29.7)	12 (32.4)

[Table/Fig-10]: Comparison of ER and PR scores in endometrioid carcinomas.

Tumour type	ER negative	ER positive	Total
Endometrioid	12	19	31
Papillary serous	4	0	4
Clear cell	1	0	1
Mucinous	1	0	1
Total	18	19	37

[Table/Fig-11]: Distribution of ER staining by tumour type.

every case of mucinous, clear cell, and papillary serous carcinoma. In general, endometrioid carcinomas tended to be ER positive. The distribution of PR staining across different tumour types in 37 endometrial cancer cases is shown in [Table/Fig-12]. Ten instances (32.3%) of endometrioid carcinomas were PR negative, whereas 21 cases (67.7%) were PR positive. Remarkably, PR negativity was present in every case of mucinous, clear cell, and papillary serous carcinomas. Most PR positive cases were found in endometrioid carcinomas. The ER and PR positivity rates for various stages of endometrial cancer are shown in [Table/Fig-13]. 17 cases (70.83%) and 19 cases (79.17%) of the Grade I cancers (n=24) were ER positive and PR positive, respectively. Forty percent of the Grade II tumours (n=5) were PR and ER positive. Remarkably, every Grade III tumour (n=2) exhibited negative ER and PR results. This suggests a possible correlation between the expression of hormone receptors and tumour grade. The scatter plot [Table/Fig-14] shows a weak negative correlation (R^2=0.103) between ER score and grade in endometrioid carcinomas, suggesting higher ER scores are slightly associated with lower grades. However, there was no statistically significant correlation between grade and ER score (Kendall's tau_b correlation coefficient=1.000, p-value=0.076), indicating ER score alone is not a strong predictor of carcinoma grade. In endometrioid carcinomas, the scatter plot demonstrates a negative connection (R^2=0.136) between the PR score and grade, suggesting that lower grades are linked to higher PR scores. As demonstrated in [Table/Fig-15], this correlation was statistically significant (Kendall's tau_b correlation coefficient=1.000, p-value=0.043), indicating that PR score is a useful predictor of carcinoma grade. As can be seen in [Table/Fig-16], out of 26 cases where there is no lymphocytic infiltration, 16 are ER negative and 15 are PR negative. There are 11 patients with a lymphocytic infiltration, of which 10 are PR positive and 9 are ER positive. There are 37 cases in all, 18 of which are ER

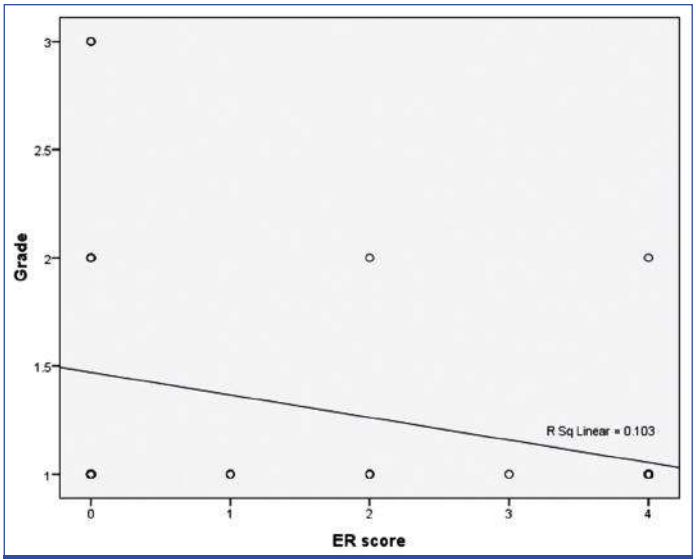
Tumour type	PR negative	PR positive	Total
Endometrioid	10	21	31
Papillary serous	4	0	4
Clear cell	1	0	1
Mucinous	1	0	1
Total	16	21	37

[Table/Fig-12]: Distribution of PR staining by tumour type.

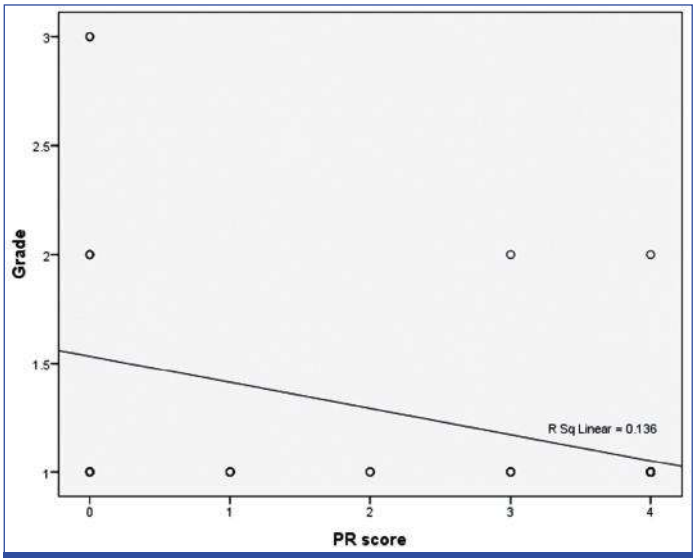
Grade	ER negative	ER positive	PR negative	PR positive	Total
1	7	17	5	19	24
2	3	2	3	2	5
3	2	0	2	0	2
Total	12	19	10	21	31

[Table/Fig-13]: Grade of endometrial carcinoma and ER and PR staining.

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[Table/Fig-14]: Scatter plot and linear regression analysis of ER score and grade in endometrioid carcinomas (Kendall's tau_b Correlation).



[Table/Fig-15]: Scatter plot and linear regression analysis of PR score and grade in endometrioid carcinomas (Kendall's tau_b Correlation)

Prominent lymphocytic Infiltrate	ER negative	ER positive	PR negative	PR positive	Total
Absent	16	10	15	11	26
Present	2	9	1	10	11
Total	18	19	16	21	37

[Table/Fig-16]: Association between lymphocytic infiltrate and hormone receptor status in endometrioid carcinomas.

negative and 21 of which are PR positive.The association between hormone receptor status (PR and ER) and lymphovascular emboli in endometrioid carcinomas is shown in [Table/Fig-17]. It is noteworthy that out of 33 cases without lymphovascular emboli, 18 have PR positive and 15 have PR negative results. Conversely, of the four cases involving lymphovascular emboli, three are ER positive and one is ER negative. The relationship between myometrial invasion and hormone receptor status (ER and PR) in endometrioid carcinomas is shown in [Table/Fig-18]. Remarkably, eight of the 19 instances with less than half of the myometrial invasion are PR negative and 11 are PR positive. Eight of the 18 cases with over half of the myometrial invasion, however, are ER negative, while the remaining 10 are ER positive. The association between the FIGO stage and the hormone receptor status (ER and PR) in endometrioid carcinomas is shown in [Table/Fig-19]. Notably, distinct patterns in hormone receptor expression appear at different FIGO stages. For example, in stage Ia, there are nine ER positive cases and 11 PR positive instances; in stage II, there are five ER negative cases

Lymphovascular emboli	ER negative	ER positive	PR negative	PR positive	Total
Absent	17	16	15	18	33
Present	1	3	1	3	4
Total	18	19	16	21	37

[Table/Fig-17]: Association between lymphovascular emboli and hormone receptor status in endometrioid carcinomas.

Myometrial invasion	ER negative	ER positive	PR negative	PR positive	Total
<half of myometrium	10	9	8	11	19
>half of myometrium	8	10	8	10	18
Total	18	19	16	21	37

[Table/Fig-18]: Association between myometrial invasion and hormone receptor status in endometrioid carcinomas.

FIGO stage	ER negative	ER positive	PR negative	PR positive	Total
Ia	4	9	2	11	13
Ib	5	6	5	6	11
II	5	1	5	1	6
IIIa	2	0	2	0	2
IIIb	2	2	2	2	4
IVa	0	1	0	1	1
Total	18	19	16	21	37

[Table/Fig-19]: Association between FIGO stage and hormone receptor status in endometrioid carcinomas.

and five PR negative cases. There was no statistically significant correlation between FIGO stage and ER score (Kendall's correlation coefficient=1.000, p value=0.360) and between FIGO stage and PR score (Kendall's correlation coefficient=1.000, p value=0.120).

DISCUSSION

Endometrial Carcinoma (EC) is a prevalent gynaecological malignancy with rising incidence and decreasing age of onset. It is more common in developed countries but has similar mortality rates worldwide. EC is classified into oestrogen-dependent (type I, mostly endometrioid) and non oestrogen-dependent (type II, including serous and clear cell) carcinomas [16]. EC is a major cancer worldwide, where the status of hormone receptors is a key factor in the characterisation and prognosis of the tumour. Oestrogen is seen as playing a role in the development of endometrial cancer, emphasising the need to assess the expressions of ER and PR. The present study found that 51.4% of EC cases were ER positive, while 56.8% were PR positive. The results align with the study done by Kounelis S et al., where ER positive cases were found in 54.1% and PR positive cases in 54.9%, suggesting a comparable pattern of hormone receptor expression in EC [17]. This constancy strengthens the trustworthiness of ER and PR as indicators in endometrial cancer. Stoian SC al., found higher rates of ER positivity (86.3%) and PR positivity (81.1%) as compared to present study. This variation might be due to differences in the study groups, such as the ratios of endometrioid to non endometrioid and low to high-grade tumours [18]. These variances highlight the importance of standardised criteria and study populations when evaluating hormone receptor status in EC. A study done by Giuffrè G et al., investigated the expression of hormone receptors and discovered strong correlations between lactoferrin expression and ER, PR, as well as proliferation markers such as Ki-67 and AgNOR. This research highlighted the importance of hormone receptor status in predicting outcomes for endometrial carcinomas [19].

In EC cases, ER positivity was seen in 61.3% and PR positivity in 67.7% in the present study. Maniketh I et al., reported similar rates, with ER positivity found in 73.3% and PR positivity in 84.4% of endometrioid carcinoma cases [13]. These findings indicate that endometrioid ECs may be more inclined to show these hormone

receptors, potentially influencing treatment choices and prognostic evaluations. This study showed that ER and PR were absent in all non endometrioid EC cases which was found to be in concordance with previous study done by Deligdisch L et al., demonstrating negative hormone receptor status in non endometrioid ECs [20]. This highlights the unique biological characteristics of non endometrioid ECs and their absence of hormone receptor expression, affecting potential treatment strategies.The present study found that 70.83% of Grade I tumours were ER positive, whereas all Grade III tumours were ER negative when it comes to tumour grade. In Grade I tumours, 79.17% tested positive for PR, while all Grade III tumours tested negative. This pattern indicates a negative correlation between tumour grade and hormone receptor positivity. Stoian SC et al., also discovered that tumours of a lower grade showed increased ER and PR positivity, but their research revealed a significant correlation between grade and receptor positivity, in contrast to the present study [18]. This variation could suggest that other factors also play a role in determining hormone receptor expression, apart from just tumour grade.

In the present study, a strong correlation was found between the presence of prominent lymphocytic infiltrate and higher ER (81.8%) and PR (90.9%) positivity. Jung IK et al., [21] corroborated this discovery by associating high lymphocytic infiltrate with lower histologic grade, while Stoian SC et al., [19] found higher ER and PR immunoreactivity in low-grade tumours. These findings indicated that a potent immune response might be associated with more positive tumour features and increased hormone receptor levels. In relation to lymphovascular invasion, the present research did not discover a notable connection with ER or PR positivity, which was consistent with the results of Maniketh I et al., who similarly found no significant correlation between lymphovascular invasion and hormone receptor status [13]. This suggests that although lymphovascular invasion is important for the spread of tumours and for predicting outcomes, it may not have a direct effect on hormone receptor levels. In the current study, there was also no notable association observed between myometrial invasion and ER or PR positivity, aligning with the outcomes of a study by Maniketh I et al., that showed similar results. This implies that hormone receptor expression is not greatly affected by myometrial invasion, underscoring the importance of considering other pathological factors when assessing hormone receptor status.

Mylonas I highlighted the importance of ERα and ERβ in predicting the prognosis of endometrioid adenocarcinomas, showing that increased ER levels are linked to improved clinical results [22]. This was consistent with the finding of the present study that lower-grade tumours, which usually have a better prognosis, tend to have higher ER positivity. A study in a Nigerian tertiary hospital by Odetola SS et al., reported ER and PR positivity rates of 29.5% and 18.2%, respectively. Their research did not establish a noteworthy link between hormone receptor expression and tumour grade, aligning with the conclusions of the current study [23]. This highlights the differences in hormone receptor expression among various populations and emphasises the importance of conducting studies specific to each region to gain a better understanding of these trends. van Weelden J al., suggested certain thresholds for ER and PR expressions to categorise EC into high-risk (0-10% positivity), intermediate-risk (20-80% positivity), and low-risk (90-100% positivity) groups in terms of clinical outcomes [24]. This categorisation emphasises the significance of accurately establishing hormone receptor threshold values for predicting disease-specific and disease-free survival in patients with EC.

Hence, the levels of ER and PR expression in endometrial cancer can differ greatly due to various factors like tumour characteristics and the extent of lymphocytic infiltration. Establishing universal thresholds for hormone receptor positivity can improve the assessment and treatment of EC. Further studies are needed to confirm the results in bigger groups and investigate the molecular pathways that regulate hormone receptor expression in EC. Also, creating standardised thresholds for hormone receptor positivity will improve the practicality of using these biomarkers to treat EC.

Limitation(s)

The small sample size was the limitation of the study.

CONCLUSION(S)

The study highlights the varying hormone receptor expression and its potential prognostic importance, specifically focusing on ER and PR positivity. Accurate identification of hormone receptor status in EC is essential for treatment decisions and prognostic assessments in a clinical setting. Acknowledging varied ER and PR expression profiles among various tumour grades and histological subtypes underscores the importance of tailored treatment approaches.

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Pathology Section

Histopathological Profile of Lung Lesions- An Autopsy Study at a Tertiary Care Centre, Kerala, India

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BY-NC-ND

ABSTRACT

Introduction: Autopsy plays a crucial role in understanding and identifying pulmonary pathology, encompassing non neoplastic lesions, neoplastic conditions and the secondary implications of the lungs in terminal events of cardiovascular diseases. Pathological analysis confirms diagnosis and identifies the prevalence of lesions, contributing significantly to medical understanding and patient care.

Aim: To estimate the prevalence of lung pathology in autopsy specimens through Histopathological Examination (HPE).

Materials and Methods: A cross-sectional one-year study was conducted to determine the histopathological alterations in 132 lung autopsy specimens from Medicolegal autopsies received in the Department of Pathology at a tertiary care centre in Government Medical College, Cochin, Kerala, India from January 2021 to December 2021. Autopsy specimens of the lung were fixed in 10% formalin. Following gross examination, tissue sections were processed with paraffin and subjected to staining, with microscopy findings recorded. The data was numerically coded and entered into a Microsoft Excel spreadsheet. Statistical Package for Social Sciences (SPSS) version 21.0 was used for descriptive statistics and graphical representations of findings.

Results: The mean age of the study population, comprising 132 autopsy cases, was 49.41±52.12 years and the male-to-female ratio was 3.71:1. Most cases 97/132 (73.50%) involved sudden deaths where the cause remained unknown. Significant microscopic findings found in 117 (88.63%) cases were as follows: Pulmonary oedema and congestion: 61 (46.21%), Pneumonia: 17 (12.87%), Diffuse Alveolar Damage (DAD): 12 (9.09%), Chronic venous congestion: 8 (6.06%), Tuberculosis: 7 (5.30%), Emphysema: 7 (5.30%), Pulmonary fibrosis: 1 (0.75%), Fat embolism: 1 (0.75%) and Pulmonary arterial hypertension: 1 (0.75%). Neoplastic lesions were identified in 7 (5.30%) cases, with primary lung cancers accounting for 3 (2.27%) cases. There were 10 cases of Real-time Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR), positive Coronavirus Disease 2019 (COVID-19) autopsies, of which 6 (60%) exhibited DAD, while 4 (40%) showed changes of bronchopneumonia.

Conclusion: Non neoplastic lesions such as pulmonary oedema, DAD and infections contributed to mortality in most cases. DAD was the most common lung finding in more than half of COVID-19 deaths. The prevalence of pulmonary neoplastic lesions in autopsies underscores their epidemiological significance in a particular geographical area.

Keywords: Coronavirus disease 2019, Diffuse alveolar damage, Lung autopsy, Pneumonia, Tuberculosis

INTRODUCTION

Autopsy is considered the definitive diagnostic test, maintaining its status as the gold standard for determining the cause of death. Autopsy pathologists are tasked with investigating a broad spectrum of sudden, unexpected and clinically unexplained deaths stemming from various natural causes [1]. Diagnosing lung diseases can pose a significant challenge to clinicians, even with access to advanced diagnostic techniques. Timely pathological diagnosis, complemented by clinical and radiological observations, are vital for enhancing patient survival [2]. The rapid progression of the disease results in less time for diagnosis; many lesions remain unidentified until after the patient has died and an autopsy has been performed [3].

Examining the lungs during an autopsy provides crucial insights into various patterns of lung injury, including DAD, stages of fibrosis, stages of interstitial pneumonitis, infectious processes and other specific pathologies. Through gross examination, valuable information is obtained about pleural lesions, the presence of collapsed or hyperinflated lungs, scarring, fibrosis, bullae, consolidation, nodules, infarction, all of which offer hints to establish a diagnosis [4]. The patterns of injury indicate damage to lung structures such as the alveolocapillary membrane, airways and blood vessels, either individually or in combination. Histologically, many diseases with distinct causes show similar tissue reactions, aiding in compiling a comprehensive list of potential diagnosis. Additionally, different disease states can affect various combinations of pulmonary microanatomy simultaneously, with conditions primarily targeting the pulmonary interstitium often also damaging small airways and vice versa [4].

Postmortem analysis of lung specimens provides valuable insights into the diverse factors contributing to prevalent respiratory infections such as bronchitis, bronchopneumonia and other types of pneumonia [5]. Some cases of active tuberculosis are not identified until after the patient has died and an autopsy has been performed [6]. Pulmonary oedema arises from fluid accumulation in the interstitium and alveoli of the lungs, which can be caused by inherent lung issues or systemic factors. It is traditionally categorised into two types: cardiogenic, resulting from acute left ventricular failure and manifesting as high-pressure oedema typically triggered by events like myocardial infarction; and non cardiogenic, characterised by low-pressure fluid build-up and arising from acute lung injury or conditions such as Acute Respiratory Distress Syndrome (ARDS) [7].

The COVID-19 infection leads to either localised or widespread inflammation in the alveoli and interstitial spaces of the lungs, causing respiratory failure primarily due to DAD and severe capillary congestion, which is the main cause of mortality [7]. Bronchopneumonia and organising pneumonia frequently manifest in patients with prolonged COVID-19 illness duration [8]. The features of COVID-19 infection include the presence of fibrinous exudates, hyaline membrane deposition, hyperplasia of type II pneumocytes and the infiltration of lymphocytes, indicative of a transition from

exudative to proliferative DAD and to fibrosis [9]. People with co-morbidities such as cardiovascular diseases and obesity are at a higher risk for multiple system involvement [8,10]. Histopathological examination of lung autopsy not only gives significant importance to diagnose the respiratory cause of death but also enriches our knowledge about lung histology [11]. The aim of the present study was to estimate the prevalence of pulmonary lesions identified in autopsies of patients who died from respiratory diseases or other causes and to shed light on the principal causes of death due to pulmonary involvement.

MATERIALS AND METHODS

The present study was a one-year cross-sectional study conducted on 132 lung specimens from routine autopsies received in the Department of Pathology at a tertiary care centre Government Medical College in Cochin, Kerala, India from January 2021 to December 2021. The specimens of lung from the Forensic Medicine Department were received in 10% formalin. The details of the autopsy cases were collected from the requisition forms. Institutional Ethical Committee clearance was obtained for conducting the study (IEC no. 50/2021).

Inclusion criteria: Specimens of whole lungs, lobes, or tissue bits from adult medicolegal autopsies above 18 years of age were included in the study.

Exclusion criteria: The decision was to exclude autolysed specimens; therefore, 8 poorly preserved specimens were omitted, resulting in a total of 132 included specimens.

Sample size calculation: It was based on a study conducted by Amin NS et al., in which the proportion of histopathological lesions in the lung among autopsy specimens was 43% [12]. Using the sample size estimation formula $N=4pq/d^2$, where 4 represents the square of the Z-value of the alpha error at 5% (approximated to 1.96), p is the proportion from the previous study (43%), q is 100-p (57%) and d is the relative precision of 20% (8.6). Therefore, the minimum sample size required for the present study was determined to be 132.

Study Procedure

The lung specimens were fixed in 10% formalin, with universal precautions observed during handling. On gross examination, parameters such as colour, volume (collapsed or inflated), consistency, presence of bullae, consolidation, nodules, infarction, oedema, congestion, abscess formation, scarring, hilum and bronchi were assessed. A minimum of four sections, with additional sections as needed, were taken from representative areas for microscopy. In addition to Haematoxylin and Eosin (H&E) stains, special stains for Acid Fast Bacilli (AFB) and Grocott-Gomori Methenamine Silver stain (GMS) and Periodic Acid Schiff (PAS) for fungal hyphae were performed when necessary. Pulmonary lesions were examined microscopically, the relative frequency of various lesions and available clinical data were recorded.

STATISTICAL ANALYSIS

Data were numerically coded and entered into a Microsoft Excel spreadsheet. Further statistical analysis was conducted using SPSS software version 21.0. Quantitative variables were summarised using frequency and percentage.

RESULTS

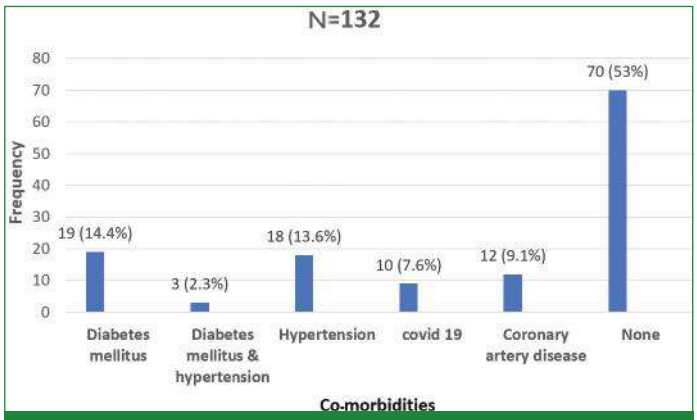
The adult autopsy cases in the study ranged in age from 18 to 88-year-old, with a mean age of 49.41 years and a standard deviation of ±52.12. Out of the 132 autopsy cases, the majority (48.50%) were in the age group of 31-40 years, followed by 41-50 years (15.90%), 20-30 years (14.40%) and 51-60 years (10.60%). The distribution of age among the patients in the autopsy cases is shown in [Table/Fig-1].

Age (years)	Frequency	Percentage
18-30	19	14.4
31-40	64	48.5
41-50	21	15.9
51-60	14	10.6
61-70	5	3.8
71-80	5	3.8
81-90	4	3
Total	132	100

[Table/Fig-1]: Distribution of age of the patients in autopsy cases.

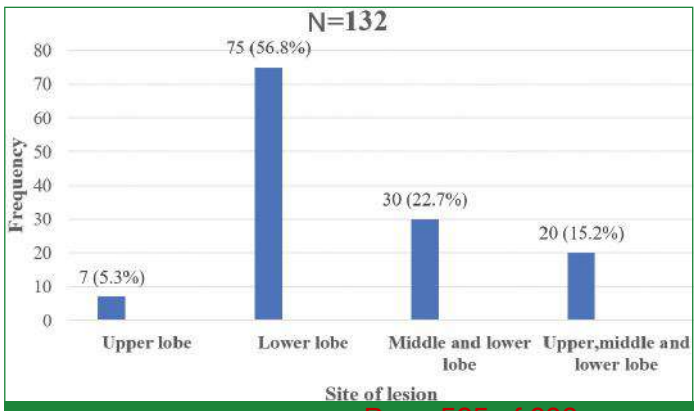
Of the 132 autopsy specimens, 104 (78.80%) cases were males and 28 (21.20%) were females, resulting in a male-to-female ratio of 3.71:1. Among the 132 cases, the cause of death for the majority, 97 (73.50%) was sudden death, while the remaining 35 cases (26.50%) were attributed to other causes such as underlying illness, suicide, electrocution, drowning, road traffic accidents, burns, etc.

Among the 132 cases, 70 cases (53%) had no associated co-morbidities. Diabetes mellitus was present in 19 cases (14.40%), hypertension in 18 cases (13.6%) and 3 cases (2.30%) had both diabetes and hypertension. RT-PCR positive COVID-19 infection was observed in 10 cases (7.60%). A history of ischaemic heart disease and coronary artery disease was seen in 12 cases (9.10%). The distribution of co-morbidities in autopsy cases is shown in [Table/Fig-2].



[Table/Fig-2]: Distribution of co-morbidities in autopsy cases.

The most common macroscopic finding was oedema and congestion, observed in 89 cases (67.40%), followed by congestion alone in 29 cases (22%). Collapse and consolidation were observed in 4 cases (3.03%). Out of the 14 cases (10.60%) with gross white lesions, seven cases showed multiple caseous lesions and necrosis suggestive of tuberculosis. Among the 132 autopsy cases, 75 cases (56.8%) showed macroscopic lesions in the lower lobe of the lung, while 30 cases (22.7%) had lesions in both the middle and lower lobes. The site of lung lesions in the lobe-wise distribution in the study is shown in [Table/Fig-3].



[Table/Fig-3]: Distribution according to site of lung lesion in autopsy cases.

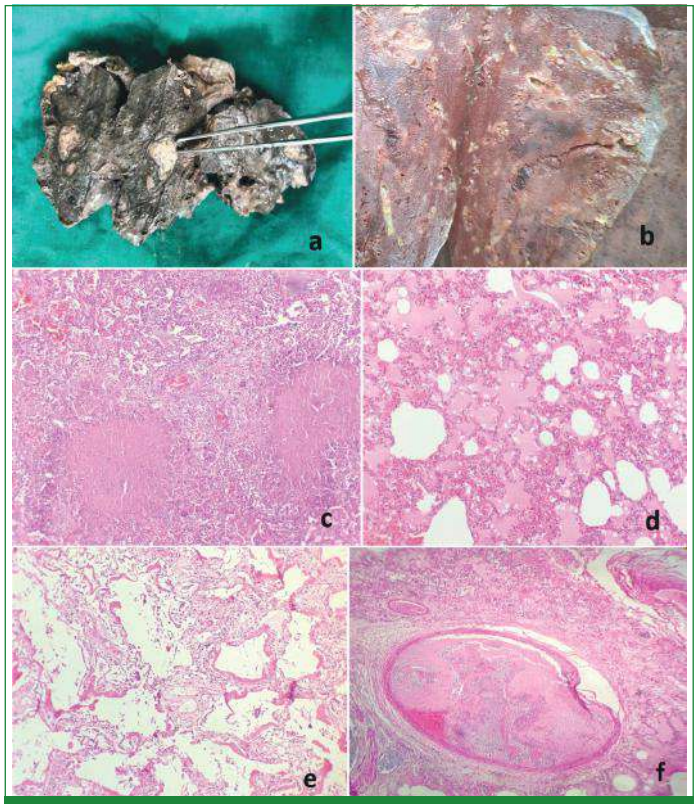
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In the present study, 11.37% of the cases were histologically unremarkable, whereas 88.63% of the cases showed histological changes of pulmonary pathology, which were further subclassified based on the type of the lesion encountered. This distribution shows the prevalence of various microscopic diagnosis in the study population given in [Table/Fig-4].

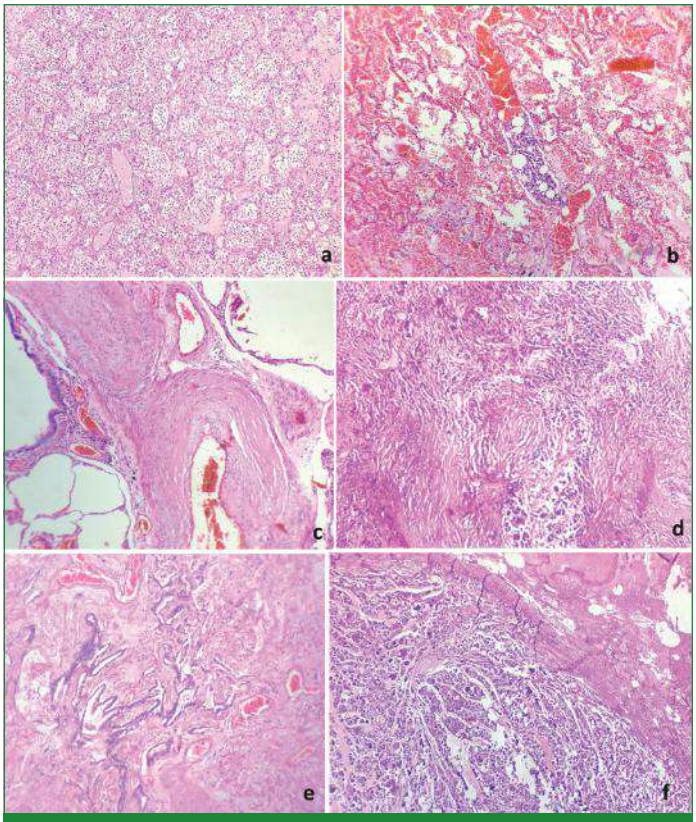
Microscopic diagnosis	Frequency	Percentage
Pulmonary oedema/congestion	61	46.21
Chronic venous congestion	8*	6.06
Emphysema	7*	5.30
Acute Respiratory Distress Syndrome (ARDS)/Diffuse Alveolar Damage (DAD)	12	9.09
Pneumonia	17*	12.87
Tuberculosis	7	5.30
Fat embolism	1	0.75
Pulmonary hypertension	1	0.75
Pulmonary fibrosis	1	0.75
Neoplastic lesions	7	5.30
No specific lesion/normal	15	11.37

[Table/Fig-4]: Microscopic findings in lung in the study (n=132).
*Overlap of findings in these lesions with pulmonary congestion and oedema

On HPE of 132 lung specimens, 61 cases (46.21%) showed pulmonary oedema and congestion. Changes of Chronic Venous Congestion (CVC) were seen in 8 cases (6.06%), Emphysema in 7 (5.30%) cases. There was overlap of findings as combined findings of pulmonary oedema with CVC were seen in 4 (3.03%) cases, pulmonary oedema with emphysematous changes were seen in 6 (5.30%) cases and pulmonary oedema with pneumonia in 8 (6.10%) autopsy cases. Pneumonia was seen in 17 (12.90%) cases which included both lobar and bronchopneumonia. Granulomatous inflammatory lesion and caseous necrosis consistent with tuberculous bronchopneumonia were found in 7 (5.30%) cases. The gross and microscopy images of lung lesions in the study is shown in [Table/Fig-5a-f, 6a-f].



[Table/Fig-5]: Gross and microscopy images of lung lesions in the study. a) Gross image of lung showing multiple caseous lesions; b) Gross-congestion and oedema; c) Caseating granuloma in Tuberculosis (H&E,10X); d) Pulmonary oedema (H&E,10X); e) DAD, ARDS. (H&E, 10X); f) Intravascular thrombi formation in COVID-19 infection lung (H&E,10X).



[Table/Fig-6]: Microscopic findings in lung in the study- images. a) Lobar pneumonia - red and grey hepatisation. (H&E,10X); b) Fat embolism in vessel-lung (H&E,10X); c) Medial hypertrophy of artery in pulmonary arterial hypertension (H&E,10X); d) Pulmonary fibrosis- extensive fibrosis (H&E,10X); e) Primary adenocarcinoma lung (H&E, 10X; f) Lung metastasis from follicular carcinoma thyroid (H&E, 10X).

The ARDS and DAD associated with multi-organ failure were seen in 12 (9.10%) of cases. Out of the 12 cases of DAD, 6 cases had COVID-19 infection as a co-morbidity. There were 10 cases of COVID-19 deaths in the study. The primary pulmonary findings in COVID-19 deaths were massive capillary congestion in all 10 (100%) cases, exudative DAD associated with hyaline membrane and type II pneumocyte hyperplasia in six cases. Four cases showed superimposed bronchopneumonia. Other findings in COVID-19 deaths were interstitial congestion, alveolar haemorrhage in three cases, platelet and fibrin thrombi in two cases.

Neoplastic lesions were seen in 7 (5.30%) out of 132 cases. There were three cases of primary lung adenocarcinoma, two cases of adenocarcinoma metastasis to lung and two cases of thyroid neoplasm metastasis to lung were found. Other lesions in the present study included one case each of pulmonary arterial hypertension (0.75%), pulmonary fibrosis (0.75%) and fat embolism (0.75%). In 15 cases (11.40%), there was no specific pathology seen.

DISCUSSION

The present study on pulmonary findings of medicolegal autopsies aimed to identify the prevalence of pulmonary pathology and the incidental lung lesions that may have contributed to fatalities associated with cardiorespiratory failure. In the current study, histopathological changes in the lungs were present in 88.63% of cases. This is similar to the findings from previous studies by Khare P et al., and by Chauhan G et al., where the prevalence of lung pathology was 65.10% and 87.47%, respectively [13,14]. The current study examined 132 autopsy cases, with patients ranging in age from 20 to 88 years. A significant portion of cases 64 (48.5%) fell within the 31 to 40 year age group and males 104 (78.8%) outnumbered females 28 (21.2%). Tahir TM et al., reported that 68.14% of cases in their study were between 20 and 49 years-old [2]. The cause of death was unknown in 97 (73.50%) cases in the present study. Road traffic accidents, suicide, poisoning and drowning were the known causes seen in 35 out of 132 (26.5%) cases. Co-morbidities present in 52 (39.39%) cases included,

diabetes mellitus, hypertension, ischaemic heart disease, coronary artery disease and COVID-19 infections.

The gross morphology of lung lesions in the study varied from congestion, heaviness, frothy appearance, whitish lesions to collapse and consolidation. Congestion and oedema were the most common gross findings, seen in 89 cases (67.40%). The second most common finding was congestion alone in 29 (22%) cases. Similar observations were seen in a study conducted by Khare P et al., which observed congestion in 42.85% of cases [13].

The spectrum of histopathological lesions included pulmonary congestion, oedema, pneumonia, tuberculosis, DAD, emphysema, neoplastic lesions and other abnormalities. Pulmonary oedema could be due to primary pulmonary pathology or secondary involvement of the lungs in the terminal stages of cardiovascular diseases. Pulmonary oedema and congestion were the most common findings in 61 (46.2%) cases in the study. Chauhan G et al., reported a similar prevalence of 53.32% [14]. Changes in the CVC were observed in 8 (6.06%) cases, while Shetty AC and Vijaya A noted a prevalence of CVC in 30 out of 349 cases (8.6%) [11]. The second most common histopathological lesion was pneumonia, including bronchopneumonia and lobar pneumonia, accounting for 12.87% of the 132 cases. This finding was consistent with studies by Chauhan G et al., and Patel CB et al., who reported pneumonia in 14.62% and 18.68% of cases, respectively [14,15].

Granulomatous inflammatory lesions with caseation consistent with tuberculosis were found in 7 (5.30%) cases out of the 132 autopsy cases in the present study. The increased frequency of sudden deaths due to undiagnosed tuberculosis, despite improved healthcare facilities, is a cause for concern. In a study on sudden unexpected deaths due to tuberculosis by Rastogi P et al., tuberculosis was identified as the most common cause of sudden unexpected death related to the respiratory system [16]. Tuberculosis poses a threat to the community, both during life and after death. Although it is a treatable disease, its fatality is often linked to its association with Human Immunodeficiency Virus (HIV) infection.

In a study by Garg M et al., which included a total of 115 autopsy cases, 10 cases (8.7%) of active tuberculosis were identified. Tuberculosis was the primary cause of death in 30% of patients, with 90% having pulmonary tuberculosis, 10% miliary tuberculosis and 30% extrapulmonary tuberculosis [17]. Emphysematous changes were observed in 7 cases (5.30%) in the present study. In a study of 441 autopsy cases by Dhruw D et al., only 3 cases (0.63%) of emphysema were reported [18]. Goswami PR et al., reported a higher prevalence of 15.8%, attributing the increase to tobacco consumption in the area [19]. A comparison of the proportions of lung lesions with other studies is shown in [Table/Fig-7] [13-15,18,19].

There were 7 (5.30%) cases of neoplastic lung lesions. Primary lung adenocarcinoma was observed in three cases and four cases of metastatic carcinoma with multiple pulmonary nodules were seen. All these findings were incidental in postmortem examinations and the lesions appeared as grey-white single or multiple nodular lesions macroscopically. Two cases of lung metastasis were from thyroid neoplasms, one from papillary carcinoma of the thyroid and another case from follicular carcinoma of the thyroid. Manser RL et al., observed 47 incidental lung cancers in a large series, with 28 being invasive non small cell lung cancers and 86% of those were stage I cancers [20]. A study on autopsy diagnosis of malignant neoplasms conducted by Burton EC et al., showed that 33% of undiagnosed malignancies were in the respiratory tract [21]. Although incidental lung cancer is uncommon, there are some lung cancers that remain undetected during life and do contribute to death. It is not possible to determine from the present study whether the incidental lesions detected were indolent or would have progressed to cause death had the individuals not died from co-morbid diseases. HPE of the autopsied specimens helps to highlight incidental findings [21]. Other lesions in the present study included a single case of pulmonary arterial hypertension associated with cardiac mitral valve stenosis and cardiac failure. Additionally, one case of fat embolism following a road traffic injury and bone fracture was noted.

Among the 10 autopsies of COVID-19-related deaths in the present study, more than half of the cases 6 (60%) showed predominantly a DAD pattern of lung injury, with the formation of hyaline membranes and interstitial fibrous tissue proliferation. Features of Bronchopneumonia were seen in 4 COVID-19 deaths. In a review article of 20 studies of COVID-19-related deaths by Sofizan NM et al., the major histological feature in the lung was DAD with hyaline membrane formation and microthrombi in small pulmonary vessels [22]. The authors concluded that there was a high incidence of deep vein thrombosis, despite the use of prophylactic anticoagulants in intensive care units. Carsana L et al., described the fibrotic phase of DAD and honeycombing, which were only focal in COVID-19 deaths, suggesting that progression to the fibrotic phase was rare due to the short duration of the disease [Table/Fig-8] [7-9,23]. Based on the comparison of COVID-19 pulmonary pathology findings between the present study and other studies, the prevalence and pattern of lesions varied based on the chronicity and complications of the cases.

Microscopic diagnosis	Present study- Kerala (2024) (N=132) N (%)	Khare P et al., (Delhi-2017) [13] (N=86) N (%)	Chauhan G et al., (Gujarat-2015) [14] (N=335) N (%)	Patel CB et al., (Gujarat-2017) [15] (N=649) N (%)	Dhruw D et al., (Chhattisgarh-2020) [18] (N=474) N (%)	Goswami PR et al., (Gujarat-2021) [19] (N=139) N (%)
Pulmonary oedema, congestion	61 (46.2%)	24 (42.85%)	-	93 (26.44%)	352 (74.25%)	-
Chronic venous congestion	8 (6.06%)	-	-	92 (26.72%)	41 (8.64%)	-
*Terminal events	-	10 (17.9%)	182 (54.32%)	-	-	42 (30.2%)
Pneumonia	17 (12.9%)	5 (8.7%)	49 (14.62%)	65 (18.68%)	25 (5.26%)	47 (33.8%)
ARDS/DAD	12 (9.1%)	1 (1.8%)	-	3 (0.86%)	-	-
Tuberculosis/Granuloma	7 (5.3%)	8 (14.3%)	21 (6.26%)	5 (1.44%)	7 (1.48%)	18 (12.9%)
Emphysema	7 (5.3%)	5 (8.75%)	26 (7.76%)	15 (4.31%)	3 (0.63%)	22 (15.8%)
Neoplastic lesions	7 (5.3%)	-	7 (2.08%)	2 (0.58%)	-	7 (5%)
Normal	15 (11.37%)	26 (30.1%)	42 (12.53%)	-	33 (7%)	-

[Table/Fig-7]: Prevalence and percentage of pulmonary pathology in various studies [13-15,17,19].
*Terminal events- Congestion, pulmonary oedema, haemorrhage, changes due to cardiovascular causes [17]

Microscopic diagnosis	Present study (2024) n=10	Elsoukkary SS et al., (2020) USA n=32 [7]	Menter T et al., (2020) Switzerland n=21 [8]	Zhao L et al., (2021) Wuhan, China n=9 [9]	Carsana L et al., (2020) Italy n=38 [23]
Interstitial congestion, oedema	10 (100%)	8 (25%)	21 (100%)	9 (100%)	38 (100%)
DAD, exudative	6 (60%)	24 (75%)	8 (38%)	9 (100%)	38 (100%)

Hyaline membrane formation	6 (60%)	24 (75%)	16 (76%)	9 (100%)	33 (87%)
Type II pneumocyte hyperplasia	6 (60%)	24 (75%)	11 (52%)	9 (100%)	38 (100%)
Platelet-fibrin thrombi in vessels/coagulopathy	2 (20%)	23 (72%)	5 (23.8%)	7 (77.77%)	33 (87%)
Alveolar haemorrhage	3 (30%)	9 (28%)	3 (14.28%)	9 (100%)	20 (50%)
Bronchopneumonia organising pneumonia	4 (40%)	14 (44%)	10 (38%)	6 (66.66%)	14 (37%)
Pulmonary embolism	-	-	4 (19%)	-	-

[Table/Fig-8]: Comparison of pulmonary pathology in COVID-19 deaths (n=10/132) [7-9,23].

Limitation(s)

Information regarding the clinical details, previous illnesses and risk factors such as tobacco smoking contributing to pulmonary diseases could not be obtained in all cases.

CONCLUSION(S)

The morphology and pattern of lung pathology are varied and complex. The present study documented the prevalence of lung lesions in sudden deaths. The terminal events of pulmonary oedema and congestion were the common findings contributing directly or indirectly to mortality. Lungs are the primary site for Novel Coronavirus infection and COVID-19 pathology is currently under extensive research. The present study showed DAD as the most common histopathological finding in the majority of COVID-19 deaths. Incidental findings reveal information regarding the epidemiology of the disease in a geographical area, which is valuable in academic research. The prevalence of lung lesions of infectious aetiology in a population depends on social and epidemiological patterns. The prevalence of tuberculosis and pneumonia emphasises the clinical significance of early diagnosis and management to reduce mortality.

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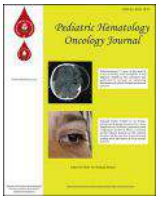
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Curative hematopoietic stem cell transplantation in a child with specific granule deficiency due to a homozygous SMARCD2 variant

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ABSTRACT

Background: Children with recurrent, severe infections that respond poorly to treatment are likely to have an underlying inborn error of immunity.
Case Report: A three-year-old male child of non-consanguineous parentage presented with recurrent severe infections from the neonatal period, including abscesses, pneumonia, diarrhea, meningitis, cystitis, and pyelonephritis. The child had subtle dysmorphic features. The dihydro rhodamine assay was abnormal, and the peripheral smear showed hypogranular, hypolobated neutrophils. Clinical exome sequencing revealed a homozygous variant in the SMARCD2 gene, confirming the diagnosis of specific granule deficiency 2. The child underwent a haploidentical hematopoietic transplant and is asymptomatic five months post-transplant. Conditioning chemotherapy included rabbit anti-thymocyte globulin/treosulphan/thiotepa/fludarabine. The CD34 dose infused was 15 x 10^6/kilogram recipient body weight. The infused product was TCR alpha/beta and CD19 depleted with preserved TCR gamma/delta cells.
Conclusion: This case demonstrates that although ultra-rare inborn errors of immunity are often diagnosed by next-generation sequencing, simple hematological and immunological tests provide valuable clues. Timely hematopoietic stem cell transplantation is curative.
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1. Introduction

Phagocytes are the predominant first responders at sites of infection. Phagocytic defects are often misdiagnosed due to the limited availability of investigative modalities and poor awareness among clinicians. Children usually present early in life with recurrent pyogenic and fungal infections. Common phagocytic defects are associated either with low absolute neutrophil counts or with functional defects that affect migration, adhesion, ingestion, degranulation, or oxidative metabolism [1].

