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MONTHLY

THE PROFESSIONAL MEDICAL JOURNAL

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- Registered with International Serials Data System of France
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- Registered with Scientific Media of Pakistan
- Indexed by Pak medinet & Medlip
- Indexed & abstracted by Extra-med U.K.
- Indexed by Science Library Index
- DOAJ, SCOPUS, ResearchGate & J-Gate

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The Professional Medical Journal

TABLE OF CONTENTS

FEBRUARY 2026 VOLUME 33 NO. 2

EDITORIAL

REVIEW ARTICLE

ORIGINAL ARTICLE

CASE REPORT

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https://doi.org/10.29309/TPMJ/2026.33.02.10145 www.theprofesional.com

ORIGINAL ARTICLE

Frequency of uncontrolled hypertension and associated risk factors attending cardiac outpatient Department Sindh Institute of medical sciences Shahdadpur.

Khiar Unisa[1], Imran Mirbahar[2], Saqiba Khali[3], Dur e Shahwar[4], Noor Samoon[5], Hanna Khair Tunio[6]

ABSTRACT… Objective: To determine the frequency of uncontrolled hypertension and its associated risk factors at Outpatient department of Sindh Institute of Medical Sciences Shahdadpur (SIMS). **Study Design:** Descriptive Cross-sectional study. **Setting:** Cardiac OPD of SIMS Shahdadpur. **Period:** 2023 to February, 2024. **Methods:** The sample size was 300 participants of both gender and were selected by convenience sampling. Data was collected on a designed questionnaire containing sociodemographic information, medical history, dietary habits, lifestyle, after taking informed consent from the participants who were fulfilling the inclusion criteria. Data was then analysed by hand sorting techniques, MS office and SPSS version 27.0. Ethical rules of the university were followed. **Results:** The research included 300 patients, with frequency of Uncontrolled Hypertension was concluded 62.6 %. A significant proportion had a history of irregular blood pressure check-ups (78.3%), while only 20.7% reported drug compliance. The education rate was relatively low, 66% were illiterate, and overweight and obesity were prevalent in 80.3% of the patients. Smoking was reported by 39.4% of the participants, and a majority (59.6%) belonged to a lower socioeconomic class and in rural residents (72.3%). **Conclusion:** Study's findings suggest that frequency of uncontrolled hypertension is more than half of the total Uncontrolled hypertension is more prevalent among rural residents, among females than males. Risk increase with age above 50years, Illiteracy, low socioeconomic groups, lack of physical activity, increase BMI, high salt diet, smoking, non-compliance to drugs, irregular checkup, stress and family history of hypertension.

Key words: Cardiac OPD, Hypertension, Risk Factor, Uncontrolled Hypertension.

Article Citation: Khair Unisa, Mirbahar I, Khali S, Dur e Shahwar, Samoon N, Tunio HK. Frequency of uncontrolled hypertension and associated risk factors attending cardiac outpatient Department Sindh Institute of medical sciences Shahdadpur. Professional Med J 2026; 33(02):190-196. https://doi.org/10.29309/TPMJ/2026.33.02.10145

INTRODUCTION

Uncontrolled hypertension, affecting 1.2 billion people and causing 1.7 million deaths annually, is a major global health issue across all socioeconomic groups. A global goal for non-communicable diseases is to reduce hypertension prevalence to 33% by 2030, aiming to lower risks of heart failure and significantly reduce stroke incidence. The reduction aims to lower the risk of cardiac failure and reduce the likelihood of strokes and cerebrovascular diseases seven-fold.[1] Around 66.8% of uncontrolled hypertensive patients are in developed countries, 61.6% in developing countries, with two-thirds residing in low- and middle-income nations.[2] Two-thirds of uncontrolled hypertensive patients live in low- and middle-income countries, with rates of 66.8% in developed and 61.6% in developing countries.[3] Key risk factors include obesity, high salt intake (>5g/day), saturated fats, excessive alcohol (>75g/day), sedentary lifestyle, smoking, stress, low education, and poverty.[4] Farhadi F et al. reported a high prevalence of uncontrolled hypertension. Noreen N et al. found that 72.7% of hypertensive patients at a cardiac clinic had uncontrolled blood pressure, mainly due to poor adherence caused by financial constraints.[5]

The Second National Diabetes Survey of Pakistan reported a hypertension prevalence of 46.2%, with a control rate of 33% overall, 34.4% in rural central Punjab, and 29.22% in urban areas.[6] Uncontrolled hypertension was highest in rural Thatta, Sindh, Pakistan (71%), compared to Bangladesh (53%) and Sri Lanka (57%). According to a survey, only 40% of hypertensive patients were aware of their condition.[7]

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Article received on:
20/10/2025
Accepted for publication:
29/12/2025

A study at Aga Khan Hospital, Karachi (July 2020–March 2022) investigated the association between uncontrolled hypertension and drug compliance. It found that 64% of patients were compliant, with 64.6% of them on monotherapy. Compliance was higher among patients aged 61–75 years and those with graduate-level education.[8] A meta-analysis and systematic review of 18 studies (from 1,240 articles) involving 42,618 participants estimated the overall prevalence of hypertension in Pakistan at 26.34%. Prevalence was higher in rural areas (31.42%) than urban areas (26.61%). Conducted due to the absence of a recent nationwide study the last being over 20 years old this review showed a rising trend in hypertension: 19.55% in the 1990s, 23.95% in the 2000s, and 29.95% in the 2010s.[9] Uncontrolled hypertension remains a major public health concern, yet awareness and focus on its modifiable risk factors are inadequate, particularly in semi-urban areas. This study, conducted in the Cardiac Outpatient Department of the Sindh Institute of Medical Science (SMIS), Shahdadpur, aims to address this gap by raising public awareness and identifying key risk factors contributing to uncontrolled hypertension. The findings are expected to enhance community understanding, support preventive strategies, and contribute to improved health outcomes in Shahdadpur and similar settings.

METHODS

A cross-sectional survey was conducted at Cardiac Outpatient Department (OPD) of Sindh Institute of Medical Science (SIMS) Shahdadpur. Patients selected were aged 40 years or above. Study was conducted from December, 2023 to February, 2024. Patients who were already diagnosed as hypertension were take conveniently into the study. Based on the prevalence of uncontrolled hypertension in Pakistan, sample size was calculated using formula and a total of 296. A predesignated questionnaire was used for data collection. The questionnaire contain sociodemographic information as age, gender, residency, educational level, monthly income, occupation. Dietary habits were assessed by history of low salt intake, use of cooking oil or ghee, lifestyle was assessed by history of exercise, physical activity, smoking, alcohol consumption. The clinical characteristics include duration of hypertension, regular blood pressure check-up, drug compliance, number of anti-hypertensive drugs used. Patients chart were also reviewed for information. Survey questionnaire was checked for errors. The data was entered into SPSS version 27.0.The variables age, gender, education, socioeconomic status, physical activity, BMI, smoking, alcohol consumption, low salt, saturated fat, stress, sleep, family history of hypertension, regular checkup, number of medicine, drug compliance, were analyzed by frequencies, percentages. The data is presented in tables. Chi Square test was applied to check related association of risk factors with uncontrolled hypertension. Results were found to be significant at p value <0.05.

RESULTS

The study included 300 participants, with a majority being female (58%) and males comprising 42% of the sample. The most represented age group was 40–49 years, accounting for 52%, followed by those aged 50–59 years (31%), and 17% were aged above 60 years. In terms of marital status, the vast majority were married (92.6%), while widowed individuals made up 6.3%, and only 1% were divorced. The educational background of participants showed that a significant portion were illiterate (55.6%), with 22.3% having secondary education, 15.3% with primary education, and only 6.6% were graduates (Table-I).

In table-III compares BMI, alcohol and smoking habits, fat usage, and salt intake between two groups of hypertensive individuals: controlled (N = 112) and uncontrolled (N = 188). Among the uncontrolled group, the majority were overweight (44.1%) or obese (34%), with a smaller percentage having normal BMI (19.6%), and only 2.6% were underweight. In the controlled group, 35.7% were overweight, 33% obese, 24.1% had normal BMI, and 7.1% were underweight, indicating a slightly more favorable BMI distribution compared to the uncontrolled group. The majority in both groups did not consume alcohol (80.3% in uncontrolled and 89.2% in controlled hypertension). A higher proportion of non-smokers was seen in the controlled group (67.8%) compared to the uncontrolled group (58.5%). Ex-smokers were minimal in both groups (2.1% and 1.7% respectively). In the uncontrolled hypertensive group, 68% used ghee for cooking,

while only 31.9% used cooking oil. In contrast, the controlled group predominantly used cooking oil (67.8%), and only 32.1% used ghee, showing a healthier fat choice in the controlled group. High salt intake was more common among the uncontrolled group (16.4%) than the controlled (11.6%). Medium salt intake was reported by 61.1% of uncontrolled and 26.7% of controlled. Notably, 61.6% of the controlled group consumed low salt, compared to only 22.3% of the uncontrolled, indicating better dietary compliance in the controlled hypertensives.

TABLE-I

Sociodemographic characteristics:

Variable	Category	Frequency N (%) N=300
Sex	Male	126 (42%)
	Female	174 (58%)
Age in Years	40-49	156 (52%)
	50-59	93(31%)
	>60	51(17%)
Marital Status	Married	278(92.6%)
	Divorced	3(1%)
	Window	19(6.3%)
Educational level	Illiterate	167(55.6%)
	Primary	46(15.3%)
	Secondary	67(22.3%)
	Graduate	20(6.6%)
Socioeconomic status	Lower	187(62.3%)
	Middle	90(30%)
	Higher	23(7.6%)
Occupational Status	Unemployed	89(29.6%)
	Skilled	65(21.6%)
	Government	117(39%)
	Labourer	29(9.6%)
Residential status	Urban	87(29%)
	Rural	213(71%)

TABLE-II

Frequency of uncontrolled hypertension among participants and their characteristics:

Variables	Category	Uncontrolled n(%)	Controlled
Hypertension	Status of hypertension	188(62.6%)	112(37.4%)
Age in Years	40-49	70(37.2%)	55(49.1%)
	50–59	86(45.7%)	35(31.2%)
	>60	32(17.1%)	22(19.6%)
Sex	Male	81(43.1%)	68(60.8%)
	Female	107(56.9%)	44(39.2%)
Residential Status	Urban	54(28.7%)	40(35%)
	Rural	134 (71.3%)	72(65%)
Educational Status	Illiterate	118(62.7%)	45(40.1%)
	Primary	25(13.3%)	19(16.9%)
	Secondary	29(15.4%)	30(26.7%)
	Graduate	16(8.5%)	28(25%)
SocioEconomic Status	Lower	112(59.6%)	75(66.9%)
	Middle	68(36.2%)	22(19.6%)
	Upper	8(4.2%)	15(13.3%)

TABLE-III

Frequency of uncontrolled hypertension among participants and their characteristics:

Variable	Category	Uncontrolled (N=188)	Controlled (N=112)
BMI	Underweight	5(2.6%)	8(7.1%)
	Normal	37(19.6%)	27(24.1%)
	Overweight	83(44.1%)	40(35.7%)
	Obese	64(34%)	37(33%)
Alcohol Consumption	Yes	37(19.6%)	12(10.7%)
	No	151(80.3%)	100(89.2%)
Smoking Status	Non Smoker	110(58.5%)	76(67.8%)
	Smoker	74(39.3%)	36(32.1%)
	Ex-Smoker	4(2.1%)	2(1.7%)
Use of Fats	Cooking oil	60(31.9%)	76(67.8%)
	Ghee	128(68%)	36(32.1%)
Salt Intake	Low	42(22.3%)	69(61.6%)
	Medium	115(61.1%)	30(26.7%)
	High	31(16.4%)	13(11.6%)

TABLE-IV

Comparison of physical activity and drug compliance

Variable	Category	Uncontrolled (N=188)	Controlled (N=112)
Physical Activity	No activity	30(15.9%)	22(19.6%)
	Domestic Activity	76(40.4%)	27(24.1%)
	Occupational Activity	82(43.6%)	63(56.2%)
Exercise	Yes	37(19.6%)	67(59.8%)
	No	151(80.3%)	45(40.1%)
Blood Pressure Check Up	Regular	41(21.8%)	79(70.5%)
	Irregular	147(78.1%)	33(29.4%)
Drug Compliance	Yes	39(20.7%)	78(69.6%)
	No	149(79.2%)	34(30.3%)

Several factors were associated with uncontrolled hypertension in our study, including age, female gender, unhealthy dietary habits (such as non-adherence to a low-salt diet and the use of ghee instead of cooking oil), physical inactivity, obesity, smoking, and alcohol consumption. These risk factors are also widely documented in literature from other regional and international studies.[20] A higher prevalence of uncontrolled hypertension has been reported in hospital settings in Afghanistan (77.3%) and in rural areas of Thatta, Sindh (71%), compared to 53% in Bangladesh and 57% in Sri Lanka. These rates indicate even worse outcomes than those found in our study. Uncontrolled hypertension was more prevalent among overweight and obese individuals, and those from low or middle socioeconomic backgrounds. Common contributing factors included smoking, physical inactivity, high salt intake, comorbid conditions, high BMI, poor medication compliance, and psychological stress, with similar patterns observed across numerous studies.[11,12,13]

Age was a significant predictor in our study. The prevalence of uncontrolled hypertension was highest in the 50–59-year age group (n=80; 45.7%), followed by the 40–49-year group (n=69; 36.7%). Similar studies have shown that individuals aged ≥50 years are more than twice as likely to have uncontrolled hypertension compared to younger age groups. Our findings are also consistent with population-based data indicating a higher prevalence of uncontrolled hypertension among older adults. Uncontrolled hypertension was more prevalent among females (n=107; 56.9%) in our study (Table 4.3), a trend also reported in international data, which indicates that after the age of 51, the prevalence tends to be higher in women. In younger age groups (30–50 years), men typically show higher rates, but this reverses with age.[13,14]

In terms of residence, the burden was higher in rural areas (n=136; 72.3%). This mirrors findings from other rural regions in Pakistan, where rates ranged from 70.78% to 77.7%. Limited access to healthcare facilities, poverty, and irregular monitoring are key contributing factors in these areas. Our study also examined multiple determinants of blood pressure control. Illiteracy was reported in 66% (n=124) of patients, regular blood pressure check-ups were reported by only 22.3% (n=42), while 63.8% (n=120) had irregular check-ups. Drug compliance was poor, reported at 20.7% (n=39), and 58.5% (n=110) were on monotherapy. These trends are consistent with findings from studies conducted across South Asia and Africa, as well as reports from the World Health Organization, all of which highlight the importance of education, monitoring, and therapy adherence in managing hypertension effectively.[7,15,16,17,18]

Among all risk factors, the most strongly associated with uncontrolled hypertension was high BMI. In our study, 43.6% of participants were overweight, and 36.7% were obese. Additionally, 80.3% reported no regular physical activity. Physical inactivity has been shown to increase the risk of uncontrolled hypertension by 1.8 times, as confirmed by studies conducted across Asia and Africa. An unhealthy diet was the third most common associated factor. Non-adherence to a low-salt diet was observed in 78% of patients, and 66.5% used ghee for cooking. High salt consumption (over 5 grams per day), especially in salt-sensitive populations such as the elderly and individuals with chronic conditions, is a well-established contributor to poor hypertension control. Alcohol consumption was reported in 19% of patients. Excessive alcohol intake more than 30 drinks per week has been linked to a 12–15% increased risk of hypertension, while cessation can reduce prevalence from 42% to 12%.[3,19,20,21,22]

Smoking was reported in 39.5% of patients, a rate likely lower due to the predominance of female participants. Smoking has been identified as a key risk factor for both the development and poor control of hypertension. Tobacco use is also associated with early complications in hypertensive patients and has been recognized as an independent risk factor for uncontrolled hypertension in national surveys. Psychological stress was reported by 84% of participants. This includes financial, family, and job-related stress, all of which are widely reported as significant contributors to uncontrolled hypertension. Stress is more frequently present in uncontrolled hypertensive patients than in those with well-controlled blood pressure. Non-compliance to medication was high in our study (79.3%). Studies show that non-compliant patients are twice as likely to have uncontrolled hypertension. Common causes include forgetfulness and financial constraints, with forgetfulness alone responsible for one-third of treatment discontinuation. Similar patterns are seen across multiple studies, emphasizing that improving medication adherence is key to managing hypertension effectively.[7,23,24,25,26]

Socioeconomic factors played a major role. In our study, 60.1% of patients were from a low socioeconomic background, 24.5% were unemployed, and 62.7% were illiterate. Poor education is linked to poor health knowledge, unhealthy behavior, and non-adherence to therapy. Socioeconomic status, influenced by both education and income, has a strong association with uncontrolled hypertension. According to the World Health Organization, medication adherence is particularly poor in developing countries due to limited access to healthcare and underutilization of available resources. Adherence rates were reported as 62.4% in Africa, 43.5% in Asia, 36.6% in the Americas, and 6.6% in Europe, highlighting how economic inequality directly impacts disease control. Global data indicate that non-compliant patients are twice as likely to have uncontrolled hypertension. Multiple studies across regions including Malaysia, South Asia, and South Africa confirm that adherence to antihypertensive therapy is a critical preventive factor. Lastly, it has been emphasized in several studies that multi-drug regimens are often necessary to achieve blood pressure control. In our study, 58.5% of patients were on monotherapy, which proved insufficient. The primary reason for monotherapy use was financial constraint, with many patients opting for the most affordable drug or one provided by the hospital.[27,28,29]

This study has some limitations, primarily due to the fact that the study population was limited to patients attending the cardiac outpatient department (OPD) of a hospital, where the majority of attendees belong to low- and middle-income groups. As such, this is not a population-based study, and the results may overestimate the frequency of hypertension, awareness levels, and compliance with medication. This is likely because a significant portion of the study population comes from rural areas, with many being illiterate and having limited health awareness, low income, and restricted access to medical facilities.