We present a three-year-old male child with phenotypic features of chronic granulomatous disease (CGD), later diagnosed as specific granule deficiency 2 (SGD2) with a variant on the *SMARCD2* (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily D, member 2) gene on exome sequencing [2,3]. To our knowledge, this is the first report from India.

2. Case

A male baby born at term to non-consanguineous parents had early-onset neonatal sepsis, hypoglycemia, and hypocalcemia. There was no history of delayed separation of the umbilical stump. He had a bulbous nose, long philtrum, thin upper lip, micrognathia, low set ears, brachydactyly, and hypertelorism (Fig. 1). Multiplex Ligation-dependent Probe Amplification (MLPA) for 22q11.2 deletion was negative.

At 5 months of age, he had a mandibular abscess, pneumonia, and pyogenic meningitis, necessitating mechanical ventilation. Blood culture yielded *Staphylococcus aureus*. Three months later, he had an axillary abscess and moderate hepatosplenomegaly. *Pseudomonas aeruginosa* was grown from pus. The Immunoglobulin profile was unremarkable. Prophylaxis with cotrimoxazole and itraconazole was started. He had recurrent diarrhea and bilateral pyelonephritis with cystitis at two years of age. All infections were severe, necessitating prolonged hospitalization. He underwent surgery for a unilateral cataract at two years of age. Complete blood count revealed moderate anemia.

Peripheral smear showed anisopoikilocytosis, tear drop cells, pseudo-Pelgher-Huet cells, and hypolobated hypogranular neutrophils with a shift to the left (Fig. 2). The nitroblue tetrazolium (NBT) test was normal, but the dihydrorhodamine (DHR) assay was abnormal (Figs. 3 and 4), suggesting neutrophil granular defect.

The assay showed an abnormal pattern with a single peak with no shift to the right, suggesting an absent oxidative burst.

A homozygous nonsense variation in exon 2 of the SMARCD2 gene was found on exome sequencing that results in a stop codon and premature truncation of the protein at codon 131 (p.Gln131Ter) and was reported as 'likely pathogenic.'

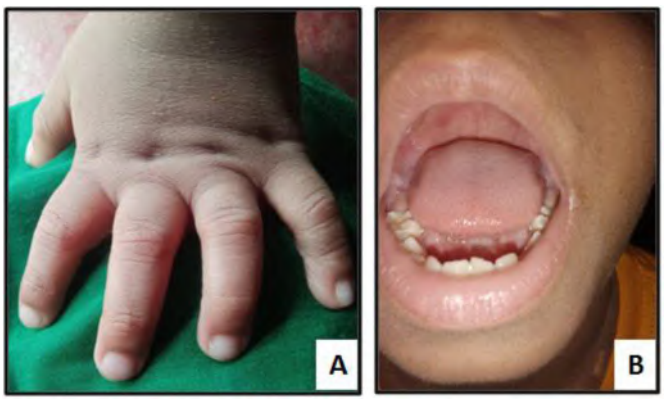


Fig. 1. Brachydactyly (A) and misaligned teeth (B).

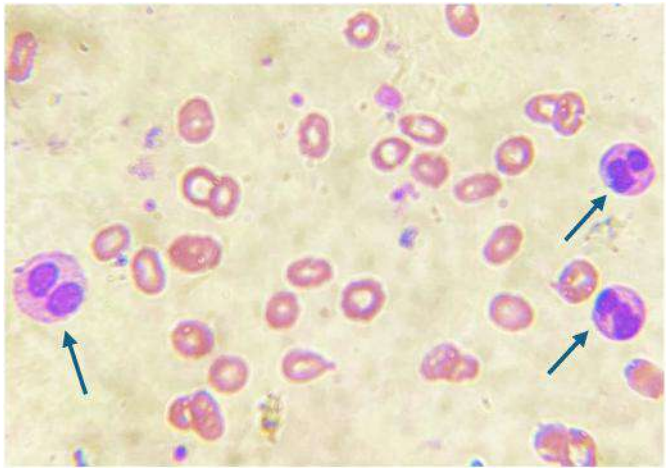


Fig. 2. Peripheral blood smear showing anisopoikilocytosis, tear drop cells, pseudo-Pelgher-Huet cells, and hypolobated hypogranular neutrophils (Leishman stain; X 100).

Since the child did not have a fully matched donor, a haploidentical hemopoietic stem cell transplantation (HSCT) was performed with the father as the donor. The donor-specific antibody test was negative.

For pre-transplant immunosuppression, one cycle of fludarabine at 40 mg/m^2/day intravenously and dexamethasone at 25 mg/m^2/day, spanning over five days, was administered. One week later, the child had a viral respiratory infection and pancytopenia. After he had recovered, he was admitted for HSCT. The conditioning regimen consisted of rabbit anti-thymocyte globulin 1.5 mg/kg/day for 3 days, thiotepa 5 mg/kg bd for one day, fludarabine for 4 days at 40 mg/m^2/day, and treosulfan at 14 gm/m^2/day for 3 days.

A total of 15 million peripheral blood stem cells per kg of TCR alpha/beta and CD19-depleted stem cells with preserved TCR gamma/delta cells mobilized from the father were infused. T-depleted product collected was documented to have 13.53 x 10^5/kg recipient body weight of CD34 cells. CD19 and TCR alpha/beta cells were 0; TCR gamma/delta cells were 21.84 x 10^6/kg recipient body weight.

The child developed grade 3 cytokine release syndrome and grade 3 mucositis. He engrafted on day 10 and was discharged on prophylactic antibiotics. The graft-versus-host disease (GVHD) prophylaxis included cyclosporine and steroids. Cyclosporine was given for 9 months, tapered, and stopped. Prednisolone at 1 mg/kg/day in two divided doses was tapered and stopped after 2 months. Topical steroids were also used.

Complete donor chimerism was documented on 15, 30, 60, 90 days, and 5 months post-HSCT. He had cytomegalovirus reactivation, which required ganciclovir and grade 2 skin GVHD, which settled with steroids. Follow-up immune reconstitution revealed that T- and B-lymphocytes gradually improved by day +100. The child remains well 5 months post-HSCT off immunoglobulin support and immunosuppressants and free of infections with 100 % donor chimerism with absolute CD4 counts of 540 cells/mm^3 and absolute CD19 counts of 356 cells/mm^3.

3. Discussion

An inborn error of immunity was suspected in the index case given neonatal sepsis and frequent severe infections since early childhood. DiGeorge syndrome was excluded by MLPA.

The next diagnostic possibility was chronic granulomatous

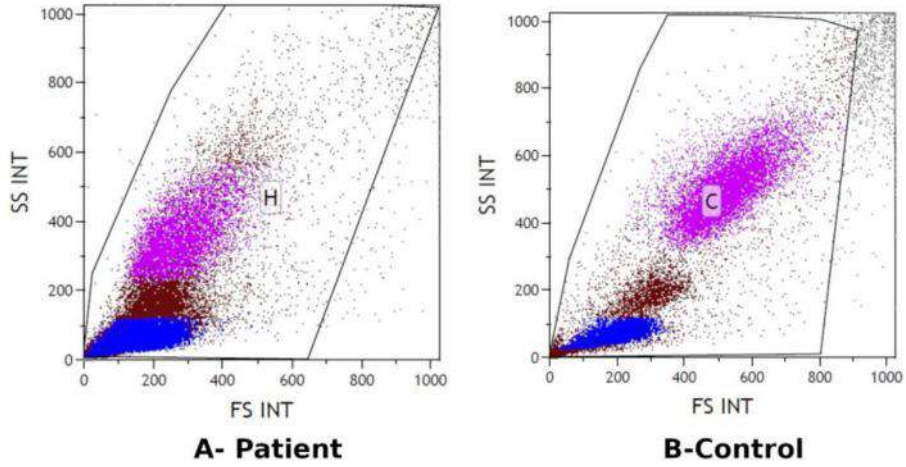


Fig. 3. Dihydrorhodamine test. The forward scatter side scatterplot of the patient (A) revealed hypogranular neutrophils, which were not easily separable from the lymphocyte population. Forward scatter side scatter plot of control (B) showed distinct, easily separable populations of neutrophils and lymphocytes.

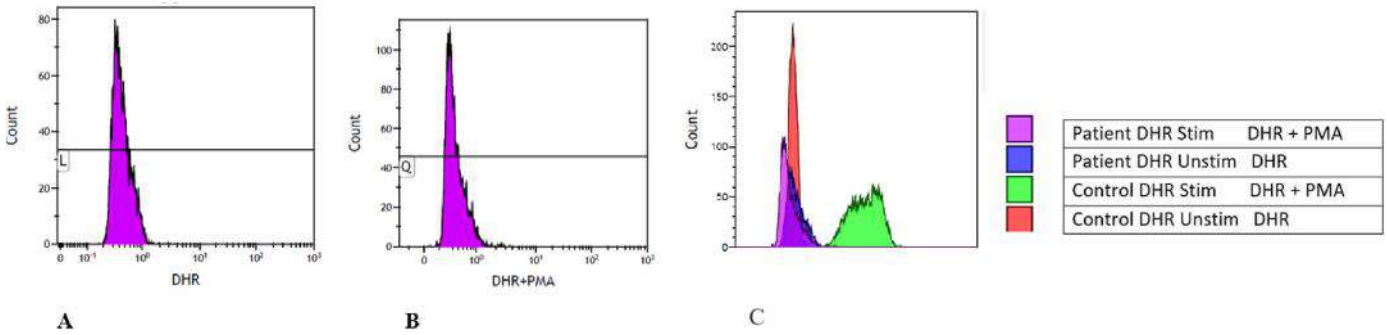


Fig. 4. Dihydrorhodamine assay: Unstimulated (A), stimulated (B), and overlay plots (C).

disease due to the early onset of recurrent abscesses, pneumonia, organ involvement, need for prolonged parenteral antibiotics, and abnormal DHR results. Infections due to *S. aureus and P. aeruginosa* were consistent with CGD [1]. Features of leukocyte adhesion defects included umbilical sepsis and delayed fall of the umbilical stump. Exome sequencing revealed an ultra-rare phagocytic defect, SGD2, due to a nonsense variant in the SMARCD2 gene (17q23.3).

SGD is a rare autosomal recessive condition where neutrophils lack the ability to express granule proteins, leading to impaired chemotaxis and bactericidal activity [2]. Patients present with recurrent pyogenic infections and may have dysmorphic facies, developmental delay, dental defects, and skeletal anomalies [3]. Pyogenic infections may result in deep organ abscesses or superficial, indolent skin infections [4].

SGD type 1 (SGD1) is caused by a defect in a myeloid-specific transcription factor, CCAAT/enhancer-binding protein epsilon (CEBPE) [5]. In SGD2, SMARCD2, a pivotal player in myeloid cell differentiation, is deficient [3,6]. SMARCD2 is also crucial for interacting with distinct transcription factors-associated expression of genes related to neutrophil function. Certain features not usually seen in CGD, including misaligned teeth, brachydactyly, facial dysmorphism, dental abnormalities, cataracts, and motor developmental delay, were observed [6–8].

The peripheral smear re-examined following the exome sequencing report, showed bilobed nuclei and pseudo-Pelgher-Huet cells. An abnormal DHR on stimulation with phorbol myristate (PMA) has been described in SGD due to loss of granularity of neutrophils and difficulty in separation from lymphocytes [9]. Detection of neutrophil granules by flow cytometry has been suggested as a rapid screening test [4].

The patient exhibited a homozygous nonsense variation in the SMARCD2 gene, the stop-gained variant c.391C > T (p.Gln131Ter). This mutation leads to a truncated SMARCD2 protein and impaired neutrophil function. Congenital neutropenia has been described in some patients with SGD [10–13].

SGD2 has been reported to be associated with myelodysplasia, and HSCT is the recommended treatment. Pre-transplant immunosuppression was employed to decrease the risk of graft rejection. The patient achieved 100 % donor chimerism 5 months post-HSCT, with successful infection management and immunological support. Good outcomes with HSCT have been reported with myeloablative conditioning [8,10,12,13]. Several studies have documented the role of TCR alpha/beta-depleted HSCT in CGD [14,15]. Neutropenia in SGD may not respond optimally to G-CSF like other severe congenital neutropenia syndromes. The efficacy of the thrombopoietin receptor antagonist, romiplostim, in combination with G-CSF has been reported [11].

To conclude, it is imperative to confirm the genomic diagnosis of a child with features of CGD since an abnormal DHR is not specific. Peripheral smear yields invaluable clues to this rare disorder and will enable life-saving antibacterial and antifungal prophylaxis even before a genomic diagnosis is made. Subtle clinical features, including mild facial dysmorphism, dental abnormalities, peripheral skeletal defects, and developmental delay, are additional pointers to the underlying diagnosis.

Patient's/Guardian's consent

Written informed consent for publication of case details, including figures depicting investigations performed, was obtained from the child's parents.

Ethical clearance

Not applicable.

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Declaration of competing interests

None.

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Treatment response of hidradenitis suppurativa with apremilast

Dear Editor,

Hidradenitis suppurativa (HS) is a chronic recurrent inflammatory skin disorder that affects the apocrine gland-bearing areas of the body, predominantly the axilla, groin, and anogenital regions.[1] The usual age of onset is postpubertal, between the second and third decades of life. Its pathogenesis is multifactorial. Treatment of HS is challenging because of the wide range of clinical manifestations of the disease and its complex pathogenesis. Here, we report a case in which apremilast showed a good therapeutic response in a patient with severe HS.

There are limited literature reviews on the effectiveness of apremilast for mild-to-moderate HS.[2-4]

A 32-year-old chronic smoker and alcoholic and otherwise healthy individual presented with recurrent episodes of multiple painful papules, nodules evolving to ulcers, and discharging sinus tracts in both axillae for 2 years duration, similar lesions in the groin and buttocks of 1-year duration. In addition, he developed bilateral knee joint pain and swelling for 1 month. Over the first 2 months, he received multiple systemic antibiotics and steroids, with little response. The results of the general examination were unremarkable. Cutaneous examination revealed ulcers measuring 10 cm × 5 cm × 6 cm–3 cm × 6 cm × 3 cm, open pseudocomedones, keloidal-type scars involving both axillae [Figure 1a and b], multiple nodules, and sinus tracts involving the groin and buttocks [Figure 1c]. Pathergy test results were negative.

A provisional diagnosis of HS Hurley stage 3 with secondary infection and arthritis was made. Pyoderma gangrenosum, scrofuloderma, autoinflammatory syndromes such as pyogenic arthritis, acne, and HS; pyogenic arthritis, pyoderma gangrenosum, acne, and HS; and cutaneous Crohn's disease were considered clinical differentials. Investigations revealed anemia (Hb 8.1 gm/dL), elevated acute-phase reactants (erythrocyte sedimentation rate = 30 mm/h), and hypoalbuminemia. Biopsy showed multiple sinus tracts surrounded by granulation tissue and multinucleated giant cells of the foreign body type, which was consistent with HS [Figure 2]. Acid-fast bacilli (AFB; Ziehl-Neelsen staining) and periodic acid shift staining results were negative. Tissue AFB, fungal culture, and cartridge-based nucleic acid amplification test results were negative. Ultrasound of the lesional area revealed multiple hypoechoic collections with sinus formation [Figure 3a and b]. Magnetic resonance imaging fistulography detected multiple fistulous tracts and infective spondylodiscitis. The rheumatoid arthritis factor was negative. No obvious fluid collection was observed in the ultrasonography knee. Abdominal contrast-enhanced computed tomography and sigmoidoscopy findings were normal. Autoinflammatory syndromes were ruled out by clinical, histopathological, and sonographic evaluation. A final diagnosis of HS Hurley stage 3 with secondary infection and seronegative arthritis was considered.

Management was initially directed toward control of the superposed infection for which systemic antibiotics were administered based on the culture and sensitivity

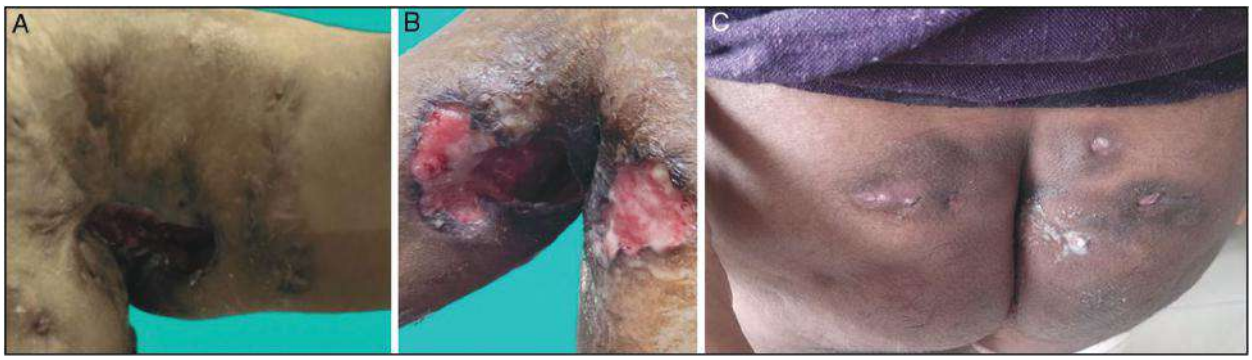


Figure 1: (a) Left axilla showing multiple ulcers with purulent exudate and open pseudocomedones. (b) Right axilla showing multiple ulcers with purulent exudate and open pseudocomedones. (c) Multiple nodules and sinus tracts involving both groin and buttocks

reports. Specific treatment measures opted for a short course of steroids and doxycycline (100 mg twice daily (BD)] for approximately 4 months. Acitretin 25 mg once a day was administered for about 7 months. Split-skin grafting was also performed. There was no response, and the patient was readmitted twice, with worsening of the lesion. A parallel workup for adalimumab was performed, but it had to be deferred due to infective spondylodiscitis.

Based on previous reports of successful treatment of HS with phosphodiesterase 4 (PDE4) inhibitors, we prescribed apremilast 30 mg BD daily.[3,4] Response was assessed by calculating the International Hidradenitis Suppurativa Severity Scoring System (IHS4) and dermatology life quality index (DLQI) before and 16 weeks after therapy. A 7-point reduction in IHS4 and 10 point reduction in DLQI (at initiation IHS4-11 DLQI-17, 16 weeks posttherapy IHS4-4 DLQI-7) was noted with no adverse effects of medication [Figures 4a and b & 5a and b].

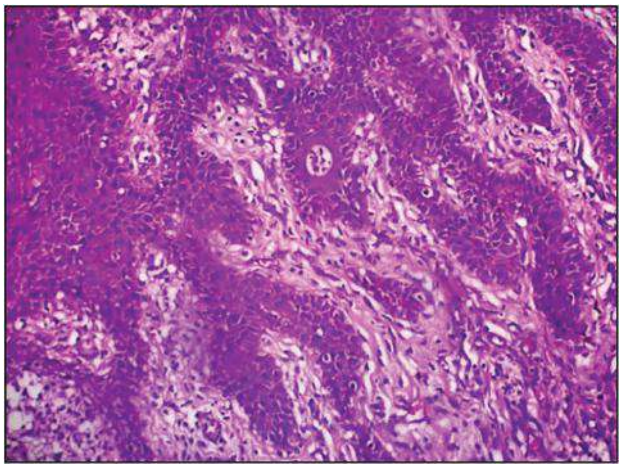


Figure 2: Dense neutrophilic infiltrates forming abscesses, sinus tracts lined by stratified squamous epithelium surrounded by granulation tissue formation, and multinucleated giant cells of foreign body type and histiocytes favoring HS (HPE 10×)

Apremilast is a small-molecule drug that inhibits phosphodiesterase and modulates the expression of several inflammatory cytokines. The off-label use of apremilast has been reported to successfully treat patients with mild to moderate HS, as evidenced by previous studies. Vossen *et al.*[2] did a randomized controlled trial in 2018 to determine the efficacy of apremilast in moderate HS and found a significant reduction in abscess and inflammatory count and a numerical rating scale for pain 16 weeks posttherapy. A case series study by Garbayo-Salmons *et al.*[3] showed a >1 point reduction in physician global assessment (PGA) in 29% of patients ($P = 0.157$), >30% reduction in DLQI in 43% of patients ($P = 0.043$), a significant reduction in IHS4 ($P = 0.068$), and >2 point reduction in the Visual Analog Scale (VAS) in 57% of patients ($P = 0.042$) at 12 and 24 weeks posttherapy.[3] Kerdel *et al.* performed a prospective open-label phase 2 study in 2019 to determine the efficacy of apremilast in mild to moderate HS and observed a significant reduction in Sartorius score ($P \leq 0.001$), PGA ($P \leq 0.01$), VAS pain score ($P < 0.05$), and DLQI ($P < 0.01$) 24 weeks posttherapy.[4]

Our case provides clinical evidence of the role of PDE4 in severe HS. The significant reduction in nodules, abscesses, and fistulous tracts underscores the effect of PDE4 in increasing the levels of proinflammatory cytokines, such as interleukin-17, tumor necrosis alpha, and interferon-gamma, majorly involved in HS.

In conclusion, the major brunt of HS is the psychosocial distress associated with the disease attributed to pain and disfigurement affecting day-to-day activities, especially in severe HS, and the dramatic response to apremilast in our patient with severe HS opens doors to a new promising modality for severe HS. Apremilast may not be uniformly effective in all patients with HS, as the pathogenesis of HS is multifactorial.

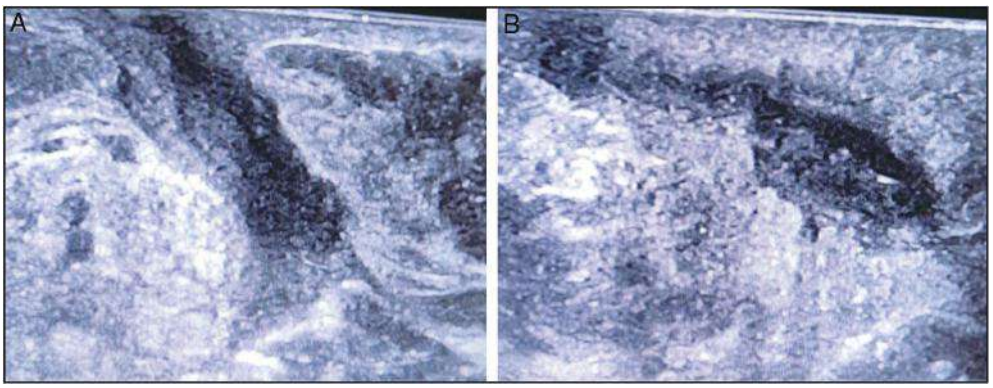


Figure 3: (a) Multiple superficial subcutaneous hypoechoic collection with sinus formation involving the left axilla. (b) Multiple superficial subcutaneous hypoechoic collection with sinus formation involving the right axilla

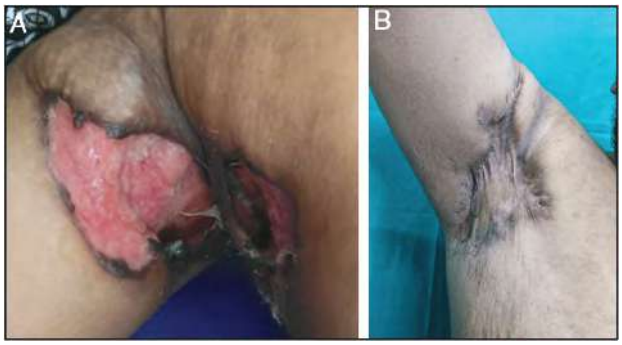


Figure 4: (a) Right axillary lesion before commencing apremilast therapy (IHS4-11 DLQI-17). (b) Right axillary lesion after commencing apremilast therapy (IHS4-4 DLQI-7)

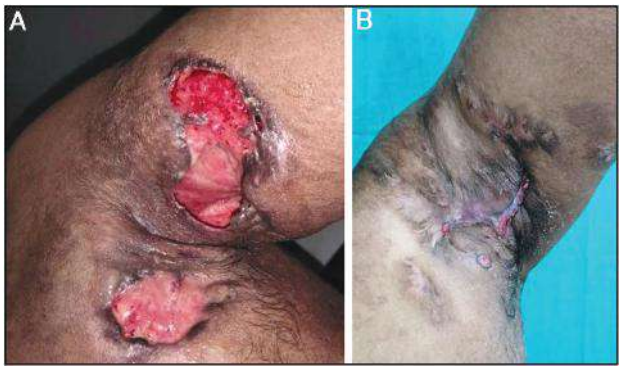


Figure 5: (a) Left axillary lesion before commencing apremilast therapy (IHS4-11 DLQI-17). (b) Left axillary lesion after commencing apremilast therapy (IHS4-4 DLQI-7)

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Conflicts of Interest

There are no conflicts of interest.

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Section: Pathology

Original Research Article

IMMUNOHISTOCHEMICAL DIFFERENTIATION BETWEEN MALIGNANT CELLS AND MESOTHELIAL CELLS IN PLEURAL EFFUSION

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ABSTRACT

Background: Differentiating malignant from reactive mesothelial cells is challenging, particularly in pleural cytology, due to overlapping cytologic features . This study evaluates the effectiveness of EMA (Epithelial membrane antigen), Desmin and Calretinin in distinguishing mesothelial cells from malignant cells in cytologic effusions and provides a comparative analysis of their diagnostic performance.

Material and Methods: This study, conducted at Government Medical College, Thrissur, from January 2017 to June 2018, focused on pleural fluid samples from patients diagnosed with reactive mesothelial cells, atypical mesothelial cell proliferation and metastatic carcinoma.Samples were examined using both cell block and conventional smear methods. Immunohistochemistry (IHC) was performed on cell block sections with markers EMA, Desmin and Calretinin using the immunoenzymatic soluble complex method.

Results: The study included 56 patients, with a mean age of 62.9 years, and found that hemorrhagic effusions were most commonly caused by malignancy. The cell block (CB) method demonstrated significantly higher diagnostic efficiency for malignancy (75.5%) compared to conventional smear (46.9%), and combining both methods improved diagnostic accuracy. Immunohistochemistry (IHC) showed strong EMA expression in adenocarcinoma cases with a sensitivity and specificity of 100% ~~.and~~ Desmin positivity was seen in a subset of reactive effusions, with sensitivity and specificity being 36.8% and 89.1% respectively.

Conclusion: This study evaluates the use of EMA, Desmin and Calretinin to differentiate mesothelial cells from malignant cells in pleural effusions. It finds that combining smear and cell block methods improves diagnostic yield, with cell block preparation offering better cellular details. EMA shows 100% sensitivity and specificity in identifying malignant cases, while Desmin helps identify reactive mesothelial cells. The combination of EMA and Desmin enhances diagnostic accuracy, making them a reliable panel for challenging effusion cases.

Key Words: Immunohistochemistry, Pleural effusion, Mesothelial cells, Malignant cells, Epithelial membrane antigen, Desmin.

INTRODUCTION

Differentiating malignant from reactive mesothelial cells is challenging, especially in pleural cytology, due to overlapping cytologic features. While various antibodies aid this distinction, clinical research continues to seek a biomarker with high sensitivity and specificity.[1] Immunocytochemical and molecular methods on cell blocks or smears improve diagnostic accuracy.[2]Various studies have

demonstrated the utility of immunohistochemical markers, such as EMA (epithelial membrane antigen), Desmin, Calretinin, Fibronectin, CEA (carcinoembryonic antigen), Vimentin, P53, and Ki-67, in distinguishing reactive mesothelial cells from malignant cells. Among these markers, Calretinin, Desmin, and EMA have been identified as particularly promising for differentiating mesothelial cells from malignant cells in effusion cytology.[4-6] However, some mesotheliomas, like sarcomatous types, are rarely detected through effusion cytology. Diagnosing mesothelioma, particularly epithelioid types, requires panels of immunohistochemical markers with both positive and negative predictive value to ensure 100% sensitivity and specificity.[3]

This study assesses the effectiveness of EMA, Desmin and Calretinin in differentiating mesothelial cells from malignant cells in cytologic effusions and provides a comparative analysis of their diagnostic performance.

MATERIALS AND METHODS

This study was conducted in the Cytology Lab of the Department of Pathology at Government Medical College, Thrissur, a tertiary care institution, from January 1, 2017, to June 30, 2018, covering a period of 18 months. Pleural fluid samples from patients diagnosed with reactive mesothelial cells, atypical mesothelial cell proliferation and metastatic carcinoma were included in the study. Cell-poor effusions and cell block preparations, fluid samples negative for malignancy, grossly purulent fluid samples, and repeat samples were excluded. The study was approved by the Institutional Ethics Committee at Govt. Medical College, Thrissur. All eligible pleural effusion samples received were subjected to both cell block and conventional smear examinations. Fluid samples were collected in clean test tubes or containers. Half of each sample was allocated for the conventional smear method, while the other half was allocated for the cell block method. Conventional Smear Technique: Fluid samples were centrifuged at 3000 rpm for 10 minutes. A minimum of 3 smears were prepared from the sediment. Two smears were fixed immediately in 85% isopropyl alcohol and stained with Papanicolaou stain. The third smear was air-dried and stained with either Leishman or Giemsa stain. Cell Block Technique: The fluid was centrifuged at 3000 rpm for 10 minutes after adding fixative (Acid-Alcohol Formalin). The supernatant was discarded, and the sediment was treated with Acid-Alcohol Formalin overnight. The sediment was processed along with routine histopathological specimens. Paraffin-embedded sections of 4-6 µm thickness were prepared and stained with H&E stain. Microscopic examination was performed to categorize the slides as either benign or malignant based on cytomorphological features. Immunohistochemistry: Immunohistochemistry (IHC) was performed on cell block sections using the markers EMA, Desmin, and Calretinin, employing the immunoenzymatic soluble complex method. 4 µm thick sections were made on poly-L-lysine-coated slides. Slides were incubated at 37°C overnight and at 60°C for 1 hour, followed by dewaxing in xylene. Antigen retrieval was performed, and staining was carried out. Immunoreactivity was scored semi-quantitatively based on the percentage of cells stained and the intensity of staining. Data were entered into Excel sheets, and the specificity and sensitivity of each immunohistochemical marker were calculated using SPSS 16 statistical software.

RESULTS

A total of 56 patients who met the eligibility criteria were included in the study. The age of the patients ranged from 29 to 91 years. The most frequent age group in this study was 61–80 years (51.8%), with a mean age of 62.9 years. Out of the 56 cases studied, 17 cases (30%) were males, and 39 cases (70%) were females, with a male-to-female ratio of 1:2.1.[Table 1]

Effusions were categorized as hemorrhagic in 32 samples and non-hemorrhagic in 24 samples. The most common cause of hemorrhagic effusions was malignancy, accounting for 28 (87.5%) of all hemorrhagic fluid samples, while only 4 (12.5%) were reactive effusions. Out of the 49 malignant effusions, 28 (57.2%) were hemorrhagic, and 21 (42.8%) were non-hemorrhagic.

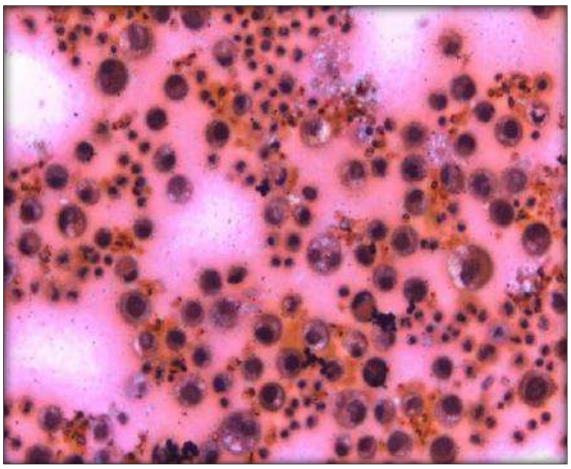
Cellularity is significantly better in cell block (CB) compared to conventional smear (CS), and nearly equal cellularity was observed in approximately 24 cases. Cytoplasmic features were superior in CB, nuclear features were enhanced in CB and architectural patterns were better appreciated in CB.

The efficiency of the cell block method in diagnosing malignancy was 37/49 (75.5%), compared to 23/49 (46.9%) for the conventional smear method. This difference was statistically significant (p-value -0.018). When combining the two tests, the diagnostic efficiency improved to 38/49 (77.6%), demonstrating a statistically significant increase in diagnostic accuracy compared to conventional smear analysis (p-value - 0.001).

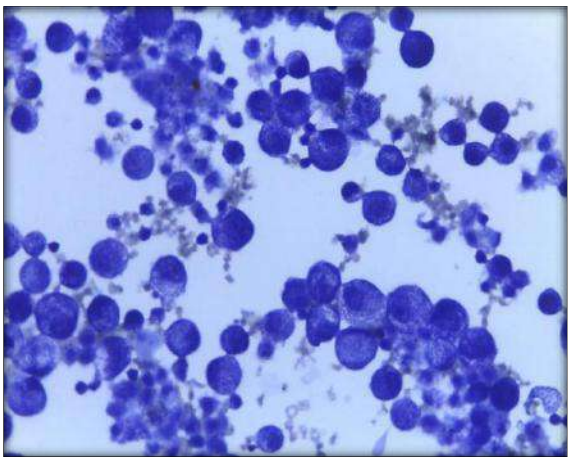
In Conventional Smear Diagnosis, 23 cases (41.1%) were adenocarcinoma, and 33 cases (58.9%) were reactive mesothelial hyperplasia.In Cell Block Diagnosis, 37 cases (66.1%) were adenocarcinoma, while 19 cases (33.9%) were reactive mesothelial hyperplasia. Immunohistochemistry (IHC) identified 49 (87.5%) adenocarcinoma cases and 7 (12.5%) reactive mesothelial hyperplasia.

When compared to conventional smear, cell block methods have demonstrated a sensitivity of 59.4%, specificity of 94.7%, positive predictive value of 95.6%, and negative predictive value of 54.5%.

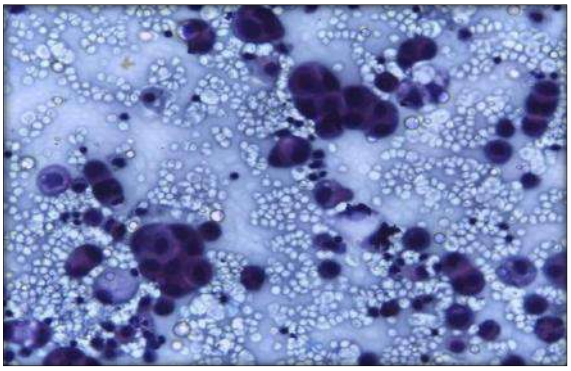
When both conventional smear and cell block methods are combined and compared with IHC diagnosis, the sensitivity increases to 77.5%, specificity reaches 100%, positive predictive value is 100%, and the negative predictive value is 38.8%. In 49 cases, strong and diffuse cytoplasmic expression of EMA was observed, with 70% of these cases showing an IHC score of 6. The sensitivity and specificity of EMA were both 100%, with a positive predictive value of 75.5% and a negative predictive value of 58.3%. For desmin expression in effusions, it was positive in 11 cases, of which 7 cases were exclusively desmin-positive. Among these, 42.9% (3/7) had an IHC score of 5, while 57.1% (4/7) had an IHC score of 6. The remaining 4 cases with IHC grade 4 exhibited strong and diffuse EMA positivity, indicating adenocarcinoma. The sensitivity and specificity of desmin were 36.8% and 89.1%, respectively, with a positive predictive value of 63.6% and a negative predictive value of 73.3%.



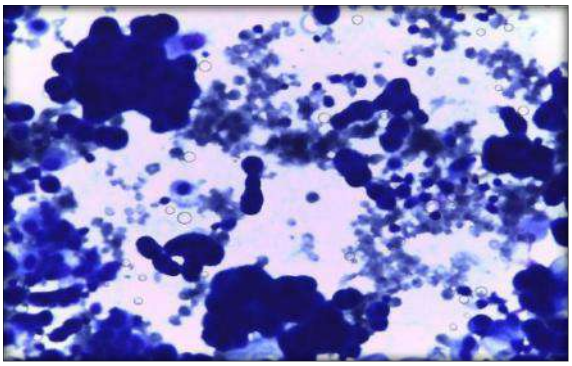
Conventional smear: pleural fluid sample showing mesothelial cells scattered singly in a bloody background (Papstain)



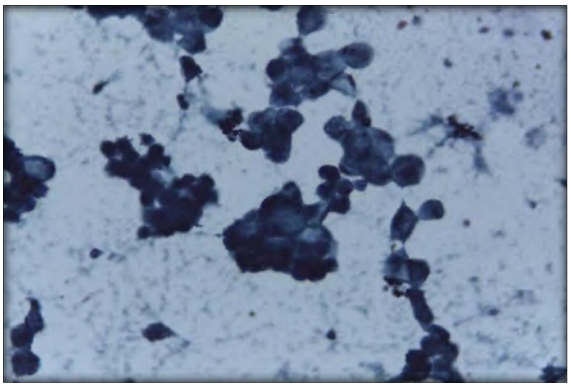
Conventional smear: pleural fluid sample showing mesothelial cells scattered singly in a bloody background (Giemsa stain)



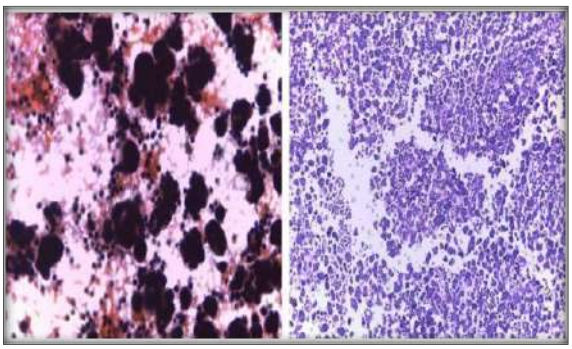
Conventional Smear: Pleural fluid showing Reactive mesothelial cells with cell window and cytoplasmic vacuolation (Pap Stain)



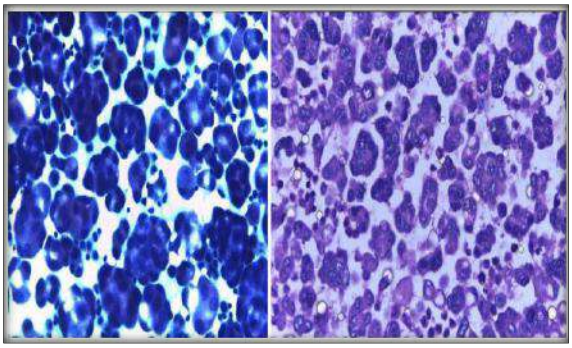
Conventional smeaer: pleural fluid showing reactive mesothelial cells with cell window (Giemsa stain)



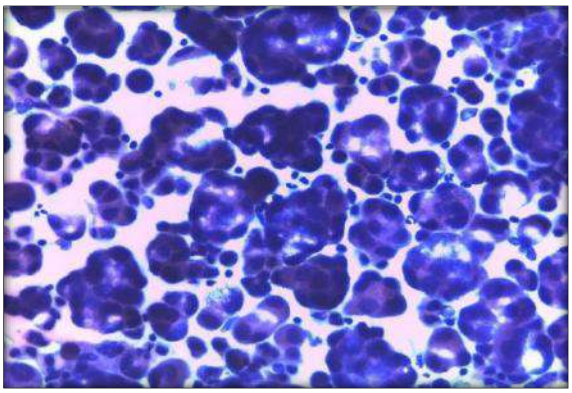
Conventional smear: Pleural fluid showing adenocarcinoma cells with a few signet ring cells (Giemsa stain)



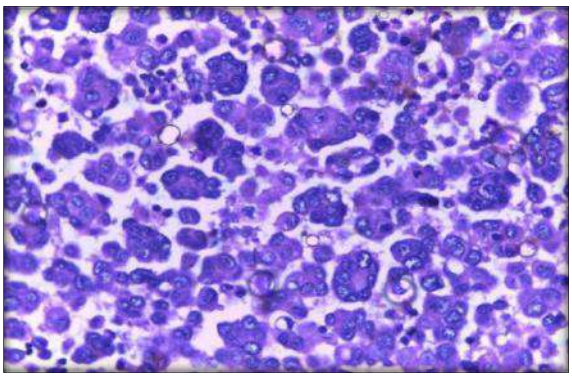
Cellularity in conventional smear compared to cell block



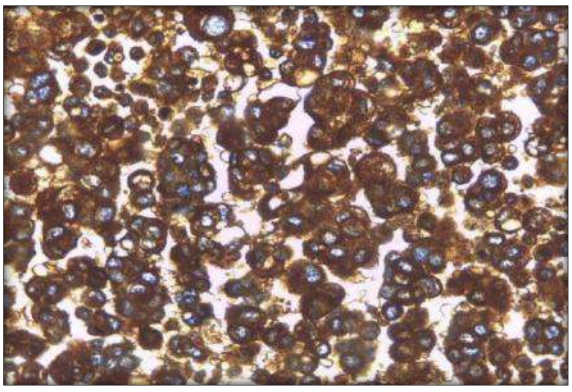
Pattern, cytoplasmic and nuclear features in conventional smear compared to cell block



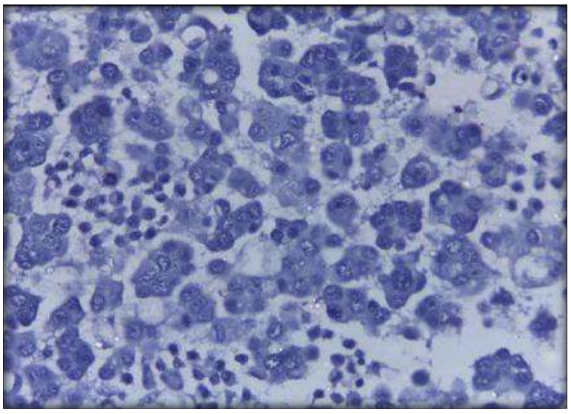
Adenocarcinoma in conventional smear (Papstain)



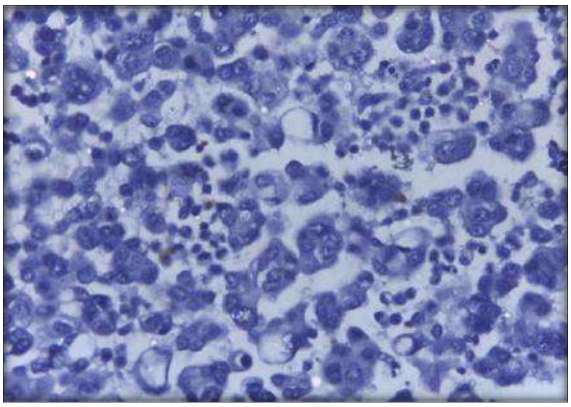
Adeno carcinoma in cell block (H&E stain)



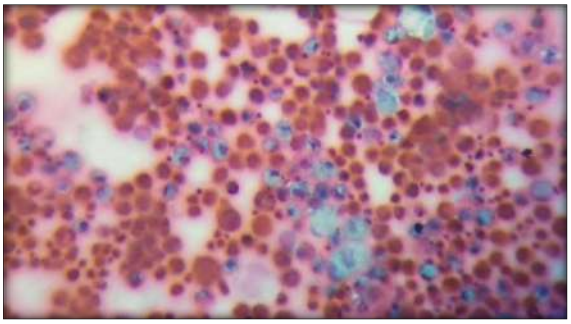
EMA Positivity in adenocarcinoma cells - diffuse strong cytoplasmic positivity. Staining Score:3; Intensity Score: 3. IHCS core: 6



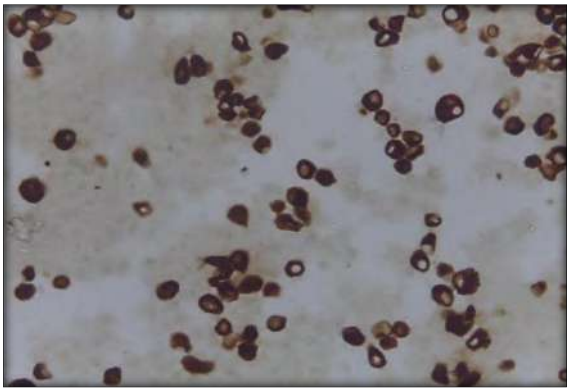
Desmin negative adenocarcinoma cells.



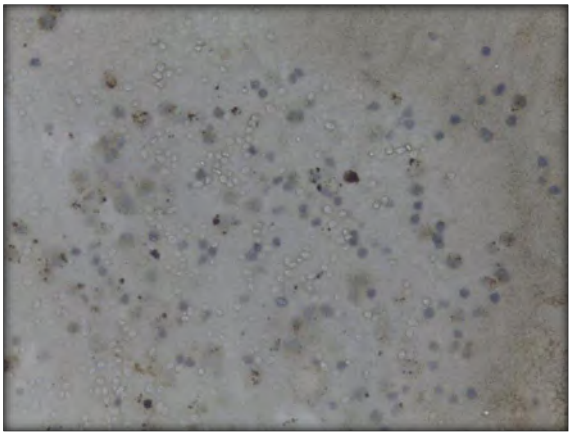
Calretinin negative in adenocarcinoma cells.



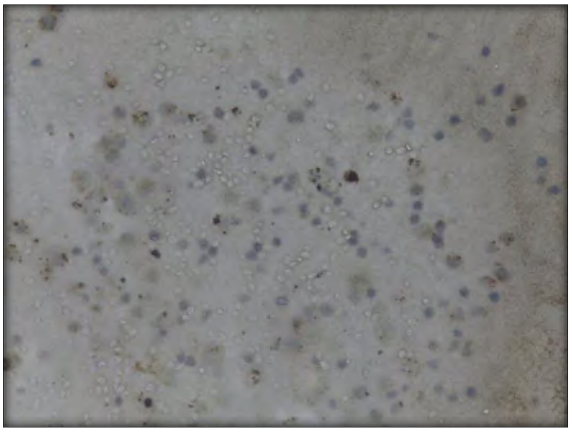
Reactive mesothelial cells in conventional smear (Pap stain)



Desmin show strong and diffuse cytoplasmic positivity. Staining score: 3; Intensity score: 3; IHC grade: 6



EMA negative in reactive mesothelial hyperplasia



Calretinin negative in reactive mesothelial cells.

Table 1:Basic characharestics of study population

Variables	N(%)
Age group	
21-40	3(5.4)
41-60	20(35.7)
61-80	29(51.8)
81-100	4(7.1)
Sex	
Male	17(30.4)
Female	39(69.6)
Colour of fluid	
Hemorrhagic	32(55)
Non-Hemorrhagic	24(45)
Distribution of primary organ in effusions	
Breast	4(7)
Colon	4(7)
Liver	2(4)
Lung	24(43)
Ovary	12(21)
Endometrium	2(4)
Stomach	5(9)
Unknown	3(5)

Table 2: Conventional smear, cell block and immunohistochemistry (IHC) comparison for final diagnosis

	Adenocarcinoma	Reactive Mesothelial Hyperplasia
Conventional Smear	23(41.1)	33(58.9)
Cell block	37(66.1)	19(33.9)
IHC	49(87.5)	7(12.5)

Table 3: Expression EMA and Desmin in effusions by immunohistochemistry

EMA Expression	
score<4	7(12)
4	4(7)
5	6(11)
6	39(70)
Expression of Desmin	
score<4	45(80.4)
4	4(7.1)
5	3(5.4)
6	4(7.1)

DISCUSSION

Pleural effusion cytology aids in diagnosing and managing malignancies but can be challenging in some cases. Ancillary techniques help differentiate between metastatic cancer, reactive mesothelial cells, and mesothelioma. This study aimed to distinguish malignant cells from mesothelial cells in pleural effusion using immunohistochemical markers (EMA, Desmin and Calretinin) on 56 cases diagnosed as reactive mesothelial hyperplasia or metastatic carcinoma .

The study analyzed 56 pleural fluid samples using smear preparation and cell block techniques. Patients ranged from 38 to 91 years, with the highest incidence (51.8%) in the 61–80 age group and the lowest in the 21–40 age group (5.4%). Pleural effusions were more common in females (69.6%) than males, with a male-to-female ratio of 1:2.1,

aligning with findings from previous studies.[7,8] Of the 56 effusions, 57% were hemorrhagic and 43% non-hemorrhagic. Malignancy was the leading cause of hemorrhagic effusions (87.5%), while 12.5% were reactive. Among 49 malignant effusions, 57.2% were hemorrhagic and 42.8% non-hemorrhagic.

In conventional smear cytology, moderate and marked cellularity were observed in 46.4% and 53.6% of cases, respectively, while in the cell block (CB) method, 80.3% showed moderate and 19.7% marked cellularity. About 43% of cases had better cellularity in CB, and 14.2% in conventional smears, with the remaining cases showing equal cellularity in both methods. CB also preserved morphological features, such as cytoplasm, cell membranes, and nuclear details, better than conventional smears, a finding consistent with previous studies.[9-11] Furthermore, CB demonstrated clearer architectural patterns, including papillae, glandular, and acinar structures. In distinguishing reactive mesothelial cells from malignant cells, CB was superior due to reduced nucleolar prominence and clearer structures, unlike conventional smears, which can mimic malignancy.[7,12,13] Out of the 56 pleural effusion samples, cytological diagnosis revealed benign effusions in 59% of the cases and malignancy in 41%. The sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were 57.9%, 94.4%, 51.5%, and 95.6%, respectively. Malignancy was diagnosed in 66% of cases using the cell block method, with sensitivity of 77.5%, specificity of 100%, NPV of 38.8%, and PPV of 100%.The cell block method improves the detection of malignant cases, with diagnostic yields ranging from 15% to 25% higher than smears alone. It is particularly effective in detecting tumors in patients with negative or atypical cytology reports. Studies consistently show that CB outperforms smears in tumor cell recovery, with some studies reporting an increase in detection rates by up to 38%.[7,11]

The study found that the cell block method for diagnosing malignancy had a higher efficiency (75.5%) compared to the conventional smear method (46.9%), with a statistically significant difference (p - 0.018). Combining both tests improved diagnostic efficiency to 77.6%, which was significantly higher than the smear method alone (p - 0.001). Previous studies support these findings, with carcinoma of the lung being the most common primary neoplasm causing pleural effusion in both sexes, followed by ovarian cancer in females and gastric cancer in males. These results are consistent with those of other researchers.[14,15]

This study aimed to assess the utility of immunohistochemical markers (EMA, desmin, and calretinin) in differentiating reactive mesothelial hyperplasia from adenocarcinoma in serous effusions. The results showed that EMA was highly effective, with 78.7% of adenocarcinoma cases showing strong and diffuse cytoplasmic positivity. Combining EMA with cell block techniques increased the diagnostic yield by 21.4%, which was statistically significant. Desmin was found to be useful in identifying reactive mesothelial cells, though its sensitivity was lower compared to EMA. Calretinin was negative in all cases, including adenocarcinoma and reactive mesothelial hyperplasia, indicating limited value in this study's context. The study confirms that no single marker can reliably distinguish between benign and malignant cells with 100% accuracy. However, the combination of EMA and desmin proved to be the most effective, with EMA positivity and desmin negativity showing the best specificity for adenocarcinoma. This highlights the importance of using a panel of markers, rather than relying on a single one, to improve diagnostic accuracy, especially given the heterogeneity of metastatic malignancy.[16-20]

CONCLUSION

This study evaluates the diagnostic efficacy of Calretinin, Desmin, and EMA in distinguishing mesothelial cells from malignant cells in pleural effusions. The study found that combining conventional smear and cell block methods improved diagnostic yield, with cell block preparation offering better cellular details. IHC analysis identified 49 malignant cases, with EMA showing 100% sensitivity and specificity. Desmin was effective in identifying reactive mesothelial cells. Overall, combining EMA and Desmin enhanced diagnostic accuracy, making them a reliable panel for challenging effusion cases.

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CASE REPORT

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Plasmodium Ovale Malaria-A Case Report from Tertiary Care Centre Central Kerala

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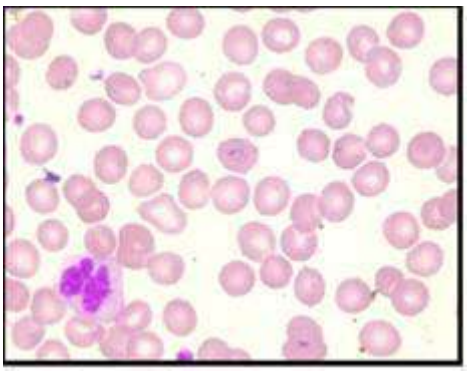
Abstract
Background: *According to World Malaria Report 2019, 3% of the global malaria cases are reported from India. Most cases of malaria in India are due to infestation by Plasmodium falciparum (65%) and Plasmodium vivax (35%). Only a few thousand cases of Plasmodium malariae has been reported from foothill areas in Orissa. Malaria due to Plasmodium ovale is not very common in India and till date only 9 cases have been reported. We are reporting a case of P. ovale malaria which was diagnosed and treated at Government Medical College, Thrissur, Kerala, in a patient who had returned from Uganda. Diagnosis was made with the specific morphological features of these parasites like oval shape of parasitised RBCs, fimbriation of RBCs and very prominent shuffners dots.*
Interpretation & Conclusion: *This is the first case of Pl. ovale reported from central Kerala. This case of plasmodium ovale malaria could be an isolated imported case and there are no reported cases of local transmission so far following detection of this case.*
Keywords: *Malaria, Plasmodium ovale, fimbriation.*

Introduction

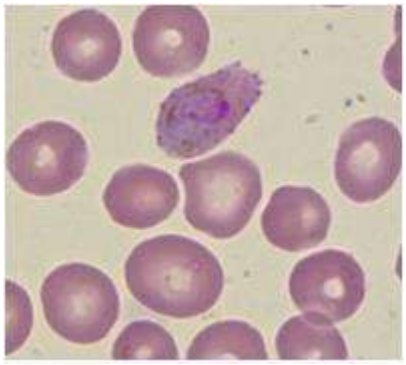
32yr old software engineer working at Bengaluru came to our Outpatient department at Government Medical college Thrissur with history of fever, myalgia, headache and abdominal pain for 5days.Fever was intermittent high grade with chills and rigor. Patient gave a history of recent visit to Uganda. On examination temperature was 104^0F. There was no jaundice, lymphadenopathy, cyanosis or pallor. Examination of abdomen showed hepatosplenomegaly. Routine blood investigations showed thrombocytopenia of 68000/cumm and normal Hb, TC, LFT, RFT, electrolytes, PT, APTT and INR. Urine examination were within normal limits. Serological tests for Dengue (NS1, IgM antibodies) and IgM antibody for Chikungunya were negative. With the history of intermittent high-grade fever with chills and rigor and history of travel outside Kerala and outside India there

was a strong suspicion of Malaria. A peripheral smear examination was done to rule out/diagnose Malaria and also for other causes of thrombocytopenia and fever. Automated haematology Analyzer showed scattergram abnormalities including merging and greying of neutrophils, eosinophil clusters, prominent blue coloured events below neutrophils due to RBC ghosts.[1]

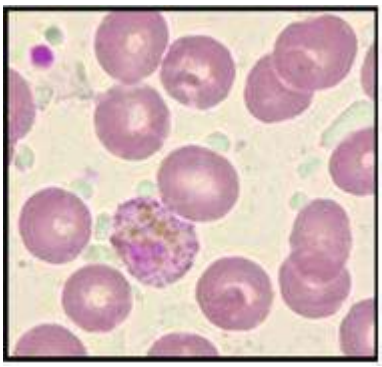
Thin smears, thick smears and buffy coat smears were prepared and stained with Leishman stain. Thick smears showed malarial parasites morphology of which was similar to P. vivax. Thin smears showed normocytic normochromic blood picture with neutrophil predominance, few reactive lymphocytes and thrombocytopenia. Malarial parasites were seen in different stages of maturation including early trophozoites, late trophozoites, schizonts and gametocytes. Examination of thin smears revealed the morphology of these parasites as that of P. ovale on the basis of peculiar morphology and changes in parasitized RBCs[2]. Infected RBCs were enlarged, oval in shape many of them showed surface fimbriations and prominent Schuffners stippling. Schizonts were seen in thick smears and buffy coat smears which were oval in shape with multiple nuclei and thick clumps of malarial pigment. Gametocytes were round to oval in shape almost filling the RBC with fimbriation. Pigment was brown and more coarse than seen in vivax. Malaria Pf/Pv bivalent Antibody Rapid Test was negative.



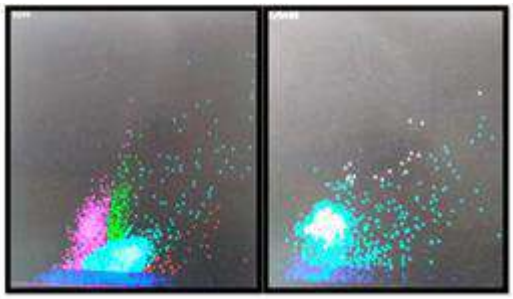
A Early trophozoite of P. ovale



B Late trophozoite with surface fimbriation of RBC and prominent Schuffners dots



C Gametocytes of P. ovale



D Scattergram showing RBC ghosts below neutrophils

Discussion

According to the latest World Malaria report there were 241 million cases of malaria globally in 2021 compared to 227 million cases in 2019.In India there were over a million reported cases of malaria in 2015.In 2019 the number reduced to around 338.5 thousand cases. As of June 2020, the numbers have been significantly low with approximately only 62 thousand cases[3].Most common species of malaria in India are P. falciparum and P. vivax. P. ovale is endemic to tropical Western Africa, it has also been detected in Philippines, Indonesia and Papua New Guinea.

Plasmodium ovale is very rare in India and till date only 9 case reports are available in the literature.[4] Rini Chaturvedi, Nimita Deora etal collated 9 reports for Plasmodium ovale infections from 1930 to 2020.[4] First case of Plasmodium ovale mono infection was reported from Delhi in 1977.[4] Three mixed infections due to Plasmodium ovale and Plasmodium falciparum were reported in 1988 from Koraput district, Odisha. Between 2000 and 2009 monoinfections were also reported from Assam and Gujarat.Mixed infection due to Plasmodium ovale and Plasmodium falciparum has been also reported from Jharkhand, Madhya Pradesh and Odisha between 2010and 2015[4]. Case reported from Johart district Assam in 2002 was in a 28 yr old male who visited Naga hills in Myanmar bordering Nagaland state, Myanmar being an endemic area for ovale malaria[5]. Recent molecular studies indicate that plasmodium ovale malaria is caused by two closely related species Plasmodium ovale curtisi and Plasmodium wallikeri. Plasmodium ovale sympatric infection have been reported from Bastar (Chhattisgarh) in a case of cerebral malaria due to mixed infection with Pf, Pv and Po[6].

This is the first case of plasmodium ovale reported from Kerala. Diagnosis was made with the morphological features of the parasites seen in thin smears. In thick smears morphology was similar to that of Plasmodium vivax. In view of patient's recent visit to East African country, Uganda we searched for P ovale malaria which is endemic in Africa. The bivalent rapid antigen kit available in our laboratory specific for Pf and Pv was negative. Even though this rapid test is 100% sensitive to Pf and Pv a negative test does not rule out the possibility of infection with P. oval and P. malariae. Automated haematology analyser showed few abnormalities in WBC-DIFF scattergram like prominent blue-colored events below neutrophil clusters due to RBC ghosts. These abnormalities which helped in the presumptive diagnosis were confirmed by peripheral smear examination[1]which is the gold standard for malaria diagnosis. Plasmodium ovale species generally produce low parasitaemia and are known to cause relapses and sometimes causes renal complications.[7] Plasmodium ovale and vivax shares similar tertian periodicity and both can cause relapse in patients without radical treatment. Treatment plan recommended by Govt of India for P. ovale is same as for Plasmodium vivax as both species tend to have hypnozoites in liver. Patient was treated with chloroquine 500mg for 3 days, primaquine15mg for 15 days and injection Artesunate 120mg. Follow-up smears showed decreased parasite load and patient became symptomatically better and was discharged. None of the family members and contact persons developed fever. This case of plasmodium ovale malaria could be an isolated imported case and there are no reported cases of local transmission so far following detection of this case.

Conclusion

Malaria Microscopists and Epidemiologist should be alert to the possibility of finding P. ovale in the routine peripheral smear examination in patients coming from endemic areas. Scattergram changes and negative rapid detection cards tests should alert the pathologists to search for the unusual forms of malaria and for mixed infections in non-endemic areas also. Species specific diagnosis is mandatory for appropriate treatment, better control of Malaria and to prevent multiple relapses and drug resistance. Ascertaining the nature of transmission whether it is local or imported is also important in malaria elimination programmes .Increased international travel increases the risk of parasite transmission between endemic and non-endemic countries and can introduce rare species of malaria to non-endemic areas. It is very important to investigate thoroughly all cases of imported malaria including conducting molecular studies in each case and to take necessary measures to prevent introduction of new species of malaria which are non-endemic to our country.

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CASE REPORT

Caseous calcification of mitral annulus: Autopsy case report of an intriguing cardiac mass

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Abstract

Caseous calcification of mitral annulus is a rare, underappreciated variant of mitral annular calcification that should be differentiated from an intracardiac abscess, tumour, or vegetation. It is a benign, usually asymptomatic condition, which may be diagnosed incidentally in autopsy and subsequent histopathological evaluation. This entity can occasionally lead on to valvular abnormalities and embolic complications. Hence, awareness about this unusual cardiac mass aiding in its early diagnosis by imaging is very important in proper management, so that unnecessary surgery can be avoided.

Keywords: Cardiac, Caseous, Vegetation, Mitral, Incidental

Introduction

Caseous calcification of mitral annulus (CCMA) is a very rare variant of mitral annular calcification (MAC). Pomerance (1970) described this uncommon entity in his autopsy series on MAC, in which he found 2.7% cases of CCMA. The condition most commonly affects elderly patients, especially women. In CCMA, there is caseous degeneration of the calcified areas in posterior mitral annulus. Due to its rarity and asymptomatic nature, it is easily overlooked or misdiagnosed as a cardiac tumour, abscess, or calcified vegetation on imaging. Although CCMA is a benign, asymptomatic, rare condition, it can result in valve dysfunctions and embolic episodes. Routine echocardiography is useful for screening, helping to arrive at an early diagnosis. Risk factors for development of CCMA are like those for atherosclerosis, and both coronary atherosclerosis and CCMA are often seen together. Here we describe an incidental diagnosis of CCMA, made during the histopathological evaluation of heart of an 84-year-old female, whose autopsy was performed following sudden death.

Case Report

An 82-year-old female was found dead at her residence. There was a history of cough and breathlessness prior to death. A medicolegal autopsy was performed in the nearby peripheral health center and the whole dissected heart was sent to our histopathology lab. Her COVID status was found to be negative before the autopsy.

The heart we received in lab, weighed 400gms. Left ventricle showed hypertrophy and areas of fibrosis. Left atrium, right atrium and right ventricle were unremarkable. Both coronaries showed pinpoint occlusion with calcification. During examination of the chambers, we noticed an incidental finding of a calcific mass measuring 2x2cms in the mitral valve annulus, which let out pultaceous, yellow tan material on cutting (Fig.1). There was extension through the myocardium and onto the epicardium.



Fig.1: Gross specimen showing calcific mass which let out caseous, yellow tan material

Microscopically, the mass showed extensive areas of calcification, caseous like necrosis (amorphous, eosinophilic, acellular material), chronic inflammatory infiltrate of macrophages and granulation tissue formation (Fig.2a, b). No evidence of tumor, abscess, granuloma (to suggest tuberculosis) or vegetation was found. With all these findings, a diagnosis of caseous calcification of mitral annulus was given. Severe coronary artery atherosclerosis with significant narrowing (>90%; AHA Type V) of right coronary artery and left anterior descending artery was also noted with left ventricular hypertrophy and evidence of an old, healed infarct.

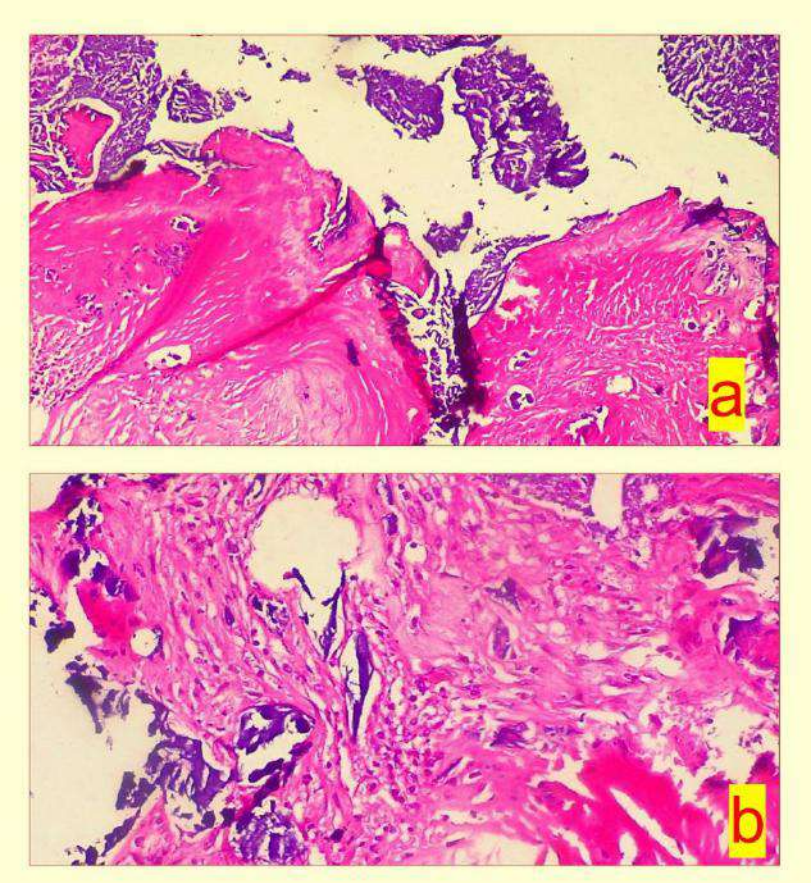


Fig.2 (a,b): Photomicrograph showing areas of calcification, caseous like necrosis, macrophages and granulation tissue formation (H&Ex200)

Discussions

Mitral annular calcification (MAC) is a chronic degeneration of the mitral valve fibrous ring affecting 10% of the population above 50[(1)]. It usually involves the mid base of the posterior leaflet. MAC is common in the elderly women but may occur in younger patients as well. It is associated with advanced renal disease and calcium disorders.

Caseous calcification of mitral annulus is a lesser-known variant of MAC, accounting for less than 1% cases of mitral valve calcification. It is a benign asymptomatic condition involving the posterior portion of mitral annulus, first described by Pomerance in 1970[(2)] In an autopsy series, he described caseous calcific necrosis of mitral annulus in 7 out of 258 cases of MAC[(2)]. CCMA presents as round, large echo dense mass with central echolucency on both transthoracic and transesophageal echocardiography. It can easily be confused with a calcific peri annular tumour or abscess in echocardiography. The prevalence of CCMA is about 2.7%

of the cases of MAC. In the autopsy series by Pomerance, CCMA is found in 0.06%–0.07% of the population [3].

Pathophysiology of CCMA is linked to altered calcium phosphate metabolism leading to the development of a calcified mitral ring due to caseous transformation of the inner material [4]. There is formation of a characteristic toothpaste-like, milky, caseous material. A large, calcified envelope that is noncollapsible surrounds this caseous material. Risk factors are thought to be similar to those for atherosclerosis, as supported by coronary atherosclerosis in our case [2,5]. CCMA lesions are associated with hypertension also [2]. In this case, there was left ventricular hypertrophy, which can probably be attributed to hypertension.

Histopathologically, a central region of amorphous eosinophilic acellular material surrounded by macrophages and lymphocytes is seen with periphery showing multiple calcifications and zones of necrosis. Differential diagnoses include cardiac tumours (Cardiac amorphous tumour, Calcified myxoma), vegetations (Organised), abscess, calcified thrombus and tuberculoma.

Cardiac complications include chronic mitral regurgitation, mitral stenosis (less likely), bradyarrhythmias, atrioventricular blocks and a higher prevalence of cardioembolic events (compared with MAC) [5]. Management is conservative in uncomplicated cases. Surgical excision with mitral valve repair is the treatment of choice in symptomatic, complicated cases. The lesion may undergo spontaneous resolution or recurrence after surgical excision.

Conclusion

Autopsy along with histopathological examination provides valuable insight into the existence of very rare cardiac lesions like CCMA, the diagnosis of which is difficult to make or easily overlooked in the antemortem period. It should be included in the differentials of intracardiac masses, especially in elderly patients with severe coronary atherosclerosis and hypertension.

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Case Report

Dermoscopy of Congenital Hemidysplasia with Ichthyosiform Erythroderma and Limb Defects Nevus with Unilateral Limb Defects

Abstract

Here, we report the dermoscopic findings of congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) nevus with left-sided ichthyosiform erythroderma and left upper-limb aplasia in a 4-month-old baby. The presence of ptychotropism and strict midline demarcation are unique features described in CHILD nevus. Dermoscopy of the CHILD nevus showed linear and dotted vessels with yellowish waxy scales on a pink background. These characteristic dermoscopic findings would also help us to differentiate it from inflammatory linear verrucous epidermal nevus.

Keywords: *Congenital hemidysplasia with ichthyosiform erythroderma and limb defects syndrome, dermoscopy, ptychotropism*

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Introduction

Congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) is a rare X-linked dominant disorder, characterized by unilateral ichthyosiform nevi with a distinct lateralization pattern and strict midline demarcation, as well as an ipsilateral skeletal defect in the form of limb hypoplasia or aplasia.[1] The term CHILD nevus was proposed by Happle *et al*. in the year 1980 due to the unique features distinguishing it from inflammatory linear verrucous epidermal nevus (ILVEN).[1] Here, we report the dermoscopic findings of CHILD nevus with left-sided ichthyosiform erythroderma and left upper-limb aplasia in a 4-month-old baby.

Case Report

A 4-month-old female child, firstborn of a nonconsanguineous marriage, presented with redness and scaling on the left half of the body with complete absence of the left upper limb since birth. There was no history of drug intake or previous miscarriages or abortions in her mother. There was no history of similar illnesses or any other genetic diseases in the family.

On examination, there was a linear erythematous plaque with coarse waxy scales involving the entire left side of the trunk with clear midline demarcation extending to involve the left groin, pubic area, and whole of the left lower limb, with complete sparing of the face [Figure 1a]. There was hypoplasia of the lateral four toes with nail dystrophy [Figure 1b]. The left labia majora showed hypertrophy. Ptychotropism was present in the form of involvement of the vulva and groin on the left side [Figure 1c]. Systemic examination was normal.

Dermoscopy showed linear and dotted blood vessels and large coarse yellowish waxy scales with a pink background [Figure 2a].

Histopathology showed psoriasiform hyperplasia with acanthosis and regular elongation of rete pegs, with few dilated vessels and moderate lymphocytic inflammatory infiltrate in the dermis [Figure 2b].

All routine investigations, echocardiogram, neurosonogram, and ultrasonogram of the abdomen were normal. X-ray whole body showed the absence of the left upper limb [Figure 2c]. ENT and ophthalmology evaluation were normal.

Due to financial constraints, genetic evaluation could not be done. Based on the clinical, histopathological, and radiological evidence, a diagnosis of CHILD syndrome was made. The child was treated with topical emollients and is on follow-up.

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Figure 1: (a) Large erythematous scaly plaque with midline demarcation involving the left half of the body sparing the face with complete absence of the left upper limb. (b) Nail dystrophy and hypoplasia of toes. (c) Ptychotropism with vulval hypertrophy of the left labia majora

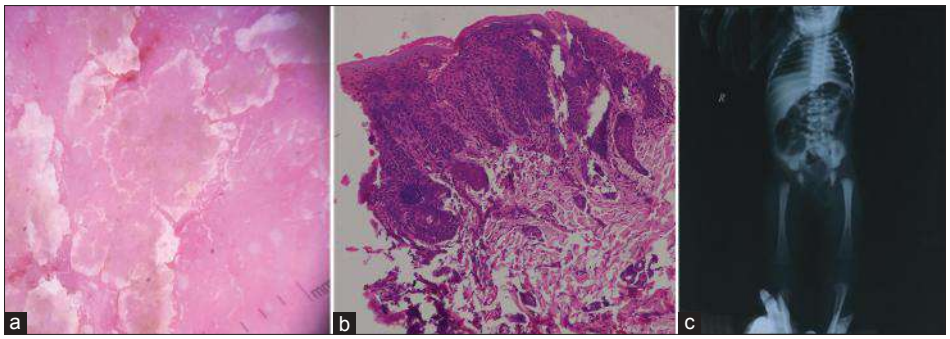


Figure 2: (a) On dermoscopy, linear and dotted blood vessels and large coarse waxy yellowish scales with a pink background (DermLite DL3N). (b) Psoriasiform hyperplasia with acanthosis and regular elongation of rete pegs, with few dilated vessels and moderate lymphocytic inflammatory infiltrate in the dermis (hematoxylin- and eosin-stained section under ×100). (c) X-ray showing absence of the left upper limb

Discussion

CHILD syndrome is due to a mutation in the NAD(P)H steroid dehydrogenase-like protein gene on chromosome Xq28, which encodes for 3-beta-hydroxysteroid dehydrogenase enzyme essential for cholesterol synthesis. Cholesterol deficiency will lead to the accumulation of toxic steroid precursors that will result in cutaneous manifestations in CHILD syndrome. Cholesterol and its precursors are required for the regulation of the sonic hedgehog pathway for skeletal development and its deficiency results in skeletal defects. Mosaicism due to lyonization leads to patchy distribution in CHILD syndrome.[2] In addition to NSDHL gene, emopamil-binding protein gene is also involved in cholesterol biosynthesis, which was initially implicated in CHILD syndrome, and later disproved by König *et al*.[3]

CHILD nevus has to be differentiated from ILVEN as skeletal defects can occur in epidermal nevus syndrome. Presence of ipsilateral skin lesions with clear midline demarcation, ipsilateral skeletal defects and ptychotropism (involvment of body folds) are unique features of CHILD nevus that differentiate it from ILVEN. Histology of CHILD nevus is unique if foamy histiocytes can be seen in the dermis.[4] However, in our case, histopathological features were similar to ILVEN.

Dermoscopy, in our case, showed linear and dotted vessels and yellowish coarse waxy scales on a pink background, whereas dermoscopy of ILVEN shows alternating brown and red glomerular structures over a white background.[5] Other patterns described in ILVEN include cobblestone pattern, cerebriform pattern, and large brown circle.[6] The waxy yellowish scales along with vascular structures over a pink background are possibly unique to CHILD nevus. More studies on ILVEN and CHILD nevus would help us to determine the characteristic dermoscopic patterns differentiating them.

We have advised the patient to use mild cleansers and topical emollients containing ceramides frequently. Topical agents like 2% simvastatin and lovastatin have shown good clinical responses for skin lesions in CHILD syndrome.[7]

The other unique feature of this case is the extensive left-sided involvement of the CHILD nevus. Left-sided involvement is rare[8] and is usually associated with severe visceral anomalies. Our baby presented with left-sided involvement without visceral anomalies.

Declaration of patient consent

The authors certify that they have obtained all appropriate consent forms, duly signed by the parent(s)/guardian(s) of the patient. In the form, the parent(s)/guardian(s) has/have given his/her/their consent for the images and other clinical information of their child to be reported in the journal. The parents understand that the names and initials of their child/children will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Clinical Challenge

Unilateral Follicular Facial Papules in a Child

INTRODUCTION

A 12-year-old boy, born of nonconsanguineous marriage, came with a 2-year history of gradually progressing, asymptomatic hyperpigmented lesion on the left cheek. He gave no history of any topical application, photoexacerbation, atopy, or similar history among family members. On examination, there were closely set follicular papules on a hyperpigmented background on the left cheek [Figure 1]. Further, the hair, nails, and mucosa appeared normal. Dermoscopy revealed round whitish areas with keratotic follicular plugs surrounded by gray spots on a reddish brown background [Figure 2]. Histopathological examination showed follicular plugging with hyperkeratosis, hyperpigmentation of the basal layer, and dermal vasodilation [Figure 3].

What is your diagnosis?

DISCUSSION

Final diagnosis: Erythromelanosis follicularis faciei

Erythromelanosis follicularis faciei (EFF) was first described by Kitamura *et al.* in 1960.[1] It is considered as a rare subtype of keratosis pilaris characterised by a clinical triad of sharply demarcated patches showing hyperpigmentation, erythema and closely set follicular papules with follicular plugging. It usually affects the preauricular areas and cheeks which gradually extend to involve the neck hence termed as EFF et colli (EFFC).[2]

In the darker skin types, erythema may not be apparent to the naked eye. In such cases, dermoscopy is a valuable noninvasive tool aiding in the diagnosis of EFFC. It shows round whitish areas with follicular plugs, some of which are centered by a hair with surrounding areas showing blue gray spots or peppering in a reddish-brown background.[3,4] The follicular papules correspond to whitish areas with keratotic plugs on dermoscopy and follicular hyperkeratosis on histology. The erythema and hyperpigmentation correspond to blue gray spots with reddish brown background on dermoscopy and basal layer hypermelanosis with vasodilatation and pigment incontinence on histology.[3]

Unusual features of our case were the unilateral presentation with erythema inapparent to naked eye and absence of keratosis pilaris elsewhere. This case also highlights the utility of dermoscopy in the diagnosis of EFFC, so that biopsy can be avoided as it involves the face.

Declaration of patient consent

The authors certify that they have obtained all appropriate



Figure 1: Left cheek showing multiple 2 mm sized closely set follicular keratotic papules with hyperpigmentation in the interfollicular areas

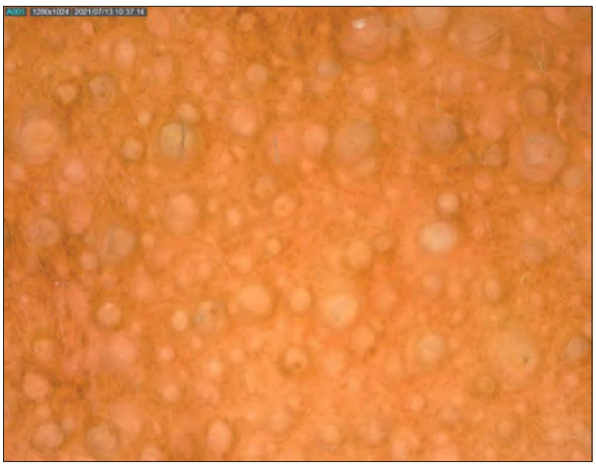


Figure 2: Whitish areas showing follicular plugging with bluegrey dots over a reddish brown background (dermoscopy, ×50)

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Figure 3: Follicular plugging, increased basal layer pigmentation with dermis showing minimal perivascular inflammatory infiltrate and vasodilatation (H and E, ×100)

patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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RESEARCH ARTICLE
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CRITICAL APPRAISAL OF DRUG PACKAGE INSERTS: A STUDY AMONG MEDICAL STUDENTS

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ABSTRACT

Background: Package inserts (PIs) are critical tools in drug labelling, offering evidence-based information to ensure the safe and effective use of medications. In India, the format and content of PIs are governed by the Drugs and Cosmetics Act (1940) and Rules (1945), specifically Schedule D, Sections 6.2 and 6.3. However, studies indicate inconsistencies in the completeness of PIs. Well-structured PIs also serve as practical learning tools for medical students. This study aimed to critically evaluate the clinical and pharmaceutical content of PIs marketed in India, using regulatory standards.
Methods: A cross-sectional study was conducted among 150 second-year medical students from a Government Medical College in Kerala, India. Each student assessed one PI using a standardized 34-item checklist based on regulatory guidelines and published literature. Each item was scored as present (1) or absent (0). Based on total scores, PIs were classified as Grade A (24–34), Grade B (13–23), or Grade C (0–12).
Results: Of the 150 PIs reviewed, only 62.67% used appropriate font size and 68% used proper font colour. Core content like generic name, dosage, and indications was present in all PIs. However, safety-related data such as ADR classification (45.33%), drug interactions (90.67%), and ADR reporting instructions (43.33%) were inconsistently reported. Among 40 injectable PIs, gaps were noted in incompatibility and storage data. Overall, 35 PIs were graded A, 53 as B, and 12 as C.
Conclusion: Significant variability in PI content highlights the need for improved standardization and regulatory oversight. Incorporating PI evaluation into medical training may enhance safe prescribing and drug literacy.

Keywords: Package Inserts, Regulatory Standards, Critical Evaluation, Medical Students.

INTRODUCTION

Drug labelling is an important aspect of pharmaceutical regulation and patient safety. It includes all printed information accompanying a medicine, such as the label, packaging, and the package insert (PI).[1] The PI is a key regulatory document that provides evidence-based information to facilitate the safe and effective use of medications. Also referred to as the prescription drug label or prescribing

information,[2,3] its content is based on current scientific data and is updated as new preclinical and clinical findings emerge.[4]

Regulatory requirements for PIs vary internationally. In India, the *Drugs and Cosmetics Act (1940)* and *Rules (1945)* govern PI content, particularly under Section 6 of Schedule D (II).[5,6] Section 6.2 mandates that PIs be written in English and include therapeutic indications, dosage, administration, contraindications, precautions, interactions, use in pregnancy and lactation, effects on machinery operation, adverse effects, and overdose management. Section 6.3 requires pharmaceutical details such as excipients, incompatibilities, shelf life, storage, container specifications, and usage instructions.[5,6]

Though primarily intended for registered medical practitioners, hospitals, and laboratories,[7] the law does not clearly indicate whether PIs are also meant for patients.[8] Nevertheless, their structured format makes them a reliable information source for healthcare providers.[9] In countries like India, with a doctor-to-patient ratio below the WHO-recommended 1:1000[10] and prevalent self-medication practices, accessible PIs are even more vital. High-quality PIs can reduce prescribing errors, which account for 29% to 56% of medical mistakes,[11] and help bridge communication gaps between providers and patients.[8,12]

PIs also serve as valuable educational tools for medical students, offering concise information on drug properties that align closely with the pharmacology curriculum. Access to standardized, real-world drug information enhances their clinical competence, supports rational prescribing, and fosters independent learning. Despite regulatory frameworks, prior studies suggest inconsistencies in the quality and completeness of PIs in India.[13-15] Against this backdrop, the present study was conducted to critically appraise the clinical and pharmaceutical content of PIs available in the Indian market, based on regulatory guidelines, with evaluations carried out by medical students.

MATERIALS AND METHODS

This was a cross-sectional, questionnaire-based study conducted among 150 second-year medical students from a Government Medical College in Kerala, India. All participants had successfully completed their pharmacology examinations at the time of enrolment, ensuring a foundational understanding of drug-related information. The study was conducted over a period of two months, from August to September 2020, following approval from the Institutional Review Board (IRB) and the Institutional Ethics Committee. The objectives and procedures of the study were clearly explained to all participants, and written informed consent was obtained in accordance with ethical research standards.

Study Procedure

The research was conducted during Pharmacology Practical Sessions held over three consecutive days. During these sessions, the Principal Investigator delivered an educational lecture on the importance of Package Inserts (PIs) and guided students on how to critically evaluate their contents. After the lecture, each participant received one PI from a pool of inserts collected from local pharmacies. A total of 150 PIs, all printed in English, were included. These encompassed a range of dosage forms, including 110 oral and 40 injectable preparations, across various therapeutic categories, such as antidiabetics, antibiotics, antihypertensives, antimalarials, hormonal agents, antihistamines, antiemetics, and analgesics. The PIs belong to various Indian pharmaceutical companies.

Exclusion Criteria for PIs Included

- Inserts from Ayurvedic or traditional medicine products
- Duplicate inserts from the same brand
- Inserts printed solely in regional languages

However, PIs printed in both English and a regional Indian language were accepted for inclusion.

Evaluation and Scoring Criteria

Prior to distribution of PIs, all participants were briefed on the objectives and methodology of the critical appraisal exercise. All 150 students who provided informed consent were included in the study. Each student was then instructed to critically evaluate a single PI using a standardized proforma, which was formulated in accordance with the Drugs and Cosmetics Rules, 1945 (Schedule D, Sections 6.2 and 6.3), and supplemented with parameters from previously published literature. Using this comprehensive 34-item checklist, participants were required to assess both the completeness and clarity of the information provided in the PI. In cases where a specific heading was absent, the insert was carefully reviewed to determine whether the relevant information was included under a different section or heading.

The following parameters were considered during the detailed assessment of each PI:

- Presence of mandatory headings as per Section 6.2, including: Therapeutic indications, posology and method of administration, contraindications, special warnings and precautions, drug interactions, use during pregnancy and lactation, undesirable effects, and antidote for overdose
- Inclusion of pharmaceutical data required under Section 6.3, such as:List of excipients, known incompatibilities, shelf life, special storage conditions, container description, and instructions for use and handling
- Evaluation of the uniformity, accuracy, and clarity of information presented under each heading
- Legibility of the PI, assessed in terms of font size and font colour

Upon completion of the appraisal, the responses from these students were reviewed for completeness and included in the final statistical analysis. Grading of PIs was also carried out. For that each checklist item was scored in a binary format: a score of '1' was awarded if the required information was present, and '0' if it was absent. The maximum possible score for a complete PI was 34. Based on the total score, PIs were classified into three quality grades:

- Grade A (Good Quality): Total score between 24 and 34
- Grade B (Moderate Quality): Total score between 13 and 23
- Grade C (Poor Quality): Total score between 0 and 12

This grading system enabled a standardized assessment of the completeness and quality of PI content and facilitated the identification of deficiencies and variations in regulatory compliance.

RESULTS

Following the critical evaluation of 150 package inserts (PIs) by the participants, it was observed that only 94 (62.67%) of the PIs employed an appropriate font size, and 102 (68%) used a suitable font colour, indicating that a considerable number failed to meet basic standards for visual accessibility. Furthermore, the lack of a standardized format and inconsistent ordering of headings impeded the convenient retrieval of specific information, adding to user difficulty. The analysis revealed that certain core elements were consistently included in all PIs. Specifically, the generic name of the active ingredients, composition of ingredients, dosage form, posology and method of administration, and therapeutic indications were present in all 150 (100%) inserts.

Moreover, critical safety-related information such as contraindications were present in 148 (98.67%), undesirable effects / ADRs were included in 143 (95.33%), special warnings and precautions were found in 140 (93.33%), use of that particular during pregnancy and lactation was documented in 143 (95.33%) and name and address of the manufacturer were stated in 147 (98%). However, some essential components were less consistently reported.