A major contributing factor appears to be a lack of awareness regarding a healthy lifestyle, which is closely linked to limited health knowledge. Poor dietary habits and unhealthy lifestyle choices such as the consumption of saturated fats (e.g., ghee and butter), excessive salt intake, and lack of structured exercise are common. Although many participants engage in physical activity through daily labor, this does not equate to regular or proper exercise. Additionally, there is little to no awareness of the health risks associated with lifestyle factors such as physical inactivity and smoking. Despite these limitations, the findings are consistent with other regional studies. Importantly, this study highlights a significantly increased number of patients with uncontrolled hypertension, along with a high prevalence of associated risk factors within the urban and neighboring rural populations of our region.

CONCLUSION

This study demonstrates a high frequency of uncontrolled hypertension among patients attending the Cardiac OPD at SIMS Shahdadpur, with a greater prevalence observed in rural populations and among women. Uncontrolled hypertension was more common in individuals over 50 years of age, particularly among the illiterate and those from lower socioeconomic backgrounds. Key contributing

factors included lack of awareness about a healthy lifestyle, physical inactivity, increased BMI, smoking, poor dietary habits (such as high intake of salt and saturated fats), and non-compliance with medication. The findings highlight the critical role of poverty and limited health education in the poor management of hypertension. These results underscore the need for targeted public health interventions focused on lifestyle modification, health education, and improved access to healthcare, especially for underserved rural and low-income populations.

Ethical Approval

This study was reviewed and approved by the ethical research committee under reference number (PUMHSW/SBA/DME 324). The study adhered to the Helsinki Declaration, as well as national, international, and institutional ethical standards at all stages, given the involvement of human participants.

Acknowledgements

We are sincerely thankful to thank our Chairman, Dr. Jawaid Hussain Laghari for supporting us in our entire academic journey.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Khiar unisa:** Concept of research, writing manuscript.
2	**Imran Mirbahar:** Writing.
3	**Saqiba Khali:** Data analysis.
4	**Dur e Shahwar:** Initial writing.
5	**Noor Samoon:** Proof reading,
6	**Hanna Khair Tunio:** Data analysis, revision.

https://doi.org/10.29309/TPMJ/2026.33.02.9989 www.theprofesional.com

ORIGINAL ARTICLE

Demographic and clinical patterns of cutaneous leishmaniasis in patients reporting to a Tertiary Care Hospital in Quetta, Balochistan.

Saima Ali Khan[1], Fareeha Imran[2], Najia Ahmed[3], Maira Wajahat[4]

ABSTRACT… Objective: To investigate the demographic profile and clinical patterns of cutaneous leishmaniasis (CL) patients presenting to a tertiary care hospital in Quetta. **Study Design:** Retrospective Cross-sectional study. **Setting:** Department of Dermatology, Combined Military Hospital (CMH), a Tertiary Care Hospital in Quetta, Balochistan, Pakistan. **Period:** June 1st, 2024, to May 31st, 2025. **Methods:** All confirmed cases of CL attending the outpatient department for the first time during the study period were included in the study. Incomplete records and repeat visits were excluded. Parameters including age, gender, occupation, month of presentation, duration of disease, number and site of lesions, and clinical morphology were recorded. Statistical analysis was performed using Statistical Programme for Social Sciences (SPSS) version 29. Continuous variables (age, duration of lesions) were presented as mean ± standard deviation (SD). Categorical variables (gender, lesion type, location, diagnostic method) were presented as frequencies and percentages. Seasonal variation was assessed by mapping monthly distribution trends. **Results:** A total of 360 confirmed CL cases were recorded during the study period. The mean age of the patients was 30.1 ± 6.2 years, with a range from 2 to 78 years. The most frequently affected age group was 21-40 years. The gender distribution showed that 89.44% of the patients were male and 10.56% were female. The mean duration of lesion was 2.3 ±1.1 months. The majority of the patients had single lesion, mostly on lower limbs. The clinical presentation exhibited a spectrum of manifestations. The predominant morphological pattern was nodulo-ulcerative, accounting for 66.67% of cases. The monthly distribution of cases demonstrated a distinct seasonal pattern, with higher number of cases in winter season. **Conclusion:** This retrospective study highlights the unique demographic profiles, clinical patterns, and seasonal trends of cutaneous leishmaniasis cases reported from a tertiary care hospital in Quetta. The findings offer valuable insights into disease patterns that are often underrepresented in regional datasets and can inform localized control strategies.

Key words: Cutaneous Leishmaniasis, Demographics, Epidemiology, Pakistan, Public Health.

Article Citation: Khan SA, Imran F, Ahmed N, Wajahat M. Demographic and clinical patterns of cutaneous leishmaniasis in patients reporting to a Tertiary Care Hospital in Quetta, Balochistan. Professional Med J 2026; 33(02):197-202. https://doi.org/10.29309/TPMJ/2026.33.02.9989

INTRODUCTION

Cutaneous leishmaniasis (CL) is a parasitic skin disease caused by protozoa of the genus Leishmania. More than twenty species of Leishmania are known to cause cutaneous disease[1], which is transmitted by the bite of infected female sandflies.[2]

Cutaneous leishmaniasis is endemic in over 90 countries and contributes significantly to the global burden of disease, with approximately 4.3 million cases reported annually.[3] Each year, an estimated 700,000 to 1 million new infections are reported, primarily originating from four eco-epidemiological regions: the Americas, East Africa, North Africa, and West and Southeast Asia.[4] Pakistan ranks amongst the high-burden countries, with endemic regions spanning Balochistan, interior Sindh, South Punjab, and Khyber Pakhtunkhwa.[5] In 2023, the World Health Organization recorded over 59,255 reported cases from Pakistan, highlighting the significant burden of disease.[6]

Cutaneous leishmaniasis continues to be a significant public health challenge in Pakistan, with Balochistan being a well-recognized endemic region.[7,8] While numerous epidemiological studies have been conducted across Balochistan, many have primarily focused on community-based prevalence rates, age-specific patterns, or ecological risk factors.[9] These studies, while valuable, often concentrate on community-based prevalence and data from primary care settings or field-based surveys[10], thus not fully capturing the comprehensive demographic and clinical profiles of patients presenting in a tertiary

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Article received on:
26/07/2025
Date of revision:
19/09/2025
Accepted for publication:
22/09/2025

care hospital.

There is a need for studies focusing on clinical patterns, seasonal trends and socio-demographic patterns in the regional population. This study aims to fill that gap by retrospectively analyzing patient profiles at a tertiary care hospital in Quetta. Our focus will be on demographic profile, lesion characteristics, and temporal trends. By enhancing this specific clinical and epidemiological insight, our findings may support more locally tailored public health planning, resource allocation and awareness efforts in a high-burden region.

METHODS

The cross sectional study was conducted at Combined Military Hospital (CMH), Quetta, Balochistan, Pakistan. after approval from ethical committe (CMH QTA-IERB/113/2025 Dated: 23 Jul 2025) The hospital serves as a major referral center for the region, serving both military personnel and civilians.

The study population included all patients attending the dermatology outpatient department with a clinical and histopathological diagnosis of cutaneous leishmaniasis from June 1, 2024 to May 31, 2025.

Inclusion criteria included confirmed diagnosis of cutaneous leishmaniasis based on both clinical presentation and histopathological findings and first-time consultation during study period.
Exclusion criteria were incomplete medical records and repeat visits.

Data Collection

Approval was obtained from the Institutional Ethical Review Board. Data of eligible patients were extracted from hospital records. The following key variables were recorded.

- Age
- Gender
- Occupation
- Month of presentation (for seasonal analysis)
- Duration of disease
- Site of lesions
- Number of lesions
- Clinical morphology (plaque, nodule, ulcer, nodulo-ulcerative, etc.)

Data Analysis

Statistical analysis was performed using Statistical Programme for Social Sciences (SPSS) version 29. Continuous variables (age, duration of lesions) were presented as mean ± standard deviation (SD) for normally distributed data or median (interquartile range - IQR) for skewed data. Categorical variables (gender, lesion type, location, diagnostic method) were presented as frequencies and percentages. Seasonal variation was assessed by mapping monthly distribution trends. Tabular and graphical representations (bar charts, pie charts, histograms) were utilized for data visualization. Statistical significance was set at a p-value of less than 0.05.

RESULTS

This study analyzed the demographic and clinical characteristics of cutaneous leishmaniasis (CL) patients presenting to the outpatient department over a one-year period (June 2024 – May 2025). A total of 360 confirmed CL cases were recorded during the study period.

Demographic Characteristics

The mean age of the patients was 32 years, with a range from 2 to 78 years. The gender distribution showed that 89.44% of the patients were male and 10.56% were female. Demographic characteristics are presented in Table-I.

TABLE-I

Demographic profile of patients of cutaneous leishmaniasis

Characteristics	Data
Mean Age (years)	30.1 ±6.2
Gender Distribution	
Males	322 (89.44%)
Females	38(10.56%)

CL was observed across all aga strata, but the highest proportion of cases were seen in the 21-40 years age group. Age-specific frequency analysis is summarized in Table-II.

Regarding occupational distribution, the majority of the patients were involved in outdoor activities, suggesting potential exposure patterns related to their daily activities.

Clinical Characteristics of Lesions

The mean duration of lesion was 2.3 ± 1.1 months, ranging from 2 weeks to 6 months. Analysis of lesion count showed that the majority of patients presented with a single lesion. The most common distribution of lesions was on the lower limbs, followed by the upper limbs and then head and neck. The clinical characteristics of study population are summarized in Table-III.

TABLE-II

Age-specific frequency analysis of patients of cutaneous leishmaniasis

Age Groups	Frequency (Percentage)
10 and less than 10 years	36(10%)
11-20 years	71(19.72%)
21-40 years	218(60.56%)
41-60 years	28 (7.78%)
61-80 years	7(1.94%)

TABLE-III

Clinical profile of cutaneous leishmaniasis

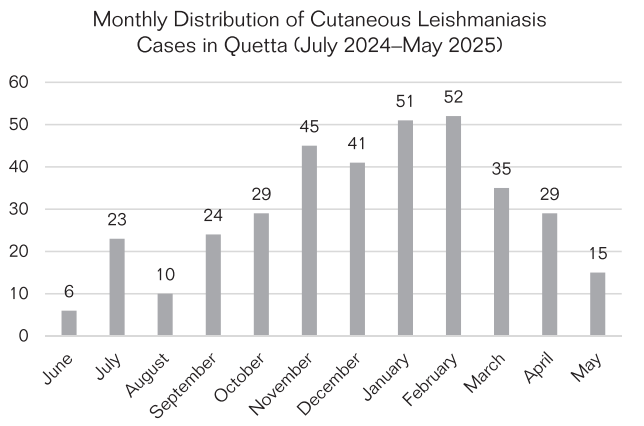
Variables	Category	n (%) / Mean ± SD / Range
Duration of lesion	Mean ±SD (months)	2.3 ±1.1
	Range (months)	0.49-4.93
Site of lesion	Head and neck	74 (20.56%)
	Upper limbs	102 (28.33%)
	Trunk	12 (3.33%)
	Lower limbs	150 (41.67%)
	Multiple sites	22 (6.11%)
Number of lesions	1	196 (54.44%)
	2	88 (24.44%)
	3 or more	76 (21.11%)
Clinical morphology	Papular/nodular	38 (10.56%)
	Nodulo-ulcerative	240 (66.67%)
	Plaque	68 (18.89%)
	Others	14 (3.89%)

Monthly Distribution of Cases

The highest number of cases were recorded during January and February. The monthly distribution of cases demonstrate a distinct seasonal pattern, with higher number of cases in winter season. The number of patients reported month-wise are summarized in Figure-1.

The clinical presentation exhibited a spectrum of manifestations. The predominant morphological pattern was nodulo-ulcerative, accounting for 66.67% of cases. The clinical spectrum of disease is depicted in Figure-2.

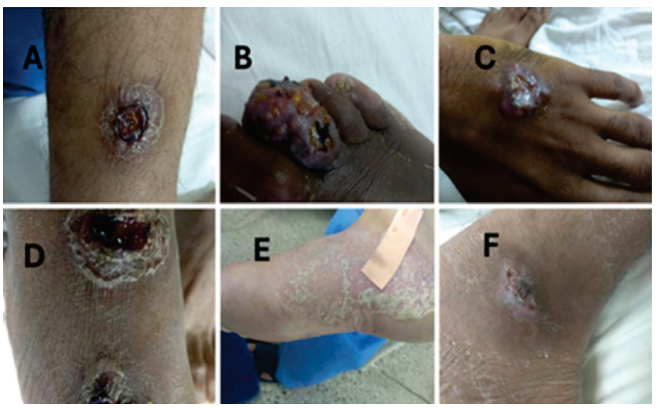
FIGURE-1



Bar Chart of Monthly Case Count for Cutaneous Leishmaniasis

FIGURE-2.

Collage illustrating the morphological diversity of cutaneous leishmaniasis lesions observed in patients from Quetta. Manifestations include ulcerative plaques, crusted nodules, papular eruptions, and infiltrated plaques across varied anatomical sites.



DISCUSSION

This study aimed to analyze the Demographic and Clinical Patterns of patients diagnosed with Cutaneous Leishmaniasis over a one year period at a Tertiary Care Hospital in Quetta, Balochistan. Our findings demonstrated a higher incidence among young males, with nodulo-ulcerative lesions being the most prevalent clinical presentation. A distinct seasonal trend was observed, with most cases occurring between November and February.

In the present study, the majority of patients affected by cutaneous leishmaniasis belonged to the 21–40-year age group, with a mean age of 30.1 ± 6.2 years. This age distribution suggests that CL disproportionately affects young individuals, potentially due to increased outdoor exposure and occupational risk.[11] Male predominance was notable, accounting for 89.44 % of cases, which aligns with findings from multiple regional studies. For instance, a study by Rashid et al. in District D.I. Khan reported that 64.2% of patients were males.[12] Similarly, Ullah S et al. observed 60.5% male prevalence in Lower Dir District (NWFP), Pakistan.[13] While most studies have identified younger age groups (≤10 years) as most affected[14], the higher burden in adults aged 21–40 years in our cohort may reflect the demographic skew due to the study setting, which was a military hospital, where military personnel represent the majority of patients. Similar trends have been documented in previous studies conducted at military medical facilities, where males are disproportionately exposed due to deployment conditions and environmental risk factors.[15] These findings reinforce the need for tailored awareness and preventive strategies targeting high-risk occupational groups.

The predominance of nodulo-ulcerative lesions (66.67%) in our cohort aligns with previous studies.[16] This study found predominant involvement of the lower limbs, with subsequent involvement of upper limbs and head and neck regions. Our findings are closely aligned with previously reported findings by Mir et al., who documented that the lower limbs and feet were most frequently affected sites in cutaneous leishmaniasis.[17] Furthermore, their study found that the majority of patients (52%) had solitary lesions, while multiple lesions were less frequent. This pattern is similar to our findings, where solitary lesions were the most common presentation.

Our study demonstrates a clear seasonal peak in CL during winter season, with the highest numbers seen in January and February. This pattern is also reported in a study in District Khyber, Pakistan by Lu C et al. The increased number of cases in winter is likely a reflection on the incubation period of CL, where sandfly biting activity peaks during the warmer summer season, leading to the clinical manifestation of disease several months later in the colder season.[18] Variations in peak months may be attributed to local climatic conditions and behaviour of specific Leishmania species prevalent in Balochistan.[19]

The epidemiological patterns observed in our study are influenced by unique environmental and socio-demographic context of Quetta and Balochistan. Factors such as arid climate, cross-border movement, poor housing, limited access to preventive measures may contribute to the sustained transmission and clinical presentation of CL in this region.[20]

These findings have significant public health implications for CL control in Balochistan. The identified seasonal peak suggests that targeted public health interventions, such as awareness campaigns and vector control measures, could be most effective if implemented prior to and during the peak transmission season. The observed concentration of cases among young adults with male predominance identifies a high-risk population. By analyzing the local clinico-demographic patterns, this study offers valuable insight for improving surveillance systems and implementing efficient public health preventive measures to control the burden of disease.

This study has several limitations. As a single-center study, relying solely on patients presenting to a tertiary care hospital, it might not capture the full burden of disease in the community. Species identification could not be performed due to limited resources. Future research should consider multi-center studies across Balochistan to provide a more comprehensive epidemiological picture. Molecular characterization of Leishmania species in different regions would be invaluable for understanding genotype-phenotype correlations.

CONCLUSION

This one-year retrospective study conducted at a tertiary care hospital in Quetta highlights cutaneous leishmaniasis as a persistent public health challenge in Balochistan. The demographic and clinical patterns observed, particularly the higher

prevalence among young males and seasonal peaks during cooler months reflect distinct epidemiological characteristics within a facility serving both military personnel and civilian populations in Balochistan. By emphasizing facility-level insights, this study bridges gaps in regional surveillance data typically derived from community settings. These findings highlight the need for integrated control strategies and targeted public health interventions in endemic regions.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Saima Ali Khan:** Drafting, Final approval.
2	**Fareeha Imran:** Analysis.
3	**Najia Ahmed:** Revision.
4	**Maira Wajahat:** Interpretation of data.

https://doi.org/10.29309/TPMJ/2026.33.02.9178 www.theprofesional.com

ORIGINAL ARTICLE

The impact of metabolic syndrome on morbidity in patients undergoing Coronary Artery Bypass Graft (CABG) surgery.

Muhammad Farooq Ahmad[1], Muhammad Hussnain Raza[2], Riaz ul Haq[3], Muhammad Mujahid[4], Sidra Masood[5], Muneeza Dilpazeer[6]

ABSTRACT… Objective: To compare the post-operative morbidity in patients undergoing coronary artery bypass graft surgery with versus without metabolic syndrome. **Study Design:** This study was a quasi-experimental study. **Setting:** Department of Cardiac Surgery, Faisalabad Institute of Cardiology Faisalabad. **Period:** 30/03/2022 to 29/03/2023 (12 month study). **Methods:** The present study involved 200 both male and female patients aged 30-65 years undergoing coronary artery bypass grafting assimilated into two equal groups containing 100 cases for each group i.e. with and without metabolic syndrome. Standard departmental protocols were adopted to manage these cases. Outcome variables were mean intubation time, mean ICU and hospital stay duration, as well as post-operative atrial fibrillation, respiratory complications and wound infection which were noted and compared between the groups. **Results:** The average age of the study participants was 51.4 ± 9.4 years, with a male predominance of 7:1. Among them, 60.5% had hypertension, and 35.5% were diagnosed with diabetes. When comparing outcomes between groups, patients with metabolic syndrome experienced significantly longer intubation times (21.35 ± 2.70 vs. 16.35 ± 1.70 hours; p=0.001), prolonged ICU stays (63.85 ± 7.81 vs. 50.38 ± 4.38 hours; p=0.001), and extended hospital stays (9.70 ± 1.92 vs. 7.17 ± 1.78 days; p=0.001) compared to those without it. Additionally, the incidence of postoperative atrial fibrillation (19.0% vs. 2.0%; p=0.001), respiratory complications (16.0% vs. 0.0%; p=0.001), and wound infections (20.0% vs. 3.0%; p=0.001) was remarkably higher among CABG recipients diagnosed with metabolic syndrome. **Conclusion:** Among patients undergoing CABG, the presence of metabolic syndrome was linked to increased post-operative morbidity, including prolonged intubation time, extended ICU and hospital stays, and a higher risk of atrial fibrillation, respiratory complications, and wound infections, irrespective of age, gender, and diabetic status. This underscores the need for routine metabolic syndrome screening in CABG candidates to enable early detection and proactive management, ultimately improving patient outcomes.

Key words: Coronary Artery Bypass Graft, Metabolic Syndrome, Post-Operative Morbidity.

Article Citation: Ahmad MF, Raza MH, Riaz ul Haq, Mujahid M, Masood S, Dilpazeer M. The impact of metabolic syndrome on morbidity in patients undergoing Coronary Artery Bypass Graft (CABG) surgery. Professional Med J 2026; 33(02):203-212. https://doi.org/10.29309/TPMJ/2026.33.02.9178

INTRODUCTION

Metabolic syndrome (MetS) includes multiple metabolic dysfunctions, such as central obesity, insulin resistance, high triglyceride levels, decreased HDL cholesterol, and hypertension.[1] The underlying mechanism linking these cardiovascular risk factors is insulin resistance, which serves as a defining feature of MetS and plays a crucial role as a causative factor in subjects undergoing CABG.[2] As metabolic syndrome (MetS) encompasses various cardiovascular risk factors, it has been linked to an increased incidence of morbidity in the early postoperative stage of CABG. Given this elevated risk, MetS should be an essential consideration in the preoperative evaluation of patients undergoing CABG. With a preventability rate of 40% to 50%, metabolic syndrome is a modifiable condition that is often overlooked and left untreated, potentially exacerbating outcomes in CABG patients.[3] It has been suggested that insulin resistance significantly contributes to the increased occurrence of ischemic events in MetS patients, though the exact mechanisms and related processes remain to be fully understood.[4] MetS has been reported to have a global prevalence of approximately 11% to 40%.[5,6] Metabolic syndrome is associated with chronic inflammation, characterized by increased adipocytokine levels, including interleukin-6, tumor necrosis factor-alpha, and C-reactive protein, along with elevated free fatty acids that contribute

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Article received on:
17/02/2025
Date of revision:
15/09/2025
Accepted for publication:
22/09/2025

to endothelial dysfunction and vasoconstriction. This condition is also regarded as a form of low-grade inflammation, marked by increased levels of circulating inflammatory cytokines. Patients with MetS exhibit reduced plasma adiponectin levels and elevated leptin and resistin levels. While leptin and resistin enhance immune system activity, adiponectin counteracts inflammation in the vascular wall by inhibiting the nuclear factor kappa B pathway.[7] The chronic pro-inflammatory condition seen in MetS patients may worsen the systemic inflammatory response triggered by cardiopulmonary bypass (CPB) and surgical trauma, increasing the risk of complications both during and after surgery.[8]

As a key component of MetS, abdominal obesity contributes to metabolic imbalances that heighten susceptibility to type 2 diabetes and CVD.[9] It has been recognized as a predictor of unfavorable outcomes after cardiovascular procedures, and recent findings suggest its association with both short- and long-term mortality and morbidity following CABG surgery.[10] various trial did not find such relationship.[11] MetS is diagnosed when at least three of the five criteria established by NCEP ATP III are met. The modified NCEP ATP III criteria are more applicable to the Asian population, as they consider ethnic-specific waist circumference values.[12,13]

METHODS

This comparative cross-sectional study was carried out in the Cardiac Surgery Department at Faisalabad Institute of Cardiology, a well-equipped tertiary care center specializing in cardiac procedures. 200 patients who underwent CABG surgery from 30-03-2022 to 29-03-2023 were included in the study. Approval was obtained from the hospital's ethical review committee (19/DME/FIC/FSD), and no conflicts of interest were reported. As part of the preoperative evaluation, systolic and diastolic blood pressure, waist circumference (cm), triglyceride levels, fasting blood glucose, and high-density lipoprotein levels were measured and recorded during admission to the cardiac surgery unit. Both male and female patients between 40 to 70 years of age with serum creatinine level of less than 1.2 undergoing elective CABG surgery were included. The study excluded patients undergoing redo surgeries, those with an eGFR below 60 ml/min, and individuals with a LVEF<30%. Patients were interviewed, explained and counseled about the procedure of the study. They were admitted in cardiac surgery ward.

TABLE

The modified criteria NCEP ATP III for metabolic syndrome

Measure (any 3 of 5 constitute diagnosis of metabolic syndrome)	Categorical Cutpoints
Elevated waist circumference*†	≥102 cm (≥40 inches) in men
	≥88 cm (≥35 inches) in women
Elevated triglycerides	≥150 mg/dL (1.7 mmol/L)
	Or
	On drug treatment for elevated triglycerides‡
Reduced HDL-C	<40 mg/dL (1.03 mmol/L) in men
	<50 mg/dL (1.3 mmol/L) in women
	Or
	On drug treatment for reduced HDL-C‡
Elevated blood pressure	≥130 mm Hg systolic blood pressure
	Or
	≥85 mm Hg diastolic blood pressure
	Or
	On antihypertensive drug treatment in a patient with a history of hypertension
Elevated fasting glucose	≥100 mg/dL
	Or
	On drug treatment for elevated glucose

*To measure waist circumference, locate top of right iliac crest. Place a measuring tape in a horizontal plane around abdomen at level of iliac crest. Before reading tape measure, ensure that tape is snug but does not compress the skin and is parallel to floor. Measurement is made at the end of a normal expiration.

†Some US adults of non-Asian origin (eg, white, black, Hispanic) with marginally increased waist circumference (eg, 94-101 cm [37-39 inches] in men and 80-87 cm [31-34 inches] in women) may have strong genetic contribution to insulin resistance and should benefit from changes in lifestyle habits, similar to men with categorical increases in waist circumference. Lower waist circumference cutpoint (eg, ≥90 cm [35 inches] in men and ≥80 cm [31 inches] in women) appears to be appropriate for Asian Americans.

‡Fibrates and nicotinic acid are the most commonly used drugs for elevated TG and reduced HDL-C. Patients taking one of these drugs are presumed to have high TG and low HDL.

As described by NCEP ATP III, the modified criteria

will be used. According to which at least three of the five criteria will have to be met for the diagnosis of Metabolic Syndrome.

The patients divided into two groups

Study Group (with metabolic syndrome)

Control Group (without metabolic syndrome)

Surgery performed utilizing standard techniques of median sternotomy, arterial and venous grafts harvesting, pericardiotomy, heparinization, cannulation, cardiopulmonary bypass, hypothermia, aortic cross clamping and ante grade cold blood cardioplegia. Required number of grafts will be anastomosed, rewarming, removal of cross clamp, restoration of normal sinus rhythm, weaning off CPB, protamine administration, placements of pacing wires and drains, hemostasis and chest closure. Patients shifted to ICU.

Postoperative outcome in term of prolonged intubation time, prolonged ICU stay (Hours), prolonged hospital stay (Days), atrial fibrillations, pulmonary complications and wound infections were recorded.

RESULTS

Patients were aged between 33 and 65 years, of 51.4 ± 9.4 years was computed as mean + sd. Most of the cases i.e. 61.5% (n=123) belonged to the 45 years and older age group. There were 175 (87.5%) males and 25 (12.5%) females. Ratio between male to female patients was of 7:1. 121 (60.5%) patients were hypertensive and 71 (35.5%) patients were diabetic as given in Table-I.

The subgroup analysis demonstrated that there was no inherent bias between the groups in study, as differences in mean age ($p = 0.881$), age subgroup distribution ($p = 0.884$), gender ($p = 0.831$), and hypertensive status ($p = 0.885$) were statistically insignificant. However, diabetes was significantly more common among MetS patients (57.0% vs. 14.0%; $p < 0.001$), Table-II.

The intubation time ranged from 13-25 hours with a mean of 18.85±3.37 hours while the length of ICU stay ranged from 44-75 hours with a mean of 57.12±9.25 hours. Length of hospital stay ranged from 5-14 days with a mean of 8.43±2.24 days. Post-operative atrial fibrillation was noted in 21 (10.5%) patients while respiratory complications and wound infection were encountered in 16 (8.0%) and 23 (11.5%) patients respectively. The mean intubation time (21.35±2.70 vs. 16.35±1.70 hours; $p < 0.001$), ICU stay duration (63.85±7.81 vs. 50.38±4.38 hours; $p < 0.001$), and total hospital stay (9.70±1.92 vs. 7.17±1.78 days; $p < 0.001$) were all remarkably longer in subjects with MetS compared to those without it. Similarly, patients with metabolic syndrome who underwent CABG exhibited a significantly higher occurrence of postoperative atrial fibrillation (19.0% vs. 2.0%; $p < 0.001$), respiratory complications (16.0% vs. 0.0%; $p < 0.001$), and wound infections (20.0% vs. 3.0%; $p < 0.001$), as shown in Table-III. Upon stratification, an equally significant difference was observed between the groups across multiple subgroups classified by gender, age, hypertension, and diabetic status, as presented in Tables-IV–IX.

TABLE-I

Demographic and Clinical Profile of the Study Cohort

Characteristics	Participants n=200
Age (years)	51.4±9.4
<45 years	77 (38.5%)
≥45 years	123 (61.5%)
Gender	
Male	175 (87.5%)
Female	25 (12.5%)
Hypertension	
Yes	121 (60.5%)
No	79 (39.5%)
Diabetes	
Yes	71 (35.5%)
No	129 (64.5%)

TABLE-II

Baseline characteristics of the study groups n=200

Characteristics	Without MetS n=100	With MetS n=100	P-Value
Age (years)	51.5±9.1	51.3±9.8	0.881
<55 years	38 (38.0%)	39 (39.0%)	0.884
≥55 years	62 (62.0%)	61 (61.0%)	
Gender			
Male	87 (87.0%)	88 (88.0%)	0.831
Female	13 (13.0%)	12 (12.0%)	
Hypertension			
Yes	60 (60.0%)	61 (61.0%)	0.885
No	40 (40.0%)	39 (39.0%)	
Diabetes			
Yes	14 (14.0%)	57 (57.0%)	<0.001*

*The chi-square test confirmed the observed difference as significant

TABLE-III

Comparison of various outcome measures between the study groups n=200

Outcome Measures	Without Mets n=100	With Mets n=100	P-Value
Mean Intubation Time (hours)	16.35±1.70	21.35±2.70	<0.001*
Mean Length of ICU Stay (hours)	50.38±4.38	63.85±7.81	<0.001*
Mean Length of Hospital Stay (days)	7.17±1.78	9.70±1.92	<0.001*
Post-Operative Atrial Fibrillation	2 (2.0%)	19 (19.0%)	<0.001*
Post-Operative Respiratory Complications	0 (0.0%)	16 (16.0%)	<0.001*
Post-Operative Wound Infection	3 (3.0%)	20 (20.0%)	<0.001*

* The observed difference was statistically significant on Independent sample t-test and chi-square test/Fisher's exact test

TABLE-IV

Comparison of mean intubation time (Hours) between the study groups across various subgroups n=200

Subgroups	Mean Intubation Time (Hours)		P-Value
	Without MetS n=100	With MetS n=100	
Age			
<55 years	16.32±1.73	21.10±2.74	<0.001*
≥55 years	16.37±1.69	21.51±2.68	<0.001*
Gender			
Male	16.32±1.75	21.33±2.71	<0.001*
Female	16.54±1.33	21.50±2.72	<0.001*
Hypertension			
Yes	16.25±1.72	21.36±2.76	<0.001*
No	16.50±1.68	21.33±2.63	<0.001*
Diabetes			
Yes	16.21±1.72	21.07±2.87	<0.001*
No	16.37±1.70	21.72±2.43	<0.001*

* The observed difference in mean intubation time (hours) was statistically significant on t- test

TABLE-V

Comparison of Mean Length of ICU Stay (Hours) between the study groups across various subgroups n=200

Subgroups	Mean ICU Stay (Hours)		P-Value
	Without MetS n=100	With MetS n=100	
Age			
<55 years	50.13±4.52	63.74±8.56	<0.001*
≥55 years	50.53±4.33	63.92±7.36	<0.001*
Gender			
Male	50.32±4.43	63.75±7.99	<0.001*
Female	50.77±4.23	64.58±6.57	<0.001*
Hypertension			
Yes	50.48±4.54	63.77±7.55	<0.001*
No	50.23±4.19	63.97±8.30	<0.001*
Diabetes			
Yes	52.29±4.53	63.23±7.47	<0.001*
No	50.07±4.31	64.67±8.25	<0.001*

* The observed difference in mean length of ICU stay (hours) was statistically significant on t- test

TABLE-IV

Comparison of mean length of hospital stay (Days) between the study groups across various subgroups n=200

Subgroups	Mean Hospital Stay (Days)		P-Value
	Without MetS n=100	With MetS n=100	
Age			
<55 years	7.13±1.66	9.64±1.95	<0.001*
≥55 years	7.19±1.86	9.74±1.91	<0.001*
Gender			
Male	7.14±1.76	9.68±1.92	<0.001*
Female	7.38±1.94	9.83±1.99	0.005*
Hypertension			
Yes	7.23±1.88	9.80±1.91	<0.001*
No	7.08±1.62	9.54±1.93	<0.001*
Diabetes			
Yes	7.28±1.77	9.84±1.85	<0.001*
No	6.50±1.70	9.60±1.97	<0.001*

* The observed difference in mean length of hospital stay (days) was statistically significant on t- test

TABLE-IIV

Comparison of Post-Operative Atrial Fibrillation between the Study Groups across Various Subgroups n=200

Subgroups	Post-Operative Atrial Fibrillation		P-Value
	Without MetS n=100	With MetS n=100	
Age			
<55 years	1/38 (2.6%)	7/39 (17.9%)	0.050*
≥55 years	1/62 (1.6%)	12/61 (19.7%)	0.001*
Gender			
Male	2/87 (2.3%)	17/88 (19.3%)	<0.001*
Female	0/13 (0.0%)	2/12 (16.7%)	0.220
Hypertension			
Yes	2/60 (3.3%)	12/61 (19.7%)	0.008*
No	0/40 (0.0%)	7/39 (17.9%)	0.005*
Diabetes			
Yes	1/14 (7.1%)	11/57 (19.3%)	0.437
No	1/86 (1.2%)	8/43 (18.6%)	0.001*

* The observed difference was significant on Fisher's exact test

TABLE-VIII

Comparison of post-operative respiratory complications between the study groups across various subgroups n=200

Subgroups	Post-Operative Respiratory Complications		P-Value
	Without MetS n=100	With MetS n=100	
Age			
<55 years	0/38 (0.0%)	6/39 (15.4%)	0.025*
≥55 years	0/62 (0.0%)	10/61 (16.4%)	0.001*
Gender			
Male	0/87 (0.0%)	14/88 (15.9%)	<0.001*
Female	0/13 (0.0%)	2/12 (16.7%)	0.220
Hypertension			
Yes	0/60 (0.0%)	11/61 (18.0%)	0.001*
No	0/40 (0.0%)	5/39 (12.8%)	0.026*
Diabetes			
Yes	0/14 (0.0%)	9/57 (15.8%)	0.189
No	0/86 (0.0%)	7/43 (16.3%)	<0.001*

* The observed difference was significant on Fisher's exact test

TABLE-IX

Comparison of post-operative wound infection between the study groups across various subgroups n=200

Subgroups	Post-Operative Wound Infection		P-Value
	Without MetS n=100	With MetS n=100	
Age			
<55 years	1/38 (2.6%)	8/39 (20.5%)	0.029*
≥55 years	2/62 (3.2%)	12/61 (19.7%)	0.004*
Gender			
Male	2/87 (3.2%)	17/88 (19.3%)	<0.001*
Female	1/13 (7.7%)	3/12 (25.0%)	0.322
Hypertension			
Yes	2/60 (3.3%)	12/61 (19.7%)	0.008*
No	1/40 (2.5%)	8/39 (20.5%)	0.014*
Diabetes			
Yes	1/14 (7.1%)	12/57 (21.1%)	0.441
No	2/86 (2.3%)	8/43 (18.6%)	0.002*

* The observed difference was significant on Fisher's exact test

DISCUSSION

Coronary artery bypass grafting (CABG) continues to be the preferred method for multivessel coronary revascularization.[14,15] Despite advancements in percutaneous coronary interventions and medical therapy, CABG continues to be a major contributor in treatment in patients diagnosed with CVD.[15] CABG has been made much safe and more acceptable by major advancements. Continuous research into various methods, approaches and medical interventions has made cardiac surgery mush safe and less invasive for future.[14,15] The rate of early versus late complications and risk factors associated with patients undergoing CABG has been attempted by many researchers. Among them are DM and COPD, number of type of graft, stroke, gender, age, serum procalcitonin level, addition, and chronic kidney disease, transfusion of blood products, ejection fraction and kind of technique (on-pump vs. off-pump).[16,17,18] In South Asia, MetS represents a significant health concern that needs urgent therapeutic and preventive actions.[19,20,21] In South Asia, paradoxically prevalence of MetS is equal between non-obese and obese populations.[19] In this region, the increased prevalence of MetS is related with increasing incidence of premature cardiovascular disease, diabetes and hypertension.[21,22] Clinicians face patients meeting diagnostic criteria for MetS in routine practice; these criteria include hypertension,central obesity, atherogenic dyslipidemia, and hyperglycemia.[23] Irrespective of variation in its definition, metabolic syndrome is related with adverse outcomes in patients undergoing non-cardiac and cardiac surgery.[23,24,25] Few recent studies reported that presence of MetS was associated with higher likelihood of post-operative complications in patients undergoing CABG and advocated that such patients should be considered as high risk.[10,11,26,27,28,29] However, the available research evidence was insufficient, and no relevant studies had been conducted on the local population, necessitating the present study.