For instance, drug interactions which are crucial for preventing adverse drug events were mentioned only in 136 (90.67%) of PIs. Information on retail price was mentioned in 131 (87.33%), pharmacokinetic and pharmacodynamic properties were detailed in 122 (81.33%), overdosage management was specified in 127 (84.67%), paediatric and geriatric indications were included in 125 (83.33%), provision for obtaining full information on request was highlighted in 121 (80.67%) and storage information was present in 112 (74.67%).

Several vital safety parameters were poorly represented. These include timing of drug intake in relation to meals was found in 98 (65.33%),effect on ability to drive or use machines was mentioned

in 76 (50.67%), ADR classification based on organ/system/class was present in 68 (45.33%), measures to be taken in case of ADR were specified in 68 (45.33%), instructions for reporting suspected ADRs were found in 65 (43.33%) and date of last update was mentioned in only 61 (40.67%).

Other sparsely documented elements included: contact details for the Pharmacovigilance Programme of India (PvPI) specified only in 56 (37.33%), qualitative frequency statements (e.g., common, rare) given only in 56 (37.33%) and guidance on missed doses specified only in 56 (37.33%).

Among the 150 PIs evaluated, 40 belong to injectable drug formulations. Within this subgroup, important data such as shelf life were mentioned in 37 (92.50%), instructions for use and handling described in 35 (87.50%), list of excipients given in 33 (82.50%), description of the container found in 31 (77.50%), incompatibilities mentioned in 29 (72.50%) and special storage precautions were found in 27 (67.50%). These findings highlight important gaps, particularly in the documentation necessary for the safe administration and storage of injectable medications. Table 1 and 2, below summarizes the percentage of PIs in which each type of information was present.

Sl. No.	Headings in the Package Inserts	Present	Percentage	Absent	Percentage
1	Legibility- Appropriate font size	94	62.67%	56	37.33%
2	Legibility- Appropriate font colour	102	68.00%	48	32.00%
3	Approved generic name of active ingredients	150	100.00%	0	0.00%
4	Composition of ingredients	150	100.00%	0	0.00%
5	Dosage form	150	100.00%	0	0.00%
6	Posology and methods of administration	150	100.00%	0	0.00%
7	Therapeutic indications	150	100.00%	0	0.00%
8	Contraindications	148	98.67%	2	1.33%
9	Special warnings and precautions	140	93.33%	10	6.67%
10	Maximum dose of drug is mentioned	116	77.33%	34	22.67%
11	Drug interactions	136	90.67%	14	9.33%
12	Pregnancy and lactation	143	95.33%	7	4.67%
13	Pediatric and geriatric indications	125	83.33%	25	16.67%
14	Effect on ability to drive and use machines	76	50.67%	74	49.33%
15	Undesirable effects	143	95.33%	7	4.67%
16	Pharmacological Properties- Pharmacokinetic and Pharmacodynamic properties	122	81.33%	28	18.67%
17	Special conditions and contraindications	124	82.67%	26	17.33%
18	Over dosage	127	84.67%	23	15.33%
19	Storage information	112	74.67%	38	25.33%
20	Instruction for use and handling	62	41.33%	88	58.67%
22	Date on which information was last updated	61	40.67%	89	59.33%
23	Name and address of manufacturer/distributor	147	98.00%	3	2.00%
24	Provision of full information on request should be highlighted	121	80.67%	29	19.33%
25	Retail price of the drug	131	87.33%	19	12.67%
26	References	56	37.33%	94	62.67%
27	Provides information on when to take the drug-(before/after/with meals)	98	65.33%	52	34.67%
28	Provides information on what to do if doses are missed	56	37.33%	94	62.67%
29	ADR classified based on organ system classes	68	45.33%	82	54.67%

30	Provides qualitative statements on frequency of side effects(rare/common)	56	37.33%	94	62.67%
31	Verbal frequency terms are explained in the form of natural frequencies (eg very common-more than 1 in 10 patients)	56	37.33%	94	62.67%
32	Describe suitable measures in case of ADR	68	45.33%	82	54.67%
33	Details on Reporting suspected ADR	65	43.33%	85	56.67%
34	Contact number of PvPI is given	56	37.33%	94	62.67%

Table 1: Presence of Key Information in Evaluated Package Inserts (n = 150)

	Headings in the Package Inserts	**Present**	**Percentage**
1	List of excipients	33	82.50%
2	Incompatabilities	29	72.50%
3	Shelf life	37	92.50%
4	Special precaution for storage	27	67.50%
5	Nature and contents of container	31	77.50%
6	Instruction for use and handling	35	87.50%

Table 2: Subgroup: Injectable Formulations (n = 40)

In addition to the qualitative evaluation, each Package Insert (PI) was subjected to a quantitative scoring and grading process based on a standardized checklist. Each item on the checklist was evaluated using a binary scoring system: a score of '1' was assigned if the required information was present, and '0' if it was absent. The maximum attainable score for a complete PI was 34. Based on the total score, PIs were classified into three quality grades to facilitate interpretation and comparison. Of the 150 PIs evaluated, 36.66% were classified as Grade A (high quality), 48.66% as Grade B (moderate quality), and 14.66% as Grade C (poor quality). This grading system provided a standardized assessment of the completeness and quality of PI content and helped identify deficiencies and inconsistencies in adherence to regulatory standards.[15]

Grade	**Score**	**Number**
Grade A	Score (24-34)	55 (36.66%)
Grade B	Score (13-33)	73 (48.66%)
Grade C	Score (0-12)	22 (14.66%)

Table 3: Scoring of Package Inserts (n = 150)

DISCUSSION

The present study critically evaluated the content and presentation of 150 package inserts (PIs) from the Indian pharmaceutical market using a 34-item structured checklist, focusing on readability, completeness of information, and regulatory compliance. The findings indicate that while core clinical information was generally well-represented, several patient-relevant and safety-related elements were frequently missing.

Essential information such as the generic name, composition, dosage form, posology, and therapeutic indications was present in 100% of the PIs, aligning with findings from Indian studies by Shivkar et al. (2009) and Barkondaj et al. (2020).[15,16] Similarly, contraindications (98.67%) and warnings and precautions (93.33%) were widely included, reflecting adherence to regulatory requirements for clinical content.

However, only 62.67% and 68% of PIs adhered to readability standards such as appropriate font size and colour, respectively. These findings mirror earlier observations by Shivkar et al.[15] Dickinson et al.[17] and Momin et al.[18] who highlighted poor formatting and the negative impact of small fonts on comprehension.

Information related to special populations was suboptimal, such as data on drug use in paediatric and geriatric populations appeared in only 83.33% of PIs, and guidance for hepatic or renal impairment in 82.67%. Shivkar et al. also noted similar gaps in PIs, which may compromise rational prescribing in vulnerable groups.[15]

Pharmacokinetic and pharmacodynamic data were included in 81.33% of PIs, overdosage management in 84.67%, and storage instructions in 84.00%, all of which are crucial for clinical safety. Comparable deficiencies have been reported by Ganguly et al.[19]

Several safety and usability parameters were inadequately addressed: only 50.67% included warnings about operating machinery or driving, 41.33% offered instructions for use and handling, and only 40.67% specified the date of the last update. Just 37.33% cited references to support the clinical content. These omissions align with findings from Shivkar et al.[15] and Ganguly et al.[19] raising concerns about accuracy and relevance.

Patient-oriented content was also lacking: only 37.33% addressed actions for missed doses, 65.33% guided food intake timing, and 37.33% used natural frequency descriptors for side effects. Thakkar et al.[20] similarly reported poor inclusion of patient-friendly information in Indian PIs.

Adverse Drug Reaction (ADR) communication was particularly deficient. Only 45.33% included ADR classification, 43.33% provided reporting instructions, and just 37.33% mentioned contact details for the Pharmacovigilance Programme of India (PvPI). Thakkar et al.[20] and Ganguly et al.[19] noted similar inadequacies, highlighting the need for improved pharmacovigilance content.

Formatting inconsistencies were another significant issue. Variations in the organization of headings and sequence of information hinder efficient use by healthcare professionals. Shivkar et al.[15] and Ganguly et al.[19] identified such structural inconsistencies as barriers to usability. Adopting international formatting standards, such as those used by the European Medicines Agency (EMA) or US FDA, could enhance readability and reliability.

While previous studies have reported that complex medical language in PIs impedes patient understanding,[15,20] this was not a limitation in our study, as the assessment was performed by medical students. Nevertheless, these findings highlight the need for dual-format PIs-one for healthcare professionals and another simplified version for patients.

In summary, while the inclusion of essential clinical content is encouraging, the overall effectiveness of Indian PIs is compromised by inadequate readability, patient-centeredness, and omission of key safety information. These concerns echo those raised in previous studies by Shivkar et al.[15] Thakkar et al.[20] and Ganguly et al.[19] To address this gap, regulatory authorities must enforce standardized, comprehensive, and patient-friendly guidelines for PI design. Aligning Indian PIs with global best practices could significantly enhance their utility in ensuring safe and rational drug use.

Limitations

This study has a few limitations that should be considered when interpreting the results. First, the analysis was based on a sample of 150 package inserts (PIs) obtained from a specific region, which may not fully represent the quality of all PIs marketed across India. Second, although a structured checklist was used to maintain uniformity, certain elements such as legibility and patient-centeredness involved subjective evaluation, potentially introducing variability in interpretation. Third, the study provides a cross-sectional assessment of PIs at a single point in time and does not reflect any updates or improvements made subsequently by manufacturers.

CONCLUSION

The present study reveals significant gaps in the content and presentation of drug package inserts (PIs) marketed in India. While essential pharmacological information such as composition, dosage, and therapeutic indications were consistently included, critical aspects related to patient safety, readability, and regulatory compliance were often missing or inadequately addressed. Key deficiencies included poor legibility, absence of patient-oriented guidance (e.g., missed doses, food interactions), lack of adverse drug reaction (ADR) reporting information, and inconsistent formatting. Furthermore, the limited inclusion of update dates and clinical references raises concerns about the accuracy and

reliability of the data presented. These findings underscore the need for uniform formatting standards, improved patient-focused content, and stricter regulatory enforcement to enhance the utility of PIs as effective tools for both healthcare providers and patients. Aligning PI design with global best practices could significantly contribute to safer and more informed drug use in India.

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A CROSS-SECTIONAL STUDY COMPARING THE KNOWLEDGE OF ESSENTIAL MEDICINES AMONG UNDER GRADUATE MEDICAL STUDENTS OF A TERTIARY CARE TEACHING HOSPITAL

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Abstract

Background: Essential medicine list of a country covers the drugs used for the treatment of prevalent diseases and commonly used drugs. The latest update of the National list of essential medicines of India was done in the year 2022. The competency based medical education in India envisages the Indian medical graduate to demonstrate the ability to prescribe therapies based on the principles of rational drug therapy, scientific validity, evidence, andcost.It is crucial for the Indian medical graduate to acquire knowledge on essential medicines asthey ensure safe and cost-effective treatment. This study evaluates and compares the knowledge of essential medicines among undergraduate medical students of MBBS (Bachelor of Medicine, Bachelor of Surgery) course.

Materials and method: 250 undergraduate medical students, 125 each from phase II and phase III of MBBS course were randomly selected for the study. A revalidated questionnaire consisting of multiple-choice questions was distributed among the students and collected after filling. Analysis was done based on the points scored by each student.

Results: Among the 250 students participated,3 % do not know the concept of essential medicines and 2 % are not sure about their understanding of essential medicines concept. The response to questionnaire showed that 20 % of students scored below 50 % points. The analysis proveda statistically significant difference in knowledge of essential medicines between phase II and phase III MBBS students.

Conclusion: The Knowledge of essential medicines among MBBS students are limited. The students of Phase III MBBS course had more knowledge on essential medicines compared to the students who had completed phase II MBBS.

Key words: Essential medicines, knowledge, MBBS, drugs,

Introduction

Essential medicines are those that satisfy the priority health care needs of the population. They are intended to be available within the context of functional health systems at all times, in appropriate dosage forms of assured quality and at prices that individuals and communities can afford. Essential

medicines are listed by governments to ensure optimum usage of these well tested and cheaper medicines which are efficacious and safe[1]. The World Health Organisation publishes a model Lists of Essential Medicines which serve as a guide for the development and updating of national and institutional essential medicine lists to support the procurement and supply of medicines in the public sector, reimbursement schemes, donations, and local medicine production[2]. A medical graduate should be capable of treating common diseases and emergency cases. As part of this, a young graduate should have thorough knowledge in the pharmacology of drugs used for routine treatment and in emergency conditions. They should be able to discuss and describe about types, mechanism of action, doses, adverse drug reactions, drug interactions, indications and contraindications of drugs. Drug is any substance or product that is used or is intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient.[3] Some of the Essential drugs are Adrenaline, Atropine, Amiodarone, Diazepam, Calcium gluconate, Lignocaine, Dopamine, Insulin, Lorazepam, Morphine, Frusemide, Salbutamol, Ondansetron and Hydrocortisone. Current National List of Essential Medicines (NLEM) of India which was revised in the year 2022 contains 384 Medicines. NLEMhelps to provide quality medical care, rational drug use and cost-effective treatment options[4]. It is important to ensure that students have proper knowledge about drugs, which instils in them the confidence to put the theory in to practice, when they study disease and treat patients in their future practice.The competency based medical education in India intends to prepare the medical students to provide health care to the evolving needs of the nation and the world.A medical student should have the knowledge about essential and commonly used drugs and should understand the Pharmacologic basis of therapeutics[5].

The competency based medical education in India divides MBBS courses in to 3 phases. Phase I, IIand III over a duration of 4.5 years. The medical students learn Pharmacology in the phase II along with other paraclinical subjects and clinical postings. The 30-month phase III includes clinical postings and learning of clinical subjects[5]. The students get acquainted with medical conditions and drugs as they advance in their course, and they should apply their knowledge of essential medicines while learning as it promotes rational prescription.The student who has completed Phase III will continue with compulsory rotatory medical internship.The study aims to evaluate and compare the knowledge of MBBS students about the knowledge of essential medicines based on phase of study.

Materials and methods

This cross-sectional comparative study was conducted among 250 medical students who have completed Phase II and Phase III of MBBS course in Government Medical College Thrissur.The study was conducted in the Department of Pharmacology, Government Medical College Thrissur, From 16th December 2024 to 16thApril 2025 after getting approval from Institutional Ethics Committee and institutional research committee. A written informed consent was obtained from the study participants. The students not willing to participatewere excluded from the study. Confidentiality and anonymity of the participants information were maintained throughout the study.

Study procedure

A questionnairewith 30 multiple-choice questions was distributed among 175 Phase II and 175 phase III MBBS students. 125 completed forms from Phase II students and 125 Phase III completed MBBS studentswereselected randomlyaccording to the inclusion and exclusion criteria. The incomplete and partially filled responses were excluded. The students were evaluated by the points scored from thequestionnaire.Total points were 30 with each correct response to the question carried one point. The questionnaire was validated by the department of Pharmacology, Thrissur government Medical College. The National List of Essential Medicines of India 2022 was referred to select the drugs and all questions on these drugs were selected fromEssentials of medical Pharmacology K D Tripathi, which is one of the textbooks prescribed by the Kerala University of Health Sciences for undergraduates.

Data analysis:
Data was collected, coded and entered in Microsoft excel and analysed using SPSS statistical software**.** The knowledge of essential drugs between Phase II and phase III students wereanalysed by independent t test.

Results
Among the 250 students,126 were females and 124 were males (Table 1). 3 % of the total 250 students did not know the concept of essential medicines and 2%were not sure about their understanding of the concept of essential medicines.Out of the total 30 points on knowledge of essential medicine drugs,20 % students scored less than 15 points, 39.6% scored 16-20 points, 29.6% scored 21-25 points and 10.8% scored 25-30 points (Table.2). The students in both groups were divided into two categories, where high knowledge group includes students with more than or equal to 50% points and low knowledge category has students with less than 50% points. The low knowledge category constitutes 20 per cent of total 250 students of which a higher proportion (66%) of phase IIcompleted studentsthan phase III completed students (34%). Also,low knowledge category has a higher proportion of male students (56%) (Table. 3) (table 4).
The mean points scoredout of the total 30 points on knowledge of essential drugs for Phase II completed students was 18.70 ± 3.97 whereas the score for Phase IIIcompleted students was 20.25 ± 4.07. The Analysis of knowledge of essential medicines of Phase II completed and phase III completed students proves that there is a statistically significant difference on knowledge of essential drugs between students of different phases of study with t value 3.056 and p value 0.002. The students who had completed phase III have a higher mean score compared to the students who have completed phase II. This shows students gain moreknowledge about essential drugs as they complete phase III. The mean points out of 30 points on knowledge of essential drugs for female students is19.36 ± 4.02 and male students is 19.58 ± 4.16. The analysis of knowledge on essential medicines of male students and female students showed there is no statistically significant difference between them with t value 4.19 and p value 0.676 (table 5).

Discussion
The practise of adhering to essential medicine list for treatment allows the people of every country to access affordable medical treatment, which leadsto better health outcomes. To ensure rational prescribing every medical graduate should have adequate knowledge on essential medicines of their region. Poor learning in clinical pharmacology and therapeutics during the undergraduate medical curriculum may underlie the lack of prescribing competencies among recent graduates[6]. Learning is a lifelong process for a doctor but it is also important to know how much knowledge about drugs they have imbibed during their MBBS course so that it can be used in future for academic policy purposes in medical pharmacology.In this study, we had compared and evaluated the knowledge of MBBS students about pharmacology of Essential Medicines

Evaluation of knowledge of essential medicine drugs among MBBS students
The concept of essential medicines was known to the majority (95%) of the students. A study done by Jani C K et al[7] showed a similar finding where 75.1% were able to define the NLEM.The knowledge of essential medicine assessed by pointsscored out of 30 revealed that 20% of 250 students scored less than 15 points, 69.2 % scored 16-25 points and 10.8 % scored 25-30 points. 20% of the students have less than 50% score on knowledge of essential medicines.This data showed that knowledge on essential medicine drugs among MBBS students is inadequate and the concept of essential medicine and the drugs in essential medicine list must be taught separately to the students emphasising their due importance. The limited knowledge of essential medicines among medical interns was reported by studies done by Hooli T V et al[8] and Hanumaiah V et al[9] and the need for regular training on essential medicines is emphasised by Sakshi Singh et al.[10]

Comparison of Knowledge of essential medicine drugs between Phase II and Phase III MBBS students

The study also proved there was difference in the knowledge of essential medicines among phase II MBBS students and Phase III MBBS students with t value 3.056 and p value 0.002. The phase III students with mean score of 20.25±4.07 out of 30 have higher knowledge on essential medicines compared to phase II with mean score of 18.70±3.97out of 30. This explicates that students become more familiar with essential drugs as they progress in their course.

These results were comparable with studies done by Tank SY et al[11]and Surendra KV et al[12].In a study by Brinkman, David J et al,there was considerable evidence that final-year medical students have insufficient prescribing competencies, and it was needed to ensure that medical students prescribe safely and effectively.[13]Thus,the study emphasises the importance to introduce awareness sessions on essential drugs in order to increase the knowledge of essential drugs during the last part of the MBBS course in order to promote rational drug therapy.

Conclusion

The current study proved that theKnowledge of essential medicine among MBBS students is not satisfactory. The phase III completed MBBS students who were at the final stage of the MBBS course had more knowledge of essential medicines compared to phase II completed students.Students during the later stages of MBBS course getmore acquainted with practical aspects of drug therapy.The study suggests that it will be beneficial if an awareness session on Pharmacology of essential medicine drugs is included in the last part of MBBS programme.

Limitations

The study was carried out in one centre.

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Conflict of interest

No conflict of interest declared.

Table.1 Distribution of students based on gender and phase of study

Gender	Phase I(group1)	Phase II (group 2)	Total
Male	63	63	126
Female	62	62	124
Total	125	125	250

Source: primary data

Table.2 The Knowledge of Essential medicines Among MBBS students on Essential medicines

Points	No of students	Percentage
≥15	50	20
16-20	99	39.6
21-25	74	29.6
26-30	27	10.8
Total	250	100

Source: primary data

Table.3 Knowledge of Essential Medicine Among Male and Female Medical Students

Category	Low Knowledge students (20%)	High knowledge students (80%)
Male	28(56%)	98(49%)
Female	22(44%)	102(51%)
Total	50	200

Low knowledge<15 points out of 30, high knowledge≥15 points out of 30
Source: primary data

Table.4 Knowledge of Essential Medicine Among Phase II and Phase III Medical Students

	Category	Low Knowledge students (20%)	High knowledge students (80%)
Phase completed	Phase II	33(66%)	92(46%)
	Phase III	17(34%)	108(54%)
	Total	50(100%)	200(100%)

Source: Primary date

Table.5 Comparison of knowledge of essential medicine based on Phase of study and Batch

		N	Mean score (30)	Std Deviation	t value	P value
Phase of study completed	Phase II	125	18.70	3.97	3.056	0.002
	Phase III	125	20.25	4.07		
Gender	Female	124	19.36	4.02	4.19	0.676
	Male	126	19.58	4.16		

Source: Primary data

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RESEARCH ARTICLE
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CUTANEOUS ADVERSE DRUG REACTIONS AMONG PATIENTS IN DEPARTMENT OF DERMATOLOGY IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Background

Skin is one of the major organ for adverse reactions. Cutaneous adverse drug reactions (CADRs) are the most common type of adverse drug reaction and the clinical presentation varies (incidence is 2-5%). They are mistaken for signs of underlying disease, resulting in unnecessary investigations and delay in treatment. The treatment of ADRs increases the costs of patient care. [1-5] So awareness about them was found to be essential for early detection and prevention. This study aimed to find the proportion of CADRs, causality, severity, preventability and drugs producing it in a tertiary care hospital.

Methods

A cross-sectional study was conducted among 160 patients attended in the outpatient department, who had a history of drug intake within a period of 1 week, in the department of Dermatology in a tertiary care hospital Kerala India. Only 40 (25%) patients had cutaneous ADRs. All the relevant information was recorded in the CDSCO[3] suspected adverse drug reaction reporting form by the Dermatologist was collected and analysed. Causality was assessed using Naranjo Algorithm.[6] Severity was assessed by Modified Hartwig and Siegel Scale.[7] The preventability was assessed using Modified Schumock and Thornton scale.[8] Data were analysed using descriptive statistics.

Results

In the present study, out of 40 patients with cutaneous ADR, the highest incidence of cutaneous ADRs was in the age group of 41 -50 years (23%), and more frequently in male patients (52.5 %). Antimicrobials were the most commonly implicated drugs (55%) followed by Non-Steroidal Anti-inflammatory drugs (NSAIDs) (28%) and anti-epileptics (5%). The most commonly observed morphological pattern was maculopapular rash (22.5%) followed by fixed drug eruptions (12.5%) and 5% had Steven Johnson Syndrome. 32.5% cases had concomitant medicines. Causality assessment was certain, probable and possible for 0%, 25% and 75% of the reactions respectively.

One case was of level 5 severity, 37 cases of mild (level 2) severities and two cases of moderate (level 4) severity. 97.5 % cases were not preventable and 2.5% cases was probably preventable.

Conclusion

Antimicrobials were the culprit drugs for most of the cutaneous adverse reactions followed by NSAIDs**.** Identification and timely reporting of cutaneous adverse drug reactions reduces their future occurrences and encourages rational prescribing and reduces the cost of healthcare.

Keywords: CADRs (Cutaneous ADRs), Causality, Preventability, Severity-Assessment, Fixed Drug Eruption (FDE)

INTRODUCTION

Adverse drug reaction is any noxious change which is suspected to be due to drug, occurs at doses normally used in humans for prophylaxis, diagnosis, treatment of disease or for modification of physiological function (WHO definition).[1-5] Adverse drug reactions cause death in 0.1% of medical and 0.01 % of surgical patients and adversely affect the quality of life. They are mistaken for signs of underlying disease, resulting in unnecessary investigations and delay in treatment. Moreover treatment of ADRs increases the costs of patient care. Cutaneous drug eruptions are the most common type of adverse reactions to drug therapy, with an incidence rate of 2–6%**.**[4,9] Cutaneous Adverse Drug Reaction (CADR) is defined as any undesirable change in the structure or function of the skin, its appendages, or mucous membranes, and it encompasses all adverse events related to the drugs, regardless of the etiology.[5] The clinical presentation of drug related cutaneous reactions ranges from mild rash to severe rash besides causing life-threatening reactions. Cutaneous drug reaction is suspected in any patient who is currently taking any medicine or recently been exposed to any medicine including the prescribed and over-the-counter medicines, herbal or homoeopathic preparations, vaccines or contrast media. In some patients non-drug components of a medicine, i.e. the pharmaceutical excipients may also cause hypersensitivity reactions like cutaneous drug eruptions. Incidence of CADRs in developed countries ranges from 1 to 3% among in-patients.[10] In developing countries such as India, it is 2–5% among in-patients and 2.6% in the out-patient setting.[11-13] The healthcare system can promote the spontaneous reporting of dermatological ADR to Pharmacovigilance centre's for ensuring safe drug use and patient care.

Different studies show variation in the data based on presentation of cutaneous drug reaction, its distribution amongst both sexes, the offending drug and causality assessment. This study was done to find the proportion of cutaneous adverse drug reactions in patients attending the department of Dermatology and describe the cutaneous ADR profile of different groups of drugs, causality of drug induced skin reactions by using Naranjo's algorithm.[6] describe the severity and preventability of adverse drug reactions by using Modified Hartwig and Seigel scale [7] and Modified Schumock and Thornton scale.[8]

MATERIALS AND METHODS

This was a cross-sectional study conducted among 160 patients in the outpatient department of Dermatology, in a tertiary care hospital Kerala. Details of all the patients of either sex, had a history of drug intake within a period of 1week, were included in the study. The study was conducted over a period of 6 months.

Exclusion Criteria

Incomplete ADR forms

Study Procedure

After obtaining IRC and IEC approval for the study, CDSCO-ADR reporting form filled and reported by the Dermatologist was collected and analyzed. All the details regarding patient's basic data like age, gender, present illness, past medical history, co-morbidities, concomitant medications, lab data, details of the drugs suspected to be causing ADR and the details of cutaneous reactions etc.

were recorded in the *ADR reporting form by the Dermatologist*. Re-challenge was not attempted due to associated risks and ethical concerns. The collected data were analysed for demographic details, drug details, causality, preventability, and severity of adverse effects. Causality was assessed by using Naranjo's Algorithm,[6] preventability by Schumock and Thornton scale[8] and severity by modified Hartwig scale.[7]

Ethical policy and Institutional Review board statement

The study was conducted in the department of Dermatology government medical college Kollam after getting IRC clearance (No.004/2018 GMCKLM dated 28/05/2018) and IEC CLEARANCE (IEC No.006/2018/GMCKLM Dated 07/06/2018)

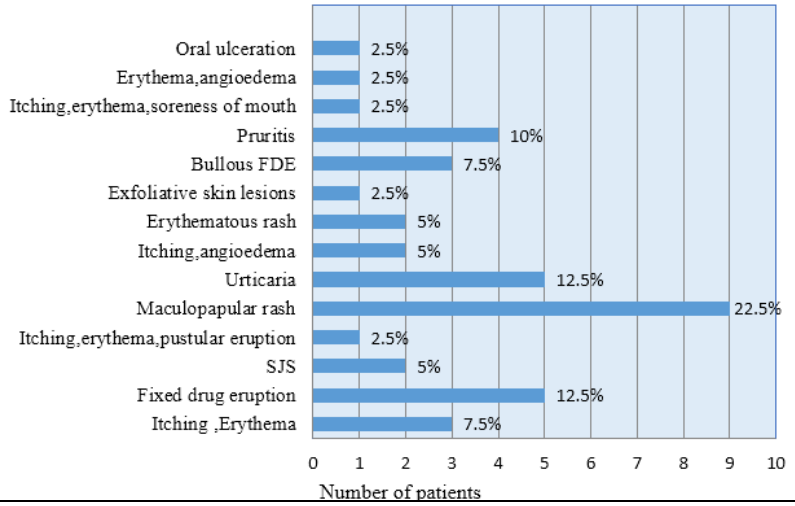
Statistical Analysis

The data were sorted, coded, and entered into Statistical Package for the Social Science (SPSS) and subsequently analysed. Variables like gender, type of CADR, causative drugs, causality, severity, preventability, and final outcome were expressed as frequency and percentage.

RESULTS

A total of 160 patients with a recent history of drug intake were enrolled in the present study. Only 40 (25%) patients had cutaneous ADRs. Majority of cases, i.e., 9 (23%) were in the age group of 41 -50 years followed by 8(20 %) in age group of 51 to 60 & 61 to 70 years and the lowest number of one case was in the age group 80years & above. In the present study, males (52.5%) were more frequently affected than females (47.5%). Out of 40 patients with cutaneous ADRs, only 3 (7.5%) patients had a positive history of previous cutaneous adverse drug reactions. Maculopapular rash was the most frequently observed morphological pattern in (22.5%) patients, followed by urticaria similar to the findings in the study.[4,5,10,13] and FDE in 5 (12.5%) patients, pruritus 4 (10%), SJS in two (5%) and were referred to higher centre.

Figure 1--Spectrum of CADRs



The common groups of drugs associated with CADRs include antimicrobials followed by NSAIDs, Antiepileptics, similar to the studies[4,5,10,13] anti-rheumatoid, anti-hypertensives and topical agents.

Drug Class	Drugs	n (%)
Antimicrobials	Amoxicillin clavulanic acid (6), Azithromycin (3), Ciprofloxacin(2),Fluconazole(2),Cloxacillin (2) , Levofloxacin(1) Ampicillin- cloxacillin(1), Doxycycline(1) Metronidazole(1) HRZE (1) Amoxicillin(1), Terbinafine (1)	22(55)
NSAIDs	Paracetamol(5),Diclofenac (4) Naproxen (1), Etoricoxib (1)	11(27.5)
Anticonvulsants	Phenytoin(1),Valproic acid(1)	2(5)
Antirheumatiod	HCQ+Sufasalazine(1)	1(2.5)
Antihypertensive	Enalapril(1)	1(2.5)
Immunomodulator	Lenalidomide(1)	1(2.5)
Topical agents	Azelaic acid+Tretinoin cream(1)glycerine magsulf(1)	2(5)
Table 1: Top drug classes causing CADRS with drugs –		

CADRs	Top Drugs	n (%)
Maculopapular rash	Azithromycin(2), Amoxicillin(2), Paracetamol(2), Levofloxacin(1)	11(22.5)
Urticaria	Amoxicillin clavulanic acid(2),Diclofenac (2)	5(12.5%)
Fixed drug eruptions	Fluconazole(2),Amoxicillin clavulanic acid (1), Doxycycline (1) , Diclofenac (1)	5(12.5%)
Pruritus	Ciprofloxacin(1),Azithromycin(1)	4(10)
SJS	Levofloxacin(1),Amoxicillin(1)	2(5)
Table 2: CADRs with drugs		

The maximum cutaneous ADRs, i.e., 32 (80%) occurred in the lag period of 2-7 days followed by 8 (20%) in less than 2 days. After the causality assessment of cutaneous ADRs as per Naranjo Algorithm, majority of cases, i.e., ten (25%) cases as probable and 30 (75%) were categorized as possible. As per Hartwig severity scale, One case was of level 5 severity, 37 cases of mild (level 2)severity and two cases of moderate (level 4) severity. The preventability was assessed using Modified Schumock and Thornton scale. 97.5 % cases were not preventable and 2.5% cases was probably preventable.

Causality	n (%)
Certain	0
Probable	10 (25)
Possible	30 (75)
Severity	
Mild	37 (92.5)
Moderate	2 (5)
Severe	1 (2.5)
Preventability	
Definitely preventable	0
Probably preventable	1 (2.5)
Not preventable	39 (97.5)
Table 3: Causality , severity and preventability	

Outcome	n (%)
Lost to follow up	2
Continuing	0
Recovering	0
Recovered	38
Table 4: Outcome	

DISCUSSION

This study included 40 patients with cutaneous ADRs, were the maximum number of patients from the age group of 41-50 years. The males in our study outnumbered the females. Most of the male patients had concomitant medicines than females. Only 3(7.5%) patients had a previous history of cutaneous ADRs to drugs. The most common cutaneous ADRs recorded were maculopapular rash followed by urticaria & fixed drug eruptions, followed by pruritus, bullous FDE, erythematous rash and Steven Johnson syndrome. The most common incriminating drug class was of antimicrobials (55%) and NSAIDs (28%).[4,5] The maximum numbers of cutaneous ADRs were induced by amoxicillin clavulanic acid (maculopapular rash, angioedema, urticaria, rash, FDE) similar to findings in studies.[9,12,14-16] Most of the cases were managed symptomatically by stopping the drugs. After Causality assessment, the implicated drug was found to be a probable cause in 25% of patients, possible in 75 % of patients. The assessment might vary with the type of scales used for the assessment of ADRs in different regions. Out of total 40 cases of cutaneous ADRs, maximum cases, i.e., 37 were of mild severities, 2 cases of moderate (level 4) and one case of severe (level 5) severities.

Limitation

This study was conducted in a single centre. Patients who developed ADRs in the hospital may not be truly reflective of the whole population. Most of the non-serious cutaneous ADRs were managed in the casualty itself. Causality assessment had some uncertainty in patients with multiple drugs, especially rechallenge was not attempted due to ethical reasons. Long-term follow-up and monitoring of the patients could not be done. There is also the problem of underreporting of mild and self-limiting cases.

CONCLUSION

CADR are common among ADRs with a reporting rate of 25%. Antibiotics contributed more to the ADRs followed by Non-steroidal anti-inflammatory drugs (NSAIDs). Most of the reactions were of mild to moderate severity and were managed symptomatically. Pharmacovigilance awareness programs should be conducted among various levels of health-care professionals to enhance the impact of understanding and timely reporting of ADRs. A careful history taking and rational prescription of drugs can prevent most of the reactions.

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Section: Miscellaneous

Original Research Article

IGURATIMOD: A NOVEL SMALL MOLECULE DISEASE-MODIFYING ANTIRHEUMATIC DRUG FOR SEROPOSITIVE RHEUMATOID ARTHRITIS-A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background: Rheumatoid arthritis (RA), is a chronic systemic inflammatory autoimmune disease. A seropositive patient has either rheumatoid factor (RA factor) or Anti-Cyclic- Citrullinated-Peptide (Anti CCP) or both in blood. They require intensive treatment approaches. Iguratimod-a new small molecule antirheumatic drug. Combined treatment with Iguratimod with Methotrexate was shown to yield result in reducing disease activity. **Objective:** To assess the effectiveness and safety of Iguratimod co-administered with Methotrexate in DMARD naive seropositive rheumatoid arthritis patients. **Materials and Methods:** This is a Prospective-observational-study which included patients coming to rheumatology clinic, Govt medical college Thrissur during the period December 2022 to June 2023. Patients with diagnosed of seropositive rheumatoid arthritis of less than two-year duration and Clinical-disease-activity-Index score (CDAI) >10 and have not received any DMARD during this period were taken. Thirty patients, who were on treatment with Methotrexate 15 mg per weekly orally and Iguratimod 25mg twice daily orally were included. Clinical effectiveness was assessed at baseline and after 2 months and 4 months using CDAI. Patients were directed to report any adverse drug reactions developed during study period. **Result:** There was markedly significant reduction in disease activity at 2nd month and 4th month. During the follow up, four patients reported dyspepsia symptoms. **Conclusion:** Methotrexate with Iguratimod combination is a better initial treatment strategy for patients with moderate to severe disease activity with favourable safety profile.

INTRODUCTION

Rheumatoid arthritis (RA) stands as a persistent autoimmune condition that incites systemic inflammation, predominantly affecting the joints.[1] Rheumatoid Arthritis significantly affects the well-being of individuals, leading to substantial morbidity, decreased functionality and independence, lower quality of life, and increased risk of mortality. Its occurrence is consistent worldwide, with a prevalence of 0.5% in our country.[1] Identifying RA early is crucial, as the condition can cause irreversible damage to joint within the first two years of activity. Therefore, prompt diagnosis is essential for achieving the most favourable outcomes. The diagnosis depends on the 2010 ACR- EULAR (American College of Rheumatology- European League Against Rheumatism) classification criteria for Rheumatoid arthritis.[2] Patients diagnosed as seropositive for RA possess either rheumatoid factor (RA factor), anti-cyclic citrullinated peptide (Anti CCP), or both within their bloodstream, which is suggesting a more severe progression of the disease, necessitating more rigorous treatment methodologies.[3]

Recent years have seen a substantial shift in how RA is managed, with current treatment objectives focusing on averting joint damage and maintaining functionality. Consequently, the initiation of Disease Modifying Antirheumatic Drugs (DMARDs) shortly after diagnosis is advocated for most individuals to mitigate the disease progression.[4] Despite ongoing debates regarding the early treatment strategy for patients diagnosed with RA, the universal

effectiveness of available medications remains elusive, compounded by potential toxicity or high costs. This situation underscores the pressing need for the development of novel, cost-effective, and safer treatment options.[5] The efficacy of single DMARD therapy often falls short, prompting the use of DMARD combination therapies, despite the scarcity of data supporting their effectiveness.[6]

The European-League-Against-Rheumatism (EULAR) has suggested for DMARD-naive patients, a combined approach of conventional synthetic DMARDs as a viable alternative to monotherapy, possibly with the inclusion of glucocorticoids, considering individual patient preferences and potential side effects. Early intervention with drug combinations not only delays and slows disease progression but also proves to be cost-effective in the long term by enhancing patient productivity.[7] Among the novel therapeutic agents in this domain is Iguratimod, a small molecule drug with significant immunomodulatory effects on the synovial tissue of individuals with RA.

Iguratimod, belonging to the methane sulfonanilide family, plays a pivotal role by suppressing the production of immunoglobulins and various inflammatory cytokines, such as IL-1, IL-6, and TNF. It promotes bone health by encouraging osteoblastic differentiation and inhibiting osteoclastogenesis, in addition to blocking the NF-kB pathway. Its inhibition of COX-2 further synergizes its analgesic and anti-inflammatory actions.[8] Published reports have confirmed that a combination therapy involving Iguratimod and Methotrexate significantly outperforms the monotherapy of either drug, positioning this combination as a potential first-line treatment option.[5] This research is intended to assess the effectiveness and safety of co-administration of Iguratimod and methotrexate in DMARD naive seropositive rheumatoid arthritis patients.

MATERIALS AND METHODS

This research is a Prospective observational study in patients coming to rheumatology clinic, Government medical college Thrissur-Kerala during the period December 2022 to June 2023. The study was initiated after getting permission from the Institutional-Research-Committee and Institutional Ethics Committee. Patients whose age more than 18 years and less than 75 years of either sex were included. Patients diagnosed with rheumatoid arthritis according to ACR/ EULAR 2010 classification criteria and those with Rheumatoid- factor or anti-cyclic-citrullinated peptides positive were taken. Patients having rheumatoid arthritis of less than two-year duration and Clinical-disease-activity-Index score (CDAI) >10 and have not received any DMARD during this period were taken. Thirty patients, who were on treatment with Methotrexate 15 mg per weekly orally and Iguratimod 25mg twice daily orally were included. Written informed consent was obtained from patients. Consecutive sampling method is used in which every subject meeting the criteria of inclusion is selected. Patients with impaired renal, liver, hematopoietic system, chronic infectious disease such as hepatitis B, hepatitis C, tuberculosis and pregnant and lactating women were excluded.

Baseline investigations like RA factor, Anti CCP, blood routine, LFT, RFT was done. LFT and blood routine repeated during follow up time. Clinical effectiveness was assessed at baseline and after 2 months and 4 months using CDAI.[9] CDAI is based on the simple summation of Tender Joint Count (TJC) and Swollen Joint Count (SJC) of 28 joints along with Patient Global Assessment (PGA) and Evaluator Global Assessment (EGA) on visual analogue scale VAS (0–10 cm) for estimating disease activity. The CDAI has range from 0 to 76. CDAI score components and its interpretations are showed in Figure 1. Paired t test was done to compare CDAI score between baseline and 2 months and between baseline and 4 months. Patients were directed to report any adverse drug reactions developed during study period.

RESULTS

Mean-age of the patients were 51.8+/-10.2 years. The median duration of illness was 12 +/- 18 months. 90% of the patients were females. The mean CDAI scores at baseline, 2nd month and 4th month were 36.47 ± 15.35, 22.27 ± 12.7 and 16.5 ± 11.11 respectively. Statistical analysis showed highly significant reduction in disease activity at 2 months (p value < 0.001) and at 4 months (p value < 0.001). These are presented in Table 1 & Figure 2. The mean changes in tender and swollen joint counts, patient and evaluator global assessment scores are depicted in Figure 3. During the follow up, four patients complained about dyspepsia symptoms which was showed in Figure 4.