The mean age of the patients undergoing CABG in this study was 51.4±9.4 years. Our observation is in line with that of another study[30] which observed similar mean age of 51.3±5.7 years among patients undergoing CABG at Choudhary Pervaiz Elahi Institute of Cardiology, Multan. In another local study[31] reported similar mean age of 51.6±10.3 years among such patients undergoing CABG at Punjab Institute of Cardiology, Lahore. Similar mean age has already been reported in a number of other local studies[32,33,34] which observed it to be 53.6±10.2 years, 55.3±9.6 years and 54.5±3.4 years respectively. In another study[35] a comparable mean age has been observed in Indian patients undergoing CABG which reported it to be 52.±11.2 years and another study[36] reported it to be 53.7±9.5 years. A similar trial[37] in Bangladesh reported comparable mean age of 54.8±2.5 years among such patients while another trial[38] reported it to be 53.4±8.9 years in Nepal.

This observed mean age in the present study matches with statistics reported by other studies conducted in local as well as other populations in south-east Asia. However in comparison with western population, this mean age is quite younger while some studies[39,40] observed much higher mean age at the time of CABG and reported it to be 67.1±10.1 years and 66.1±9.9 years respectively. Another study[41] also reported higher mean age of 67.3±9.1 years among Chinese such patients. This difference in the mean age can be attributable to geographical as well as life style and genetic factors associated with coronary artery disease. It implies public health measures in this regard to increase the public awareness about this aspect to reduce the burden of disease and delay its development as much as possible.

We observed that there was a male predominance among patients undergoing CABG with a male predominance to female. In another similar study[32] reported alike predominance of males with male to female ratio of 7.2:1. Observations in this study are in line with that of another trial[42] as well, who stated similar male predominance with male to female ratio of 6.2:1 in patients undergoing CABG. Comparable male predominance with male to female ratio of 6.2:1 has also been reported in another study.[33] Some other studies[35,36] described comparable predominance of male patients with male to female ratio of 7.1:1 and 7.9:1 respectively in Indian CABG patients. Another study[43] observed it to be 7.3:1 among Italian such patients.

In the present study, among patients undergoing CABG, 60.5% patients were hypertensive and 35.5% patients were diabetic. A similar frequency of hypertension (83.0%) and diabetes (38.0%) has also been observed in another trial[44] among patients undergoing CABG. Another study[33] observed similar frequency of hypertension and diabetes among such patients at Chaudhary Pervaiz Elahi Institute of Cardiology Multan and reported it to be 47.0% and 36.3% respectively. Another local study[32] reported comparable frequency of 46.0% and 36.0% for hypertension and diabetes respectively among patients undergoing CABG at Punjab Institute of Cardiology, Lahore. Our observation is also in line with that another study[35] which reported similar frequency of hypertension (76.1%) and diabetes (38.1%) in Indian such patients. Another Indian study[36] reported similar frequency of hypertension (71.6%) and diabetes (37.5%) among patients undergoing cardiac bypass surgery. Similar distribution has also been reported by another study[37] which reported the frequency of hypertension and diabetes to be 81.3% and 34.1% respectively in Bangladesh. Another study[40] also observed similar frequency of hypertension (76.1%) and diabetes (32.6%) in American patients undergoing cardiac bypass surgery. Our results are also in line with a Chinese study[41] which reported similar frequency of 78.4% for hypertension and 31.2% for diabetes among patients undergoing CABG.

Thus middle aged males with hypertension and diabetes contributed major share of patients undergoing CABG in the present study.

Patients diagnosed with metabolic syndrome experienced significantly longer intubation periods (21.35±2.70 vs. 16.35±1.70 hours), extended ICU stays (63.85±7.81 vs. 50.38±4.38 hours), and prolonged hospitalization (9.70±1.92 vs. 7.17±1.78 days), with statistical tests confirming p-values below 0.001 in each case. Similarly, they had a markedly higher incidence of post-operative atrial fibrillation (19.0% vs. 2.0%), respiratory complications (16.0% vs. 0.0%), and wound infections (20.0% vs. 3.0%), all reaching statistical significance at $p<0.001$. Subgroup analysis indicated that these differences remained significant across stratifications based on age, sex, hypertension, and diabetes.

A similar study[45] supports our findings, as it assessed operative morbidity in 40 Indonesian CABG patients with metabolic syndrome, compared to 34 patients without it. Their results demonstrated a significantly prolonged mean intubation time (30.2±4.4 vs. 16.4±4.2 hours; $p < 0.001$) and longer hospital stays (9.44±1.50 vs. 7.31±1.13 days; $p < 0.001$) in the metabolic syndrome group. The study also reported a notably higher wound infection rate (20.5% vs. 2.9%; $p < 0.001$) among these patients.

Another study[29] investigated 11,021 CABG cases in the USA, identifying 3,881 (35.2%) as having metabolic syndrome. Their study highlighted a significantly prolonged mean intubation period (30.9±93.8 vs. 24.6±81.1 hours; $p<0.001$), an extended ICU stay (68.50±150.2 vs. 55.3±105.1 hours; $p<0.001$), and a longer hospitalization duration (7.3±6.3 vs. 6.3±5.2 days; $p<0.001$) among patients with metabolic syndrome compared to those without.

A study[46] on Chinese CABG patients reported that individuals with metabolic syndrome had extended intubation times (18.23±22.63 vs. 15.86±24.17 hours) and ICU stays (60.33±67.79 vs. 48.26±38.29 hours), with the differences reaching statistical significance at a 99.9% confidence level ($p<0.001$).

Another study[10] on American CABG patients, observed significantly longer ICU stays (2.3±4.3 vs. 1.9±2.8 days) and hospital stays (8.3±7.8 vs. 6.6±6.0 days), with statistical testing confirming $p<0.003$ for both outcomes. Similarly, a study[3] on Chinese patients found that those with metabolic syndrome had a significantly increased intubation duration (19.53±34.45 vs. 15.86±24.17 hours) and ICU stay (61.11±82.09 vs. 48.26±38.29 hours), with p-values indicating highly significant differences ($p<0.001$).

Another study[11] analyzed Turkish CABG patients and found that those with metabolic syndrome had significantly prolonged ICU stays (2.6±0.8 vs. 2.1±0.3 days) and hospital stays (7.9±2.7

vs. 7.1±1.1 days), with p-values demonstrating strong statistical significance (p<0.001). The study also highlighted a significantly higher frequency of atrial fibrillation (15.0% vs. 9.3%; p<0.05) and wound infections (30.0% vs. 4.7%; p<0.001). Similarly, another study[24] identified elevated rates of atrial fibrillation (20.3% vs. 4.5%; p=0.005), wound infections (21.9% vs. 3.4%; p<0.001), and pulmonary complications (17.2% vs. 3.4%; p<0.001) in patients with metabolic syndrome undergoing CABG.

Another study[26] on Iranian patients undergoing CABG, noted a significantly higher frequency of atrial fibrillation in the metabolic syndrome group (15.0% vs. 2.9%), with statistical evaluation yielding p<0.05.

This study is the first of its kind conducted in the local population and adds to the limited international literature on the topic. The study's strengths include a robust sample size of 200 cases and strict exclusion criteria. Additionally, we stratified the data to minimize the influence of confounding factors. Our results indicate that among CABG patients, metabolic syndrome was linked to increased post-operative morbidity, including prolonged intubation duration, extended ICU and hospital stays, and a higher risk of atrial fibrillation, respiratory complications, and wound infections. These associations were observed regardless of patient age, gender, or hypertensive and diabetic status. This validates our initial hypothesis, confirming that metabolic syndrome contributes to higher post-operative morbidity in coronary heart disease patients undergoing CABG. Based on these findings, we recommend that metabolic syndrome screening be incorporated into routine preoperative assessment for CABG candidates to facilitate timely intervention and improve surgical outcomes.

One key limitation of this study was the short follow-up period. A longer follow-up would have allowed for a more comprehensive evaluation of long-term outcomes such as the need for repeat surgery and mortality, providing a clearer picture of the prognostic impact of metabolic syndrome. Future research addressing this aspect is essential.

CONCLUSION

In the present study, we observed that among patients undergoing CABG, the presence of metabolic syndrome was linked to increased post-operative morbidity, including prolonged intubation time, extended ICU and hospital stays, and a higher risk of atrial fibrillation, respiratory complications, and wound infections, irrespective of age, gender, and diabetic status. This underscores the need for routine metabolic syndrome screening in CABG candidates to enable early detection and proactive management, ultimately improving patient outcomes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Muhammad Farooq Ahmad:** Manuscript writing, Data collection.
2	**Muhammad Hussnain Raza:** Data entry.
3	**Riaz ul Haq:** Data analysis.
4	**Muhammad Mujahid:** Revisions.
5	**Sidra Masood:** Study design.
6	**Muneeza Dilpazeer:** References.

https://doi.org/10.29309/TPMJ/2026.33.02.9787 www.theprofesional.com

ORIGINAL ARTICLE

Evaluating the impact of neutrophil-to-lymphocyte ratio on disease severity in acute ST-segment elevation myocardial infarction.

Munir Ahmad[1], Muhammad Yasir[2], Bazgha Niaz[3], Ahmad Salman[4], Jasia Raham Din[5], Farah Naz[6]

ABSTRACT… Objective: To evaluate the impact of NLR on disease severity and clinical outcomes presenting with acute STEMI. **Study Design:** Cross-sectional study. **Setting:** Faisalabad Institute of Cardiology (FIC). **Period:** March 2024 to August 2024. **Methods:** A quantitative, cross-sectional study was conducted at the Faisalabad Institute of Cardiology over six months. A total of 385 patients with confirmed STEMI were included through stratified random sampling. Data on demographics, comorbidities, laboratory parameters, and clinical outcomes were collected. The TIMI risk score and the left ventricular ejection fraction (LVEF) were used to assess disease severity. Experiments, statistical analyses include t tests, chi square tests, correlation, and logistic regression were implemented with SPSS. **Results:** Patients with NLR > 5 demonstrated significantly worse outcomes, including higher TIMI risk scores (5.4 ± 1.5 vs. 3.8 ± 1.2, $p < 0.001$) and lower LVEF (44.3 ± 5.7% vs. 52.2 ± 5.8%, $p < 0.001$). Strongly associated with adverse events including cardiogenic shock, recurrent myocardial infarction, and 30 days' mortality (21.9% vs. 4.4%, $p < 0.001$), increased NLR levels were. NLR over 5 (OR 3.75, $p < 0.001$) and LVEF < 45% (OR 4.12, $p < 0.001$) were identified using the multivariate analysis. **Conclusion:** The patients with elevated NLR have been shown to be reliable markers of increased disease severity and adverse outcomes in STEMI patients. An addition of NLR to routine clinical assessment would improve risk stratification and could guide management strategies. The integration of NLR with other biomarkers can improve predictive accuracy, and further researches should be performed.

Key words: Cardiovascular Risk, Disease Severity, Inflammatory Biomarkers, Left Ventricular Ejection Fraction, Neutrophil-to-Lymphocyte Ratio, Pakistan, ST-Segment Elevation Myocardial Infarction, TIMI Risk Score.

Article Citation: Ahmad M, Yasir M, Niaz B, Salman A, Raham Din J, Naz F. Evaluating the impact of neutrophil-to-lymphocyte ratio on disease severity in acute ST-segment elevation myocardial infarction. Professional Med J 2026; 33(02):213-218. https://doi.org/10.29309/TPMJ/2026.33.02.9787

INTRODUCTION

Ischemic Heart Disease (IHD) constitutes a Globel Health Burden with high morbidity and mortality rates.[1] Recent advances in STEMI pathophysiology have emphasized the key role of inflammation in the genesis, propagation or complications of atherosclerotic plaque rupture.[2] As a result, inflammatory biomarkers have come to prominence as important markers of cardiovascular risk and prediction of disease outcomes. The NLR is one such biomarker among these that has become a simple but powerful predictor of systemic inflammation. NLR is derived from routine complete blood counts and indexes the balance between the neutrophil driven innate immune responses and lymphocyte driven adaptive.[3] An elevated NLR reflects an overinflamed state that is linked to a more severe clinical course in diverse cardiovascular conditions, including STEMI.[4] Its dual components form the mechanistic basis underlying association of NLR with STEMI severity.[5] First responders to vascular injury are neutrophils that propagates inflammation, oxidative stress and extracellular matrix degradation.[6] For instance, in acute inflammatory states, lymphopenia is seen, rather, reflecting failure to properly regulate the immune response and heightened stress responses.

Together, these processes create a pro-inflammatory milieu that exacerbates myocardial injury and fosters adverse remodeling.[7] Several studies from Western and Asian populations have validated the prognostic value of NLR in STEMI, linking higher ratios to larger infarct size, impaired left ventricular function, and increased rates of major adverse cardiovascular events (MACE).[8]

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Article received on:
15/04/2025
Accepted for publication:
26/06/2025

However, data from South Asia, particularly Pakistan, remain limited despite the region's high prevalence of cardiovascular risk factors such as diabetes, hypertension, and dyslipidemia.[9] Local dietary habits, genetic predispositions, and healthcare disparities further underscore the need for region-specific research. In Pakistan, cardiovascular disease accounts for a substantial proportion of non-communicable disease burden. Studies such as Gitto et al. (2022) and Rehman et al. (2022) have documented the rising incidence of STEMI and its associated risk factors in the Pakistani population.[10,11] However, there is a paucity of research exploring the utility of inflammatory biomarkers like NLR in this context. Understanding the impact of NLR on STEMI severity in Pakistani patients could offer valuable insights into its prognostic relevance and guide therapeutic strategies tailored to this population.

With an increasing appreciation for the role of inflammation in STEMI pathophysiology, evaluation of NLR as a marker of disease severity is timely. The objective of this study is this gap in regional literature by exploring the relationship between NLR and clinical outcome in Pakistan STEMI patients. The findings may help improve risk stratification protocols and facilitate incorporation of inexpensive, easily available biomarkers into routine clinical practice. This research also echoes the international effort to optimize STEMI management using personalized and evidence based approaches.

METHODS

This cross-sectional study was conducted at Faisalabad Institute of Cardiology (FIC), a tertiary care hospital renowned for its comprehensive cardiac services. The study spanned six months from March 2024 to August 2024, Ethical Approval was obtained (Ref No. CPSP/REU/CRD-2021-130-2584, dated: February 16, 2024) from the Ethical Review Board with a sample size of 385 patients diagnosed with acute STEMI, calculated based on previous studies and statistical considerations for adequate power and precision. Stratified random sampling was employed to ensure equal representation of patients with varying degrees of disease severity, considering demographics and clinical characteristics like age, gender, and comorbid conditions. Inclusion criteria required patients aged 18 and above with acute STEMI, diagnosed through clinical presentation, ECG changes, and cardiac biomarkers, with informed consent obtained from all participants. Exclusion criteria included patients with a history of malignancy, autoimmune diseases, chronic inflammatory conditions, those on immunosuppressive therapy, or those with incomplete medical records or missing laboratory data. Data were collected through both primary (patient interviews and laboratory tests) and secondary (hospital records) sources, with clinical and demographic data, laboratory parameters (neutrophil and lymphocyte counts), and disease severity assessed using Killip classification and ECG findings. Ethical approval was obtained from FIC's ethical review board, and written informed consent was secured from all participants.

Statistical analysis was performed using SPSS, with continuous variables summarized using descriptive statistics and categorical variables using frequencies and percentages. Comparative analysis of NLR values across different severity levels was conducted with independent sample t-tests and chi-square tests. Pearson correlation coefficients assessed the relationship between NLR and disease severity markers, and multivariate logistic regression identified independent predictors of disease severity, with statistical significance set at $p<0.05$.

RESULTS

In the study population of 385 patients, those with a neutrophil-to-lymphocyte ratio (NLR) > 5 (n = 160) were significantly older (65.7 ± 11.2 years) compared to those with NLR ≤ 5 (60.4 ± 9.8 years, p = 0.001). Hypertension was more prevalent in the higher NLR group (62.5%) than the lower NLR group (48.9%, p = 0.01), while diabetes mellitus (43.8% vs. 35.6%, p = 0.12) and smoking status (46.9% vs. 46.7%, p = 0.97) showed no significant differences. The TIMI risk score was markedly higher in the NLR > 5 group (5.4 ± 1.5 vs. 3.8 ± 1.2, p < 0.001), and left ventricular ejection fraction (LVEF) was significantly reduced in this group (44.3 ± 5.7%) compared to those with NLR ≤ 5 (52.2 ± 5.8%, p < 0.001). The male gender distribution was similar between the groups (75.0% vs. 75.6%, p = 0.89). These findings

underscore the association between elevated NLR and worse clinical and functional outcomes in STEMI patients. Table-I

The analysis of Table 2 reveals a significant relationship between increasing neutrophil-to-lymphocyte ratio (NLR) and worsening disease severity in acute ST-segment elevation myocardial infarction (STEMI) patients. Patients with NLR ≤ 3.0 (n = 140) exhibited the lowest TIMI risk score (3.5 ± 1.1) and the highest left ventricular ejection fraction (LVEF) (54.3 ± 6.0%), with a minimal incidence of major adverse cardiovascular events (MACE) (10.7%, p < 0.001). Conversely, patients with NLR > 7.0 (n = 70) demonstrated the highest TIMI risk score (6.3 ± 1.6) and lowest LVEF (40.5 ± 5.4%), along with the highest MACE incidence (57.1%, p < 0.001). Intermediate groups, including NLR 3.1–5.0 and 5.1–7.0, showed a progressive increase in TIMI risk scores (4.2 ± 1.3 and 5.1 ± 1.4, respectively) and MACE rates (23.5% and 38.9%, respectively), alongside a decline in LVEF (50.1 ± 5.8% and 46.2 ± 5.9%, respectively, p < 0.001). These findings underscore a clear trend of increased disease severity and adverse outcomes with higher NLR levels. Table-II

Age was associated with an increased risk (Odds Ratio [OR] 1.12, 95% Confidence Interval [CI] 1.08–1.17, p < 0.001), while a neutrophil-to-lymphocyte ratio (NLR) > 5 demonstrated a strong predictive value for MACE (OR 3.75, 95% CI 2.45–5.72, p < 0.001). Hypertension also significantly increased the risk of MACE (OR 1.80, 95% CI 1.15–2.80, p = 0.01). Patients with a TIMI risk score ≥ 5 had a 2.65-fold higher risk (95% CI 1.85–3.79, p < 0.001), and those with a left ventricular ejection fraction (LVEF) < 45% had the highest odds of MACE (OR 4.12, 95% CI 2.68–6.34, p < 0.001). Table-III

In this study, the neutrophil-to-lymphocyte ratio (NLR) demonstrated a significant association with adverse clinical outcomes in patients with acute ST-segment elevation myocardial infarction (STEMI). Patients with NLR > 5 experienced substantially higher 30-day mortality (21.9%) compared to those with NLR ≤ 5 (4.4%, p < 0.001), as well as a markedly increased incidence of cardiogenic shock (15.6% vs. 3.6%, p < 0.001). Similarly, the occurrence of heart failure was significantly greater in the high-NLR group (28.1%) than in the low-NLR group (8.9%, p < 0.001). Additionally, recurrent myocardial infarction (MI) was more frequent in patients with NLR > 5 (7.5%) compared to those with NLR ≤ 5 (2.2%, p = 0.03). These findings underscore the prognostic value of NLR as an indicator of disease severity and adverse outcomes in STEMI. Table-IV

TABLE-I

Baseline characteristics of the study population (n = 385)

Variable	Total (N=385)	NLR ≤ 5 (n=225)	NLR > 5 (n=160)	P- Value
Age (years, mean ± SD)	62.8 ± 10.5	60.4 ± 9.8	65.7 ± 11.2	0.001**
Male (%)	290 (75.3)	170 (75.6)	120 (75.0)	0.89
Hypertension (%)	210 (54.5)	110 (48.9)	100 (62.5)	0.01**
Diabetes Mellitus (%)	150 (39.0)	80 (35.6)	70 (43.8)	0.12
Smoking (%)	180 (46.8)	105 (46.7)	75 (46.9)	0.97
TIMI Risk Score (mean ± SD)	4.5 ± 1.7	3.8 ± 1.2	5.4 ± 1.5	<0.001**
Left Ventricular EF (%)	48.5 ± 6.5	52.2 ± 5.8	44.3 ± 5.7	<0.001**

Note: Statistical significance is indicated by P < 0.05.

TABLE-II

Neutrophil to lymphocyte ratio and disease severity (n = 385)

NLR Group	Number of Patients (n)	TIMI Risk Score (Mean±SD)	LVEF (%) (Mean±SD)	Incidence of MACE (%)
NLR ≤ 3.0	140	3.5 ± 1.1	54.3 ± 6.0	15 (10.7)
3.1 - 5.0	85	4.2 ± 1.3	50.1 ± 5.8	20 (23.5)
5.1 - 7.0	90	5.1 ± 1.4	46.2 ± 5.9	35 (38.9)
> 7.0	70	6.3 ± 1.6	40.5 ± 5.4	40 (57.1)

TABLE-III

Predictors of MACE (n=385) using multivariate logistic regression analysis

Variable	Odds Ratio (95% CI)	P-Value
Age	1.12 (1.08 - 1.17)	<0.001**
NLR > 5	3.75 (2.45 - 5.72)	<0.001**
Hypertension	1.80 (1.15 - 2.80)	0.01**
TIMI Risk Score ≥ 5	2.65 (1.85 - 3.79)	<0.001**
Left Ventricular EF < 45%	4.12 (2.68 - 6.34)	<0.001**

TABLE-IV

Association of NLR with clinical outcomes (n = 385)

Outcome	NLR ≤ 5 (n=225)	NLR > 5 (n=160)	P-Value
30-day Mortality (%)	10 (4.4)	35 (21.9)	<0.001**
Cardiogenic Shock (%)	8 (3.6)	25 (15.6)	<0.001**
Heart Failure (%)	20 (8.9)	45 (28.1)	<0.001**
Recurrent MI (%)	5 (2.2)	12 (7.5)	0.03**

DISCUSSION

In 385 patients with acute ST segment elevation myocardial infarction (STEMI), we evaluated the impact of neutrophil to lymphocyte ratio (NLR) on disease severity and outcomes. Results showed that an increased NLR (NLR > 5) was associated with poorer clinical and functional outcomes, including greater TIMI risk scores and lower LVEF, and more frequent occurrences of MACE. These findings establish that NLE is a valuable prognostic marker in STEMI patients.

Patients with NLR > 5 were significantly older (65.7 ± 11.2 years) than those with NLR ≤ 5 (60.4 ± 9.8 years, p = 0.001) indicating that higher NLR is linked to higher age. This is consistent with Selanno et al. study (2022), who found an association of NLR with age in STEMI patients.[12]especially in remote areas require an easy and inexpensive examination such as Neutrophil Lymphocyte Ratio (NLR Consistent with the study by Dieden et. al (2022), hypertension prevalence was higher in the high-NLR group (62.5% versus 48.9%, p = 0.01).[13] However, diabetes mellitus and smoking status showed no significant differences between groups, a result partially supported by Sharma et al. (2023), who found only weak associations of these factors with NLR in STEMI patients.[5]

The TIMI risk score, a marker of clinical severity, was significantly elevated in patients with NLR > 5 (5.4 ± 1.5 vs. 3.8 ± 1.2, p < 0.001). This finding underscores the association of high NLR with severe disease profiles. Supporting this, a study by Bedel, Korkut and Armağan et al. (2021) demonstrated that patients with high NLR exhibited higher clinical risk scores, emphasizing the utility of NLR as a predictor of adverse outcomes.[14]

Patients with NLR > 5 had markedly reduced LVEF (44.3 ± 5.7% vs. 52.2 ± 5.8%, p < 0.001). Table-II, likewise, shows increasing NLR and corresponding declining LVEF with increasing NLR, from 54.3% in the lowest NLR group (≤ 3.0) to 40.5% in the highest NLR group (>7.0, p < 0.001). Consistent with the study by Tey et al. (2023), which also found a strong inverse relationship between NLR and LVEF, these results also show a strong inverse relationship between NLR and LVEF.[15] On the other hand, some researchers Begic et al., (2020) have been suggesting that LVEF does not always decrease significantly in various subsets of patients with STEMI and high NLR but this may vary with other confounders.[16]

The relationship between NLR and MACE incidence was shown to be direct. Patients with NLR < 3.0 had the lowest MACE rate (0.000, p < 0.001) compared to patients with NLR > 7.0 (57.0%) and patients with NLR less than or equal to 4.0. Further, multivariate analysis showed that NLR > 5 was a strong, independent predictor of MACE (OR 3.75, 95% CI 2.45–5.72, p < 0.001). Similar to these findings, Shah et al. (2016) also found an elevated NLR did prognosticate with greater rates of recurrent MI, cardiogenic shock and mortality.[17] But other studies, such as that by Nielsen et al (2020) have little or weaker associations which might be a result of difference in sample size and patient population.[18]

Furthermore, the 30 days mortality was significantly higher in patients with NLR > 5 (21.9% vs. 4.4%, p < 0.001) and increased rates of cardiogenic shock (20.1% vs. 15.6%, p < 0.001). These findings are consistent with Fatima et al. (2022) who found

elevated NLR to be a robust predictor of short term mortality and complications of STEMI patients.[19] Furthermore, NLR also identifies high risk patients as those having higher incidence of heart failure in the high NLR group compared to the low NLR group (28.1% vs. 8.9%, $p < 0.001$). On the other hand, Citu et al. (2022) found that NLR may be insufficient to entirely predict mortality, and multiple biomarkers should be integrated.[20]

The findings of the present study are consistent with the current literature regarding the prognostic potential of NLR in the cardiovascular diseases. While the association between elevated NLR and more severe disease and poorer outcomes has been corroborated by several studies, for example those by Pirsalehi et al. (2020) and Pujari Y et al. (2021), there are conflicting results in some cohorts.[21,22] For instance, it was reported that weaker associations are seen in populations with lower baseline inflammation, which implies that systemic inflammation levels may modulate the prognostic value of NLR, Nielsen et al., (2020).[18] This study's detailed stratification of NLR levels further allows novel insights into the gradient of risk posed by increasing NLR, where this aspect of NLR is not emphasized in the bulk of previous research. The progressive worsening of TIMI risk scores, LVEF, and MACE rates within NLR strata highlights the inherent dynamic nature of NLR as an in vivo marker of risk.

CONCLUSION

This study revealed that elevated NLR is a salient marker of worse clinical outcomes in patients with STEMI and reinforces its potential as a marker of worsening outcome in risk stratification in this setting. The results are in line with previously reported literature, and provide an added level of sophistication in our understanding of the relationship between NLR and disease severity. Future work should harness NLR to augment predictive power of other biomarkers and determine its potential utility to guide therapeutic interventions.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Munir Ahmad:** Manuscript writing.
2	**Muhammad Yasir:** Study design.
3	**Ahmad Salman:** Data analysis.
4	**Farah Naz:** Results, References.
5	**Jasia Shahid:** Proof read.
6	**Bazgha Niaz:** Data collection.

https://doi.org/10.29309/TPMJ/2026.33.02.9878 www.theprofesional.com

ORIGINAL ARTICLE

Association of long duration of cardiopulmonary bypass with adverse outcomes in patient undergoing coronary artery bypass grafting.

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ABSTRACT… Objective: To investigate the association between long duration of cardiopulmonary bypass and various adverse postoperative outcome in patients undergoing coronary artery bypass grafting for coronary artery disease. **Study Design:** Cohort study. **Setting:** Department of Cardiac Surgery, Azra Naheed Medical College, Lahore. **Period:** January'2023 to June'2023. **Methods:** Non-probability consecutive sampling done for 180 cases; 90 cases in each group is calculated with 80% power of test, 5% level of significance and taking expected percentage of ARF i.e. 1.3% in patients having short duration of surgery while 12.5% in patients having long duration of surgery. The in-hospital mortality in two groups was 2% vs. 12.9% (p=<0.001) exposed vs non-exposed. **Results:** According to study renal failure and mortality was significant among patients who had longer bypass time. According to chi square test p value was 0.014 with high significance of renal failure in group 46-75years and strong association of Age with ARF RR of 2.16. According to chi square test p value was 0.039 in male group with high significance of mortality in 27-30 BMI group and strong association of gender with mortality RR of 6.3. **Conclusion:** Longer CPD in patients undergoing CABG significantly associated with increased risk of postoperative renal failure and mortality. Key risk factors include Age >46 years and Male gender with BMI 27-30. Prolonged bypass time should be considered a predictor of adverse outcomes, warranting closer monitoring in high-risk patients.

Key words: Acute Renal Failure, Body Mass Index, Cardiopulmonary Bypass Time, Cardiac Surgery, Coronary Artery Bypass Grafting, In-Hospital Mortality, Postoperative Mortality, Risk Factors, Relative Risk, Serum Creatinine.

Article Citation: Khan T, Shabbir M, Ammar M, Tufail Z, Kazim AH, Shahryar. Association of long duration of cardiopulmonary bypass with adverse outcomes in patient undergoing coronary artery bypass grafting. Professional Med J 2026; 33(02):219-224. https://doi.org/10.29309/TPMJ/2026.33.02.9878

INTRODUCTION

Coronary artery bypass grafting (CABG) is conventional and gold standard treatment for patients having coronary artery disease.[1,2] Cardiopulmonary bypass machine (heart lung machine) is the miracle of new age which made cardiac surgery possible but at the cost of its adverse effects on human body.[3,4]

Once bypass is established human blood is directly exposed to cardiopulmonary bypass circuit which can induce severe allergic reactions and can cause complications involving brain, kidneys, lungs and GIT.[5-7] The duration of time in which patient remains on heart lung machine is known as cardiopulmonary bypass time (CPB). Prolonged CPB time increases the chances of harmful Effects and complications. Bypass time is one of the major periprocedural factor determining patient outcome.[8-10]

AKI following coronary artery bypass grafting (CABG) is a common complication with high morbidity and death. AKI is linked to cardiopulmonary bypass (CPB).[11] Acute kidney damage affects up to 30% of coronary artery bypass grafting patients, depending on criteria. Kidney injury increases the risk of infectious complications, short-term and long-term mortality, and hospital problems. In addition to preoperative renal impairment, peripheral artery disease, diabetes, and age, cardiopulmonary bypass technique and duration are risk factors for AKI.[12]

In a study, it was noticed that ARF was higher in long duration of CPB as compared to short duration i.e. 1.3% vs. 12.5% (p=0.018). The in-hospital mortality in two groups was 2% vs. 12.9% (p=<0.001).[14]

Rationale of this study was to find the association between long duration of cardiopulmonary bypass

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Article received on:
03/07/2025
Accepted for publication:
17/09/2025

and adverse postoperative outcomes in patients undergoing coronary artery bypass grafting. Literature has showed that longer duration of cardiopulmonary bypass is associated with post-operative complications and even may lead to mortality within 5-7 days after surgery, which are usually in-hospital stay. Though international studies are there but data reflecting our population is not available and there is only one study found in literature which showed significant results. This study will help us generating information as well as enable us to confirm the evidence in local population.

METHODS

The cohort research was conducted in the department of cardiac surgery at the Azra Naheed Medical College, Lahore, more than six months (from January'2023 to June'2023) after the synopsis was approved from the CPSP and Ethical Review Board (ANMC/ME/01/23/058, Dated: 04-January-2023 in the name of Dr M. Ammar). The expected percentage of ARF is 1.3% in patients with a brief duration of surgery and 12.5% in patients with a long duration of surgery, as determined by non-probability consecutive sampling of 180 cases. The power of the test is 80%, the level of significance is 5%, and the number of cases in each group is 90. The in-hospital mortality rate was 2% in the exposed group and 12.9% in the non-exposed group (p=<0.001). Selection Criteria:

Patients of either gender who are scheduled to undergo coronary artery bypass grafting (CABG) for coronary artery disease under general anesthesia will be included in the study. The age range is 40 to 70 years. Group A will consist of patients who are undergoing surgery with a short cardiopulmonary bypass (CPB) duration (non-exposed), while Group B will consist of patients who are undergoing surgery with a long CPB duration (exposed). Therefore, the study population will be divided into two categories.