Table 1: Paired t test

Disease activity score		Mean ±SD	t value	p value
CDAI score	0 weeks	36.47 ± 15.35	6.21	0.000
	2 weeks	22.27 ±12.71		
CDAI score	2 weeks	22.27 ±12.71	7.35	0.000
	4 weeks	16.5 ± 11.11		
CDAI score	0 weeks	36.47 ± 15.35	7.65	0.000
	4 weeks	16.5 ± 11.11		

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CDAI Variables	Range
Tender joint score (TJC)	(0-28)
Swollen joint score (SJC)	(0-28)
Patient global score (PGA)	(0-10)
Evaluator global score (EGA)	(0-10)
CDAI score	(0-76)

CDAI score interpretation score interpretation	
0.0-2.0.0-2.88	Remission
2.9-10.0	Low activity
10.1-22.01-22.0	Moderate activity
22.1-76.01-76.0	High activity

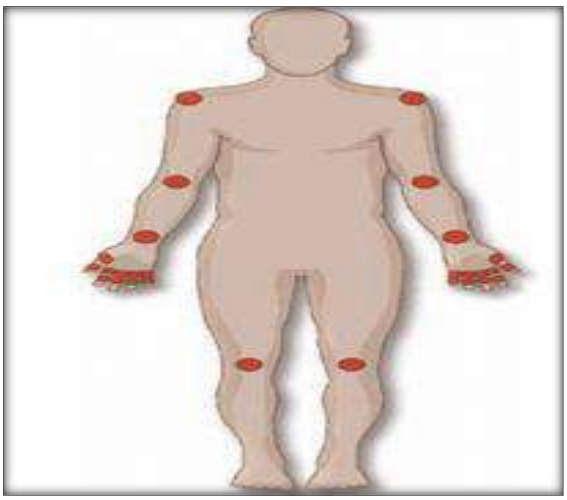


Figure 1: Clinical Disease Activity Index

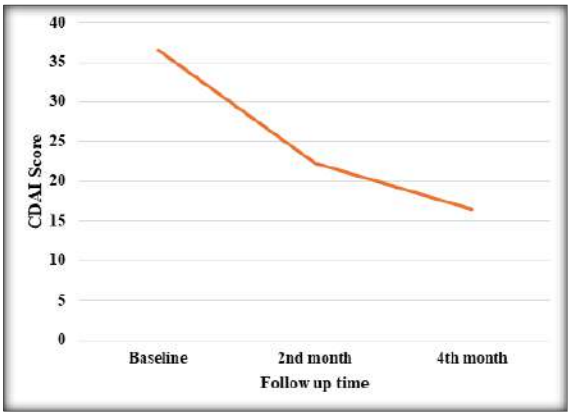


Figure 2: Clinical Disease Activity Index

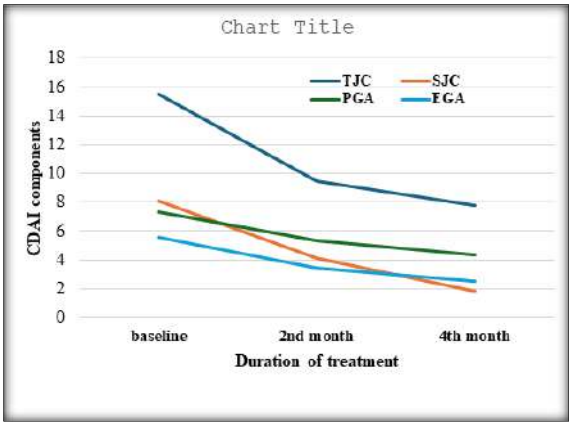


Figure 3: CDAI Components

TJC- Tender joint count, SJC- Swollen joint count PGA- Patient global assessment, EGA- Evaluator global assessment

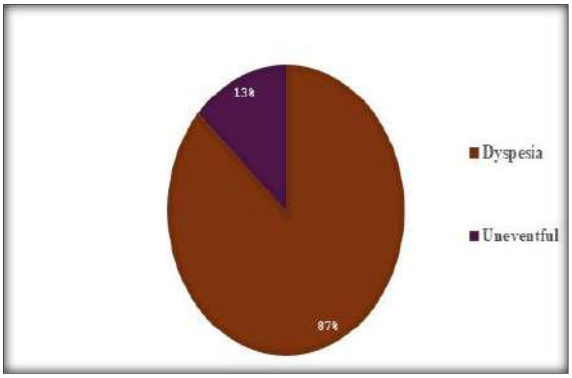


Figure 4: Adverse drug reactions

DISCUSSION

This study demonstrated a significant marked reduction in disease activity in the 2nd and 4th months post-treatment with Methotrexate at a dose of 15 mg weekly and Iguratimod at 25 mg twice daily, when taken orally. Merely four individuals reported symptoms related to dyspepsia because of the treatment. These findings are consistent with those of a national prospective real-world study conducted by Rong Mu et al., which verified the effectiveness and safety of Iguratimod in treating active rheumatoid arthritis, suggesting it as an affordable option for either solo or combined treatment regimes.[10] The primary safety concern identified in our research was gastrointestinal symptoms, mirroring the outcomes observed in the study by Mu et al. Comparable outcomes were noted in several other studies: L.J. Chen et al.'s meta-analysis of Randomized Controlled Trials (RCTs) suggested that a combination therapy of Iguratimod and Methotrexate was superior to Methotrexate monotherapy for rheumatoid arthritis, with adverse events being similar to Methotrexate treatment alone.[11] Jingya Tan et al. highlighted that combining Methotrexate with Iguratimod enhanced clinical results for patients with rheumatoid arthritis without raising the risk of

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adverse events.[12] Lastly, a systematic-review by Chao-Jun Hu et al. concluded that Iguratimod serves as reliable and tolerable option as either a standalone treatment or in combination, particularly with Methotrexate, for those suffering from active RA.[13] Additionally, a systematic review by Dan Ouyang et al. stated that combining Methotrexate with Iguratimod significantly enhances ACR 20 response rates without significant adverse effects.[14] Liuting Zeng et al.'s systematic review indicated that, compared to standard therapy, the combination of Iguratimod with Methotrexate may offer a safer and more efficacious treatment for RA patients, without noticeable side effects.[15]

CONCLUSION

Rheumatoid arthritis is a chronic and severely debilitating condition. Despite the availability of numerous treatment options, achieving complete remission remains challenging, and many treatments come with significant side effects. Iguratimod, a novel small molecule disease-modifying antirheumatic drug, has shown promising results. This research indicates that combining Iguratimod with methotrexate significantly lowers disease activity in patients newly diagnosed with seropositive moderate to severe rheumatoid arthritis, and this combination has been well-received by patients. Therefore, this approach could function as a initial treatment choice for individuals with moderate to severe seropositive rheumatoid arthritis.

The primary limitation of the study is short duration of assessment. Therefore large scale long term and comparative studies are recommended to more conclusively establish the effectiveness and tolerability of this drug combination in rheumatoid-arthritis.

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PSYCHIATRY

Mephentermine misuse: an emerging challenge and the potential role of mirtazapine-a case report

Abstract

Mephentermine is a sympathomimetic amine with structural and pharmacological similarities to amphetamines. Despite its increasing misuse, particularly among athletes and bodybuilders, there is limited literature on its management. No pharmacological treatments have been approved for mephentermine misuse. We describe two cases of young adult males presenting with symptoms of mephentermine withdrawal, including insomnia, anxiety, and craving. Both had histories of prolonged intravenous mephentermine use, with one managed on an outpatient basis and the other as an inpatient. Mirtazapine was initiated in both cases and was associated with improvements in sleep, anxiety, craving and hyperarousal. Psychotic symptoms in one patient resolved with short-term risperidone. Both patients received brief motivational enhancement therapy and remained abstinent from all substances except tobacco during two months of follow-up. These cases highlight the potential utility of mirtazapine in managing mephentermine misuse, particularly for addressing withdrawal symptoms and craving. Given its noradrenergic and serotonergic profile and its demonstrated efficacy in methamphetamine use, mirtazapine may be a promising candidate for treatment. However, the findings are limited by the case series design and larger, controlled studies are needed to confirm its role in clinical management.

PULMONOLOGY

Section: Physiology

Original Research Article

SERUM ZINC LEVELS AND ASTHMA: IS THERE A RELATION TO BE EXPLORED? A PILOT STUDY

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ABSTRACT

Background: Asthma is a chronic inflammatory disease with increasing prevalence in developing countries. The role of trace elements such as zinc in the pathophysiology of asthma has been explored due to its antioxidant and immunomodulatory properties. We investigated a possible correlation between serum zinc levels and both the incidence and symptom control in individuals with bronchial asthma. **Materials and Methods:** This cross-sectional observational study was conducted at Government Medical College, Thrissur, Kerala, involving 49 asthmatic patients and 48 age and gender matched healthy controls. Serum zinc levels were measured using Plasma Optical Emission Spectrometry (POES). Data were analysed using SPSS version 27, with independent t-tests and ANOVA for statistical analysis. **Result:** Mean serum zinc levels were significantly lower in asthmatic patients (13.03 ± 3.98 µmol/L) compared to controls (15.06 ± 2.30 µmol/L, $p < 0.05$). However, no significant correlation was observed between serum zinc levels and the degree of asthma control based on GINA classification ($p = 0.093$). **Conclusion:** Asthmatic patients had significantly lower serum zinc levels compared to healthy individuals, but no correlation was found between zinc levels and the degree of asthma control. Further multicentric trials involving larger sample sizes are warranted to investigate serum zinc levels in asthma and their potential therapeutic role.

INTRODUCTION

Asthma, a chronic respiratory disorder characterized by airway inflammation and hyperresponsiveness, affecting an estimated 262 million individuals globally as of 2019.[1] In India, asthma remains a significant public health issue, with a prevalence of 2.05% and an estimated burden of over 17 million cases.[2] The Global Initiative for Asthma (GINA) provides standardized criteria for assessing asthma control and severity, enabling uniform management approaches worldwide.[1]

The aetiology of asthma is multifactorial; involving genetic predisposition, environmental exposures and immunological dysregulation. Oxidative stress plays a crucial role in the pathogenesis of asthma, driven by an imbalance between reactive oxygen species (ROS) and antioxidant defences. Zinc, an essential trace element, is known to contribute to both antioxidant activity and immune function. Zinc deficiency has been linked to increased oxidative stress and an exaggerated T-helper 2 (Th2) immune response, both of which are implicated in airway inflammation and asthma exacerbations.[3]

Several studies have reported lower serum zinc levels in patients with asthma, suggesting a possible role of zinc in asthma pathophysiology and disease control.[4,5] However, the relationship between zinc levels and asthma severity remains unclear. This study aims to explore the relation between serum zinc bronchial asthma and its severity of among the study population.

MATERIALS AND METHODS

Study Design and Participants: After ethical committee and Institutional Review Board approval (IEC/GMCTSR/192/2021), this cross-sectional observational study was conducted during a period of one year [October 2021 to October 2022] at Government Medical College, Thrissur. We included 49 adult asthmatic patients and 48 age and gender matched healthy controls. The inclusion criteria were adult asthmatic patients, who voluntarily participated. Those with Chronic respiratory diseases

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other than asthma, who received Zinc supplementation in the preceding three months of study period, pregnant or lactating mothers and patients with comorbidities altering serum zinc levels were excluded from the study. The severity of asthma was classified using GINA guidelines

Sample Size Calculation: The sample size was calculated using serum zinc levels in study and control population as the primary outcome. Based on previous studies [5,6], mean zinc levels were 10.85 ± 2.60 µmol/L in asthmatics and 12.54 ± 1.83 µmol/L in healthy controls. With 90% power at a 5% significance level, 35 participants per group were required. To allow for possible dropouts, 48 participants were enrolled in each group.

Serum Zinc Measurement: Venous blood samples were collected using trace element-free tubes. Serum was separated via centrifugation (3000 rpm for 10 minutes) and stored at −20°C. Zinc concentrations were determined using Plasma Optical Emission Spectrometry (POES) at College of Veterinary and Animal Sciences Mannuthy, Thrissur, Kerala. POES is known method for the detection of trace elements, it involves the ionization of the sample using plasma and measuring the light emitted at zinc's characteristic wavelength. Calibration was done using certified zinc standards (PerkinElmer India Pvt. Ltd.). Normal reference values ranged from 12-18 µmol/L [6,7]

Statistical Analysis: Statistical analyses were performed using SPSS version 27. Independent t-tests were used for comparing mean serum zinc levels between cases and controls. One-way ANOVA was used to compare the mean values among the different asthma control groups. A p-value <0.05 was considered statistically significant.

RESULTS

Serum Zinc Levels in Asthmatic Patients vs Controls

[Table 1] presents a comparison of serum zinc levels between asthmatic patients (cases) and healthy individuals (controls). The mean serum zinc level among cases was 13.03 ± 3.98 µmol/L, which was significantly lower than that of controls (15.06 ± 2.30 µmol/L). This difference was statistically significant (t = 3.08, p = 0.0028), indicating that asthmatic individuals tend to have reduced serum zinc levels compared to healthy counterparts. These findings suggest a potential association between lower serum zinc levels and the presence of bronchial asthma.

Serum Zinc and Control of Asthma (GINA Classification)

Based on the GINA classification of asthma control, out of the 49 asthmatic patients evaluated, 14% were classified as well-controlled, 51% as partially controlled, and 35% as uncontrolled.

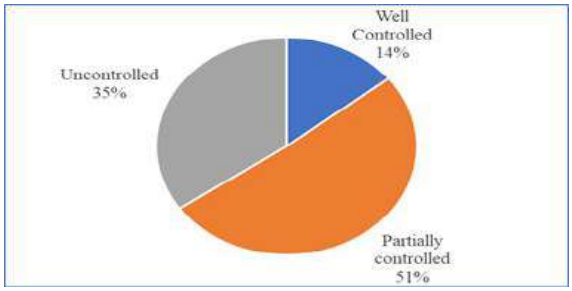


Figure 1: Classification based on degree of asthma control

Table 1: Comparison of Serum Zinc Between Cases and Controls

Group	N	Mean (µmol/L)	SD µmol/L	t-value	p-value
Cases	49	13.03	3.98	3.08	0.0028
Controls	48	15.06	2.30		

Table 2: Comparison of Serum Zinc Based on GINA Classification.

GINA Scoring	N	Mean (µmol/L)	SD (µmol/L)
Well Controlled	7	13.13	3.63
Partially controlled	25	13.55	4.08
Uncontrolled	17	12.20	4.16
F-value =2.51; P-value = 0.093			

[Table 2] depicts the comparison of serum zinc levels among asthmatic patients categorized according to the GINA classification of asthma control. The mean serum zinc level was 13.13 ± 3.63 µmol/L in the well-controlled group, 13.55 ± 4.08 µmol/L in the partially controlled group, and 12.20 ± 4.16 µmol/L in the uncontrolled group. Although the mean serum zinc level was lower in the uncontrolled group, one-way ANOVA revealed no statistically significant difference in serum zinc levels across the three groups (F = 2.51, p = 0.093). This suggests that while a trend toward lower zinc levels with worsening asthma control was observed, the difference did not reach statistical significance.

DISCUSSION

This study investigated the association between serum zinc levels and bronchial asthma, with a focus on both the presence of the disease and its severity as classified by GINA (Global Initiative for Asthma) guidelines. GINA provides detailed criteria for assessing asthma control, categorizing it into well-controlled, partly controlled, and uncontrolled levels. These classifications are based on symptom frequency, activity limitations, nocturnal symptoms, and the need for reliever medications.[8-10] The results

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revealed a statistically significant reduction in mean serum zinc levels in asthmatic patients compared to healthy controls. However, no statistically significant differences were observed when serum zinc levels were compared among asthma severity groups.

Table 3: Asthma Control Levels Based on GINA 2024 Guidelines [9]

In the past 4 weeks, has the patient had:	Yes	No	Well controlled	Partly controlled	Uncontrolled
• Daytime asthma symptoms more than twice/week?	☐	☐			
• Any night waking due to asthma?	☐	☐			
• Short-Acting Beta$_2$-Agonist (SABA) reliever for symptoms more than twice/week?	☐	☐			
• Any activity limitation due to asthma?	☐	☐			
			None of these	1–2 of these	3–4 of these
Exacerbations			None	One or more in past year	Frequent or severe exacerbations

In our observation, asthmatic patients had significantly lower serum zinc levels (13.03 ± 3.98 µmol/L) compared to controls (15.06 ± 2.30 µmol/L) aligns with a growing body of evidence indicating a potential role for trace elements in the pathophysiology of asthma.

Several studies have reported significantly lower serum zinc levels in asthmatic individuals compared to healthy controls, supporting the hypothesis that zinc deficiency may contribute to asthma pathophysiology. A meta-analysis by Chen et al. (2020) revealed a consistent reduction in circulating zinc levels among asthmatic patients, highlighting zinc's potential role in immune regulation and airway inflammation.[11] Similarly, Ghaffari et al. (2021), in a systematic review and meta-analysis of paediatric populations, confirmed lower serum zinc levels in asthmatic children.[12] Mohamed et al. (2018) found significantly reduced zinc levels in atopic asthmatic patients compared to non-atopic individuals, suggesting zinc's influence on allergic mechanisms in asthma.[13] Additionally, Srivastava et al. (2023) identified low serum zinc, selenium, and vitamin D3 as biomarkers associated with poor asthma control and increased airway inflammation.[14]

Conversely, some studies have not demonstrated a clear association between serum zinc levels and asthma. Seo et al. (2017), analysing data from the Korean National Health and Nutrition Examination Survey, found no significant correlation between serum zinc status and allergic sensitization, implying that serum zinc alone may not predict asthma risk.[15] Furthermore, a study by Abdul Wahab et al. (2018) reported that the Zn may not play a major role in the degree of asthma control, indicating that zinc's therapeutic role may be limited or dependent on additional factors.[16] These contrasting findings highlight the complexity of trace element interactions in asthma and underscore the need for further research to clarify zinc's exact role in disease modulation.

Zinc is a crucial micronutrient involved in numerous biological processes, including antioxidant defence, immune modulation, and regulation of inflammatory responses. Its deficiency has been associated with increased oxidative stress, impaired T-cell function, and an upregulated pro-inflammatory state all of which are recognized contributors to asthma pathogenesis.[17] Reduced serum zinc levels in asthma may be a consequence of chronic inflammation leading to increased consumption or redistribution of zinc within tissues.[18] It is also plausible that dietary insufficiencies, poor absorption, or zinc sequestration during acute or chronic immune activation could contribute to these findings.[19]

The significantly lower levels observed in this study reinforce the hypothesis that zinc deficiency may either predispose individuals to asthma or exacerbate existing disease through immune dysregulation. A comprehensive review by Rajkumar et al. (2022) highlights that zinc deficiency disrupts the T-helper 1 (Th1) / T-helper 2 (Th2) balance, favouring Th2 responses, which are associated with allergic conditions like asthma. This imbalance leads to increased eosinophil counts and elevated IgE levels, exacerbating airway inflammation3. In a murine model by Bao et al. (2011) zinc supplementation prior to allergen exposure resulted in decreased neutrophil infiltration and TNF-α release in the airways. This effect was mediated through the inhibition of the NF-κB pathway, suggesting zinc's potential in modulating inflammatory responses in asthma.[20]

Interestingly, the analysis of zinc levels in relation to asthma severity as per GINA classification did not reveal statistically significant differences ($F = 2.51$, $p = 0.093$). Although mean zinc levels tended to be lower in the "Uncontrolled" group (12.20 ± 4.16 µmol/L) compared to the "Well-Controlled" (13.13 ± 3.63 µmol/L) and "Partially Controlled" (13.55 ± 4.08 µmol/L) groups, the variation did not reach statistical significance.

This lack of significant association between serum zinc and asthma control status could be due to several factors. First, the relatively small sample size within each subgroup particularly "Well-Controlled" ($n = 7$) and "Uncontrolled" ($n = 17$) categories may have limited the power to detect subtle but clinically relevant differences. Second, asthma severity is multifactorial and may not be solely influenced by micronutrient status. Environmental triggers, adherence to treatment, comorbidities, and genetic predispositions also play critical roles.[21,22]

Moreover, while serum zinc measurement is a commonly used biomarker, it may not fully reflect

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total body zinc status or the functional availability of zinc at the cellular level.[3] Intracellular zinc levels or other markers of zinc-dependent enzyme activity could potentially provide a more accurate assessment of zinc's role in disease severity.

Clinical and Research Implications: The significant difference in zinc levels between cases and controls suggests that zinc may have a protective or modulatory role in asthma.[23,24] This opens avenues for further research into whether zinc supplementation could benefit asthmatic individuals, particularly those with documented deficiencies. However, the lack of a clear relationship between serum zinc and asthma severity underscores the need for larger, longitudinal studies that explore zinc status in conjunction with other biomarkers of inflammation and oxidative stress.

Additionally, future studies should investigate whether serum zinc levels change with asthma exacerbations, treatment responses, or during periods of remission, to better elucidate the dynamic role of zinc in disease progression.

CONCLUSION

Asthmatic patients in this study exhibited significantly lower serum zinc levels compared to healthy controls, indicating a possible protective role of zinc in asthma pathophysiology. However, no correlation was found between zinc levels and asthma severity. Further studies are required to understand the underlying mechanisms and to assess whether zinc supplementation might serve as a supportive therapy in asthma management.

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Multidetector Computed Tomography in Evaluation of Lung Masses: Study from South India

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Abstract

Background: *Bronchogenic carcinoma is the leading cause of cancer-related death worldwide in men and second most-common in women after breast cancer. Patients with bronchogenic carcinoma have poor prognosis with an overall survival rate of 10-15%. The early detection and accurate staging of bronchogenic cancer is crucial in planning the optimal treatment modalities and further management. Radiological imaging plays a critical role in the initial detection and diagnosis of lung cancer. Multi Detector computed tomography (MDCT) is the standard modality of choice for evaluating the lung cancer because of its better spatial resolution. CT has a role in identifying the lung nodules and characterizing them as benign or malignant.*

Objectives: *The study aims to assess the accuracy of Multi detector computed tomography in diagnosis and staging of Bronchogenic carcinoma. The study also intends to identify the various imaging characteristics types of bronchogenic carcinoma by MDCT.*

Methodology: *This study was a descriptive study conducted on 80 subjects with clinically or radiologically suspicious bronchogenic carcinoma who were referred to department of radio diagnosis, Govt Medical college, Thrissur for undergoing contrast enhanced CT over a period of one year, and were selected based on inclusion and exclusion criteria. Pre and post contrast CT scans were performed. Lung lesions were analysed based on various variables and staging and provisional diagnosis were made and then correlated with histopathology. The data was managed using Microsoft Excel 2016 and statistical analysis was done with IBM SPSS Statistics v25. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of each characteristic as well as the combined values in comparison to histopathological findings were obtained.*

Results: *Majority of the patients belonged to 60 – 70 years age group (47.5%) with male predominance (77.5%). About 66.8 % patients had history of smoking. Cough and dyspnea were the commonest symptoms. Most common radiological finding was central hilar mass lesion (57.5 %) followed by peripheral lesion in 42.5 %. Squamous cell carcinoma was the most common histopathological type*

(46.3%), followed by adenocarcinoma (22.5%) then small cell carcinoma (12.5%). The most common lobe affected by bronchogenic carcinoma was right upper lobe. The most common site of distant metastasis was adrenal gland (42.6%) followed by pleura (35.3%) and then liver (29.4%). Majority of the patients (69.1%) presented with TNM stage IV.

Conclusions: *Overall, CT had a sensitivity of 95.7% and specificity of 81.8%, positive predictive value of 97.1% and negative predictive value of 75 %. Multi detector computed tomography has high positive predictive value suggestive of great diagnostic accuracy in the evaluation of bronchogenic carcinoma. MDCT is a useful tool in the staging of Bronchogenic Carcinoma.*

Keywords: *Multidetector Computed Tomography (MDCT), Bronchogenic Carcinoma, Histopathology.*

Background And Introduction

Bronchogenic carcinoma is the leading cause of cancer-related death worldwide in men and second most-common in women after breast cancer. Its incidence is raising at alarming rates at developing countries. Although the underlying aetiology for this malignancy is multifactorial, approximately 85% of bronchogenic carcinoma deaths are attributable to cigarette smoking (1).Multi Detector computed tomography (MDCT) is the standard modality of choice for evaluating the lung cancer because of its better spatial resolution (2) MDCT provides precise characterisation of the size, contour, extent and tissue composition of the suspicious lesion. It identifies small nodules not visible by radiography. It also has role in characterizing them as benign or malignant. MDCT accurately stages the tumours because of the superior multiplanar reformatted images. Staging of lung cancer plays a vital role in deciding the treatment and helps in accessing the prognosis. The present study is aimed at assessing the diagnostic accuracy of MDCT in the evaluation and staging of bronchogenic carcinoma and at evaluating the imaging characteristics of bronchogenic carcinoma with histopathological correlation.

Objective

1. To document the imaging characteristics of bronchogenic carcinoma using multidetector computed tomography in adult patients referred for evaluation of lung masses in a tertiary care centre in South India.
2. To calculate the diagnostic efficiency of MDCT in detection of malignancy in patients referred for evaluation of lung masses, taking Histopathology as gold standard

Methodology

It was conducted as a cross sectional analytical study over a period of one year in the department of radio diagnosis.

Patients included in the study were adults with clinically or radiologically suspected bronchogenic carcinoma who were referred to the department of radio diagnosis, in whom histopathology correlation was available.

Previously diagnosed cases of carcinoma lung were excluded from the study. The examinations were performed using Siemens Somatom16 slice CT scanner with 5mm section thickness, and reformed to 1.5mm section thickness. Scanning images included pre and post administration of contrast medium in all patients. Sections were taken from the level of lung apices to up to adrenals.

Patients were followed up with histopathological examination of the specimen obtained from FNAC/ biopsy of the lesion and results were compared with CT findings. The data was managed using Microsoft Excel 2016 and statistical analysis was done with IBM SPSS Statistics v25. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of each characteristic as well as the combined values in comparison to histopathological findings were obtained.

Observations and Results

A total of 80 subjects were included in the study, ranging in age group from 40 to 75.

In this study, 5 (6.3%) participants were in the age group of 40-50 years, 14 (17.5%) were in the age group of 51-60 years, 38 (47.5%) were in the age group of 61-70 years and 23 (28.8%) were in the age group of more than 71-75 years.

In the study, 62 (77.5%) participants were male and 18 (22.5%) were females.

Of the 80 patients, 55 (68.8%) gave a history of smoking.

The most common presenting symptoms were cough in 75 participants (93.8%) followed by dyspnea in 70 (87.5%) participants.

All patients had masses detected in X Ray. The various findings have been elaborated in tables that follows.

Table 1 gives the distribution of site of mass lesion, most common being central in 57.5% of cases

Table 1: Distribution of site of lung mass in CT

Site of Lesion	Frequency (n=80)	Percentage
Right Upper Lobe	33	41.3
Right Middle	13	16.3
Right Lower	16	20.0
Left Upper	18	22.5
Left Lower	17	21.3
Central	46	57.5
Peripheral	34	42.5

Most of the lesions were more than 4 cm, highest number of cases being more than 7 cm (30%)

Table 2: Distribution of size of lung mass in CT

Size of lesion	Frequency	Percentage
1-2 cm	3	3.8
2-3 cm	3	3.8
3-4 cm	12	15.0
4-5 cm	18	22.5
5-7 cm	20	25.0
> 7 cm	24	30.0
Total	80	100.0

The margins were classified into 5 types, the most common being lobulated irregular margins in 42 (52.5%) cases

Table 3: Distribution of contour of lung mass in CT

Contour of Lesion	Frequency	Percentage
Spiculated	28	35.0
Lobulated/irregular	42	52.5
Smooth	4	5.0
Irregular thick-walled cavity	4	5.0
Ill-defined	2	2.5
Total	80	100.0

Different CECT characteristics were studied. In the study, contrast enhancement of the lesion was present in 79 (98.8%) participants. Contrast enhancement was absent in only one case. There were 13 other CT findings looked for in the study as given in table 4..

Table 4: Distribution of other features of lung mass in CT

Other Findings	Frequency (n=80)	Percentage
Calcification	18	22.5
Cavitation	13	16.3
Necrosis	31	38.8
Bronchial cut off	37	46.3
Satellite lesions	24	30.0
Pleural thickening	35	43.8
Collapse	37	46.3
Consolidation	17	21.3
Interstitial thickening	30	37.5
Chest wall infiltration	11	13.8
Mediastinal infiltration	40	50.0
Vocal cord palsy	2	2.5
Diaphragmatic palsy	3	3.8

Enlarged lymph nodes were documented at peri bronchial, mediastinal, hilar and distant sites (supraclavicular and scalene). The distribution is as given in table 5.

Table 5: Distribution of Mediastinal and Hilar Lymphadenopathy in CT

Nodes	Frequency (n=80)	Percentage
Peri bronchial	23	28.8
Mediastinal		
Ipsilateral	58	72.5
Contralateral	17	21.3
Subcarinal	54	67.5
Hilar		
Ipsilateral	37	46.3
Contralateral	8	10.0
Supraclavicular	14	17.5
Scalene	0	0.0

Table 6: Distribution of presumed metastatic lesions in CT

Metastases	Frequency (n=68)	Percentage
Opposite lung	33	48.5
Liver	20	29.4
Bone	16	23.5
Adrenal	29	42.6
Pleural nodules	24	35.3
Pleural effusion	23	33.8
Extra thoracic nodes	12	17.6
Others	6	8.8

Table 6 gives the distribution of enhancing masses presumed to be metastasis.

In the study, metastasis to the opposite lung was noted in 33 (48.5%) participants. Adrenal gland was the most common site of distant metastasis, in 29 (42.6%), followed by liver in 20 (29.4%), then bone in 16 (23.5%). Metastasis to extra thoracic nodes noted in 12 (17.6%) and 6 (8.8%) of participants had metastases to other sites like brain, kidney. Pleural nodules were seen in 24 (35.3%) and pleural effusion in 23 (33.8%),

Table 7: Distribution of final diagnosis from CT

Impression from CT	Frequency	Percentage
Malignant	68	85.0
Benign	5	6.3
Infection	7	8.8
Total	80	100.0

In the study of 80 participants, from CT evaluation, a final impression were made. As described in table 7, 68 (85.0%) lesions were diagnosed as malignant, 5 (6.3%) were benign and 7 (8.8%) belonged to infective etiology based on impression from Computed Tomography evaluation.

Table 8: Of the 68 with impression of Malignancy in CT, the staging were given as follows:

Tumour (T)	Frequency	Percentage
T1a	1	1.4
T1b	2	2.9
T2a	3	4.4
T2b	4	5.8
T3	11	16.1
T4	47	69.1
Total	68	100.0

Based on CT based approach, Tumor Node Metastasis (TNM) staging was done, which is provided in Table 9, 10 and 11 respectively.

Table 9: Distribution of stages of nodes of study participants

Nodes (N)	Frequency	Percentage
N1	3	4.4
N2	42	61.8
N3	23	33.8
Total	68	100.0

Table 10: Distribution of Metastasis of study participants

Metastasis (M)	Frequency	Percentage
M0	11	16.2
M1a	11	16.2
M1b	25	36.8
M1c	21	30.9
Total	68	100.0

On histopathology follow up, the 68 malignant cases were divided into 3 major histo pathological types, viz Squamous cell, adeno, small cell types. The most common type being Squamous cell carcinoma in 48 cases (70.6%).

Table-11: Distribution of types of Malignant lesions based on CT

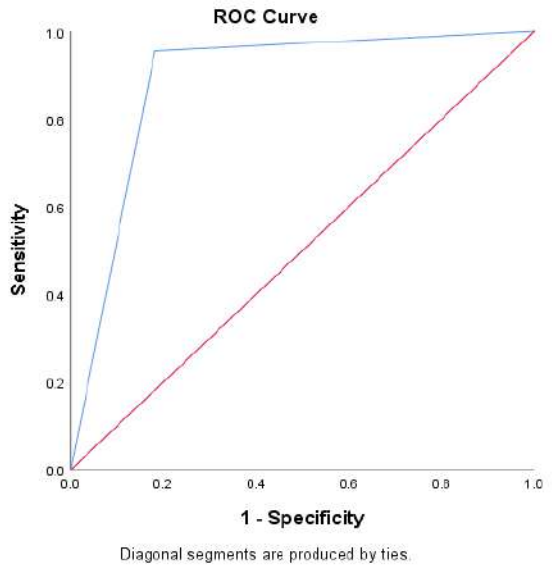
Malignant- types (by CT)	Frequency	Percentage
Squamous cell carcinoma	48	70.6
Adenocarcinoma	18	26.5
Small cell carcinoma	2	2.9
Total	68	100.0

Table 12: Comparison of CT diagnosis with Histological diagnosis of bronchogenic carcinoma.

CT	HPE				p Value
	Malignant		Benign		
	n	%	n	%	
Malignant	66	95.7	2	18.2	1.000
Benign	3	4.3	9	81.8	
Total	69	100.0	11	100.0	

From the above 2X2 table (table 12) , for finding the diagnostic accuracy of CT as a tool for detection of metastasis with Histopathology as gold standard,
The sensitivity: TP/ (TP+FN)= 66/(66+3)= 95.7%
Specificity= TN/(FP+TN) = 9/(9+2)= 81.8%
Positive predictive value to diagnose bronchogenic carcinoma = TP/TP+FP = 66/(66+2)= 97.1%
The Kappa measurement value of 0.746 revealed that almost perfect agreement between CT diagnosis and Histopathological diagnosis.

Figure-1: ROC curve for CT diagnosis and Histopathological diagn



Discussion

80 cases who had lung masses and had histopathology confirmation were included in the study. Majority were males(77.5%) with maximum patients in the age group of 61-70 years : 38 cases (47.5%).

This is in keeping with usual detection of lung masses in adult males.

There were 14 CT findings looked for in the study. All lung masses showed enhancing areas, except for one which was non enhancing, probably because of near complete necrosis of the lesion. Necrosis , viz non enhancing areas within the solid areas which again may be attributed to benign and malignant causes, was seen in 31 cases.

Definitive evidence of malignancy , viz chest wall infiltration and mediastinal infiltration were noted in 11 and 40 cases respectively. Other features like satellite lesions (24 cases), pleural thickening (35 cases), bronchial cut off (37 cases), vocal cord (2 cases) and diaphragmatic palsy (3 cases) , which directed towards malignancy were also documented in this study. Collapse (37 cases), interstitial thickening (30 cases), consolidation (17 cases), calcification (18 cases) and cavitation (13 cases) were other CT features which were equivocal for benign and malignant. Multiple CT characteristics were elaborated by Purandare et al,[3] and that was used in staging of carcinoma lung.

In histopathology, most cases were Squamous cell carcinoma, possibly reflecting smoking incidence in the study population.

In this study, Multi detector computed tomography showed a high positive predictive value (97%) suggestive of great diagnostic accuracy in the evaluation of bronchogenic carcinoma. The Kappa measurement value of 0.746 revealed that almost perfect agreement between CT diagnosis and Histopathological diagnosis

These results were similar to studies conducted by Mohammed et al[4].

In this study having 68 participants with bronchogenic carcinoma, 1 (1.4%) of the participants had T1a stage, 2 (2.9%) participants

had T1b stage, 3 (4.4%) had T2a stage, 4 (5.8%) had T2b stage, 11 (16.1%) had T3 stage and 49 (72.1%) had T4 stage. Majority of the patients were presented at advanced stages as in stage 4 and stage 3 where surgical treatment is no longer an option. This finding correlated with the study done by Rawat et al[5], Shetty et al[6], Prasad R et al[7], Malik PS et al[8], and Shah D et al[9].

Multi detector Computer tomography with precise anatomic details is the imaging modality of choice for evaluating bronchogenic carcinoma. CT provides precise characterization of the size, contour, extent and tissue composition of the suspicious lesion. In the diagnosis of bronchogenic carcinoma, CT is a highly sensitive and specific test. Multi Detector Computed Tomography has a high positive predictive value. Similar results has been reported in previous studies [10, 11]

Representative Images.

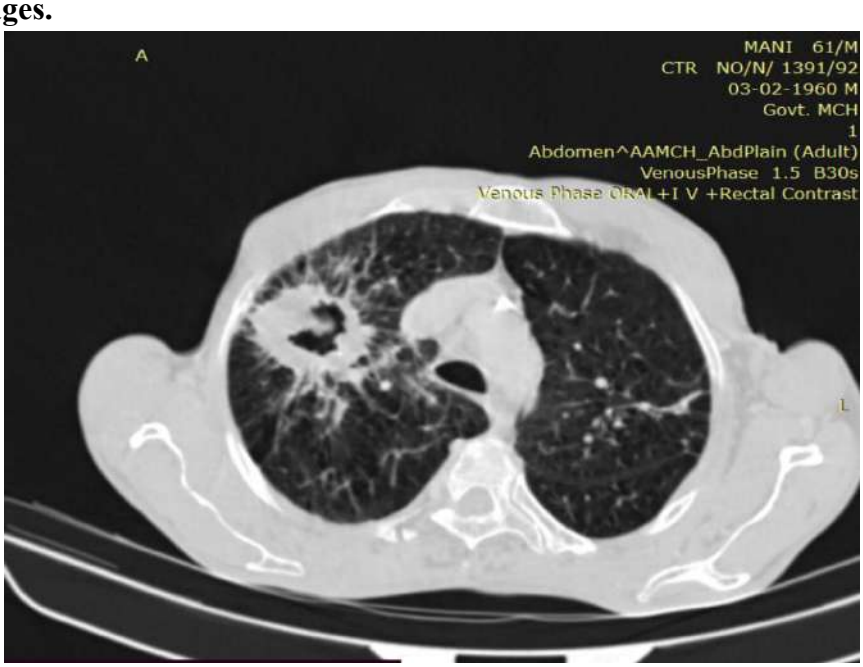


Fig. 2 Axial- CT showing Thick-walled cavity lesion – Squamous Cell Carcinoma



Fig.3: Coronal CECT showing cavity lesion in right upper lobe.

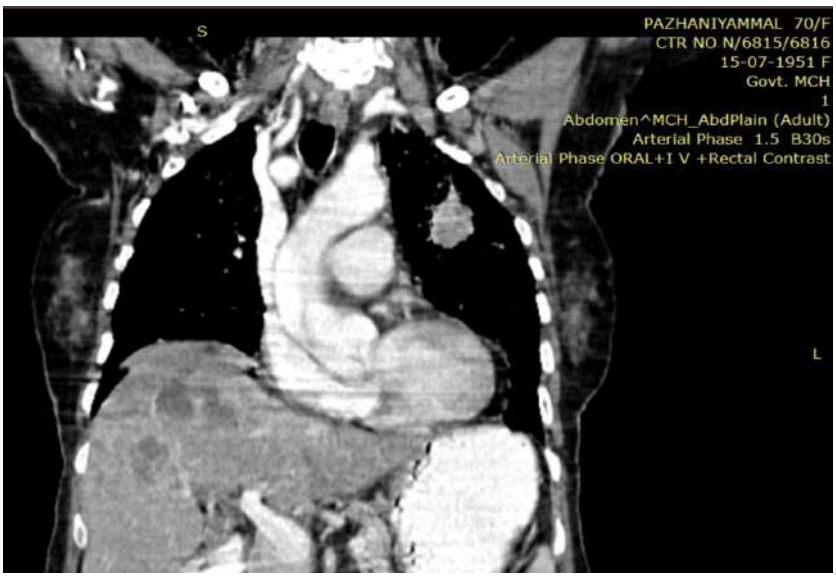


Fig. 4: CECT coronal plane showing left upper lobe mass lesion with liver metastasis. (diagnosed as adenocarcinoma in histopathology)

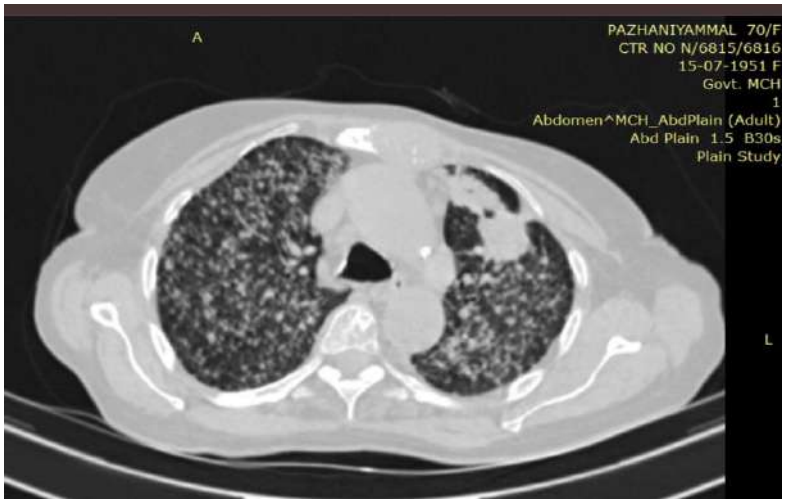


Fig. 5: CT axial plane showing left upper lobe lesion with miliary metastasis & bone metastasis in sternum.

Small cell carcinoma lung

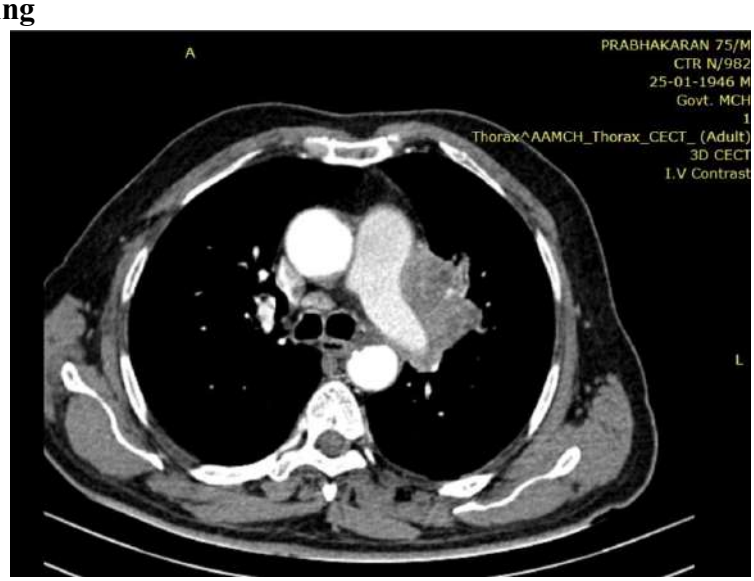


Fig. 6 Axial-CT image showing central mass lesion, diagnosed as small cell carcinoma by histopathology.

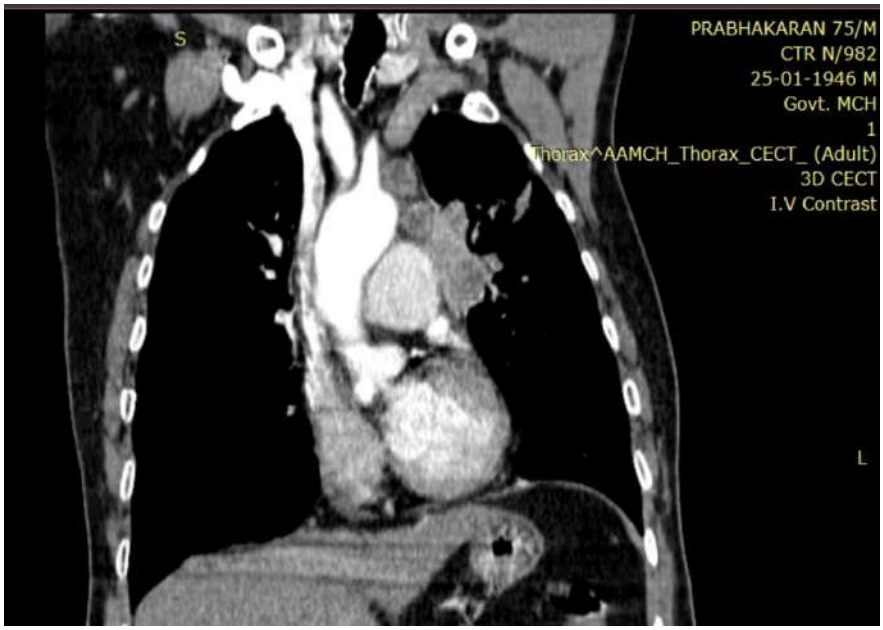


Fig.7: Coronal image of small cell carcinoma with necrotic mediastinal nodes.

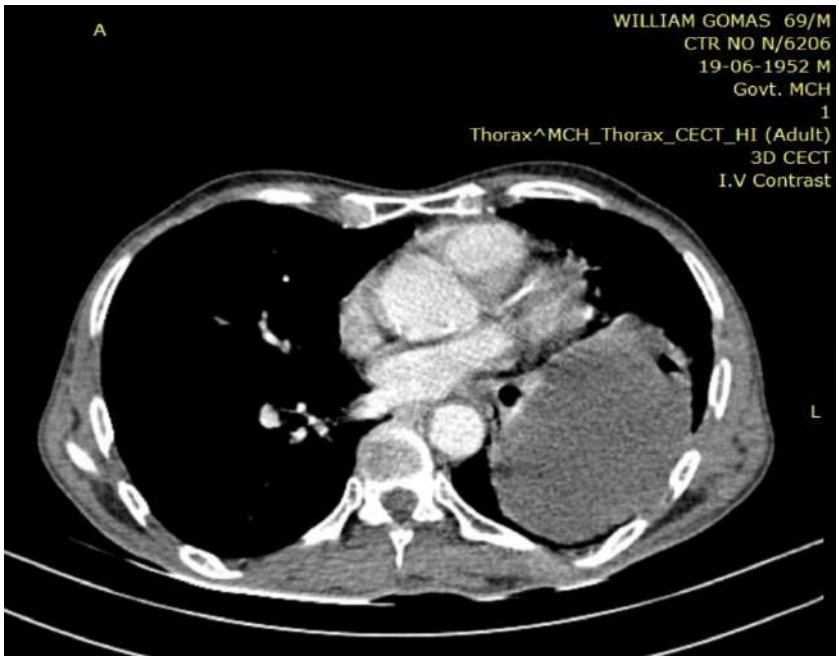


Fig. 8 Axial CT showing large cell carcinoma left lung, by histopathology (Undifferentiated large cell carcinoma)

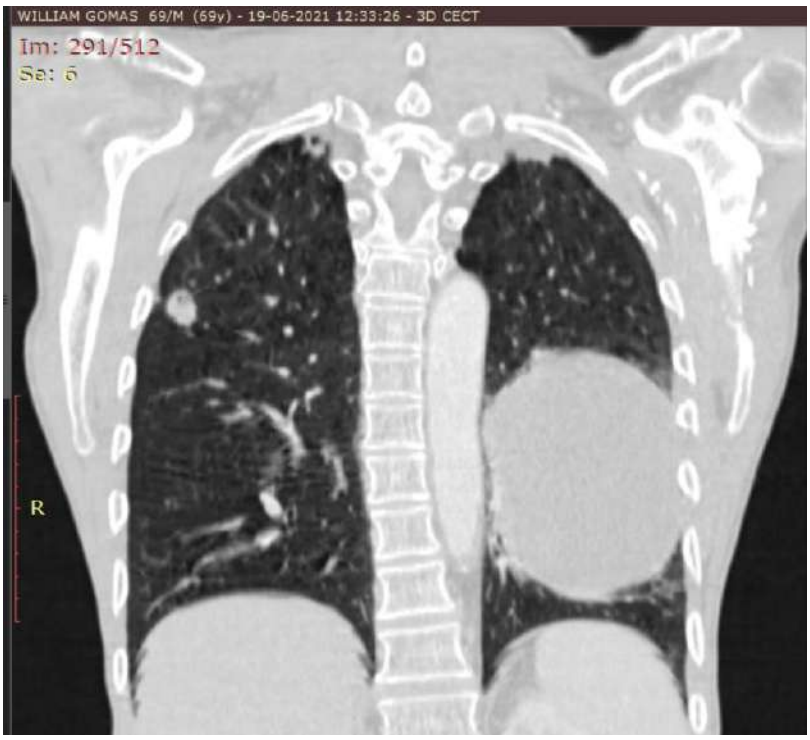


Fig. 9 Coronal CT showing large cell carcinoma with metastasis in opposite lung

Distant metastasis

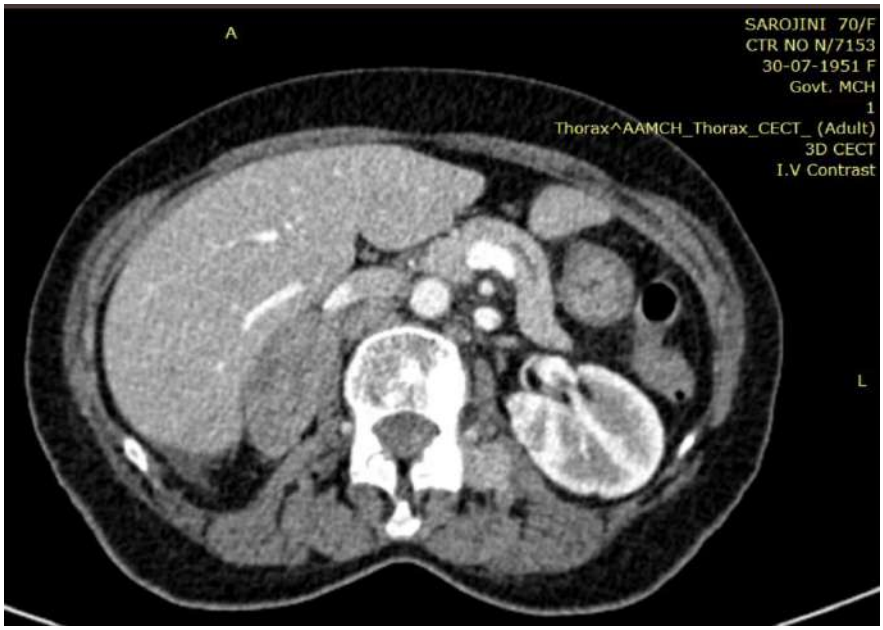


Fig. 10 Axial image showing right adrenal gland metastasis.

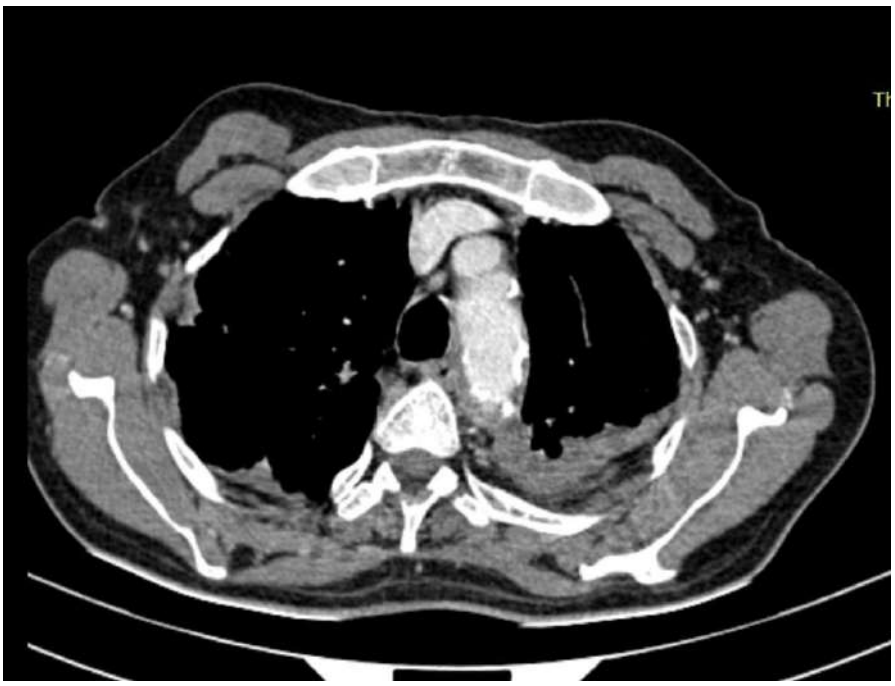


Fig. 11 Axial image with pleural metastasis



Fig.12 Sagittal image , bone window showing lytic-sclerotic lesions in multiple vertebra

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Conflict of Interest: None

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High Resolution Computed Tomography of Temporal Bone Pathologies with CT based Diagnosis - An Experience from Tertiary Health Centre in Kerala

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Abstract:- Background: HRCT plays an important role in evaluation of middle ear, particularly for ossicles, bony structures and inner ear canals.This study is an attempt to document HRCT/CECT findings in middle ear pathologies and to categorize these pathology into radiological diagnosis.
Methods: 40 cases of HRCT temporal bone were studied which included all age groups and both sexes. The radiological diagnosis were defined and broadly classified into infection, neoplastic or radiologically normal.
Results and observation: Among the 40 cases, there were 67.5 percent cases of infections (30% Otomastoiditis: , 32.5% Cholesteatoma: 5% Mastoiditis:), 5% of neoplasms and 27.5% radiologically normal.
Conclusions: HRCT is a non-invasive easily available investigation for middle and inner ear, best suited for the preoperative evaluation of temporal bone anatomy and ossicular chain disruption.

Keywords*: High Resolution Computed Tomography, Radiological Diagnosis, Temporal Bone.*

I. INTRODUCTION

The non-invasive evaluation of the middle ear has been revolutionized by the use of modalities like CT and MRI. CT allows excellent delineation of calcifications, cortical bone, air, and fat. Hence, CT of temporal bone can be used to visualize external ear, middle ear soft tissue and bony structures (ossicles, tegmen, facial nerve canal) and inner ear structures like semicircular canal, cochlea etc. Although MRI offers much better, more specific, and more distinctive soft tissue characterization, (1) CT can easily assess ossicles, their erosions and extent of soft tissue lesions . High Resolution Computed Tomography outweighs the conventional modalities of investigations and provides higher spatial resolution and better soft tissue contrast.(2)

Contrast Enhanced CT of temporal bone is rarely indicated, except for documenting the enhancement in some tumors (where again, MRI is preferred, but use is restricted due to its availability). (3)

For the assessment of middle-ear infections, a close clinical correlation is essential to evaluate the nature of middle-ear soft tissue masses as cholesteatoma is mimicked by many other middle-ear pathologies.

Antico Antral Disease is an "unsafe" type of chronic otitis media (COM) due to its association with cholesteatoma which has a property of bone erosion and intraoperative complications. (4)

The hallmarks of cholesteatoma are soft tissue mass-like opacity in the middle ear cavity and mastoid antrum associated with smooth bony erosion of the ossicles and expansion of adjacent structures (5,6)

HRCT scan of temporal bone correlates well for the detection of disease presence and shows good radiosurgical agreement for sinus plate erosion, LSCC erosion but fair agreement for dural plate erosion and malleus erosion. (7,8)

This study is to document CT findings in temporal bone of patients referred for middle ear pathologies to the Department of Radiodiagnosis, Government Medical College, Thrissur, Kerala and simplify them by categorizing into "radiological diagnosis".

II. MATERIALS AND METHODS

- Study setting-Dept of Radiodiagnosis,Govt medical college Thrissur.
- Study design- Cross sectional Descriptive study
- Study population-Patients with signs and symptoms of middle ear pathology such as ear discharge, hearing loss,

vertigo, headache, cerebellar signs and tinnitus, where CT is indicated.

- Inclusion criteria-Patients who came for HRCT temporal bone with signs and symptoms of temporal bone (middle ear) pathologies.
- Exclusion criteria: Any radical surgery (like radical /modified radical mastoidectomy) done to temporal bone.
- Study period- March 2023 to September 2023 - 6 months
- Study procedure-Patients selected on the basis of inclusion criteria were scanned using Seimens 16 slice MDCT in axial plane with thin 0.6mm sections of formatted axial, coronal and sagittal non-enhanced images. Intravenous Iohexol was used as contrast in indicated cases. CT scans were evaluated for the presence of findings in temporal bone. Results were entered in Excel sheets and tabulated using percentages.

Few definitions were used in the study

For the purpose of convenience, to aid a radiological diagnosis.

- Cholesteatoma –Non enhancing soft tissue density with ossicular erosion.
- CSOM/Otomastoiditis- Middle ear soft tissue/fluid density without bony erosion with or without mastoid involvement.
- Mastoiditis –Soft tissue /fluid density with or without bony erosion and isolated involvement of mastoid.

III. RESULTS

Forty cases of temporal bone CT were included in the study.

- Sex distribution: The study sample included 21 females (52.5) and 19 males (47.5%)

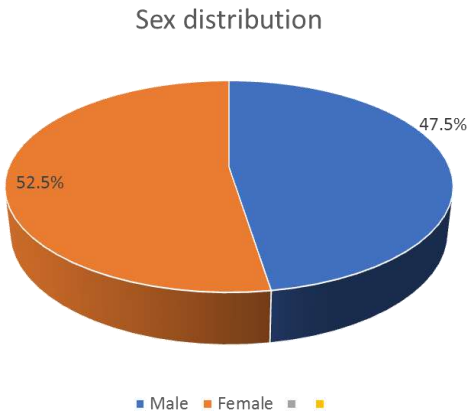


Fig 1: Sex distribution of cases

- Age distribution: The age ranged from 5 years to 72 years mean of 36.6 years. Most number of patients were in 20 to 29 age group.

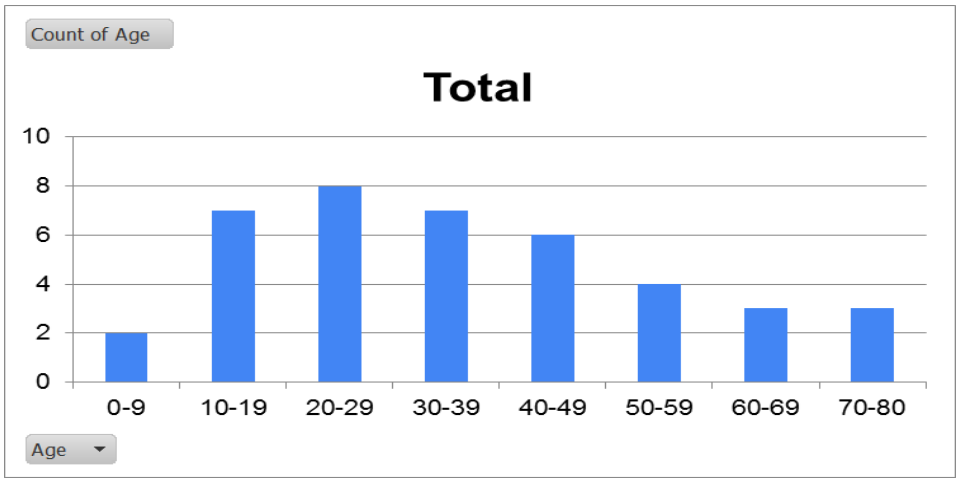


Fig 2: Age distribution of cases

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- Side affected: In our study, of the 29 cases with CT findings in ear, it was found that the left ear was involved in 14 cases, Right ear in 11 cases and both ears in 4 cases.

- Symptoms: The main symptom is each patient was noted. Most common symptom was decreased hearing/hard on hearing, in 15 cases(37.5%) , followed by discharge from ear in 14 cases (35%) . Other symptoms documented, included pain, tinnitus and vertigo.Radiological diagnosis:

With the CT findings, a radiological diagnosis was assigned to each case. The "radiological diagnosis" were Otomastoiditis , Cholesteatoma, Mastoiditis, Tumors and radiological normal.

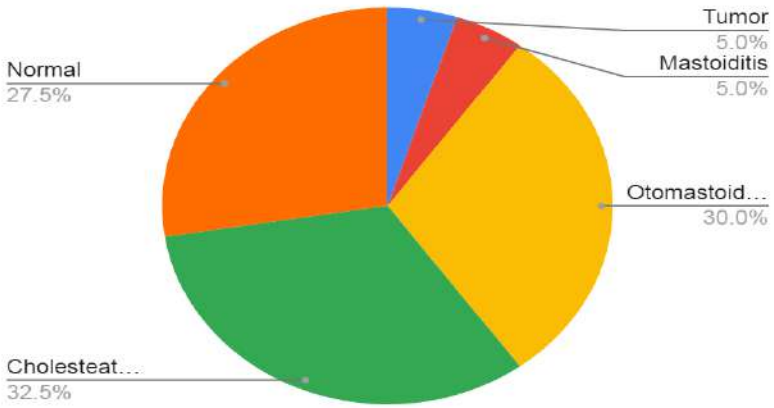


Fig 3: Pie diagram showing distribution of final radiological diagnosis



Fig 4: Radiology of isolated mastoid soft tissue opacification in the right mastoid.

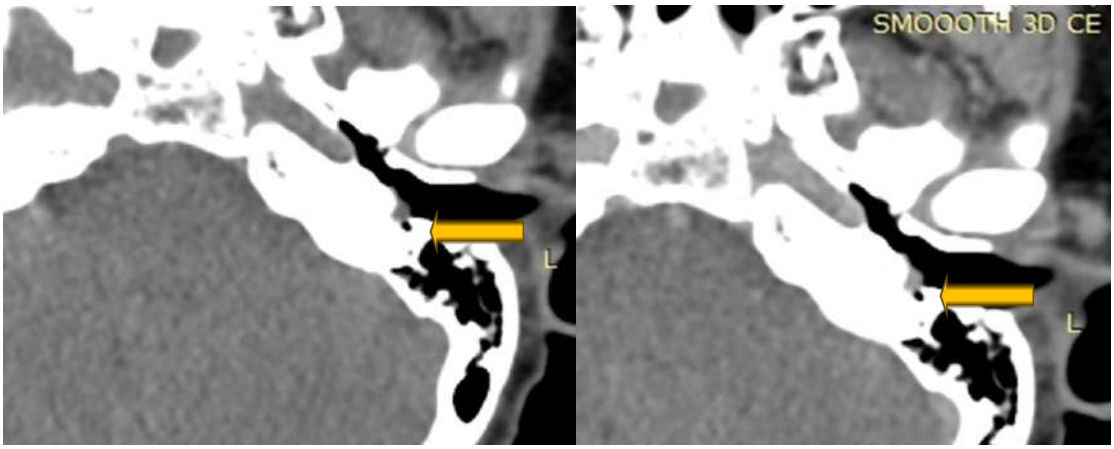


Fig 5, 6: Soft tissue density in middle ear which is Intensely enhancing on contrast (Fig 6)

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Fig 7, 8: Soft tissue density in left middle ear with ossicular disruption

IV. DISCUSSION

High Resolution Computed Tomography is one of the easiest available non invasive modality for evaluation of temporal bone. Its importance in studying pre operative anatomy of the middle ear is well documented. Although, MRI is better in discriminating soft tissue masses, yet another importance of CT is in establishing the complications of middle ear pathology like ossicular discontinuity and bony defects.

Our study included 40 patients in the age range of 5 to 72 years with almost equal male female distribution. Of the most important symptom documented, the highest complaints were decreased hearing (37.5 %), followed by ear discharge (35 %, n=14)

External ear abnormality was not documented in any case. Tympanic membrane was not well visualized in most cases and hence, perforation was not separately commented upon.

Soft tissue masses in the middle ear was noted in 27 cases amounting to 67.5 percentage.

Of these, two were identified as neoplasms and 13 had bone erosions, hence categorized as Cholesteatoma.

The term Otomastoiditis was used for soft tissue filling the middle ear and mastoid without bony erosion, and so, 12 cases were radiologically diagnosed as Otomastoiditis.

Scutum showed erosion in 13 cases with all of them showing soft tissue in Prussacs space.

Those cases with soft tissue mass and bony erosion of middle ear was categorized as Cholesteatoma.

Ossicular erosion, particularly involving incus (8 cases) and malleus(6 cases) was noted.

Tegmen erosion was noted in one case.Other bony discontinuity like bony facial canal defect was not seen. Including all these cases, a final radiological diagnosis of Cholesteatoma was given in 13 cases (32.5%).

No obvious defects/ erosion or sclerosis of inner ear structures were noted in any of the cases in the present study.

Mastoid sclerosis was noted in 4 cases, and soft tissue exclusively filling mastoid air cells were noted in 2 cases. These cases with soft tissue filling only in mastoid was given a radiological diagnosis of isolated mastoiditis, 5%

These above radiological diagnoses were included in the heading of "infection", which accounted for 67.5 % of cases.

11 cases were "radiologically normal" without any obvious soft tissue/ bone erosion. A normal CT does not mean there is no pathology as some like mild otitis externa, facial palsy,etc may not be detected in CT. HRCT images may not well delineate tympanic membrane and it's perforations, hence ASOM or a quiescent CSOM may not be well diagnosed. (These are clinical diagnosis which may not be diagnosed in CT).

The other major radiologically detected pathology was neoplasms. In this study, two cases of soft tissue masses with intense enhancement, hence diagnosed as glomus tympanicum, the most common middle ear tumor according to literature. (9)

These findings are comparable with similar studies from elsewhere in literature. A study by Santhosh Patil et al, in 2021 from Raichur, India,notes infection to be the most common pathology, of which Cholesteatoma was around 39% being the most common. Although they have reported more number of neoplasms (6 cases), majority was acoustic neuroma(60%) (9)

In yet another 2017 study from Ahmednagar, India with 100 patients, infection was the most common pathology (78%) followed by trauma (12%) and 6% cases of neoplasms (2)

A 2019 study from Udaipur, India (10) also reports the most common pathology to be Infections (61%), but they have included more trauma cases as HRCT has high accuracy in detecting fracture lines.

Most authors suggest HRCT as a tool for detailing middle ear anatomy in preoperative work up for middle ear pathology (3,4,8,11)

V. CONCLUSION

HRCT of temporal bone can be used to detect soft tissue density and bony erosions in middle ear diseases and a broad radiological diagnosis can be suggested in individual cases. These can be interpreted in adequate clinical context. However, HRCT is best indicated as a preoperative work up for middle ear diseases.

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Case 18480

Eurorad

X-linked adrenoleukodystrophy: A case report

Published on 11.03.2024

DOI: 10.35100/eurorad/case.18480
ISSN: 1563-4086
Section: Neuroradiology
Area of Interest: CNS
Imaging Technique: MR
Case Type: Clinical Case
Authors: Akhil R. Nambiar, Fiza Hamza, Deepa S.
Patient: 12 years, male

Clinical History:

A 12-year-old boy presented with increasing pigmentation of the face. He was the only boy born of a non-consanguineous marriage. The antenatal period and infancy were uneventful. He had complaints of tiredness and fatigue, with one episode of syncope at school. The mother reported normal intelligence and school performance. No history of fever, head injury seizure or focal neurological deficits. MRI brain was done.

Blood investigations were normal except for raised ACTH levels (1456 pg/dL) and cortisol level of 2 g/dL.

Imaging Findings:

MRI showed T2 (Figures 1 and 2), FLAIR hyperintensity (Figure 4) in periventricular white matter, splenium of the corpus callosum, posterior limb of the internal capsule, white matter tracts of pons and medulla (Figure 3) (Schaumberg zones). T1 showed hypointensity (Figure 5) in the middle zone with enhancement.

There was no significant diffusion restriction.

The subcortical and anterior region was normal.

Discussion:

Background

X-linked adrenoleukodystrophy (X-ALD) is a metabolic disorder characterised by impaired peroxisomal beta-oxidation of very long-chain fatty acids (VLCFA; ? C22), which is reduced to about 30% of control levels [1]
X-ALD is the most common peroxisomal disorder. The disease is caused by mutations in the ABCD1 gene that encodes the peroxisomal membrane protein ALDP which is involved in the transmembrane transport of very long-chain fatty acids (VLCFA; ? C22). A defect in ALDP results in elevated levels of VLCFA in plasma and tissues [2].

VLCA accumulation may impair the capacity of oligodendrocytes and Schwann cells to maintain axonal integrity through mitochondrial dysfunction and calcium deregulation [3].

Clinical perspective

The clinical spectrum in males with X-ALD ranges from isolated adrenocortical insufficiency and slowly progressive myelopathy to devastating cerebral demyelination [2,4].

Addison only, cerebral ALD, and adrenal leucomyelopathy are the different manifestations of male X-linked ALD. The childhood cerebral form manifests most commonly between ages 2.5 and 10 years and is characterised by behavioural and cognitive disorders as well as extensive white matter lesions on MRI. Some cases may be asymptomatic too [2].

Imaging perspective

Depending on the anatomical location of the first T2 signal hyperintensity, of the five MRI patterns described by Loes et al. [5], parieto-occipital involvement is the most common (pattern 1: parieto-occipital white matter; pattern 2: frontal white matter; pattern 3: corticospinal tract; pattern 4: cerebellar white matter; pattern 5: concomitant parieto-occipital and frontal white matter).

In MRI, signal alterations might differ depending on the zonal distribution of the damaged white matter. The central zone is hypointense in T1-weighted images and significantly hyperintense in T2-weighted MRI images. The intermediate zone is isointense to hypointense, and the peripheral zone is moderately hyperintense in T2-weighted images [6].

MR spectroscopy reveals signs of neuronal loss manifested by a drop in NAA peak in the central part of the lesion, and a decrease in NAA with an increase in lipid/lactate peak in the peripheral region [6].

Outcome

For the majority of patients with X-ALD, there is currently no curative or preventive treatment.

Allogeneic HCT in the early stage of CCALD and endocrine replacement therapy for adrenocortical insufficiency may be recommended. Bezafibrate is a compound which can lower the levels of VLCFA in X-ALD cells by inhibiting VLCFA synthesis and in trials [2].

Take home message

T2 hyperintensity detected in MRI in the appropriate clinical setting (adrenal dysfunction) is important in identifying X-linked ALD.

All patient data have been completely anonymised throughout the entire manuscript and related files.

Differential Diagnosis List: Krabbe disease, Posterior reversible encephalopathy, Metachromatic leukodystrophy, X-linked adrenoleukodystrophy, Leukoencephalopathy with axonal spheroids and pigmented, Alexander disease

Final Diagnosis: X-linked adrenoleukodystrophy

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Figure 1

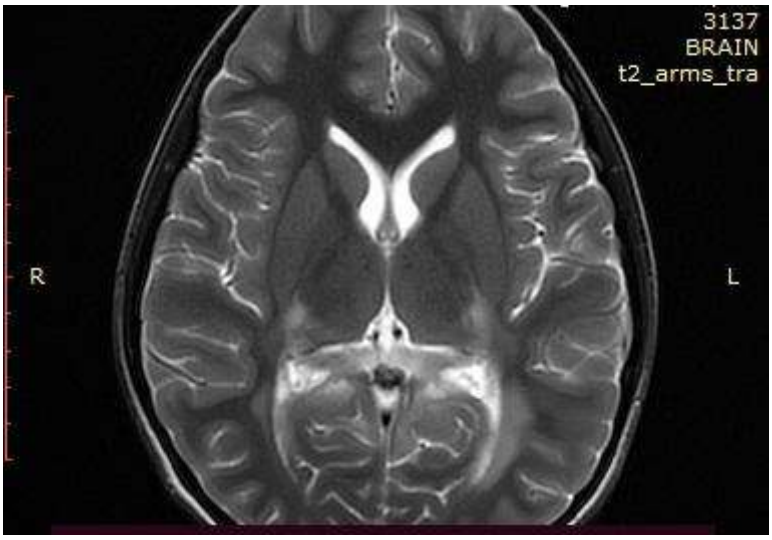
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Description: Brain axial T2 image, showing hyperintensity in the posterior periventricular region, splenium of the corpus callosum and posterior limb of the internal capsule. **Origin:** © Department of Radiodiagnosis, Government Medical College, Thrissur, India, 2023

Figure 2

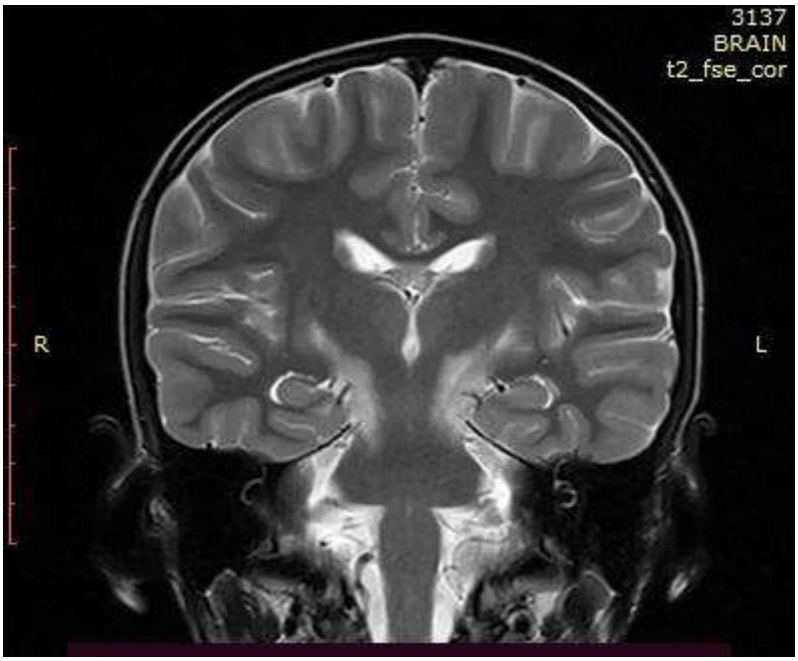
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Description: Brain axial T2 image, showing hyperintensity in the posterior periventricular region, splenium of the corpus callosum and posterior limb of the internal capsule. **Origin:** © Department of Radiodiagnosis, Government Medical College, Thrissur, India, 2023

Figure 3

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Description: Brain coronal section T2 image, showing hyperintensity in white matter tracts of pons and medulla. **Origin:** © Department of Radiodiagnosis, Government Medical College, Thrissur, India, 2023

Figure 4

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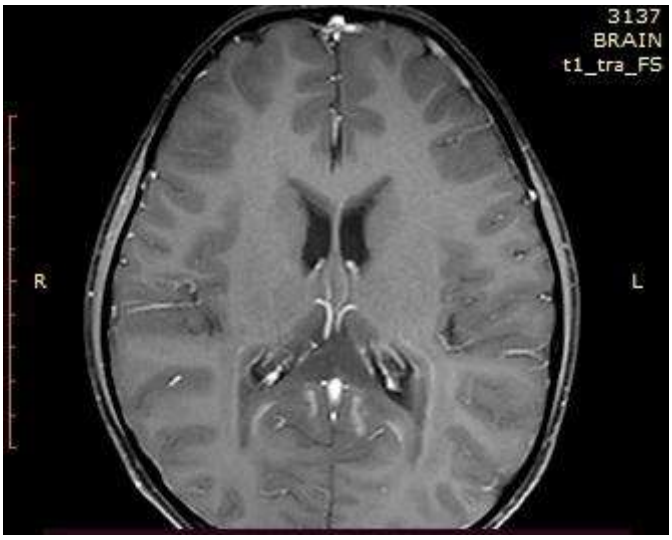


Description: Brain axial FLAIR image, showing hyperintensity in areas as in T2. **Origin:**

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Figure 5

a



Description: Brain axial T1 image, showing hypointensity in the region of the splenium of the corpus callosum, white matter tracts in the periventricular region. **Origin:** © Department of Radiodiagnosis, Government Medical College, Thrissur, India, 2023

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Original Research Article

The Predictive Accuracy of Magnetic Resonance Imaging (MRI) Findings in Identifying Anorectal Fistula over Intraoperative Findings

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Received: 18-12-2023 / Revised: 21-01-2024 / Accepted: 26-02-2024
Corresponding author: Dr. Praveen R Krishnan
Conflict of interest: Nil

Abstract:

Introduction: Fistula-in-ano, also referred to as the anal fistula, is an abnormal tract or cavity between the anal canal and perianal skin. The treatment of fistulas requires surgery. Proper manipulations, such as curettage and drainage of blind sinuses, abscess cavities, and accessory tracts, are the key for successful treatment. Owing to high soft tissue resolution of MRI, radiologists can provide detailed anatomic descriptions of the relationship between the fistula and the anal sphincter complex, localization of the site of internal opening of anal fistula, definition of the primary and secondary tracts and their relationships with the sphincter muscles, and presence of horseshoe fistulas and abscesses, thereby allowing surgeons to choose the best surgical treatment, significantly reducing recurrence of the disease or possible secondary effects of surgery, such as fecal incontinence

Methodology: Diagnostic test evaluation to compare the predictive accuracy of MRI findings in identifying anorectal fistula over intraoperative findings in 30 patients referred with clinical diagnosis of perianal fistula from Department of Surgery, Govt TD Medical College, Alappuzha.

Result: The study sample included 22 males and 8 females. MRI had 100% sensitivity and specificity in identifying external opening, type of ano rectal fistula and in detecting abscesses. MRI and surgery correlation was excellent for St James hospital university classification Grades 3, 4 and 5 perianal fistula with sensitivity and specificity of 100%. For grade 1 and 2 perianal fistula, MRI and surgery finding had significant correlation; with sensitivity of 87.5% and specificity of 100% for grade 1 and for grade 2 fistulas the sensitivity was 100% and specificity 95.7%. For identifying secondary tract MRI had sensitivity of 84.6% and 88.2%. For all statistical interpretations, $p<0.05$ was considered the threshold for statistical significance.

Conclusion: Correct identification of perianal fistulae and proper grading of fistulae are possible by MRI with very good predictive accuracy and thereby ensuring best surgical outcome to patient.

Keywords: MRI- Magnetic Resonance Imaging.

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Introduction

Fistula is an abnormal connection between two epithelized surfaces. Fistula-inano, also referred to as the perianal fistula, is an abnormal tract or cavity between the anal canal and perianal skin [1] Many anal fistulae are suspected to arise from infected anal glands that open into the anal crypts at the dentate line, a theory known as the crypto glandular hypothesis [2], whereby inter sphincteric gland infection represents the initial event, which leads to formation of an inter-sphincteric fistula track or abscess if the draining duct becomes obstructed.

Chronic infection in the primary site in the inter-sphincteric plane produces a persistently discharging fistula or recurrent abscess. [3] Around 35% of patients develop recurrent disease after initial presentation for crypto glandular perianal abscess [2]. Perianal fistulas may also be caused by several inflammatory conditions and events including Crohn's disease, pelvic infection, tuberculosis, and diverticulitis, trauma during childbirth, pelvic malignancy, and radiation therapy.

However, most are idiopathic. [3] The incidence of perianal fistula ranges from approximately 1 to 2 per 10,000 individuals with an approximate 2:1 male to female predominance and causes significant morbidity to the patient.2 The treatment of fistulas requires surgery. [3] Proper manipulations, such as curettage and drainage of blind sinuses, abscess cavities, and accessory tracts, are the key for successful treatment. [1] While this

is successful in most cases, it is associated with a significant prevalence of recurrence. Successful surgical management of anal fistulas requires accurate preoperative assessment of the course of the primary fistulous track and the site of any secondary extension or abscesses. [3] Physical examination alone may not be sufficient in detecting these features of the fistula, and imaging modalities play a very important complementary role. [1]

Although imaging techniques played a limited role in evaluation of perianal fistulas in the past, it is now increasingly recognized that imaging techniques, especially magnetic resonance imaging, may play a crucial role. [3] MRI use in anal fistulas was first reported in the early 1990s.

In that initial report, MRI showed 87.5% concordance with the surgery. MRI has the ability to differentiate soft tissues, identify tracts outside the anal canal, and demonstrate the images compatible with the surgically relevant plane. [1] The Association of Coloproctology of Great Britain and Ireland defined MRI as an imaging technique with high sensitivity and specificity for the diagnosis of the primary fistula tract and recommended this technique for imaging assessment of the complex or recurrent fistulas.

Owing to high soft tissue resolution of MRI, localization of the site of internal opening of anal fistula, definition of the primary and secondary tracts and their relationships with the sphincter muscles, and presence of horseshoe fistulas and abscesses can be more accurately depicted preoperatively compared with physical examination. [1]

MR imaging allows identification of infected tracks and abscesses that would otherwise remain undetected. Furthermore, radiologists can provide detailed anatomic descriptions of the relationship between the fistula and the anal sphincter complex, thereby allowing surgeons to choose the best surgical treatment, significantly reducing recurrence of the disease or possible secondary effects of surgery, such as fecal incontinence.

Materials and Methods

Aim: To assess the diagnostic accuracy of MRI in delineation of anorectal fistula tract.

Objectives

Primary Objective: Comparison of the predictive accuracy of MRI findings in identifying anorectal fistula over intraoperative findings in patients referred with clinical diagnosis of perianal fistula from Department of Surgery, Govt TD Medical College, Alappuzha.

Secondary Objective:

- Assess the type of anorectal fistula
- Position of internal opening
- Grading of fistula by St James University hospital MRI classification.

Inclusion Criteria:

- All patients referred from Department of Surgery with clinical diagnosis of perianal fistula
- All patients presenting with local pain and discharge through perianal region with a past history of perianal abscess.
- Patient who had given consent for this study.
- No contraindication for MRI study.

Exclusion Criteria:

- General contraindications for MRI (metallic implants in their body, foreign body in their eyes, pacemaker, pregnancy and claustrophobia).
- All congenital fistulas.
- Fistula associated with Malignancy.
- Inflammatory bowel disease patients 54.
- Incontinent patients.
- Patients with rectovaginal fistula.
- Patient with deranged renal function test.
- Cases unfit or refused for surgery.

Study Design: Diagnostic test evaluation.

Study Period: 1 year.

Study Setting: The study was conducted in Department of Radiodiagnosis of Govt. TD Medical College, Alappuzha in patients referred from department of Surgery with clinical diagnosis of perianal fistula.

Study Population: All patients who came to Department of Radiodiagnosis with clinical diagnosis of anorectal fistula.

Sampling Method: Probability sampling.

Sample Size: Sample size of 30 was used in the study.

Result

In our study, the youngest patient was aged 17 years and oldest was 68 years. The age distribution in the patient population studied was between 17-68 years with the most number of patients (33.3%) falling in the groups 21- 30 and 41-50 years.

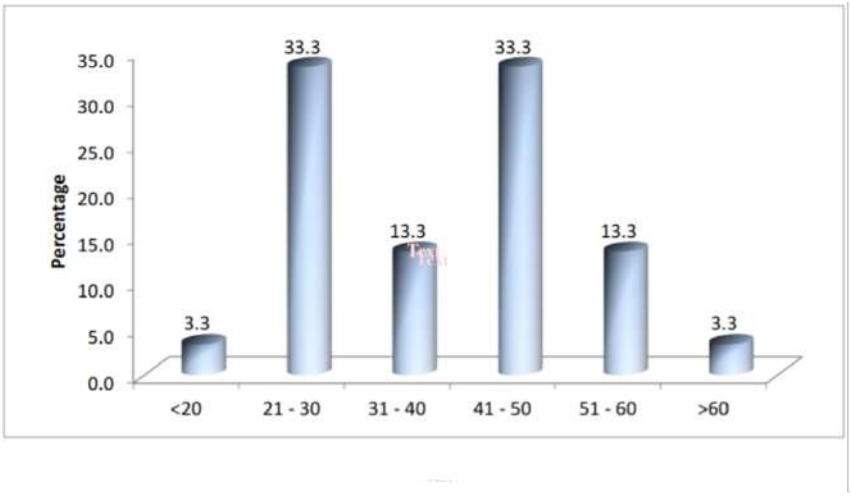


Figure 1: Percentage distribution of the sample according to age

In this study of 30 patients with perianal fistula, majority of patients were males constituting 73.3 % and 26.7 % were females.

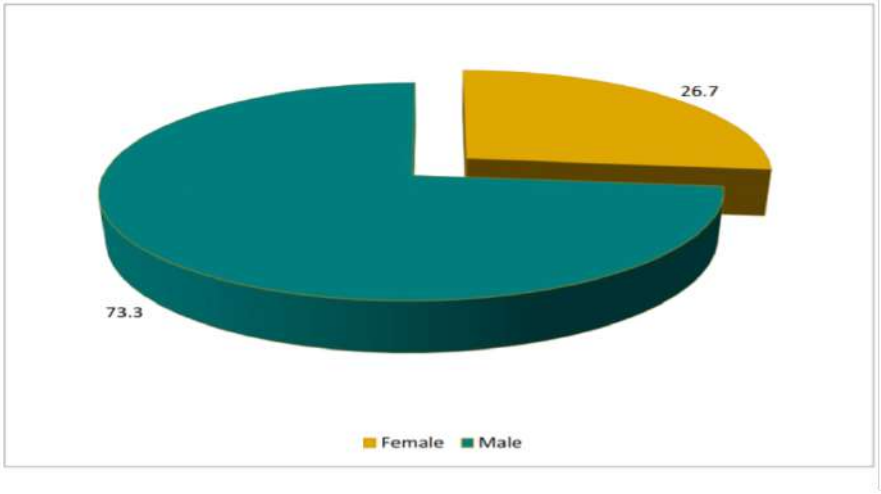


Figure 2: Pie chart showing sex distribution

In our study, when the fistulous tracts were analysed, majority of the patients (29 out of 30) had a single external opening (96.67%). Multiple external openings were seen in 1 patient (3.33%)

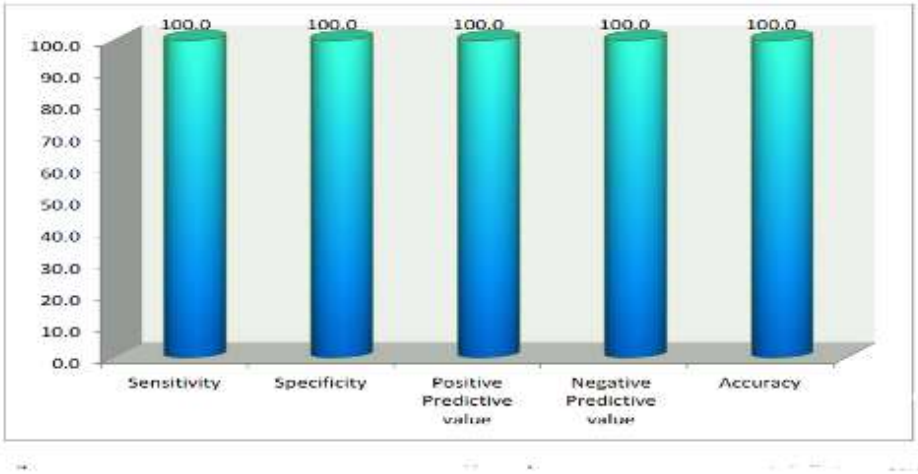


Figure 3: Predictive accuracy of MRI finding in identifying anorectal fistula over intra operative finding in patients for number of external opening.

Most commonly the opening was found between 4 and 6'o clock position (11 patient).The next common location being 7 to 9'o clock position which was found in 8 patients. One patient in the study had 2 external openings one between 1 to 3 'o' clock and other between 4 to 6 'o' clock position in MRI and was categorized in column named 1-3/ 4-6 'o' clock position of table 6 and 7. The intraoperative findings were in agreement with MRI finding.

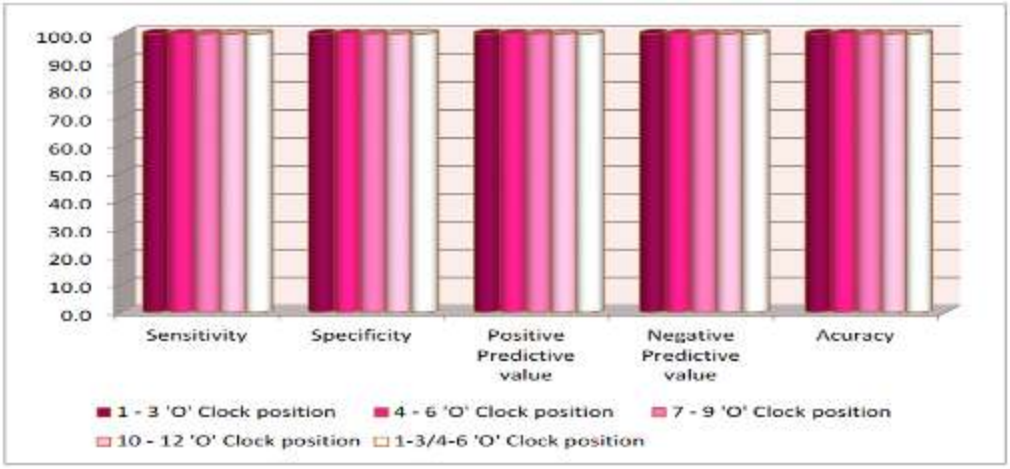


Figure 4: Predictive accuracy of MRI finding in identifying anorectal fistula over intra operative finding in patients for number of external opening clock position.

When analyzing the internal opening, it was single in 96.67 % of patients (29 out of 30) and multiple in about 1 patient (3.3 %) (Table 8, figure 31). Most commonly, the internal opening was found in 6'o clock position in 13 patients (26%). The operative findings were well correlating with the study with regard to the site of the internal openings.

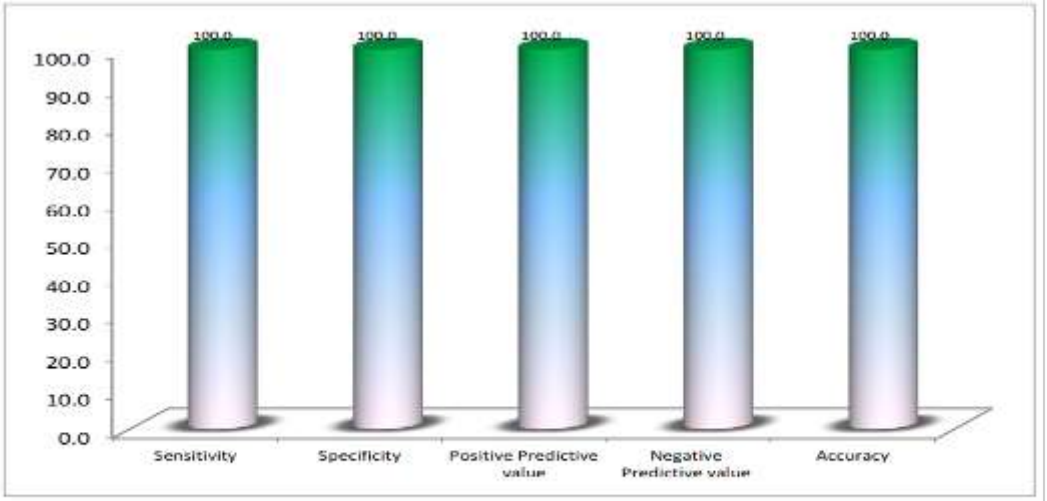


Figure 5: Predictive accuracy of MRI finding in identifying anorectal fistula over intra operative finding in patients for internal opening

In our study MRI was not able to delineate secondary tract in 2 cases which was found to be present during surgery. In 2 other cases reported to have secondary tract in MRI, the operating surgeon could not find any secondary tract In our study the predictive accuracy of MRI in identifying secondary tract had a sensitivity of

84.6 % and specificity of 88.2 % In our study, abscesses were identified in 17 out of 30 patients (56.67 %).Our study showed sensitivity and specificity of 100% and 100% for abscesses.