If the medical record indicates that the patient is undergoing CABG in conjunction with any additional procedure, such as for valvular disease, they will be excluded. Additional exclusion criteria include a left ventricular ejection fraction (LVEF) of less than 30% on echocardiography, intraoperative technical difficulties resulting in a bypass time exceeding 240 minutes, and preoperative renal impairment or a serum creatinine level greater than 1.2 mg/dL.

Demographic information, including name, age, gender, BMI, diagnosis, and baseline creatinine level, was also recorded. Patients were transferred to the intensive care unit following surgery and will be monitored there. A 3cc BD syringe will be used to collect a blood sample, which will be sent to the hospital's laboratory for the evaluation of the basal creatinine level following the surgery. A rise in creatinine was observed. ARF was classified as such if the absolute increase in serum creatinine was 0.3mg/dl or greater, and the urine output was decreased, as per the operational definition. Then, patients were monitored until their discharge. In-hospital mortality was designated for patients who passed away within 30 days of surgery. The proforma was used to record all of this information.

We entered all the data into SPSS version 21 and looked at it. Mean and standard deviation were used to show quantitative factors like age, BMI, and a rise in blood creatinine. Qualitative characteristics including gender, ARF, and death in the hospital were shown as percentages and frequencies. We looked at ARF and in-hospital death rates in both groups and figured out the proportional risk. A relative risk of more than 1 was seen as important. The data was broken down by age, gender, and BMI. We used the post-stratification chi-square test and found that a p value of less than 0.05 was significant.

RESULTS

In this study, 72.8% of the patients were male (131) and 27.2% were female (49). There was no statistically significant difference (p>0.05) between the two groups for most of the factors, such as height and age. Patients in Group B, who had longer bypass times, had a higher BSA (1.71±0.17) (p<0.05) than patients in Group 1, who had shorter bypass times (1.67±0.27). Also, the people in Group B, who had longer bypass times, weighed more (65.88±12.1) (p<0.05) than the people in Group 1, who had shorter bypass times (64.41±17.51). The research of body mass index found significant differences between the two groups: group A had a value of 24.9±1.83 and group B had a value of 25.7±2.12 (p value 0.016). Group B had a higher

BMI. Table-I summarizes perioperative variable like bypass time and postoperative variables were urine output, serum creatinine levels and mortality.

TABLE-I

Perioperative and postoperative variables

Variables	Group-1	Group-2	Overall
	Mean ± SD	Mean ± SD	Mean ± SD
Serum creatinine (mg/dl)	1.00±0.24	3.32±1.38	1.16±0.63
Mortality	1.00±0.00	1.05±0.23	1.05±0.21

Bypass time calculated in minutes in group 1 was (61.1±18.49) and group 2 showed results with wide variation (120.68±33.09) with overall mean of 90.25 min± 39.3

Renal failure was more common in group with longer bypass time. Among males 48.8% were in group A with a frequency of 61 and 51.2% were in group B with a frequency of 64. Males in group A had low incidence of renal failure of only 9.8% with frequency of only 6. Whereas incidence of renal failure among males in group B was significant 78.1% with frequency of 50. On the other hand among females 59.1% were in group A with frequency of 29 and 40.8% were in group B. Females in group A showed lesser incidence of renal failure 13.7%with frequency of 4 while group B had significant result of 70% with frequency of 14. Group stratification showed renal failure in group B was more common in age ranging 45-60 years highest from 55-60 years. The serum creatinine levels of the patients having higher values of bypass time (Group-2) were greater (3.32±1.38) ($p<0.05$) than in group-1 (1.00±0.24) that had shorter bypass time values. Relative risk calculated for above mentioned results is 6.9, showing longer bypass time to be a strong risk factor for postoperative renal failure.

In group A 34 out of 90 candidates had ARF whereas in group B 71 out of 90 patients had ARF. According to chi square test p value was 0.001 with high significance of renal failure in group B and strong association of long bypass time with ARF RR of 2.1 Group stratification on age for ARF age group 46-75 years had 91 out of 124 candidates had ARF whereas in group 30-45 years 29 out of 56 patients had ARF. According to chi square test p value was 0.014 with high significance of renal failure in group 46-75years and strong association of Age with ARF RR of 2.16.

Group stratification on gender for ARF male group 90 out of 131 candidates had ARF whereas in Female group 30 out of 49 patients had ARF. According to chi square test p value was 0.001 in male group with high significance of renal failure in male group and strong association of gender with ARF RR of 2.04 Group stratification on BMI for ARF 23-26 group had 29 out of 80 candidates had ARF whereas in 27- 30 group 91 out of 100 patients had ARF. According to chi square test p value was 0.02 in male group with high significance of mortality in male group and strong association of gender with mortality RR of 1.48. Hence high BMI have clear association with acute renal failure.

Hence analysis showed that bypass time proved to be significantly associated with higher postoperative serum creatinine levels and justified the objective of study.

TABLE-II

Comparison between both groups for ARF

	ARF		Total	P-Value	RR
	No	Yes			
Group A	41	49	90		
Group B	19	71	90	0.001	2.15
Total	60	120	180		

The mortality among patients having higher values of bypass time (Group-2) was greater (1.05±0.23) ($p<0.05$) than in group-1 (1.02±0.00) that had shorter bypass time values. There were 2 mortalities among females and 9 mortalities among males. 9 mortalities belonged to group B.

In group A 2 out of 90 candidates had mortality whereas in group B 9 out of 90 patients had mortality. According to chi square test p value was 0.02 with high significance of mortality in group B and strong association of long bypass time with mortality RR of 4.50. Group stratification on age for Mortality age group 46-75 years had 6 out of 124 candidates had ARF whereas in group 30-45 years 5 out of 56 patients had ARF. According to chi square test p value was 0.006 with not a significance result of mortality among two groups. Though relative risk

calculation showed strong association of Age with ARF RR of 5.61

Group stratification on gender for Mortality male group had 8 out of 131 candidates had ARF whereas in Female group 3 out of 49 patients had ARF. According to chi square test p value was 0.037 in male group with high significance of mortality in male group and strong association of gender with mortality RR of 6.4.

Group stratification on BMI for mortality 23-26 group had 3 out of 85 candidates had mortality whereas in group 8 out of 95 test p value was 0.039 in male group with high significance of mortality in 27-30 BMI group and strong association of gender with mortality RR of 6.3. Therefore, it also showed that higher bypass time was associated with mortality and it is an important risk factor.

TABLE-III

Comparison between both groups for mortality

	Mortality		Total	P-Value	Relative Risk
	No	Yes			
GROUP A	88	2	90		
GROUP B	81	9	90	0.02	4.50
Total	169	11	180		

DISCUSSION

According to data analysis preoperative parameters like age, gender did not show any significance, but weight and body surface area had significant relation with postoperative adverse outcome. Weight of the patients having higher values of bypass time were higher than in group-1 that had shorter bypass time values. Weight and body surface area are associated with adverse outcome.

Patients in group-2 had significant renal failure. They showed rise in serum creatinine levels postoperatively and slow recovery. Drop in urine output was also significant in patients with longer bypass time. On other hand group-1 had low incidence of serum creatinine levels rise.

According to one international study by Fischer UM, Weissenberger WK, Warters RD[15] done in 2002 showed significance of CPB time with renal failure. In above mentioned study ARF group requiring postoperative dialysis, CPB duration was longer (166 +/- 77 [standard deviation, SD] min) compared to CREATININE group showing renal dysfunction had CPB time (115 +/- 41 min; $p < 0.001$) compared to Control groups who had no renal dysfunction had CPB time (107 +/- 40 min; $p < 0.001$).

Another study done in 2007 by Taniguchi, Souza AR, Martins AS[13] showed very significant results supporting longer CPB time to be strong predictor of post op rise in creatinine levels. The median increases in serum creatinine were 0.18 + 0.41(CPB<70min) and 0.42 + 0.44 (CPB>90min p=0.005). Dialysis was indicated in 1.3% (CPB<70min) and 12.5% 90min - p = 0.018).

Another study by Tolpin D, el. al.[16], emphasized high 30 days mortality among patients who had renal failure after long CPB time. Results of study stated that negative change in serum creatinine was associated with reduced 30-day all-cause mortality. Even subclinical increases in serum creatinine were associated with increased mortality relative to patients with negative changes in serum creatinine (odds ratio, 3.93; 95% confidence interval, 1.68-9.22; P < .01). After propensity matching, subclinical increases in serum creatinine were still associated with increased mortality (odds ratio, 4.13; 95% confidence interval, 1.37-12.45; P = .01).

According to our study Bypass time calculated in minutes in group 1 was (61.1±18.49) and group 2 showed results with wide variation (120.68±33.09) having The serum creatinine levels of the patients having higher values of bypass time (Group-2) were greater (3.32±1.38) ($p<0.05$) than in group-1 (1.00±0.24) that had shorter bypass time values. Bypass time had significant impact on postoperative parameters like urine output and mortality. Postoperative renal failure is one the most important indicator of postoperative recovery of the patient.

It was observed in this group of patients had longer time towards recovery, respiratory failure and arrhythmias. There are number of studies available that have shown renal failure to be important factor determining patients recovery after cardiac surgery. Most of studies compared preoperative factors and

postoperative outcomes. I have studied association of intraoperative parameter with postoperative outcome. The results of our research are sufficiently convincing and demonstrate the direct impact of bypass time on renal function and mortality. The incidence of renal failure and mortality is significantly higher in the group with a longer bypass time.

CONCLUSION

Cardiopulmonary bypass time is an intraoperative variable that is both objective and easily accessible. It has a direct and robust correlation with mortality and morbidity. This is due to two factors. CPBT is indicative of certain unforeseen occurrences, such as technical difficulties in revascularization that result in a longer CPBT or issues with weaning from bypass. Simultaneously, cardiopulmonary bypass has a time-dependent impact on the human organs(organism). It induces a systemic inflammatory response by activating complement pathway and injuring platelets, which becomes more severe as CPBT is prolonged.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Taimoor Khan:** Data collection, Paper Writing
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4	**Zafar Tufail:** Review of Manuscript.
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https://doi.org/10.29309/TPMJ/2026.33.02.9964 www.theprofesional.com

ORIGINAL ARTICLE

Induction mortality and remission rate after 1st cycle of standard 7+3 regimen chemotherapy in patients of acute myeloid leukemia.

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ABSTRACT… Objective: To determine the remission rate, mortality rate, and induction failure after standard 7+3 induction chemotherapy in patients with AML in Pakistan. **Study Design:** This study utilized a descriptive design. **Setting:** The study was conducted at the National Institute of Blood and Marrow Transplant Rawalpindi (NIBMT/AFBMTC). **Period:** August 2018 to May 2021. **Methods:** The study cohort comprised 88 patients aged 15 to 55 years, inclusive of both genders, diagnosed with acute myeloid leukemia (AML). All participants received standard induction chemotherapy. Remission status was evaluated either upon hematologic recovery or on Day 42 of treatment, whichever occurred first. Patients who died prior to initiating induction chemotherapy or discontinued hospitalization before completing the induction course were excluded from the analysis. Written informed consent was obtained from each enrolled patient. **Results:** A total of 88 patients were enrolled, with a mean age of 29.18±10.6 years. Sixty-one percent of the patients were 30 years or younger, while the remaining 38.6% were aged between 31 and 55 years. Among the patients, 50 (57%) were male and 38 (43%) were female, resulting in a male-to-female ratio of 1:1.3. The mean blast percentage in the diagnostic bone marrow was 75±21.9%. The majority of patients belonged to the AML M2 subtype (50%), followed by AML M4 (15.9%), AML M1 (13.6%), and AML M0, M5, and AML-MRC (6.8% each). Remission was achieved in 71.6% of the total patients, while 4.5% were not assessed for remission due to death, and 23.9% were refractory to the first cycle of chemotherapy. The frequency of induction mortality in our study was 4.5%. **Conclusion:** The 7+3 regimen is an effective intensive induction chemotherapy for fit patients to achieve remission with an acceptable treatment-related mortality rate.

Key words: Acute Myeloid Leukemia, Induction Mortality, Remission Rate, Induction Chemotherapy, 7+3 Chemotherapy.

Article Citation: Shah SAA, Hussain M, Ali M, Chaudhry Q, Shamshad G, Hussain F, Mahmood SK, Iftikhar R. Induction mortality and remission rate after 1st cycle of standard 7+3 regimen chemotherapy in patients of acute myeloid leukemia. Professional Med J 2026; 33(02):225-230. https://doi.org/10.29309/TPMJ/2026.33.02.9964

INTRODUCTION

Acute Myeloid Leukemia (AML) is a clonal proliferative malignancy of the myeloid lineage, marked by the infiltration of the bone marrow, peripheral blood, and extramedullary sites by poorly differentiated blast cells. Historically considered incurable five decades ago, AML treatment has undergone transformative advancements, leading to cure rates of approximately 35–40% among adults under 60 years of age, and between 5% to 15% in individuals aged above 60. However, outcomes remain dismal for elderly patients who are ineligible for intensive chemotherapy, with median survival ranging from 5 to 10 months.[1] The median age at diagnosis in Western populations is reported to be around 70 years, with a strong correlation observed between increasing age and AML incidence.[2,3] Annually, AML is diagnosed in approximately 2 to 3 children per 100,000, compared to around 15 cases per 100,000 adults.[4]

Management of acute myeloid leukemia (AML) is traditionally structured into two main phases: induction and consolidation. The induction phase involves administering intensive combination chemotherapy with the primary goal of attaining complete remission (CR) by swiftly decreasing the leukemic cell load and promoting the restoration of normal bone marrow function.

A commonly employed induction protocol consists of a continuous seven-day infusion of cytarabine alongside a three-day course of anthracycline, commonly recognized as the "7+3" regimen.[5,6]

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Article received on:
12/07/2025
Accepted for publication:
25/09/2025

In young adults, the CR rate with standard induction therapy ranges from 60% to 80%. However, older age groups have lower CR rates with intensive chemotherapies.[7]

Historically, there has been significant treatment-related mortality (TRM) associated with chemotherapy, particularly in older age groups and patients with poor performance status.[8] However, over the past several decades, treatment-related mortality (TRM) has declined markedly, reflecting advancements in supportive care, patient stratification, and therapeutic protocols. For instance, TRM decreased from 18% in South West Oncology Group (SWOG) trials and 16% at MD Anderson (MDA) during the 1991–1995 period, dropping to 3% at SWOG and 4% at MDA by 2006-2009.[9]

A multi-center study conducted in India reported a CR rate of 52.8% and induction mortality ranging from 6.1% to 43% across different centers.[10] Similarly, a single-center study in India showed a CR rate of 70% and an induction mortality rate of 18.4%.[11] However, there is currently no recent similar study available from Pakistan. A single-center study conducted in 1996 in Pakistan reported a CR rate of 65% and an induction mortality rate of 29%.[12]

Given the lack of recent data from Pakistan and the evolving landscape of AML treatment, it is essential to investigate the outcomes of induction therapy, including CR rates and induction mortality, in AML patients in the Pakistani population. Therefore, the aim of this study is to evaluate the efficacy and safety of standard induction chemotherapy in patients with AML in Pakistan, providing valuable insights into the current landscape of AML treatment outcomes in this region.

METHODS

This descriptive study was carried out at the Armed Forces Bone Marrow Transplant Centre in Rawalpindi over a period spanning August 2018 to May 2021. Patients aged 15 to 55 years of both genders, diagnosed with AML and undergoing induction chemotherapy, were included. The cohort was stratified into two age groups: 15–30 years and 31–55 years. Due to resource limitations, germline mutation testing was not performed. Patients with therapy-related AML, acute promyelocytic leukemia (APL), those deemed unfit for chemotherapy, and individuals who did not provide informed consent were excluded. Institutional ethical approval was obtained from the Hospital's Ethical Review Committee on 20th February 2019.

Baseline data included complete blood count, blast percentage, AML morphological subtype, and relevant prognostic molecular and cytogenetic markers. All patients received standard 7+3 induction chemotherapy and were monitored until recovery of blood counts, Day 42 post-induction, or death—whichever occurred first during the initial cycle of treatment. Remission status was evaluated via bone marrow examination.

Treatment response was categorized according to the European LeukemiaNet (ELN) criteria. Complete remission (CR) was defined by the presence of <5% blasts in the bone marrow, absence of circulating blasts and blasts containing Auer rods, no evidence of extramedullary disease, an absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L, and a platelet count $\geq 100 \times 10^9$/L. CR with incomplete hematologic recovery (CRi) fulfilled all criteria for CR except in cases of persistent neutropenia (ANC $< 1.0 \times 10^9$/L) or thrombocytopenia (platelet count $< 100 \times 10^9$/L). Partial remission (PR) was defined by fulfilment of all hematologic parameters for CR with a bone marrow blast percentage between 5–25%, accompanied by at least a 50% reduction from the pretreatment blast count. Not in remission (NR) Bone marrow blasts >25% and/or presence of circulating blasts and/or presence of extramedullary disease. Induction mortality was when death occurring within 42 days after initiating chemotherapy. Remission included cases of CR and CRi.

Data were analyzed using SPSS version 23.0. Numerical variables—including age, white blood cell (WBC) count, and bone marrow blast percentage—were summarized using mean ± standard deviation (SD) and median values. Categorical variables such as gender, AML subtype, cytogenetic risk classification, remission status, and mortality rates were presented as frequencies and percentages. To account for potential effect modifiers, data

were stratified based on age, WBC count, and blast percentage. Following stratification, the chi-square test was applied to assess associations with remission status, with a p-value ≤ 0.05 considered statistically significant.

RESULTS

A total of 88 patients were enrolled in the study, with a mean age of 29.18±10.6 years.54 (61.4%) patients belonged to the 15-30 years age group, and 34 (38.6%) were in the 31-55 years age group. Gender distribution revealed 50 (56.8%) males and 38 (43.%) females, establishing a male-to-female ratio of 1:1.3. The mean blast cell count in the bone marrow before treatment was 75±21.9%. According to the French-American-British (FAB) classification, the prevalent subtype was AML M2 (50%), followed by AML M4 (15.9%), AML M1 (13.6%), and AML M0, M5, and AML-MRC (6.8% each).

Risk stratification based on European Leukemia Net criteria revealed 45.5% of patients with intermediate risk, 31.8% with favorable risk, and 22.7% with adverse risk disease. The most frequent chromosomal translocation, t(8;21), occurred in 13% of patients, with NPM1 mutation being the most common molecular mutation (22%). FLT3 was detected in 11.4% of patients. Remission was successfully achieved in 71.6% of patients, while 4.5% did not undergo repeat biopsy due to mortality, and 23.9% were refractory to chemotherapy. The study observed a 4.5% frequency of induction mortality.

Statistical analyses demonstrated no significant impact of age groups on the remission rate (p-value 0.116) or blast cell percentage (p-value 0.325). Similarly, the leukocyte count at presentation showed no significant relationship with the frequency of remission (p-value 0.359). Additionally, there was no significant effect of age on the mortality rate (p-value 0.104), blast cell percentage on induction mortality rates (p-value 0.852), or total leukocyte count at presentation on induction mortality rate (p-value 0.562).

TABLE-I

Demographic distribution of the study population

Age	
Mean age	29.18±10.6 years
Age groups	
15-30 years	54 (61.4%)
31-55 years	34 (38.6%)
Gender	
Male	50 (56.8%)
Female	38 (43.2%)
Mean blast cell count	75±21.9%
FAB sub types	
AML M2	50%
AML M4	15.9%
AML M1	13.6%
AML M0	6.8%
AML M5	6.8%
AML-MRC	6.8%
Risk stratification based on ELN	
Favorable	31.8%
Intermediate	45.5%
Adverse risk	22.7%

TABLE-II

Frequency of remission and induction mortality

		Frequency	Percent
Remission post chemo-therapy	Remisson	63	71.6%
	Refractory	21	23.9%
	Not done	4	4.5%
Induction mortality	Alive	84	95.5%
	Death	4	4.5%
	Total	88	100%

TABLE-III

Association between remission and age / blast percentage

Variable	Remis-sion (n, %)	Refrac-tory (n, %)	Not As-sessed (n, %)	Total (n)	P-Value
Age Group					
15–30 years	40 (74.1%)	10 (18.5%)	4 (7.4%)	54	0.116
31–55 years	23 (67.6%)	11 (32.4%)	0 (0.0%)	34	
Blast % in BM					
< 85%	34 (72.3%)	11 (23.4%)	2 (4.3%)	47	0.325
≥ 85%	29 (70.7%)	10 (24.4%)	2 (4.9%)	41	

TABLE-IV

Association between remission status and total leukocyte count

Total Leukocyte Count	Remission (n,%)	Refractory (n,%)	Not Assessed (n,%)	Total (n)	P-Value
< 50,000 /cmm	43 (76.8%)	11 (19.6%)	2 (3.6%)	56	0.359
> 50,000 /cmm	20 (62.5%)	10 (31.2%)	2 (6.2%)	32	

TABLE-V

Association between induction mortality and total leukocyte count

Total Leukocyte Count	Alive (n,%)	Death (n,%)	P-Value
< 50,000 / cmm	54 (96.4%)	2 (3.6%)	0.562
> 50,000 / cmm	30 (93.8%)	2 (6.2%)	

DISCUSSION

An essential step to achieve a cure for AML involves reducing the leukemic burden through intensive cytotoxic chemotherapy to induce complete remission (CR). Upon reaching CR, to sustain remission and achieve long-term cure, patients may undergo additional cycles of cytotoxic chemotherapy or hematopoietic stem cell transplantation.[14] Seminal investigations by the Cancer and Leukemia Group B (CALGB) during the 1980s identified the most efficacious albeit still imperfect induction regimen: three days of daunorubicin (45–60 mg/m^2) combined with a seven-day course of cytarabine (100–200 mg/m^2.[15] Subsequent investigations have focused on enhancing the efficacy of remission induction, with the overarching aim of improving overall survival (OS) as a clinically meaningful outcome. This study was conducted to determine remission rate and induction mortality in patients undergoing the 7+3 chemotherapy regimen within our population.

In our study, 88 patients were enrolled, with a mean age of 29.18±10.6 years. The majority of patients (61.4%) belonged to the younger age group, while 38.6% were in the older age group. Among the participants, 56.8% were male and 43.6% were female. The mean blast percentage in the bone marrow prior to treatment initiation was 75±21.9%. The most prevalent AML subtype in our study was AML M2, accounting for 50% of patients, followed by AML M4 (15.9%), AML M1 (13.6%), and AML M0, M5, and AML-MRC (6.8% each). Remission was achieved in 71.6% of the total patients, while 4.5% of patients did not have their remission assessed due to death during the induction phase. Additionally, 23.9% of patients were refractory to chemotherapy. The observed frequency of mortality during the induction phase in our study cohort was 4.5%, which aligns with reported rates in comparable clinical settings utilizing the standard 7+3 induction protocol.

Our findings align with previous studies and yield even better results, particularly when compared to older studies conducted in our region. Notably, our results remain consistent with more recent studies conducted in Western countries. A multicenter study in India reported a CR rate of 52.8% and an induction mortality rate ranging from 6.1% to 43% across different centers.[16] A single-center study in India demonstrated a CR rate of 70% and an induction mortality rate of 18.4%.[17] While no similar recent studies were found in Pakistan, a single-center study from 1996 reported CR and induction mortality rates of 65% and 29%, respectively.[12] Another study conducted in 2017 found similar treatment outcomes, with an induction mortality rate of 4.8% and increased mortality observed in patients over 55 years. Our study did not include cases over 55 years, but induction mortality in younger patients was comparable to the reported findings. In this same study, the remission rate after chemotherapy was 71%, and remission was more common in younger patients, which is consistent with our study.[18] Another study highlighted the benefits of a 7+3 regimen with daily infusion, including reduced hospital stay and decreased financial burden associated with chemotherapy.[19] A retrospective study reviewing 113 patients treated with the 7+3 regimen reported a remission rate of 87.6%, which is similar to our study.[20] A study conducted at the National Institute of Medical Sciences and Nutrition Salvador Zubirán, Mexico City, between

November 2010 and November 2016, involving 40 patients aged 18–55 years, reported outcomes comparable to those observed in our cohort. The remission rate was 76.2%, the induction mortality rate was 5%, and the mean overall survival was 17.2 months.[21] Additionally, earlier reports from the same institution documented complete remission (CR) rates of 39.5% following a single cycle of the 7+3 regimen, which increased to 62.6% with two cycles in patients with a median age of 44 years (range: 15–79 years).[22]

Regarding the influence of various patient factors on treatment outcomes, older age has historically been considered a poor prognostic marker.[18] Our study demonstrated a trend toward higher remission rates in younger patients; however, this difference did not reach statistical significance. This observation may be influenced by the limited sample size and the disproportionate distribution of patients within the younger age cohorts. Additionally, neither elevated white blood cell (WBC) count at diagnosis nor blast percentage were found to be significant predictors of treatment response or survival, a finding consistent with previously published data.[20] A review of the literature suggests that the remission rate has been increasing with the use of the 7+3 regimen, accompanied by a decrease in induction mortality rates over time.[10,11,12,22] The reduction in induction mortality is likely due to improvements in supportive care in recent years, as observed worldwide.

Our study has few limitations, including its single-center design, with relative a small population, and a predominantly younger patient population up to the age of 55, which may impact the generalizability of the findings. Exclusion criteria, such as patients leaving before completing induction chemotherapy, introduce potential bias. Resource limitations prevented testing for germline mutations and molecular classification. The study period, spanning from August 2018 to May 2021, may not fully capture evolving treatment practices. The focus on fit patients aged 15-55 may restrict the applicability of the results to older or less fit individuals. As this study yields important clinical insights, its limitations should be carefully considered when interpreting the findings.

CONCLUSION

The 7+3 standard chemotherapy regimen is an intensive yet effective induction chemotherapy for fit patients to achieve remission. While historically linked to significant treatment-related mortality, the progress made in supportive care has rendered mortality rates associated with 7+3 chemotherapy acceptable in the present day.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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2	**Mussawair Hussain:** Data analysis, Manuscript writing, Draft making.
3	**Murad Ali:** Draft making.
4	**Qamar Un Nisa Chaudhry:** Methodology, supervision..
5	**Ghassan Shamshad:** Data collection, Supervision.
6	**Fayyaz Hussain:** Data analysis.
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https://doi.org/10.29309/TPMJ/2026.33.02.9954 www.theprofesional.com

ORIGINAL ARTICLE

The relationship of patent infarct-related artery with time to thrombolysis in patients with ST-Segment Elevation Myocardial Infarction.

Zia Ullah Khan[1], Rukhshanda Afsar[2], Mohammad Imran Khan[3], Saad Shams[4], Aftab Ahmed[5], Matiullah Khan[6]

ABSTRACT… Objective: To find out the spectrum of TIMI flow in the infarct-related artery amongst the patients who are thrombolysed in different time zones from pain to thrombolysis. **Study Design:** Prospective, Comparative study. **Setting:** Department of Cardiology, Ayub Medical Teaching Institute. **Period:** August 2022 to January 2023. **Methods:** A total of 122 consecutive patients with their first STEMI thrombolysed within 12 hours of pain were included in the study. Data on demographics, medical history, and physical examination findings were collected using a specially designed proforma. Patients were assessed for the success or failure of thrombolysis according to our prespecified criteria. All patients underwent coronary angiography as per our institutional protocol. TIMI flow in the infarct-related artery was documented. Results were analyzed using SPSS statistical software version 21.0. **Results:** 77% were male, 43% were hypertensives, one-third of patients were smokers, and 26% were diabetic. Anterior STEMI was seen in 38% of patients, while 57% had inferior STEMI. 46% of patients were thrombolysed within 3 hours, 33% within 3 to 6 hours, 10% between 6 to 9 hours, and 11% between 9 to 12 hours. The rate of TIMI III flow was the highest (89%) in patients thrombolysed within 3 hours, 85% in patients thrombolysed between 3 to 6 hours, 83% in patients thrombolysed between 6 to 9 hours, and 78% in patients thrombolysed between 9 to 12 hours. There were significantly more patients with ≥70% resolution of ST-segment elevation amongst those thrombolysed within 3 hours since the onset of pain, compared to those thrombolysed after 9 hours since the onset of pain. **Conclusion:** The highest frequency of TIMI III flow was seen when patients were thrombolysed within 3 hours. The rate of TIMI III flow decreased as the time to thrombolysis increased from less than 3 hours to 12 hours. However, the differences in TIMI III flow were not statistically significant. There was a statistically significant relationship between the degree of ST-segment resolution and time since pain to thrombolysis.

Key words: Infarct-related Artery, STEMI, Thrombolysis, TIMI III Flow, Time Since Pain-to-thrombolysis.

Article Citation: Khan Z, Afsar R, Khan MI, Shams S, Ahmed A, Khan M. The relationship of patent infarct-related artery with time to thrombolysis in patients with ST-Segment Elevation Myocardial Infarction. Professional Med J 2026; 33(02):231-236. https://doi.org/10.29309/TPMJ/2026.33.02.9954

INTRODUCTION

The primary goal of thrombolytic therapy is rapid, complete, and sustained restoration of TIMI III flow in the occluded infarct-related artery. Studies have shown that early thrombolysis results in smaller infarct size after STEMI.[1] Occluded infarct-related artery at 90 minutes was associated with 8.9% mortality at 30 days compared to only 4% mortality with normal TIMI III (Thrombolysis in Myocardial Infarction grade III) flow.[2]

Streptokinase is a leading Thrombolytic agent used for thrombolysis in STEMI patients across Pakistan. There is some evidence that non-fibrin specific agents may lose their fibrinolytic efficacy as the time from the onset of symptoms to the start of treatment increases.[3] An angiographic study to assess the efficacy of Streptokinase has never been done in our institution. For emerging centers that are in their developing phases and who cannot offer primary PCI to all patients, such a study would be useful to select patients for primary PCI rather than thrombolysis if a certain threshold of time since pain is established, beyond which Streptokinase would start losing its ability to establish TIMI III flow. We therefore wanted to find out how the hours since pain to thrombolysis influence the rate of TIMI III flow in patients with STEMI who are eligible for and treated with timely thrombolysis.

METHODS

122 consecutive patients presenting with STEMI were prospectively included in the study between August 2022 and January 2023.

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Article received on:
07/07/2025
Date of revision:
23/08/2025
Accepted for publication:
15/09/2025

The study was conducted in the Department of Cardiology Ayub Medical Teaching Institute, Abbottabad. Informed consent was taken from all patients. Data was collected using a specially designed proforma, which included demographics like age, gender, time from the onset of pain, contraindications to thrombolysis, co-morbidities, and complete physical examination findings. Categorical values were summarized as percentages, and numerical values were summarized as means. Data was analyzed using SPSS statistical software version 21.0. The chi-square test was used to test the significance of the difference in TIMI flow across different time zones from pain to thrombolysis. A p-value of 0.05 was considered significant. The study was approved by the institutional ethical review committee (RC-2022/EA-01/116).

Inclusion Criteria

1) Age 20 to 75 years
2) Patients with first STEMI as per the operational definition
3) Those who received thrombolytic therapy within 12 hours of the onset of chest pain.

Exclusion Criteria

1) All patients who did not receive thrombolytic therapy.
2) Patients who did not consent for the study.
3) All patients who did not undergo angiographic studies.
4) Patients who died before thrombolytic therapy and/or angiography
5) Patients with prior CABG or STEMI
6) Patients with Cardiogenic shock
7) Patients with valvular heart diseases
8) Patients with left bundle branch block.

All patients with STEMI presenting within 12 hours of the onset of chest pain and fulfilling our inclusion criteria who consented to the study were included. Patients received Streptokinase uninterrupted within one hour. Anterior STEMI was defined as ST elevation of ≥0.2 mV at the J point in V1, V2, or more anterior leads. Lateral STEMI was defined as ≥0.1 mV ST elevation in AVL and Lead I. Inferior STEMI was defined as ≥0.1 mV ST elevation in Leads II, III, AVF. Successful thrombolysis or otherwise was assessed based on pain relief and ECG criteria 90 minutes after finishing Streptokinase infusion by an experienced postgraduate cardiology fellow as follows:

1. Categorical verbal rating scale as described by T Bendinger and N Plunkett (Measurement in pain medicine. BJA Education, Vol16. Issue 9, Sept 2016. Pages 310-315.) was used to assess the severity and relief of pain. The magnitude of pain was categorized as none, mild, moderate, or severe.

Significant pain relief was defined as follows:

i. Significant pain relief in patients with severe pain was defined as no to mild residual pain.
ii. Significant pain relief in patients with moderate pain was defined as no to mild residual pain.
iii. Significant pain relief in patients with mild pain was defined as no residual pain.

2. Successful thrombolysis was defined as ≥70% resolution in ST segment measured in mm, at 90 minutes after stopping Streptokinase infusion in the lead showing the highest ST elevation and significant pain relief.
3. Unsuccessful thrombolysis was defined as persistent pain and/or <70% resolution in ST segment measured in mm, at 90 minutes after stopping Streptokinase infusion in the lead showing the highest ST segment elevation.
4. Patent-Infarct-Related Artery was defined as TIMI III flow in the artery most likely to be the culprit artery.

Streptokinase was administered at a dose of 1.5 MU over 1 hour. All patients received a loading dose of Aspirin 300 mg, Clopidogrel 300mg, and high-dose Statins. Baseline pulse rate, blood pressure, and oxygen saturation by pulse oximetry were recorded. The vertical height of ST segment elevation in the lead with the maximum ST segment elevation, before and at 90 minutes after finishing thrombolysis, was measured in mm, 80 ms from the J point. ECG interpretation of successful or failed thrombolysis was performed by a single observer who was not involved in performing angiographies of these patients. All patients underwent coronary angiography by experienced operators. All angiographies were analyzed by a single expert who classified coronary flow as per the TIMI

criteria. According to our protocol, angiography was performed in patients who underwent successful thrombolysis within 72 hours after discharge. The patients who did not fulfil the criteria of successful thrombolysis underwent angiography as inpatients.

RESULTS

Table 1 displays the baseline characteristics of the patient population and information about the types of Myocardial Infarction and a summary of angiographic findings. The majority of the patients were males, predominantly between the ages of 41 years to 70. 43% of patients had hypertension, 35% were smokers, and about 26% of the patients were diagnosed with diabetes. Of the total population, 47 (38%) patients had Anterior STEMI and 70 (57%) patients had Inferior STEMI. All patients underwent angiography. 40% of patients had single-vessel coronary artery disease, 30% had double disease, while 24% had multi-vessel coronary artery disease. A small number had left main disease and a nonobstructive recanalized artery on angiography.

Overall, 46% of patients were thrombolysed within 3 hours, and another 33% were thrombolysed within 3 to 6 hours. The rest of the patients were thrombolysed within 6 to 9 hours and 9 to 12 hours. (Table-II)

All patients were thrombolysed within 12 hours. There was a significantly higher percentage of patients achieving ≥70% ST-segment resolution in patients thrombolysed within 3 hours compared to those who were thrombolysed between 9 to 12 hours. There was a statistically significant relationship between the time since pain to thrombolysis and the degree of ST-segment resolution ($p = 0.0075$).