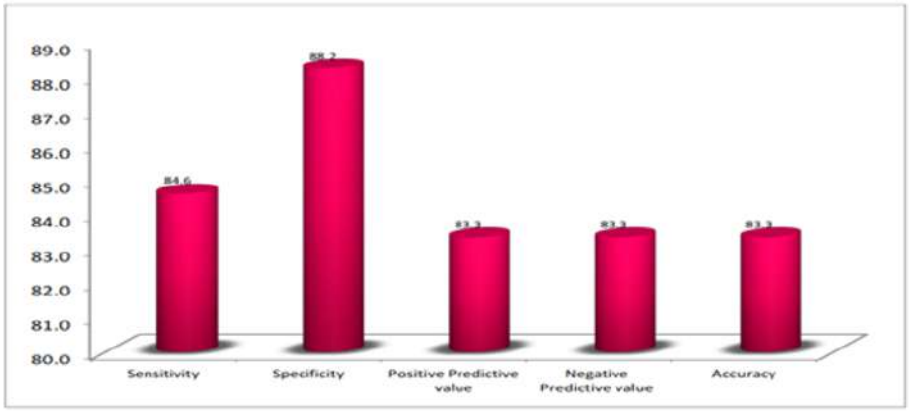


Figure 6: Predictive accuracy of MRI finding in identifying anorectal fistula over intra operative finding in patients for number of secondary tract

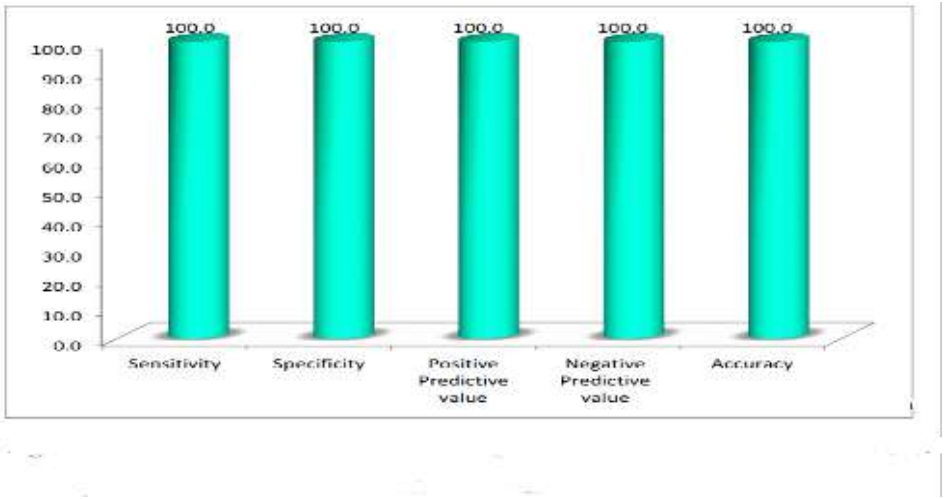


Figure 7: Predictive accuracy of MRI finding in identifying anorectal fistula over intra operative finding in patients for number of abscess.

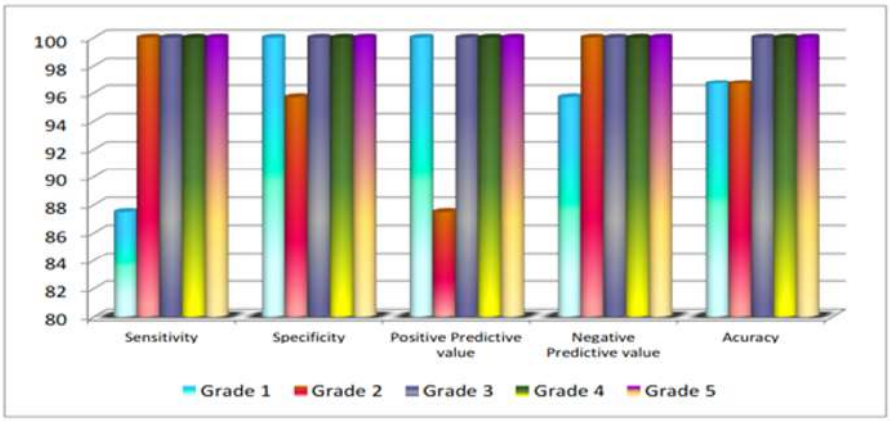


Figure 8: Predictive accuracy of MRI finding in identifying anorectal fistula over intra operative finding in patients for ST James grading of fistula

MRI findings for Grade 1 and 2 fistulas showed discrepancies in identification (One patient classified as St James grade I as per MRI was found to be St James grade II intraoperatively as the operating surgeon found an additional secondary tract). When the St James's University Hospital MRI grading according to which patients were classified was compared with that of the peroperative findings, the correlative value was the best for the fistulas of grades III, IV and V. The per operative findings correlated exactly with the MRI findings for grades 3 to 5.

Discussion

Of the total 30 patients included in the study, 22 patients were males 73.3% and 8 patients were females (26.7%). Most of them were in the age group of 21 to 30 years (10 out of 30) and 41 to 50 years (10 out of 30).

Among the 30 patients included in the study group, the most prevalent type of fistula was intersphincteric type 50% (15 out of 30 patients) followed by trans sphincteric type 43.33% (13 out of 30 patients).

The operative findings were well correlating with the study with regard to type of fistula. This was correlated with the results of study done by Parks et al (1976) who also reported intersphincteric type of fistula to be the commonest in their study. [5] The results were also consistent with the study done by Morris et al. who in their study mentioned that most common perianal fistulas were intersphincteric fistulas**.** [6]

In our study, when the fistulous tracts were analyzed, majority of the patients (29 out of 30) had a single external opening. Most commonly the opening was found between 4 and 6'o clock position (11 out of 30 patients). The next common location being 7 to 9'o clock position (7 out of 30 patients). The operative findings were well correlating with the study with regard to the site of the openings.

When analyzing the internal opening, it was single in majority of patients (29 out of 30). Most commonly, the internal opening was found in 4 to 6'o clock position (13 out of 30 patients). There was discrepancy between MRI and operative findings in 2 cases with regard to clock position of internal opening. One case reported to have internal opening at 4 to 6'o' clock position in MRI, during surgery was found to have internal opening at 7 to 9 'o'clock position.

And another case reported to have internal opening at 7 to 9'o' clock position in MRI, during surgery was found to have internal opening at 4 to 6 'o'clock position In our study, we classified perianal fistulas on the basis of St James's University Hospital Classification. This revealed that grade IV fistulas were the commonest which was found in 9 patients. The second most common type is grade II fistulas which were found in 8 patients. This is in accordance with the study done by Esra Ozakavukcu et al. [7]

In our study, 13 out of 30 patients had secondary tracts. Identification of all these tracts is essential for complete eradication of the disease. Failure of preoperative identification of secondary tracts is the most common cause for recurrence of the disease. [8] As already known, active fistulous tracts enhance well with gadolinium contrast.

This helps in better delineation of fistulous tracts. In our study MRI was not able to delineate secondary tract in 2 cases which was found to be present during surgery. In 2 other cases reported to have secondary tract in MRI, the operating surgeon could not find any secondary tract. Retrospective Radiodiagnosis – surgery interdepartmental discussion and analysis was done about these 2 cases and the conclusion made was that, these 2 patients had underwent fistulotomy 3 months after MRI during which they were on conservative medical management and the secondary tracts might have healed.

In our study the predictive accuracy of MRI in identifying secondary tract had a sensitivity of 84.6 % and specificity of 88.2 %. In our study, abscesses were identified in 17 out of 30 patients. MRI and surgery correlation had 100 % sensitivity and 100% specificity for detecting abscesses. This is superior to the result given by Maier et al in his study [9] that showed an 84% sensitivity of MRI for the identification of perianal fistulas and abscesses. His study gave 15% false positive results which were eliminated in our study.

The better results of our study may be attributed to the use of contrast enhanced imaging. So, contrast enhanced imaging should be routinely included in MRI protocols of anal fistula examination, even with no abscess or collection seen at the precontrast images. This was in correlation with the study done by M.E. Agha et al. [10]

In our study, there was significant correlation between the fistulous tracts identified on MRI and the surgical findings. Fistulectomy was done in all 30 patients and intraoperative findings correlated well with the MRI findings for grades 3 to 5. Grade 1 and 2 fistulas showed discrepancies in identification of tracts. MRI in our study could not delineate the secondary tracts in 1 patient and was wrongly classified as grade 1. The result obtained (86.78%) was comparable with the result obtained from the previous study conducted by Lunniss et al which reported a concordance rate of 86- 88% between MRI and surgical findings. [11] In another study by Beets- Tan et al, who compared the results of MRI with that intraoperative findings, the

sensitivity and specificity were 100% and 86% respectively. [12]

Conclusion

Perianal fistula, though an uncommon problem may be chronic and recurrent. It may present with numerous complications like secondary tracks and abscess cavities. Incomplete evaluation of these complications can result in residual and recurrent disease. So, complete preoperative evaluation of perianal fistulas is warranted. Also, to prevent the injury to external sphincter and resultant fecal incontinence, it is necessary to establish the relationship of sphincter with the fistulous tracks. MRI satisfies all these needs of surgeons and helps in planning of surgery. MRI provides finer anatomic details of fistula and also identifies secondary tracks and abscesses. Contrast enhanced MRI can identify active inflammation of tracks. Correct identification of perianal fistulae and proper grading of fistulae are possible by MRI with very good predictive accuracy and thereby ensuring best surgical outcome to patient.

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Response And Clinical Outcome of Locally Advanced Epithelial Ovarian Cancer to Neoadjuvant Chemotherapy with Paclitaxel and Carboplatin

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Abstract

This is a single institutional study of stage 3 and 4 epithelial ovarian cancer treated with neoadjuvant chemotherapy, paclitaxel and carboplatin during 2018- 2020 and underwent interval cytoreduction and was done to evaluate the pathological response in patients treated with neoadjuvant chemotherapy (NACT) for unresectable advanced-stage ovarian cancer. Response were classified into complete pathological response (cPR) and partial pathological response (pPR). Partial pathological response is again classified as microscopic residual and macroscopic residual disease with size <1cm or >1cm. Clinical outcome of the patient assessed as on January 2022 and classified as no evidence of disease(NED), relapsed treated and NED, relapsed treated and is having persistant disease, relapsed and progressed on palliative care, relapsed and progressed to death. Fifty-one patients (36 stage 3 and 15 stage 4) who fulfilled inclusion criteria after a median follow up of 22 months had Pathological complete response and partial response of13.7% and 86.3% respectively. Majority of patients relapsed and only 29.4% of patients were disease free and 17.6% of patients progressed to death. Clinical outcome is found to be better in patients with complete pathological response or microscopic residual disease or macroscopic residual disease < 1cm (p value- 0.00092). Complete pathological response of advanced carcinoma ovary is rare. Patients with complete pathological response or microscopic residual disease or macroscopic residual disease of size <1cm after NACT has less incidence of relapse.

Keywords: Ovarian Cancer, Neoadjuvant Chemotherapy, Pathological Response

Introduction

sOvarian cancer is the fourth most common cancer in Indian women. Age standardised incidence rate of the same is 6.6 cases per 100000 (GLOBOCON 2020).[(1)]Epithelial ovarian carcinoma is the most common type ovarian cancer which includes high grade serous carcinoma (70%), endometrioid carcinoma (10%), clear cell carcinoma (10%), mucinous carcinoma (3%), low grade serous carcinoma (<5%).[(2)] Germ cell

tumours account for 5% of ovarian cancers and sex cord stromal tumours account for 7% of ovarian cancers.[3] All these cancers vary in their prognosis based on the difference in their molecular profile, clinical presentation, pattern of spread and response to chemotherapy. 70% of epithelial ovarian carcinoma presents in stage 3 or 4. Delay in diagnosis occurs due to non specific symptoms in patients and absence of effective screening modalities. Management of carcinoma ovary depends on the stage of the disease. Surgery is the primary modality of management in carcinoma ovary. In stage 1A and 1B tumours fertility sparing surgical approaches can also be considered. Complete resection during cytoreductive surgery is the most important independent prognostic factor in advanced epithelial ovarian cancer. Neoadjuvant chemotherapy(NACT) is a treatment approach that is getting popularity as an alternative to primary cytoreductive surgery for management of advanced epithelial ovarian cancer. Several studies suggest that neoadjuvant chemotherapy offers better optimal debulking with less surgical morbidity in females with ovarian carcinoma compared with primary cytoreductive surgery.[4,5]

The treatment of surgically unresectable epithelial carcinomas of ovary with neoadjuvant chemotherapy using paclitaxel and carboplatin is popularized world wide recently. This is an effort to analyse the response to the above mentioned treatment conducted in an Indian setup as a single institutional study done at a Government Medical College in Kerala.

Patients and methods

This is a single arm retrospective observational study done in the Department of Radiation oncology, Government Medical College, Thrissur, Kerala, India.

Patients who attended the Radiotherapy OPD of Government Medical College, Thrissur with histologically proven, previously untreated, carcinoma of ovary during 2018 - 2020 with inclusion criteria:

1 Tumours of clinical stage 3 - 4
2 Surgically inoperable, loco regionally advanced disease
3 Age between 18 and 70 years
4 Perfomance score of 0- 2
5 WBC count greater than 4000 cells/ml
6 An absolute neutrophil count greater than 37.5%
7 Platelet count more than 1 lakh cells/ml
8 Serum creatinine < 1.5mg/dl
9 Creatinine clearance >80ml/min
10 Hemoglobin value > 8gm%
11 Received neoadjuvant chemotherapy with paclitaxel (175mg/m2)and carboplatin (5AUC) 3 weekly cycle

Were selected to apply the exclusion criteria:

1 Operable carcinoma of ovary
2 History of coronary artery disease, renal disease, uncontrolled hypertension.
3 Previous history of any carcinoma and irradiation

Datas of the patients fulfilling the above criterias including age, performance score, stage of the disease, initial imaging modality, number of chemotherapy cycles are recorded from the medical records library All operable patients after neoadjuvant chemotherapy who were send for cytoreductive surgery are selected from the cohort and response to chemotherapy is assessed with postoperative histopathology report and is classified as partial pathological response and complete pathological response depending on the residual disease. Patients who drop out or do not complete planned course of treatment are excluded. Patients are clinically assessed as on January 2022 and response is assessed as follow up with no evidence of disease (NED), relapsed treated and NED, relapsed treated and is having persistent disease, relapsed and progressed on palliative care and relapsed and progressed to death

Results

51 patients treated between 2018- 2020 was selected. 36 patients had stage 3 disease (70.6%) and 15 patients had stage 4 disease (29.4%). Patient characteristics are detailed in Table 1. Median age of patients was 55 years (range, 36- 75 years).

7 patients underwent ultrasound (USG) abdomen as initial imaging modality whereas 37 patients underwent contrast enhanced computed tomography (CECT) abdomen and pelvis and 6 patients underwent magnetic resonance imaging (MRI) pelvis. Only 6 patients underwent positron emission tomography (PET).

All underwent chemotherapy with paclitaxel and carboplatin chemotherapy. Number of chemotherapy cycles varied ranging from 3- 8 cycles. 4 patients received less than 4 cycles of chemotherapy whereas 41 patients received 4- 6 cycles of chemotherapy and only 6 patients received more than 6 cycles of chemotherapy.

General characteristics of patients- Table 1

	NO. of patients
Age	
</=40 years	5 (9.8%)
41- 50 years	10 (19.6%)
51- 60 years	16 (31.4%)
>/61 years	20 (39.2%)
Stage	
3	36 (70.6%)
4	15 (29.4%)
Imaging modality	
USG	7(13.7%)
CECT	37(72.5%)
MRI	6 (11.8%)
PET	1(2%)
Number of chemotherapy	
<4	4 (7.8%)
4- 6	41 (80.4%)
>6	6 (11.8%)

All patients underwent interval cytoreduction after completion of chemotherapy and reevaluation with imaging. Histopathological report was studied and the pathological response to chemotherapy was classified as complete pathological response which was seen in 7 patients (13.72%) and partial pathological response seen in 44 patients (86.27%)

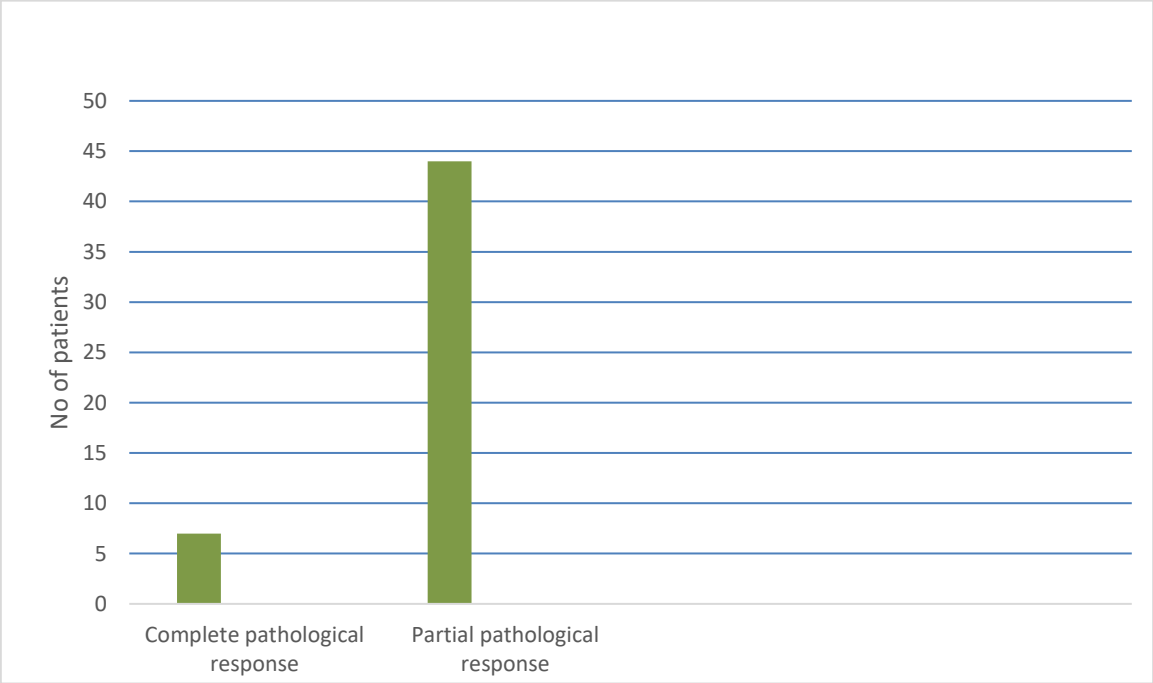


Figure 1- pathological response

Partial pathological response was then classified as microscopic and macroscopic residual tumour. Out of 44 patients with partial response, 7 patients had microscopic partial response (15.9%) and 37 patients had macroscopic partial response (84.1%).
The size of the residual tumour in macroscopic disease was assessed and it was noted that 3 patients only had a residual tumour of size <1cm (6.82%) and 31 patients had tumour size >1cm (70.45%)- Table 2

Residual disease- Table 2

Residual disease	No of patients
Microscopic disease	7 (15.9%)
Macroscopic disease < 1cm	3(6.82%)
Macroscopic disease > 1cm	34(77.27%)

After a median follow up of 22 months (5- 42 months) patients were reassessed on January 2022 and were identified to have NED in 15 patients (29.4%), relapsed treated and NED only in 1 patient (1.96%), relapsed treated and is having persistent disease in 16 patients (31.37%), relapsed and progressed on palliative care in 10 patients (19.6%) and relapsed and progressed to death were 9 patients (17.65%)- Table 3

Clinical outcome- Table 3

Clinical outcome	No of patients
NED	15 (29.4%)
Relapsed, treated and NED	1 (2%)
Relapsed, treated with persistent disease	(31.4%)
Relapsed and progressed on palliative care	10 (19.6%)
Relapsed and progressed to death	9 (17.6%)

So while comparing the response with the outcome by combining the above two associations we can see that 15 patients has attained a complete pathological response or microscopic pathological response or macroscopic residual tumour <1cm to the neoadjuvant chemotherapy. In these 15 patients 11 patients have clinically NED at the time of reevaluation (p- 0.00092)

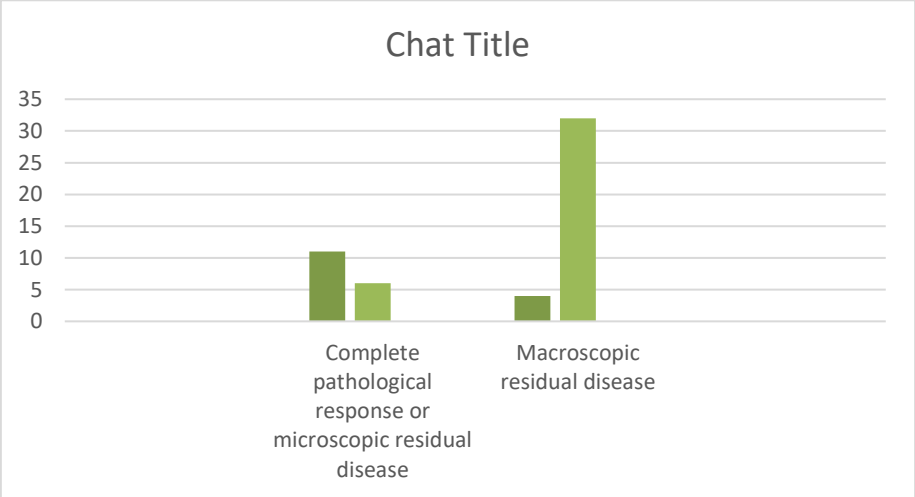


Figure 2- Complete pathological response and microscopic disease vs macroscopic disease

Discussion

The main treatment modality of stage 1 to 4 epithelial ovarian carcinoma is surgery. Complete resection during the cytoreductive surgery is one of the prognostic factor in advanced epithelial ovarian carcinoma. Survival is found to have an inverse relationship with the residual disease after the surgery. In a meta analysis of stage 3 and 4 epithelial ovarian cancer which included 6885 patients found that 5.5% increase in median survival rates were seen with every 10% increase in the maximal cytoreduction rates.(6)

Another review of 11999 patients with advanced carcinoma of ovary found that median overall survival was 70 months in patients who had no residual disease compared with 53 months in patient s with 1-5mm residual lesion, 40 months in patients with 1-10mm residual lesion and 30 months in patients with >10mm residual lesion.(7) So the aim of the cytoreductive surgery should be to achieve a complete resection with no residual disease.

Patients with advanced stage carcinoma ovary rarely achieves optimal debulking by primary cytoreductive surgery. So NACT before cytoreductive surgery was extensively studied in carcinoma ovary aiming at improving the debulking and thereby improving the survival of the patient. But EORTC and MRC trials has shown no benefit in the progression free survival(PFS) and overall survival(OS) between patients who underwent primary cytoreductive surgery and who underwent NACT followed by cytoreduction. (8,9)

The optimal duration for NACT is not defined in the literature. Platinum agents are the most active class of compounds in the adjuvant treatment of ovarian cancer. Before 1980s alkylating based regimens including cyclophosphamide and doxorubicin were used with a clinical response rates of 15- 20%. GOG 47 demonstrated an improvement in the clinical complete response rates(51% vs 26%) and PFS (13 vs 8 months) with addition of cisplatin with cyclophosphamide and doxorubicin.(10) since then cisplatin was used extensively in both single agent and multi agent drug trials.

GOG 111 compared cisplatin and paclitaxel vs cisplatin and cyclophosphamide in womens with suboptimally debulked large ovarian carcinomas and found thatimproved clinical response rates (73% vs 60%) and PFS (18 vs 13 months) and OS (38 vs 24 months) was seen in patients with paclitaxel containing arm.(11) Similarly a non inferiority trial of GOG compared paclitaxel cisplatin with paclitaxel and carboplatin with comparable median PFS and OS.(12) Hence paclitaxel and carboplatin based chemotherapy is more preferred as the regimen in NACT for advanced ovarian carcinoma.

Only few studies are there which evaluates the pathological response of ovarian cancer to the NACT. According to the studies pathological complete response is rarely observed in carcinoma ovary and ranges from 0- 14% and is demonstrated to have improved clinical outcomes. (13,14,15,16,17,18)

Till date no histopathological criteria has been established to describe treatment response after neoadjuvant chemotherapy. Residual tumour size after neoadjuvant chemotherapy was the only criterion significantly correlated with treatment response and subsequent overall survival. Studies has shown an overall survival of 45.6 months with NACT in advanced ovarian carcinoma.(13)

In a small retrospective study done in 16 patients with advanced epithelial ovarian cancer a complete pathological response of 12.5% and a partial pathological response of 50% is noted.(14)

Retrospective study done in 58 patients who evaluated the pathological response and event free survival has shown that 13.79% patients has attained complete pathological response but the degree of histological response has a limited impact on the survival when complete debulking surgery is achieved at interval cytoreduction.(15)

A retrospective study done by Petrillo et al in 322 patients assessed the pathological response after NACT as complete pathological response, microscopic and macroscopic residual disease. cPR is an uncommon event in patients receiving NACT and is associated with a longer progression-free survival and overall survival compared with women showing no cPR, even in patients receiving IDS with no gross residual disease. And the proposed classification of pathological response is expected to serve as an easily assessable and highly valuable prognostic tool in this clinical setting in the future. This was the classification that we considered in our study too.

No data evaluated relationship between the clinical outcome and the pathological response so far. Newer neoadjuvant regimens including PDL1 inhibitors are tried in the treatment of carcinoma ovary and the possibility of a personalised treatment with the help of molecular markers are under trial[19]

Conclusion

In our study, pathological complete response was noted in 13.7% of patients similar to the data available till date showing that complete response with NACT is a rare observation. In patients who completed NACT and cytoreductive surgery, the incidence of disease relapse is very high and majority of such patients are managed with second or third line chemotherapy. There is good clinical response with decreased incidence of relapse for patients with complete pathological disease, microscopic residual disease or macroscopic residual disease <1cm after NACT than those with macroscopic residual disease >1cm after NACT, who relapsed after the treatment. This is a potential area of research.

Limitations

Our data is single institutional retrospective data with small sample size. Hence prospective studies with large sample size is recommended for the confirmation of the result

Conflict of Interest

Nil

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Statements and declarations

Study is done to emphasise and compare results of the standard treatment options at our centre with the national and international data for general welfare. The study is completely funded by the institution and the investigators and there is no other funding agencies and the study has no financial interests

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CASE REPORT

ORIGINAL RESEARCH PAPER

Oncology/Radiotherapy

A RARE CASE OF CARCINOMA OROPHARYNX WITH SYNCHRONOUS PRIMARY LARYNX- A CASE REPORT

KEY WORDS: Carcinoma oropharynx, carcinoma larynx, synchronous primary

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ABSTRACT

This is the case report of a 60 year old patient presented with hoarsness of voice, evaluated by ENT examination was found to have two primaries, in larynx and oropharynx.Treated with concurrent chemoradiation with three weekly cisplatin and radiation dose of 66Gy/30# to both primaries and positive nodes and nodal station .60Gy/30# to other lymph node stations with 6 MV IMRT. The case being reported here is unusual as the index tumour is in the oropharynx which is the least common site when compared with other studies and Synchronous primary tumours with primaries in oropharynx and larynx has not yet reported.

INTRODUCTION

Head and neck region have a global incidence between 400,000 and 600,000 new cases per year and 223,000 and 300,000 yearly deaths[1]. They are the sixth leading human cancer worldwide[2]. More than 90% of these cancers arise from the mucosal surfaces of the oral cavity, oropharynx and larynx[3-4].

Carcinoma oropharynx constitute 10% of annual incidence of head and neck cancers[5], where the incidence of carcinoma oropharynx is increasing despite decrease in overall head and neck cancer incidence. In India oropharyngeal cancer is the 18th most common cancer with incidence of 1.6%[6].

Oropharyngeal cancers have predilection of submucous extension and are seen as erythematous region without distinct border or ulceration.

They have lymphatic spread to level 1,2,3 and 4 cervical lymph nodes with 0.3% skip metastasis. Distant metastasis is uncommon and is seen in about 4- 26% of patients during the whole course of disease where the most common site is lung and then comes bone and liver[7].

Highest risk of second primary cancer is in head and neck followed by esophagus and lung[8].Second primary cancers are the leading cause of death in patients with head and neck cancers. Oropharyngeal cancers have lowest risk of second primary cancer.

Multiple malignancies can be of two types; synchronous (second primary neoplasm (SPN) is diagnosed within 2-6 months of diagnosis of index tumour) or metachronous (second primary tumour is diagnosed 6 months following diagnosis of primary tumour)[9-10]. 46.9% patients with second primary head and neck present as synchronous[11].

Synchronous malignancies in head and neck cancers are mainly due to field cancerisation and oncogenic viruses. In patients with squamous cell carcinoma of head and neck the index cancer site and smoking status effect the risk and distribution of second primary malignancy.

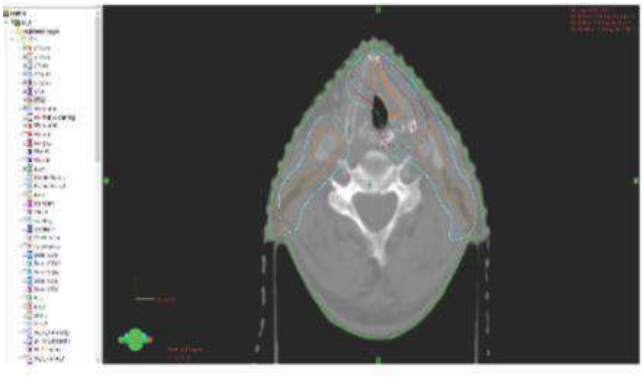


Figure 1: Contour of lesion treated with IMRT at the level of larynx

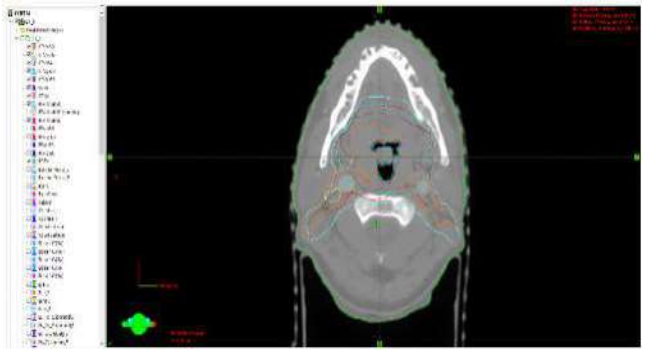


Figure 2: Contour of lesion treated with IMRT at the level of oropharynx

Case Description

61 year old chronic smoker and alcoholic with pack year 40 presented with complaints of hoarsness of voice for 3 months. There was no associated symptoms including throat pain, dysphagia, odynophagia, noisy breathing, ear ache, breathlessness, foreign body sensation in throat, difficulty in hearing. There was no associated systemic symptoms including cough, hemoptysis, neck pain ,back pain, swelling in neck or elsewhere in the body, visual symptoms, headache, bone pain. There was no associated loss of weight and loss of appetite.

He was evaluated in a nearby hospital with ENT examination suggestive of irregular growth in bilateral posterior pillar and under surface of uvula and pharyngeal arch. Video laryngoscopy was suggestive of slough covered whitish growth in left entire length of true vocal cord with impaired mobility of left vocal cord. On neck examination patient had a 2x2cm firm mobile right level 2 lymph node.

He underwent a direct laryngoscopy and biopsy from the laryngeal lesion and a biopsy from the oropharyngeal lesion. Histopathology is suggestive of squamous cell carcinoma well differentiated. Patient was referred to our centre for further evaluation and management. He was further evaluated from our centre with and MRI neck suggestive of a 2x1.8x1.6 cm ill-defined nodular mass in the lower part of soft palate more on right side with lesion extending to tonsillar region on right side suggestive of carcinoma soft palate. Bilateral palatine tonsils were bulky and a soft tissue thickening of left vocal cord with irregular surface was seen suggested skip metastasis. Few enlarged deep cervical lymph nodes were noted at level 1b and 2 on right side and largest was 2.3x

1.9cm with few enhancing lymph node at level 1b and 2 on left side. CECT thorax was done suggestive of no lung metastasis.

Patient was diagnosed as Carcinoma soft palate extending to tonsil on right with regional lymph node metastasis and a synchronous primary larynx. TNM stage- cT2N2bM1- IV.

Patient was planned for neoadjuvant chemotherapy with TPF(docetaxel 75mg/m2 D1, cisplatin 75mg/m2 D1, 5FU 1000mg/m2 D1-2) 2-3 cycles followed by radical concurrent chemoradiation. Patient after completion of first cycle of TPF chemo had complaints of chest discomfort and ECG change suggestive of T inversion in V2 and was diagnosed with NSTEMI and was treated for the same. So further cycles of chemotherapy was deferred and was started on radical CCRT.

Radical radiation 66Gy/30# was given to GTV primary, GTV nodes and 60Gy/30# to other lymph node stations with IMRT with 6MV photons.

GTV PRIMARY- soft palate lesion extending to tonsil and left vocal cord
GTV NODE- enlarged positive lymph node
CTV PRIMARY- GTV primary+ 1cm
CTV NODE- GTV node + 1cm
PTV PRIMARY- CTV primary + 0.5cm
PTV NODE- CTV node + 0.5cm

Dose-
PTV PRIMARY+ PTV NODE + RIGHT LEVEL 1B+ RIGHT LEVEL 2= 66Gy/30#

Right level 3+ right level 4+ level 1a +left level 1b, 2, 3 = 60Gy/30#

Concurrent cisplatin chemotherapy given with 100mg/m2 dose three weekly schedule on D1 and D22

On completion of treatment patient had grade 1 RT reaction and grade 2 oral mucositis with maintained general condition and well fed through the ryles tube.

A videolaryngoscopy was done after 1.5 months and 6 months of completion of treatment which was within normal limits and no lymph node was palpable in the neck. Suggesting patient has completed 6 months post treatment with no evidence of recurrence or residual disease.

DISCUSSION AND CONCLUSION

The first case of synchronous cancers was reported by Billroth in 1889. That was a case of stomach cancer and second primary in external ear. Incidence of synchronous primary larynx is 0.6% and primary oropharynx is 0.3%[12]. Few case reports are seen in the literature on head and neck synchronous primary cancers.

The criteria used for diagnosis of multiple primary cancers was first given by Warren and Gates includes:

1. Each of the tumours must be malignant and confirmed on histology
2. Each must be geographically separate and distinct.
3. The lesions should be separated by normal mucosa and Probability of one being the metastasis of the other must be excluded

Development of multiple malignant lesions can be explained by the phenomenon of "field of cancerization". Tobacco is a common risk factor responsible for the occurrence of both oropharyngeal carcinoma and laryngeal carcinoma and our reported case can be explained by theory of the "field of cancerization".

A study with 851 patients with head and neck cancer, incidence of primary head and neck cancer is 19% of which 41% are synchronous tumours and 59% are metachronus tumours[5]. 46% in base of tongue, 34% in pyriform sinus, 23% in larynx, 18% in oral cavity, 15% in tonsil and 10% in oral tongue had a second primary.

Tobacco smoking and alcohol intake was statistically significant in predicting likelihood of developing second malignancy. 8% non smokers vs 26% smokers with less than or equal to 20 pack years, 42% with more than 20 but less than and equal to 40 pack years and 30% with more than 40 pack years had incidence of second primary. 5% drinkers vs 32% non drinkers had incidence of second primary.

In a retrospective study about distant metastasis and synchronous malignancies on FDG PET/CT in patients with head and neck cancer was suggestive of low frequency of synchronous malignancy (4.2%) in primary head and neck cancer and less metastasis(3%)[13]

Case report of synchronous ca buccal mucosa and larynx is also reported where patient was treated with excision and total laryngectomy followed by external beam radiotherapy[14]. Synchronous dual malignancy of larynx with hepatocellular carcinoma and with intrahepatic cholangiocarcinoma is also reported[15].

In our case this patient has tumours at two sites that is oropharynx and larynx. Eventhough MRI suggests the presence of drop metastasis to larynx from oropharynx, literature shows no evidence for drop metastasis in head and neck squamous cell carcinoma. Drop metastasis are common in intracranial malignancies with intradural extramedullary spinal metastasis. So possibility of a synchronous primary can be considered

The case being reported here is unusual as: (a) In our case the index tumour is in the oropharynx which is the least common site when compared with other studies. (b) synchronous primary tumours with primaries in oropharynx and larynx has not yet reported.

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ORIGINAL RESEARCH PAPER

Radiotherapy

ATYPICAL PAEDIATRIC EXTRA VENTRICULAR NEUROCYTOMA– A RARE CASE REPORT

KEY WORDS: Paediatric tumors, extra ventricular neurocytoma, radiotherapy

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ABSTRACT

Central neurocytoma (CN) and extra ventricular neurocytoma (EVN) are rare intracranial tumors. Central neurocytomas are well-differentiated, intraventricular lesions mainly seen in adults. Similar tumors may develop in the brain parenchyma or spinal cord referred to as extra ventricular neurocytomas. Here we are reporting a case of 10-year-old boy with intracranial mass lesion for which left parieto-occipital craniotomy was done with histopathology showing atypical extra ventricular neurocytoma, recurred after for which gross total excision was done and histopathology report confirmed neurocytoma recurrence. Postoperative MRI showed residual disease and treated with radiation therapy 50 Gray in 28 fractions using IMRT technique. Post radiation MRI showed no residual disease and was kept under follow up.

INTRODUCTION:

Central neurocytoma (CN) and extra ventricular neurocytoma (EVN) are rare intracranial tumors First identified as histologically distinct entities in 1982[1]. Central neurocytomas are well-differentiated, constituting approximately one-half of all intraventricular lesions in adults[2] . Similar tumors have occasionally been identified in the brain parenchyma or spinal cord; in which case they are referred to as extra ventricular neurocytomas. They are classified under glioneuronal and neuronal tumors according to 2021 WHO classification of tumors of the central nervous system [3]. Microscopically sheets, clusters, ribbons or rosettes of monotonous tumor cells with round and regular vesicular nuclei and distinct nucleoli [4].

Immunohistochemically, extra ventricular neurocytomas are characterized by the robust expression of synaptophysin, but with a lack of oligodendrocyte transcription factor 2, isocitrate dehydrogenase enzyme isoform 1 (IDH1) R132/IDH2 R172 mutations and p53 immunoexpression[5]. Atypical lesions are characterized by a MIB-1 labelling index >3% and atypical histologic features such as necrosis, increased mitotic activity, and vascular proliferation [6]. Intracerebral haemorrhage and transformation to a more aggressive malignant lesion are considered serious complications [7]. The treatment for extra ventricular neurocytomas in paediatric and adult populations is gross total resection, with post- operative radiation reserved for subtotal resection or recurrent disease [8]. There is a lack of data on chemotherapy for both typical and atypical extra ventricular neurocytoma.

Case Report:

10-year-old boy with normal developmental milestones presented with persistent headache and projectile vomiting in 10/2021. MRI brain showed left parieto-occipital cystic lesion. Left parieto-occipital craniotomy done under general anaesthesia and histopathology came as atypical extra ventricular neurocytoma (figure 1,2). Immunohistochemistry shows Ki 67- 45%(figure 3). Synaptophysin(figure 4:), Glial fibrillary acidic protein(GFAP) negative (figure 5) and neuron specific enolase (NSE) positive (figure no:6).

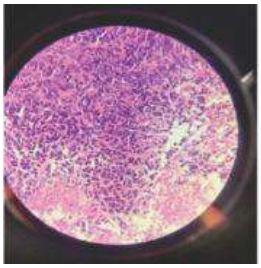


Figure. 1

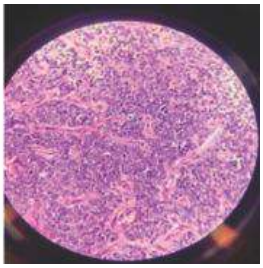


Figure. 2



Figure3: Ki 67



Figure 4: Synaptophysin Positive



Figure 5: Gfap Negative

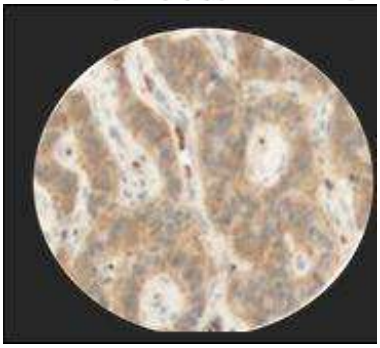


Figure 6 : NSE positive

Post-operative MRI showed no residual disease and he was kept under follow up. Follow up MRI after 6 months showed peripherally enhancing lesion with heterogeneously enhancing solid component measuring 46 x 48 x51 mm involving left parieto- occipital lobe-suggesting recurrence (figure no:7). Gross total excision was done on 13-8-22 with histopathology report atypical extra-ventricular neurocytoma- recurrence. Post-surgery MRI detected 1.9x1.4x0.5 cm lesion with diffusion restriction – most likely residual lesion. Post operatively he was treated with radiotherapy 50Gy in 28 fractions using IMRT technique. (figure no:8 and 9) MRI taken after 6 weeks of Radiation showed no residual mass lesion. Patient was clinically better with no neurological deficits, and kept under follow up.

Clinical Diagnosis : Extra ventricular neurocytoma

Differential Diagnosis:

1. Ependymoma,
2. Oligodendroglioma,
3. High grade astrocytoma.

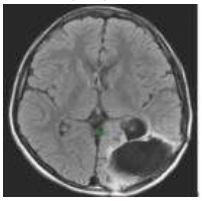


Figure 7

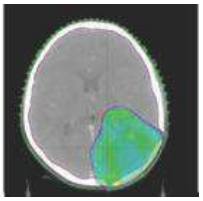


Figure 8

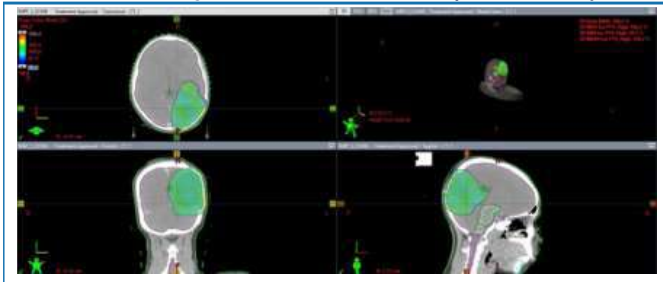


Figure 9

RESULTS:

Patient was clinically better post radiation with no neurological deficits, and MRI suggestive of no significant recurrent or residual disease and is under follow up for past 1 year 10 months.

DISCUSSION ON MANAGEMENT

Extra ventricular neurocytoma is classified under glioneuronal and neuronal tumors by WHO. It is due to alteration in FGFR (FGFR1-TACC1 fusion), and is of IDH-wild type [3]. Paediatric extra ventricular neurocytoma accounts for approximately 0.1% of central nervous system tumors[8]. Tumors are classified into typical or atypical categories, and atypical histological criteria. Extra ventricular neurocytoma generally have a good clinical outcome if completely resected. However, extra ventricular neurocytoma with atypical features are associated with an aggressive clinical outcome and higher recurrence rates as compared with extra ventricular neurocytoma without atypical features. In a study comprising 35 patients with extra ventricular neurocytoma it was found that when MIB-1 ranged from 3% to 18% in the context of cellular atypia, the recurrence rate was the highest[9]. The 5-year overall survival rates were 91% after complete tumor resection, 93% after complete tumor resection and radiotherapy, 46% after incomplete tumor resection and 69% after incomplete tumor resection followed by radiotherapy[9]. The higher rates of recurrence and mortality is detected in neurocytoma with atypical features. 40% recurrence and 20% mortality in atypical central neurocytoma compared with 68% recurrence and 44% mortality, respectively, in atypical extra ventricular neurocytomas [10].

The treatment of atypical neurocytoma has not been distinguished from treatment of typical extra ventricular neurocytoma. Complete resection would provide better local control and survival rates than incomplete resection and that local control and survival rates are improved with postoperative radiation therapy in cases of incomplete resection. In adults, 50–54 Gy is sufficient for typical lesions, whereas atypical lesions require 56–60 Gy. After incomplete tumor resection in children, post-operative radiation significantly improves local control, but not overall survival. Doses of 50 Gy appear appropriate[11]. The evidence for use of chemotherapy is low due to rarity of the condition. Brandes et al. reported a favourable outcome of chemotherapy in progressive and recurrent central neurocytoma; they used a platinum-based agent in three patients. However, there is a lack of data on chemotherapy for both typical and atypical extra ventricular neurocytoma [11].

In this case it was an atypical neurocytoma with synaptophysin positive and Ki 67- 45%. The child was initially treated with gross total excision, which is considered the standard of care, but recurrence occurred within 6 months. Repeat excision was done, but residual disease persisted. In view of age and recurrence in spite of resection multidisciplinary tumor board decided for radiation therapy. He was treated with 50 Gy in 28 fractions using IMRT technique. He had a good disease control and was kept under follow up. Clinical experience of neurocytoma treatment with different modalities like chemotherapy and targeted therapy has not been explored to the fullest due to the rarity of this type of tumor.

Final Diagnosis

Extra ventricular neurocytoma

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GeoChromNet: Declustering Metaphase Chromosomes via Topology-Informed Deep Instance Segmentation

Abstract:

Accurate segmentation and declustering of metaphase chromosomes are crucial for automated karyotyping and diagnosing genetic disorders. However, the complex arrangements in metaphase spreads, including overlapping and touching chromosomes, challenge existing segmentation approaches. This paper presents GeoChromNet (Geometric Chromosome Network), a novel deep learning architecture utilizing topological information to enhance metaphase chromosome instance segmentation and declustering. Our model combines a modified Mask R-CNN backbone with a topology-aware module to effectively segment and decluster chromosomes. We evaluate GeoChromNet on two datasets along with augmentation: The Cell Image Library (CIL), with 5,000 metaphase cell images and 229,852 annotations across 24 chromosome classes, and the BioImage Chromosome Classification Dataset (BICCD), containing 42 chromosome objects with various annotations. Experimental results show GeoChromNet outperforms state-of-the-art methods like ChroSegNet, Mask R-CNN, PSPNet, and DeepLabV3. On the CIL dataset, GeoChromNet achieves a Mean Pixel Accuracy (MPA) of 96.8%, an F1 score of 0.945, a Mean Intersection over Union (MIoU) of 0.921, a Jaccard index of 0.893, and a Dice similarity coefficient of 0.937. These results represent improvements of 2.3%, 3.1%, 3.7%, 4.2%, and 2.8% respectively over the next best model, ChroSegNet. GeoChromNet's topology-informed approach is particularly effective in declustering challenging cases of overlapping and touching chromosomes, as evidenced by a 15.% increase in cluster separation accuracy compared to ChroSegNet. On the BICCD dataset, GeoChromNet maintains its superior performance, achieving an MPA of 95.7% and an F1 score of 0.932, demonstrating its robustness across different datasets. Our work highlights the potential of integrating topological information into deep learning models to improve the accuracy and robustness of metaphase chromosome segmentation and declustering, paving the ...

Original Article

Aspiration or Drain? A Prospective Insight into Minimally Invasive Strategies for Intra-abdominal Abscesses

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Abstract

Background: Intra-abdominal abscesses are a common clinical problem requiring timely intervention. Percutaneous drainage techniques, including percutaneous aspiration (PA) and percutaneous catheter drainage (PCD), are minimally invasive alternatives to surgical drainage. However, their relative efficacy remains debated. **Aim:** The study aimed to compare the outcomes of PCD and PA in the treatment of intra-abdominal abscesses. **Materials and Methods:** A longitudinal comparative study including 60 patients with intra-abdominal abscesses where 30 patients underwent PCD and 30 underwent PA. The outcomes compared included cavity size reduction, white blood cell (WBC) count trends, length of hospital stay, percentage reduction in cavity size at days 1, 4 and 7 and procedure-related complications. **Results:** Baseline abscess size was significantly larger in the PCD group (162.57 ± 184.58 mL) compared to PA (25.57 ± 10.94 mL, $P < 0.001$). Cavity size remained larger in PCD group at all time points. The percentage reduction from baseline was consistently greater with PCD (day 1: 66.16% vs. 51.06%; day 4: 82.38% vs. 71.62%; day 7: 92.18% vs. 82.98%; all $P < 0.001$). No significant intergroup differences observed in WBC count trends. Mean hospital stay was longer in the PCD group (9.80 ± 1.97 days) compared to PA (8.67 ± 2.01 days, $P = 0.031$). Complications occurred in two PCD patients (catheter blockage and local infection), whereas no complications were noted in the PA group. **Conclusion:** PCD offers greater and faster cavity reduction, suitable for larger or multiloculated abscesses, although with slightly longer stay and minor risk. PA is safer and less invasive for smaller unilocular abscesses.

Keywords: Abscess management, image-guided drainage, intra-abdominal abscess, minimally invasive surgery, percutaneous aspiration, percutaneous catheter drainage

Introduction

Abdominal abscesses are the localised collections of pus walled off from the peritoneal cavity by adhesions, omentum or adjacent viscera and may occur intraperitoneally, retroperitoneally or within solid organs.[1] They most often develop postoperatively, particularly after colorectal or pancreaticobiliary surgery but may also arise from localised perforations (appendicitis, diverticulitis and Crohn's disease) or hematogenous spread.[2-4]

Percutaneous drainage, guided by ultrasound or CT, has become the standard of care for most abdominal abscesses not requiring emergency surgery, achieving success rates of 80%–90% when combined with antibiotics.[5-7] While both percutaneous aspiration (PA) and percutaneous catheter drainage (PCD) are widely employed, debate persists regarding their relative efficacy. Aspiration is less invasive, avoids catheter-related morbidity, and is suitable for smaller collections (≤5 cm), whereas catheter drainage provides continuous decompression and is generally preferred for larger or multiloculated abscesses.[8-10]

This study was undertaken to compare the outcomes of PCD and PA in the management of intra-abdominal abscesses, focusing on cavity reduction, white blood cell (WBC) response, hospital stay and procedure-related complications.

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Materials and Methods

This was a longitudinal and comparative study conducted in the Department of General Surgery, at a tertiary care centre, over 1 year. IEC approval was taken on October 25, 2023 (IEC/GMCTSR/2023/117). Our study aimed to investigate the difference in treatment outcomes for intra-abdominal abscesses between PCD and PA. Informed written consent was obtained from every participant. We assessed the difference in the outcome of treatment of PCD versus PA in the treatment of intra-abdominal abscess, and we also assessed the indications and complications of PCD and PA.

Sample size estimation

The minimum required sample size was calculated using the following formula:

$$n = \frac{2Sp^2\ (Z1 - \alpha 1^2 + Z1 - \beta)^2}{Ud^2}$$

Where,

$S1^2$ = Standard deviation of duration of hospital stay of percutaneous needle aspiration (2)

$S2^2$ = Standard deviation of duration of hospital stay of PCD (2.7)

α = significance level (5%)

$1-\beta$ = study power (90%)

Participants were recruited using consecutive sampling, including all eligible patients during the study period. Patients aged over 18 years with intra-abdominal abscesses were considered for inclusion if the abscess cavity was well defined, unilocular and without internal septations. Bilocular cavities were also included provided there was free communication between compartments and sufficient side holes could be positioned to ensure adequate drainage through a single catheter. Only cases with a safe access route that avoided injury to bowel loops, vessels, viscera or sterile cavities were enrolled. Post-operative or critically ill patients, particularly those at high risk for general anaesthesia, were also regarded as suitable candidates. Patients were excluded if they presented with poorly defined phlegmonous collections, lacked a safe access pathway or had multiple abscesses or multiloculated collections (considered relative contraindications). Additional exclusions included suspected echinococcal cysts, owing to the risk of anaphylactic reaction from spillage and patients with abnormal coagulation profiles.

Data collection

Demographic details, clinical findings, radiological data, procedure notes and laboratory reports of patients undergoing ultrasound-guided PA and PCD were prospectively recorded and analysed. The study compared three outcome variables: Duration of hospital stay, time required for reduction in abscess cavity size (assessed on serial ultrasonography) and trends in WBC counts.

PCD was carried out using the Seldinger technique under ultrasonographic guidance. The abscess was punctured with an 18G needle, pus was aspirated and sent for microbiological analysis and a 10–14 Fr pigtail catheter was introduced and secured to the skin. Maximal aspiration was performed initially, after which the cavity was allowed to drain by gravity. Patients received four daily saline irrigations (10 mL each), with careful monitoring of catheter output. The catheter was removed once fever subsided, drainage reduced to <10 mL/day and ultrasound confirmed near-complete resolution.

PA was performed under ultrasonographic guidance using an 18-gauge disposable trocar needle (10–20 cm depending on depth). Abscess fluid was completely aspirated into sterile containers for microbiological and serological evaluation. Repeat aspirations were undertaken if the collection persisted or reaccumulated on follow-up imaging.

Results

A total of 60 patients were included in the study, with 30 undergoing PCD and 30 undergoing PA. Amongst patients managed with catheter drainage, 18 (60%) were male and 12 (40%) were female, whereas in the aspiration group, 23 (76.7%) were male and 7 (23.3%) were female. Although the aspiration group had a relatively higher proportion of male patients, the difference in sex distribution between the two groups was not statistically significant (χ^2 =1.926, P = 0.165).

The mean abscess size in patients undergoing catheter drainage was 162.57 ± 184.58 mL, with a median of 80 mL (interquartile range [IQR]: 65.5–165.0). In contrast, the aspiration group had a significantly smaller mean abscess size of 25.57 ± 10.94 mL, with a median of 22 mL (IQR: 18.0–30.0). Statistical analysis using the Mann–Whitney U-test demonstrated that the abscess size was significantly larger in the catheter drainage group compared to the aspiration group (U = 474.000, P < 0.001).

At all measured time points, the cavity size remained significantly larger in the catheter drainage group compared to the aspiration group. On day 1, the mean cavity size was 48.87 ± 53.30 mL in the catheter drainage group versus 12.65 ± 7.34 mL in the aspiration group (P < 0.001). By day 4, cavity size decreased to 22.55 ± 22.39 mL in the catheter drainage group and 7.50 ± 5.61 mL in the aspiration group (P < 0.001). On day 7, the mean cavity size further reduced to 8.48 ± 4.99 mL with catheter drainage and 4.18 ± 2.56 mL with aspiration (P < 0.001). These findings indicate a consistently higher residual cavity size in patients managed with catheter drainage throughout the 1st week of follow-up [Figure 1].

The mean WBC counts demonstrated a progressive decline in both groups during the 1st week of treatment. On day 1, the mean WBC count was 13,690 ± 4278.83 cells/mm^3 in the catheter drainage group and 12,741.07 ± 5370.98 cells/mm^3 in the aspiration group. By day 4, counts had decreased to 11,212.27±3171.66 cells/mm^3 and 10,800.53±4333.69 cells/mm^3, respectively. On day 7, further reduction was observed, with

the values of 8832.73 ± 1916.49 cells/mm^3 for catheter drainage and 8975.47 ± 3215.46 cells/mm^3 for aspiration. Statistical analysis using the Mann–Whitney U-test revealed no significant difference in WBC counts between the two groups at any of the evaluated time points (day 1: $P = 0.375$; day 4: $P = 0.701$; day 7: $P = 0.779$) [Figure 2].

The average hospital stay was significantly longer amongst patients who underwent catheter drainage compared to those treated with aspiration. The catheter drainage group had a mean hospitalisation period of 9.80 ± 1.97 days, while the aspiration group had a shorter mean stay of 8.67 ± 2.01 days. Statistical analysis confirmed this difference to be significant ($t = 2.207$, $P = 0.031$) [Figure 3].

The mean percentage reduction in cavity size from baseline to day 1 was significantly greater in the catheter drainage group compared to the aspiration group. Patients managed with catheter drainage showed a mean reduction of 66.16% ± 16.01% (median 68.72%, IQR 58.55–78.29), whereas those in the aspiration group demonstrated a lower reduction of 51.06% ± 15.02% (median 50.0%, IQR 41.61–60.00). The difference was statistically significant (Mann–Whitney $U = 3.638$, $P < 0.001$) [Figure 4].

By day 4, the percentage reduction in cavity size remained significantly higher in patients treated with catheter drainage compared to those undergoing aspiration. The catheter drainage group showed a mean reduction of 82.38% ± 11.49% (median 85.22%, IQR 79.15–87.50), whereas the aspiration group demonstrated a mean reduction of 71.62% ± 12.45% (median 72.77%, IQR 63.56–80.00). This difference was statistically significant (Mann–Whitney $U = 3.867$, $P < 0.001$) [Figure 5].

By day 7, both groups showed marked reduction in cavity size compared to baseline; however, the catheter drainage group demonstrated a significantly greater reduction. The mean percentage decrease in cavity size was 92.18% ± 4.27% (median 93.04%, IQR 89.83–94.66) with catheter drainage, compared to 82.98% ± 8.43% (median 82.34%, IQR 76.50–89.24) in the aspiration group. This difference was statistically significant (Mann–Whitney $U = 4.252$, $P < 0.001$) [Figure 6].

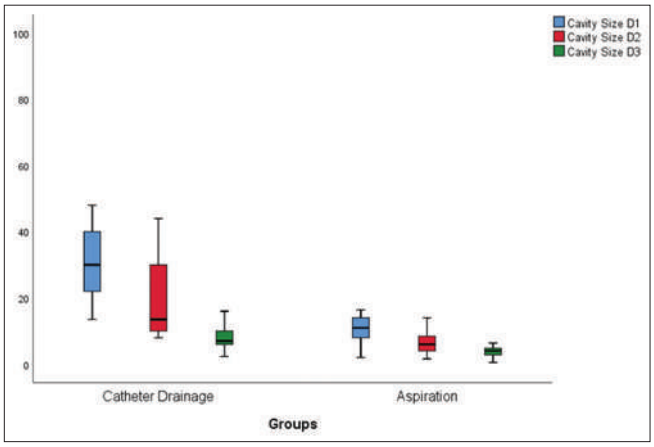


Figure 1: Box plot for cavity size between groups (day 1, day 4 and day 7)

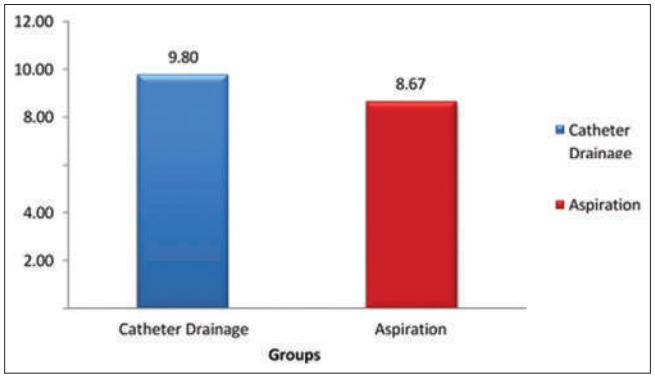


Figure 3: Simple bar diagram of days of hospitalisation between groups

Discussion

This study compared PCD and PA in the management of intra-abdominal abscesses across a cohort of 60 patients with diverse etiologies, including hepatic, pancreatic, appendicular,

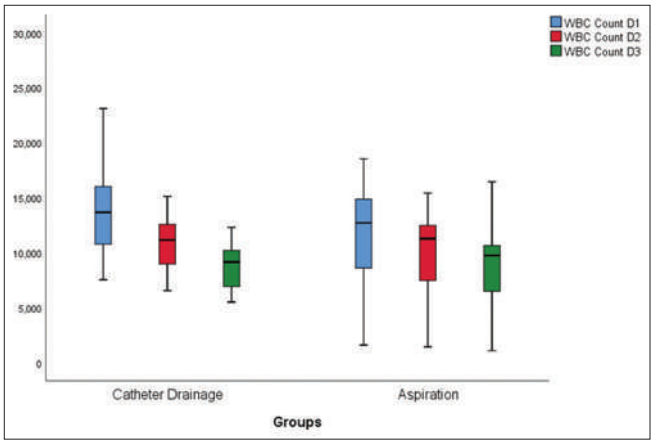


Figure 2: Box plot for white blood cell count between groups (day 1, day 4 and day 7) WBC: White blood cell

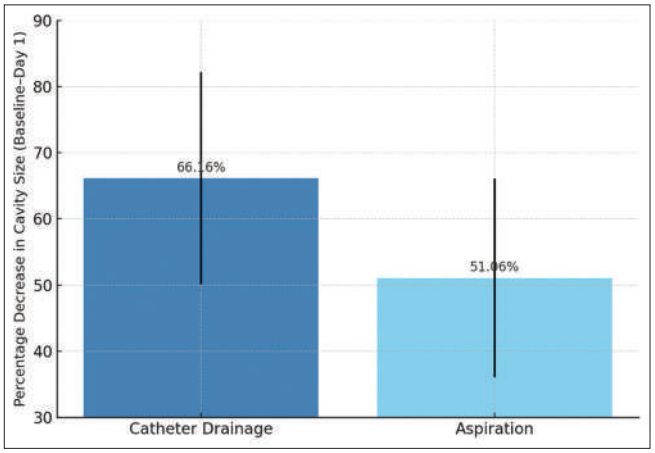


Figure 4: Box-plot for percentage decrease in cavity size (baseline-day 1) size between groups

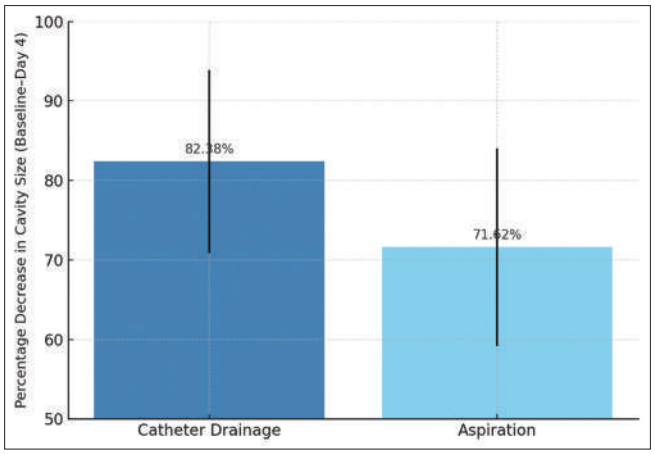


Figure 5: Box-plot for percentage decrease in cavity size (baseline-day 4) between groups

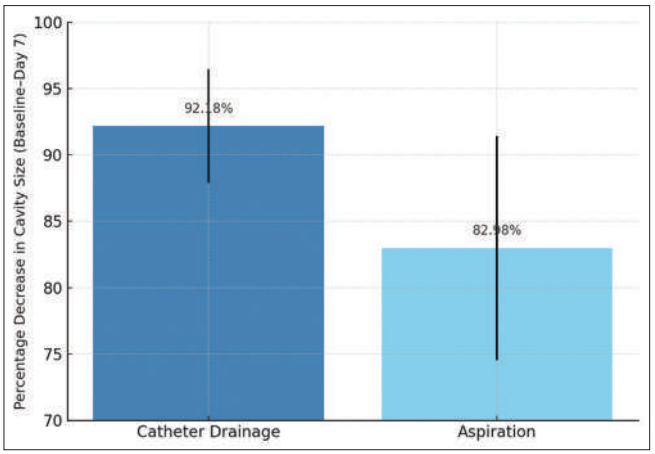


Figure 6: Box-plot for percentage decrease in cavity size (baseline-day 7) between groups

renal, pelvic and post-operative collections. Thirty patients underwent catheter drainage and thirty were managed with aspiration, enabling a direct comparison of outcomes.

Patient demographics

There were no significant differences in age or gender distribution between the two groups, suggesting that demographic factors did not influence treatment outcomes. This aligns with earlier studies, which similarly reported that neither age nor sex has a major impact on the efficacy of percutaneous abscess drainage techniques.[11-14]

Abscess size and cavity reduction

In our study, baseline abscess size was significantly larger in patients who underwent catheter drainage compared to those managed with aspiration (162.6 mL vs. 25.6 mL). During the follow-up, cavity size reduction was consistently greater in the catheter drainage group at day 1, day 4 and day 7. The superior efficacy of PCD in larger or multiloculated abscesses has been reported in several studies. Singh *et al*.[12] observed that catheter drainage was particularly advantageous for abscesses >5 cm in diameter and for those with multiple loculations, where aspiration alone often necessitated repeated procedures. Similarly, Zerem and Hadzic[3] reported that catheter drainage achieved higher success rates in large liver abscesses compared with needle aspiration.

White blood cell count

Although both groups showed a steady decline in WBC counts during treatment, the intergroup differences at day 1, day 4 and day 7 were not statistically significant. This finding indicates that both techniques were equally effective in controlling systemic inflammatory response once drainage was achieved. Comparable results were noted by Rajak *et al*.[10] in their prospective analysis, where WBC normalisation did not differ significantly between aspiration and drainage groups.

Hospital stay

Mean duration of hospitalisation was slightly longer in the catheter drainage group (9.8 ± 1.97 days) compared to aspiration (8.7 ± 2.01 days), with the difference reaching statistical significance. Similar observations have been reported in prior studies, where aspiration was associated with a shorter length of stay, likely due to the absence of catheter care requirements and reduced risk of catheter-related complications.[15] However, this needs to be weighed against the higher recurrence rate after aspiration, especially in larger abscesses.

Percentage reduction in cavity size

One of the notable findings of our study was that PCD achieved a significantly higher percentage reduction in cavity size at all follow-up intervals (day 1, day 4 and day 7) compared to aspiration. These results are in concordance with studies by Seewald *et al*.[13] and Singh *et al*.,[12] who also reported faster cavity resolution with catheter drainage. While aspiration may suffice for smaller unilocular collections, continuous drainage appears superior in ensuring rapid collapse of the abscess cavity in larger lesions.

Complications

In our series, two patients in the PCD group developed procedure-related complications (catheter blockage and local site infection), whereas no complications were recorded in the aspiration group. The relatively higher complication rate with catheter drainage has been noted previously, primarily due to catheter dislodgement, blockage or secondary infection.[11,15] Nonetheless, these complications are generally manageable and rarely outweigh the benefits of definitive drainage in large or complex abscesses.

Clinical implications

Taken together, our findings suggest that PA is a safe, effective and less invasive option for smaller abscesses (<5 cm, unilocular, with safe access), offering advantages such as shorter hospital stay and fewer complications. PCD, however, remains the treatment of choice for larger, multiloculated or recurrent collections, as it provides continuous decompression and faster cavity resolution, despite a slightly longer hospital stay and risk of catheter-related morbidity.

The study is limited by its small sample size, single-centre design and potential geographical and selection biases, which may restrict the generalisability of its findings. Furthermore, only short-term outcomes were assessed, without a long-term follow-up for recurrence or cost-effectiveness. These limitations underscore the need for larger multi-centre studies across diverse populations, incorporating long-term outcomes, quality of life and cost analyses. Future research should also explore patient stratification based on abscess characteristics and evaluate newer or hybrid drainage techniques to refine the treatment protocols and improve patient outcomes.

Conclusion

Both PCD and PA are effective, minimally invasive techniques for the management of intra-abdominal abscesses. In this study, PCD demonstrated superior outcomes in terms of cavity size reduction and overall percentage decrease at the serial follow-up intervals (day 1, day 4 and day 7). However, this advantage came at the cost of a slightly longer hospital stay and a small risk of catheter-related complications. PA, on the other hand, was associated with fewer complications and shorter hospitalisation, making it a suitable option for smaller, unilocular collections.

Therefore, the choice between the two modalities should be individualised: PCD is recommended for larger, multiloculated or recurrent abscesses, whereas PA remains a safe and effective alternative in smaller, uncomplicated cases.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Determinants of Recurrent Acute Pancreatitis: Findings from a Cross-sectional Study in South India

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Abstract

Background: Recurrent acute pancreatitis (RAP) is a major clinical issue that may progress to chronic pancreatitis. While global data exist, evidence from South India is limited, where demographic and lifestyle patterns differ. **Objectives:** To identify demographic, clinical, etiological, lifestyle and outcome-related factors associated with RAP amongst patients at a tertiary care hospital in Kerala. **Materials and Methods:** A cross-sectional study was conducted in the Department of General Surgery, Government Medical College, Thrissur, including 203 RAP patients over 12 months. Data were collected using a structured questionnaire and analysed with SPSS v16. Descriptive statistics and univariate/multivariate analyses were performed. **Results:** The mean age was 45.1 ± 10.6 years, with most cases between 30 and 50 years. RAP showed a striking male predominance (97.5%) and 75.9% were married. Alcohol consumption (85.2%) and smoking (56.2%) were the major lifestyle factors, with most alcohol users reporting daily intake for >10 years. Most had normal body mass index (77.3%) and disease duration was 2–5 years in 63.1%. Interstitial pancreatitis was the predominant radiological finding (92.1%). Alcohol was the leading aetiology (85.2%), followed by biliary causes (11.3%). Nearly all patients (99.0%) were managed conservatively, and most episodes were mild (Glasgow score <3 in 92.6%). Hospital stay was usually 5–10 days (68.0%). Almost all patients (98.5%) were aware of their disease, but sustained abstinence from alcohol was rare. **Conclusion:** RAP in Kerala predominantly affects middle-aged men, strongly linked to alcohol and smoking. Targeted preventive strategies, including structured de-addiction, smoking cessation and lifestyle interventions, are essential to reduce recurrence and disease burden.

Keywords: Alcohol, cross-sectional study, Kerala, recurrent acute pancreatitis, risk factors, smoking

Introduction

Acute pancreatitis (AP) is a significant gastrointestinal disorder associated with severe pain, frequent hospitalisations and substantial healthcare costs. A subset of patients experience recurrent acute pancreatitis (RAP), defined as two or more distinct episodes of AP separated by at least 3 months of complete recovery in a morphologically normal pancreas.[1] Initially described in the Marseille classification[2] and later incorporated into the TIGAR-O system,[3] RAP remains clinically distinct from chronic pancreatitis, although its progression to chronic disease is incompletely understood.[4,5]

The global prevalence of pancreatitis in 2017 was 76.2 per 100,000 population, with an incidence of 20.6 per 100,000. While overall incidence is declining, South Asian countries, including India, report increasing disease burden within younger populations.[6] In India, AP occurs at a rate of 7.9 per 100,000 (8.6 in men; 8.0 in women),[7] with southern states reporting the highest incidence (114–200/100,000).[8] RAP is more common amongst men and typically presents between 30 and 40 years of age.[9]

Alcohol, smoking, gallstones, obesity, hypertriglyceridaemia and delayed cholecystectomy are amongst the recognised risk factors for recurrence.[10-16] Preventive strategies such as abstinence from alcohol, early gallbladder removal and triglyceride control can significantly reduce risk.[14,17] Despite these insights, up to 16%–20% of patients experience recurrent

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attacks, which not only increase morbidity and mortality but also impose a considerable socioeconomic burden.[10,18,19]

Data from India on RAP remain sparse, particularly in Kerala, where unique demographic and lifestyle patterns exist. National Family Health Survey (NFHS-5) (2019–2020) reported alcohol use in 19.9% of men and 0.2% of women in Kerala, slightly higher than national averages.[20] However, the specific contribution of alcohol and other risk factors to RAP in this region is poorly characterised. This study therefore seeks to identify demographic, lifestyle and clinical determinants of RAP in a central Kerala cohort, with the aim of informing preventive strategies and optimising long-term outcomes.

Materials and Methods

The study was designed as a hospital-based cross-sectional analysis conducted over 12 months, extendable to 18 months with appropriate ethical clearance and undertaken in the Department of General Surgery, Government Medical College, Thrissur, with the primary objective of identifying the demographic distribution and the various risk factors associated with RAP. Specific areas of interest included the influence of age, sex and body mass index (BMI); lifestyle determinants such as alcohol intake, smoking and dietary habits and environmental and clinical factors contributing to the recurrence and severity of the disease. In addition, the study sought to explore the common aetiological causes, the average duration of hospital stay, the severity of clinical episodes and the diagnostic as well as therapeutic strategies employed in the management of RAP. By addressing these facets, we aimed to delineate the patterns and determinants of recurrence in patients presenting to our institution, thereby contributing region-specific insights to the literature.

All patients admitted with AP were screened, and those fulfilling the diagnostic criteria for RAP were recruited. RAP was defined as two or more distinct attacks of AP with complete recovery between episodes, in the absence of features suggestive of chronic pancreatitis. Eligible participants were between 12 and 79 years of age. Patients with proven chronic pancreatitis or those unwilling to participate were excluded.

The sample size was calculated using the finite population correction method, with an assumed prevalence of 7%,[6] an absolute precision of 2% and a 95% confidence level. Considering an annual patient load of approximately 300 cases of RAP at our hospital, the minimum required sample size was estimated at 203.

Data collection was carried out using a standardised, validated questionnaire in both Malayalam and English, along with a structured pro forma. Information regarding socio-demographic characteristics, clinical presentation, laboratory and imaging findings, etiological factors, alcohol and smoking patterns, dietary habits and awareness about the disease was obtained through the direct interviews and case records. The diagnosis of AP was based on the Revised Atlanta Classification, requiring the presence of at least two of the following: (a) characteristic abdominal pain, (b) serum amylase or lipase more than three times the upper normal limit or (c) imaging features consistent with pancreatitis. Responses were documented through Google forms, collated and compiled into a master database for the analysis.

Data analysis was performed using the SPSS software version 16 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as proportions for the categorical variables and as means (standard deviation) or medians (interquartile range) for the continuous variables. Continuous variables were compared using the one-way analysis of variance or the Kruskal–Wallis test, with subsequent two-group comparisons by *t*-test or Mann–Whitney test when appropriate. Categorical data were analysed using the Chi-square test. Associations between alcohol consumption, smoking, BMI categories (<25, 25–30, >30) and RAP were further examined using the Cochran–Armitage trend test and Spearman correlation. To adjust for confounding factors such as age, sex and BMI, multivariable logistic regression was employed, with stratified analyses performed for sex, drinking and smoking categories. Model adequacy was assessed using the Hosmer–Lemeshow goodness-of-fit test, and a two-sided $P < 0.05$ was considered statistically significant.

Results

Of the 203 patients studied, most were between 30 and 60 years of age, with the highest proportion in the 40–50 year group (33.5%). Very few participants were <20 years (1.0%) or >70 years (0.5%). The mean age was 45.1 ± 10.6 years, indicating that RAP predominantly affected middle-aged adults.

Amongst the 203 participants, the vast majority were male (97.5%), while only 2.5% were female, demonstrating a clear male predominance in RAP. 154 (75.9%) were married and 49 (24.1%) were unmarried, indicating that the majority of patients with RAP were married. 46 participants (22.7%) were underweight, while the majority, 157 (77.3%), had a normal BMI. The mean BMI of the study population was 20.03 ± 1.88 kg/m². Most participants were from Thrissur district (69.5%), followed by Palakkad (21.7%) and Malappuram (6.4%), while only a small proportion (2.5%) were from Ernakulam.

More than half of the participants (51.2%) had experienced three episodes of pancreatitis, while 42.9% reported four episodes. Only a small proportion had five (5.4%) or six (0.5%) episodes. The majority of participants (63.1%) had a disease duration of 2–5 years, while 22.7% reported illness for ≤2 years and 14.3% for more than 5 years.

On imaging, the majority of patients had interstitial pancreatitis (92.1%). Other findings included gallstones in 4.4%, pseudocysts in 3.4%, necrotising pancreatitis

in 2.5% and walled-off pancreatic necrosis in 1.5% of cases [Figure 1].

Alcohol was the predominant aetiology, accounting for 85.2% of cases, followed by biliary pancreatitis in 11.3% and idiopathic causes in 3.4%. Nearly all patients (99.0%) were managed conservatively. Only one patient (0.5%) required endoscopic retrograde cholangiopancreatography (ERCP) and another (0.5%) underwent laparotomy with drainage [Figure 2].

Based on the Glasgow severity score, most patients (92.6%) had mild attacks with scores <3, while only 7.4% experienced severe episodes (score ≥3). The majority of patients (68.0%) required hospitalisation for 5–10 days, while 20.7% were discharged within 5 days and 11.3% stayed for more than 10 days. Most patients (58.6%) had hospital admissions lasting 5–10 days, while 31.0% stayed ≤5 days and 10.3% required admission beyond 10 days. Nearly all participants (98.5%) were aware of their diagnosis, while only 1.5% reported no awareness of their existing disease.

Alcohol was the predominant risk factor, reported by 85.2% of participants. Amongst drinkers, most had consumed alcohol for more than 10 years (72.3%), while 26.0% reported 4–10 years and 1.7% had a shorter duration of 2–4 years. The majority consumed alcohol daily, with 65.5% drinking 6–7 times per week. Regarding quantity, two-thirds (66.7%) consumed 100–200 ml/day, while 22.6% reported 90–100 ml/day and 10.2% consumed about 90 ml/day. Amongst alcohol users ($n = 177$), the most commonly consumed beverages were vodka, rum, whiskey and brandy (each reported by 98.9% of drinkers). Beer was consumed by 48.6%, while local toddy use was uncommon (2.3%).

Amongst alcohol users ($n = 177$), 95.5% reported abstaining from alcohol after the first episode of pancreatitis, while 4.5% continued drinking. The majority abstained for 2–8 weeks (65.7%), whereas 27.8% abstained for 9–24 weeks and only 6.5% maintained abstinence beyond 24 weeks. The mean duration of abstinence was 11.6 ± 16.3 weeks [Figure 3].

More than half of the participants (56.2%) reported smoking, while 43.8% were non-smokers. Amongst smokers, cigarettes were the most common form (74.6%), followed by combined cigarette and beedi use (17.5%) and beedi alone (7.9%). The mean duration of smoking was 18.0 ± 9.0 years, with 28.9% smoking for 10–15 years and 26.3% for more than 20 years. In terms of quantity, nearly half (46.5%) smoked 5–8 times daily, 31.6% smoked 2–5 times and 21.9% smoked more than 8 times per day [Figure 4].

The majority of participants (94.1%) reported a mixed diet, while 4.9% were exclusively non-vegetarian and only 1.0% were vegetarian. Among non-vegetarian eaters, meat (98.0%) and fish (96.5%) were the most common items, followed by eggs (75.6%). Chicken (96.4%) and beef (82.7%) were the predominant meat types consumed, while mutton (55.8%) and pork (40.1%) were less common.

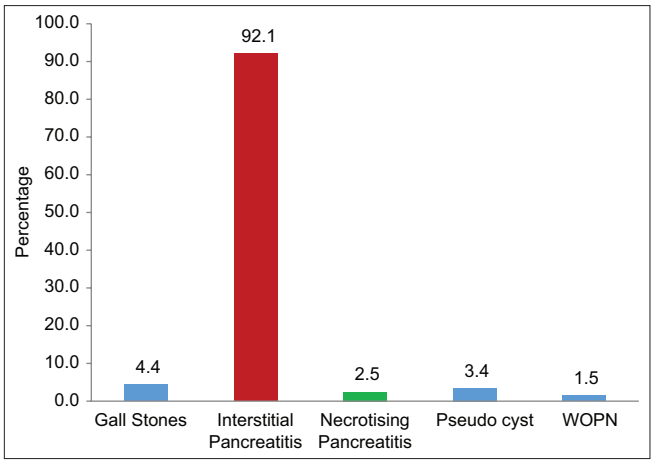


Figure 1: Distribution of computed tomography findings amongst study participants. WOPN: Walled-off pancreatic necrosis, computed tomography

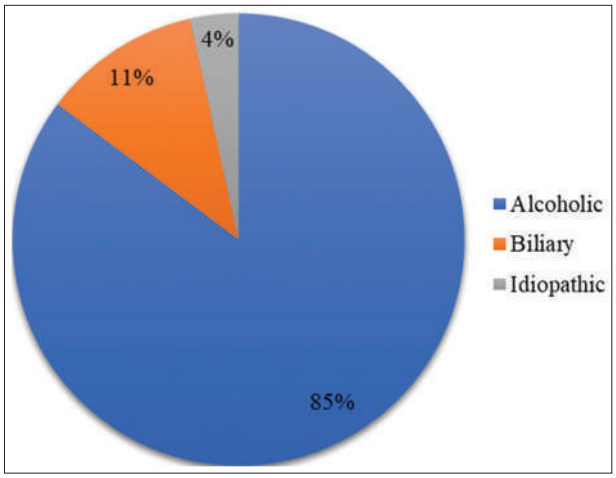


Figure 2: Distribution of diagnosis amongst study participants

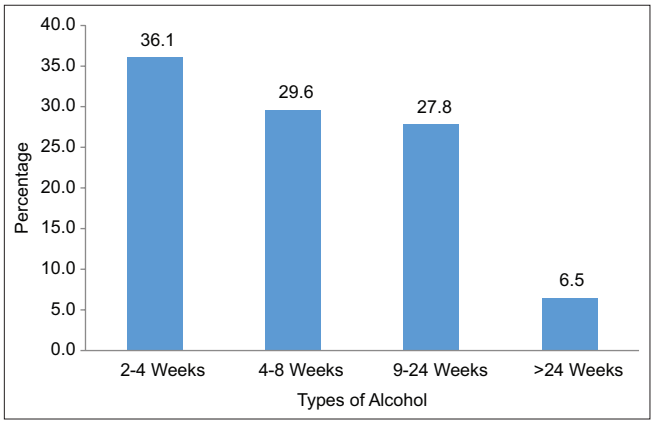


Figure 3: Distribution of duration of abstain from alcohol

Apart from alcohol and smoking, only a small proportion of participants reported other addictions, including gudka (4.9%), pan (3.9%) and betel chewing (0.5%). The majority (90.6%) had no additional addictive habits [Figure 5].

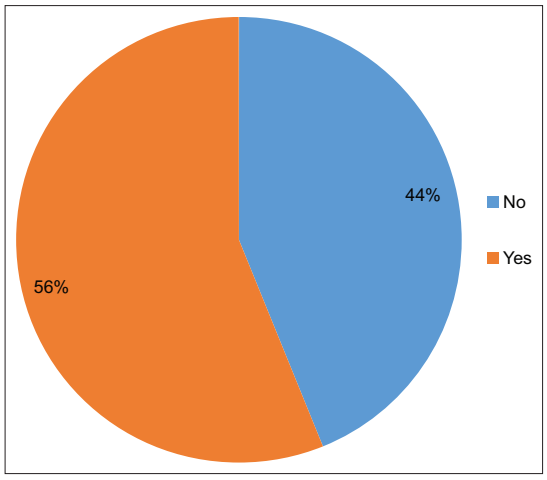


Figure 4: Shows smoking status amongst study populations

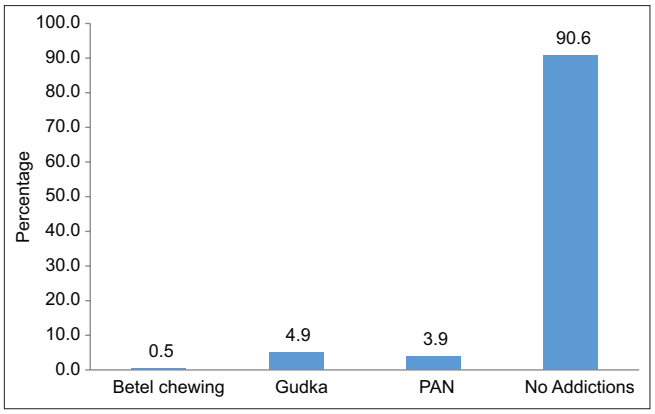


Figure 5: Shows distribution of any other addictions amongst study population. PAN: Pan masala

Discussion

This study provides a comprehensive profile of RAP in a South Indian cohort. The majority of patients were middle-aged men, with alcohol and smoking identified as the predominant risk factors. These findings echo the global consensus that lifestyle factors, particularly alcohol, remain the principal drivers of RAP.[1]

The strong male predominance in our cohort (97.5%) is consistent with prior Indian data[7,8] and with international studies showing higher rates of alcohol- and tobacco-associated RAP amongst men, while gallstone-related RAP is more frequent in women.[12] Historically, early classifications of pancreatitis[2-5] recognised the challenge of distinguishing RAP from early chronic pancreatitis, and our findings similarly highlight this overlap.

Age distribution in our study peaked between 30 and 50 years, which aligns with Scandinavian data showing a younger age of onset for RAP compared to single-episode AP.[9] The Global Burden of Disease study[6] demonstrated that pancreatitis prevalence increases with age, peaking later in women, reinforcing the sex-and age-related differences we observed.

Alcohol accounted for 85.2% of RAP cases in our series, a higher proportion than reported in European[10] or Chinese cohorts.[19] This likely reflects Kerala's unique epidemiological profile, as the NFHS-5 survey[20] showed alcohol use in nearly one-fifth of adult men in the state. Our results align with North American[11] and Asian data,[13,14] which emphasise alcohol, hypertriglyceridaemia and smoking as critical contributors to recurrence.

Most patients experienced three to four attacks within 2–5 years of their first episode. This parallels the findings of Yu *et al*.,[13] who noted recurrence in about 11% within 3 years and long-term studies summarised by Guda *et al*.,[1] where the majority of recurrences occurred in the first 4 years. Our data confirm that the early years after an initial episode represent the highest-risk window.

While nearly all patients in this study were managed conservatively, disease burden remained significant, with frequent hospitalisations of 5–10 days. This reflects global observations that, despite reduced mortality, RAP continues to carry substantial morbidity, economic costs and impaired quality of life.[17,21]

Importantly, awareness of disease was high (98.5%), and most patients attempted abstinence, yet relapse was common. This gap between awareness and sustained behaviour change underscores the need for structured de-addiction and lifestyle modification programs. Prior work has shown that alcohol abstinence and early management of gallstones or hypertriglyceridemia reduce recurrence risk.[14-16] However, in practice, adherence remains a challenge.

Limitations

Our study is cross-sectional and single-centre, limiting generalisability. Genetic factors and biochemical markers were not assessed. Nonetheless, it adds valuable region-specific data from Kerala, where alcohol dominates the aetiological spectrum far more than in Western populations.

Conclusion

RAP in Kerala predominantly affects middle-aged men with long-standing alcohol and smoking exposure. Compared with Western populations where gallstones are more frequent, the aetiological profile here is strongly alcohol-driven. These findings underscore the urgent need for region-specific prevention strategies, focusing on alcohol control, smoking cessation and early management of metabolic risk factors.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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