Table-IV shows the results of a logistic regression analysis of ≥70% ST-segment resolution and time since pain to thrombolysis with < 3 hours as a reference group.

The 3 to 6 hour and 6 to 9 hour groups did not differ significantly from the less than 3 hour group in the odds to achieving ≥70% ST-Segment resolution. Patients thrombolysed between 9 to 12 hours had 88% less odds of achieving ≥70% ST-Segment resolution than those thrombolysed less than 3 hours since pain.(OR=0.12, P=0.002)

TABLE-I

Baseline characteristics and summary of Angiographic findings.

Serial No.	Parameter	Number	Percentage
1	Age 30 to 40 years	1	0.8
2	Age 41 to 50 years	29	24
3	Age 51 to 60 years	40	33
4	Age 61 to 70 years	41	33
5	Age 71 to 80 years	12	10
6	Males	94	77
7	Diabetes Mellitus	32	26
8	Hypertension	53	43
9	Smokers	43	35
10	Anterior Wall MI	48	39
11	Inferior Wall MI	70	57
12	High Lateral Wall MI	4	3
13	Postero-lateral Wall MI	1	0.8
14	Single Vessel disease	49	40
15	Double Vessel disease	37	30
16	Multi-Vessel Disease	29	24
17	Left Main Disease	2	1.6
18	Recanalized non-obstructive plaque	3	2.4

TABLE-II

Summary of Time since pain to thrombolysis.

Pain To Needle Time	Number of Patients	Percentage
< 3 Hours	56	46
3 to 6 Hours	40	33
6 to 9 Hours	13	10
9 to 12	14	11

Over all 86% of patients had TIMI III flow in their infarct-related arteries. 10% had TIMI 0 flow.

TABLE-III

ST-Segment resolution among time to thrombolysis groups

Time Since Pain To Thrombolysis	Number of Patients	>70% St-Segment Resolution	<70% St-Segment Resolution
< 3 HOURS	56	50	6
3 TO 6 HOURS	40	33	7
6 TO 9 HOURS	13	12	1
9 TO 12 HOURS	14	7	7
Total	123	102	21

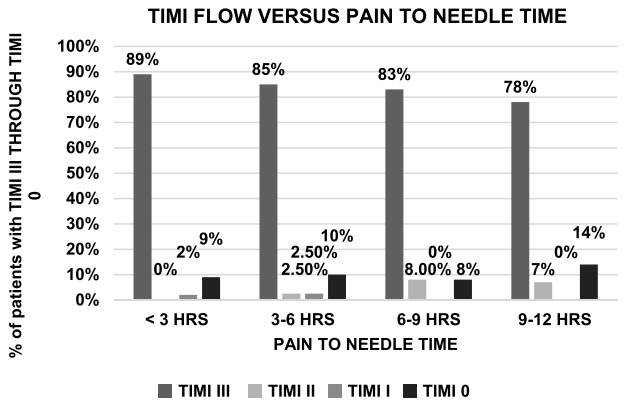
TABLE-IV

Time groups compared to < 3 hour group.

Time Group vs < 3 h	Odds Ratio	95% CI	P-Value
3-6 hours	0.50	0.16-1.56	0.23
6-9 hours	1.44	0.16-13.1	0.75
9-12 hours	0.12	0.03-0.46	0.002

FIGURE-1

Variable TIMI III flow in patients with different times to thrombolysis since pain.

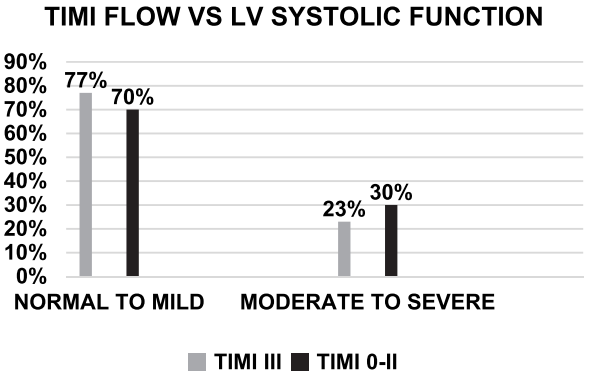


The differences in TIMI flow grades across the pain-to-needle categories were not statistically significant (p=0.79). Similarly, there was no significant difference among the pain-to-needle time groups in the proportion of patients achieving TIMI III flow (p=0.74). However, the power to detect any significant differences was low since the later pain-to-needle groups had only 13 and 14 patients.

There were equal proportions of patients with normal to mildly impaired left ventricles in patients with TIMI III flow and TIMI II to 0. There were equal proportions of patients with moderate to severely impaired Left ventricles in patients with TIMI III and TIMI II to 0 flows in their infarct related arteries. (Figure-2).

FIGURE-2

TIMI flow and Left Ventricular Function



DISCUSSION

Since 1994 when Schroeder et al showed in their retrospective analysis of ISAM study, more than 70% resolution of ST segment in post thrombolytic ECG has been considered a sign of good short and long term prognosis.[4] Around the same time other researchers[5] correlated the resolution of ST segment with the presence of TIMI III flow in infarct related arteries.

Our study adds to the existing body of literature by showing that the rate of TIMI III flow declines with time. There was a nonsignificant trend of declining rate of TIMI III flow from 89% to 78% as the time since pain to thrombolysis increased from less than 3 hours to 12 hours. When the patients were categorized according to hours since pain to thrombolysis, from less than 3 hours through 3-6 hours, 6-9 hours, and 9-12 hours, the percentage of patients achieving ≥70% decreased significantly.

In a study by P.Gabriel Steg et al, the 90-minute patency of the infarct-related artery reduced from 81.7% when Streptokinase was given in less than three hours compared to 53.6% when Streptokinase was given after 3 hours.[3] In a similar study, U Zeymer et al studied TIMI flow in patients treated with either fibrin-specific or non-fibrin-specific thrombolytic agents within 3 hours or beyond 3 hours of symptom onset. It was observed that front-loaded Alteplase and Reteplase were equally effective within 3 hours

and beyond 3 hours. But the ability to achieve TIMI III flow at 90 minutes beyond 3 hours was reduced significantly for Streptokinase, Urokinase, and Anisoylated plasminogen streptokinase activator complex.[6] This difference in the thrombolytic ability to achieve TIMI III flow at 90 minutes is reflected also in ultimate sizes of the infarcts[7] and also in mortality differences between Fibrin specific and non-fibrin specific agents.[8] Previous research has also shown the importance of TIMI rather than just Infarct related artery patency, with higher ejection fractions in patients with not only patent infarct related arteries but also effective (TIMI III) compared to those with patent arteries but ineffective (TIMI II or less) flow. This difference was seen in patients with similar times from symptom onset to thrombolysis.[9]

Streptokinase is a bacterial protein that combines with Plasminogen to generate plasmin that has proteolytic activity.[10] The trial that comprehensively proved its efficacy after its intravenous use for ST-segment elevation Myocardial infarction was the GISSI[11] published in the Lancet. This trial also showed the declining efficacy of Streptokinase as the time from pain to Thrombolysis increased, with the highly significant 23% mortality reduction when patients were treated within 3 hours and falling to a nonsignificant benefit when patients were treated after 6 hours.

Our study is consistent with the results of the previous trials that the efficacy of Streptokinase in achieving TIMI III flow reduces in a time-dependent fashion, with the highest likelihood of achieving TIMI III flow when the patients are treated within 3 hours of pain and the least likelihood of TIMI III flow when patients are treated after 9 to 12 hours. ST-segment resolution dropped in a time-dependent fashion as the time to thrombolysis since pain increased. The highest proportion of ≥70% appeared amongst those thrombolysed within 3 hours and declined thereafter. This finding is also consistent with the previous studies of ST-segment resolution analysis, both in the settings of Thrombolysis and Mechanical reperfusion.[12,13]

We were not able to show any association of time to treatment with left ventricular function nor was there any association with achievement of TIMI III flow or otherwise with better left ventricular systolic function or otherwise. It is possible, as shown in previous studies of acute vs convalescent left ventricular function studies, that the left ventricular function does not improve acutely due to the fact that it might be stunned and recovers only over a passage of time.[14,15]

CONCLUSION

We conclude that the highest likelihood of achieving TIMI III flow post-streptokinase is when the lytic agent is administered within 3 hours and up to 9 hours since the onset of pain. After 9 hours, the likelihood of achieving TIMI III flow reduces to 78%. The likelihood of achieving TIMI III was 89% when thrombolysis was administered within 3 hours, reducing to 85% and 83% respectively, with thrombolysis administered between 3 to 6 hours and 6 to 9 hours. There was therefore a trend towards reduction in TIMI flow in the infarct-related artery, as the time to thrombolysis window increases. This reduction in TIMI III flow did not reach statistical significance. A larger study is required to confirm or otherwise the efficacy of Streptokinase to achieve TIMI III flow in patients who are thrombolysed after 9 hours of the onset of pain.

LIMITATIONS

Patients in the 6 to 9 hours and 9 to 12 hours categories were small, which reduced the power of the study to detect any significant differences in the efficacy of Streptokinase to achieve TIMI III flow across all time zones.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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https://doi.org/10.29309/TPMJ/2026.33.02.10055 www.theprofesional.com

ORIGINAL ARTICLE

The role of diffusion weighted (DWI) MRI and apparent diffusion coefficient (ADC) in assessment of diabetic kidney disease.

Jawairia Warriach[1], Zeeshan Nawaz Bandesha[2], Asim Shaukat[3]

ABSTRACT… Objective: To evaluate the diagnostic value of ADC derived from DW-MRI in staging and assessing progression of DKD. **Study Design:** Cross-sectional Validation study. **Setting:** Department of Radiology, Allied Hospital Faisalabad. **Period:** [6/12]-month period between January and July 2025. **Methods:** Using a 1.5-Tesla MRI scanner a total of 120 adult patients with DKD and 20 age- and sex-matched healthy volunteers were enrolled. All subjects underwent renal DW-MRI and ADC mapping. ADC values were measured from multiple regions of interest in both kidneys. Clinical and laboratory parameters, including serum creatinine and eGFR, were recorded for correlation. **Results:** Mean ADC values were significantly reduced in DKD patients compared with controls ($2.1 \pm 0.3 \times 10^{-3}$ mm²/s vs $2.4 \pm 0.1 \times 10^{-3}$ mm²/s; $p < 0.001$). A progressive decline in ADC was observed with advancing disease stage, showing inverse correlation with serum creatinine and positive correlation with eGFR. **Conclusion:** ADC values derived from DW-MRI reliably reflect renal dysfunction and disease progression in DKD. ADC may serve as a noninvasive biomarker for staging and early detection, potentially guiding therapeutic decisions and improving prognostic evaluation.

Key words: Apparent Diffusion Coefficient, Chronic Kidney Disease, Diabetic Kidney Disease, DW-MRI, Renal Imaging.

Article Citation: Warriach J, Bandesha ZN, Shaukat A. The role of diffusion weighted (DWI) MRI and apparent diffusion coefficient (ADC) in assessment of diabetic kidney disease. Professional Med J 2026; 33(02):237-242. https://doi.org/10.29309/TPMJ/2026.33.02.10055

INTRODUCTION

As a major microvascular complication of diabetes, diabetic kidney disease (DKD) affects over 40% of diabetic individuals and stands as the leading contributor to kidney failure worldwide.[1] Its growing prevalence is attributed to inadequate early detection methods and the scarcity of effective interventions.[2] Although renal biopsy is the definitive diagnostic tool, it is invasive and susceptible to sampling error, which limits its application to a minority of patients where the diagnosis remains unclear. For broader clinical practice, current guidelines emphasize the use of blood and urine biochemical markers for the diagnosis and evaluation of DKD.[3]

Assessment of renal function is typically achieved by estimating the glomerular filtration rate (eGFR), either through serum creatinine measurements or 24-hour creatinine clearance (CrCl). Of these methods, eGFR based on serum creatinine is considered the most accurate indicator of global renal function. Nonetheless, both eGFR and CrCl estimations have limitations, particularly their inability to evaluate the function of a single kidney.[4]

In recent years, magnetic resonance imaging (MRI) has demonstrated considerable potential in the evaluation of diabetic kidney disease (DKD). This non-invasive modality enables the measurement of structural and functional parameters of the kidneys without requiring contrast agents.[5] Diffusion-weighted imaging (DWI) MRI leverages the natural diffusion of water molecules within tissues, providing insights into microscopic renal changes. The apparent diffusion coefficient (ADC) values derived from DWI are significantly reduced in DKD compared with normal kidneys. A decline of 10–20% in ADC values has been observed with each progressive stage of DKD, highlighting its value as a reliable tool for disease staging and monitoring.[6,7] In a study assessing diabetic kidney disease with diffusion-weighted MRI, the apparent diffusion coefficient (ADC) was found to provide 86% sensitivity and 100% specificity for diagnosing chronic kidney disease, with an optimal cutoff point of less than 1.91×10^{-3} mm²/s, when validated against eGFR.[8]

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Article received on:
26/08/2025
Accepted for publication:
30/10/2025

The rationale for conducting study on the diagnostic utility of DWI and apparent diffusion coefficient (ADC) in assessing DKD: Current diagnostic methods like eGFR detect functional decline but often miss early structural changes. Diffusion-weighted MRI (DW-MRI) and apparent diffusion coefficient (ADC) offer non-invasive imaging of renal microstructure. Their diagnostic accuracy in DKD remains underexplored. This will enable earlier diagnosis, timely intervention, and improved patient outcomes, while reducing reliance on invasive or late-stage diagnostic methods.

METHODS

This cross-sectional validation study was conducted at the Department of Radiology, Allied Hospital Faisalabad, over a duration of six months following the approval by ethical review committee (ERC/FMU-202324/505) of the synopsis. The aim was to assess the diagnostic accuracy of diffusion-weighted magnetic resonance imaging (DW-MRI) and apparent diffusion coefficient (ADC) in the diagnosis of diabetic kidney disease (DKD), using laboratory findings—serum creatinine and estimated glomerular filtration rate (eGFR)—as the gold standard. The sample size was calculated using a standard calculator based on sensitivity and specificity estimates. With an anticipated DKD prevalence of 40%, expected sensitivity of 86%, specificity of 100%, a 10% margin of error, and a 95% confidence level, the required sample size was determined to be 120 patients. A non-probability, consecutive sampling technique was employed.

Patients aged 18 to 75 years of either gender with diagnosed type 1 or type 2 diabetes mellitus and suspected DKD based on serum creatinine levels (>1.2 mg/dL in females, >1.3 mg/dL in males) or BUN >20 mg/dL were included. Patients were excluded if they were pregnant, had contraindications to MRI, were undergoing dialysis or kidney transplant, had known allergies to gadolinium-based contrast agents, had other renal conditions such as polycystic kidney disease or glomerulonephritis, or had unstable medical histories. Following ethical approval, eligible patients were enrolled. Demographic data including age, gender, symptom duration, and provisional diagnosis were recorded. Blood samples were obtained to measure serum creatinine, and eGFR was calculated using the CKD-EPI equation, taking into account serum creatinine, age, sex, and race. DKD was defined as an eGFR <60 ml/min/1.73 m^2 persisting for at least three months in patients with known diabetes.

All patients underwent MRI scans using axial diffusion-weighted multi-section echo-planar imaging with b-values ranging from 0 to 800 s/mm^2. Imaging parameters included an echo time of 70 ms, repetition time of 1535 ms, a 1 mm interslice gap, slice thickness of 7 mm, field of view 435 × 350 mm, matrix size 224, and a flip angle of 90°. All sequences were performed during a single breath-hold. Regions of interest (ROIs) were placed bilaterally in the renal parenchyma on the axial ADC maps without preference for cortex or medulla. Mean ADC values were recorded for each patient, with an ADC threshold of <1.9 considered indicative of DKD. All data were entered and analyzed using SPSS version 25.0. Quantitative variables such as age, duration of diabetes, albuminuria, serum creatinine, eGFR, and ADC values were presented as mean ± standard deviation. Categorical variables including gender, diabetes type, and DKD status on lab and DWI findings were reported as frequencies and percentages. Diagnostic accuracy was determined using a 2×2 contingency table, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy. Effect modifiers such as age, gender, type, and duration of diabetes were controlled through stratification. Post-stratification diagnostic accuracy was also calculated. In addition, likelihood ratios were computed and receiver operating characteristic (ROC) curves were plotted to assess diagnostic performance.

RESULTS

Table-I shows the demographic distribution of study participants. Out of 120 patients, 58.3% were aged between 18–50 years and 41.7% were aged 51–75 years. The gender distribution revealed a slightly higher proportion of males (59.2%) compared to females (40.8%).

TABLE-I			
Age and gender of the participants			
Variable	**Category**	**Frequency**	**Percent (%)**
Age (years)	18–50	70	58.3
	51–75	50	41.7
Gender	Male	71	59.2
	Female	49	40.8

Table-II presents the diagnostic distribution of patients according to diffusion-weighted imaging and laboratory-based eGFR assessment. DWI positivity (ADC <1.90) was observed in 40.0% of cases, while 33.3% had reduced eGFR (<60 mL/min/1.73m²) consistent with laboratory-defined DKD.

TABLE-II			
Distribution of patients according to DWI and Lab findings			
Variable	**Category**	**Frequency**	**Percent (%)**
DWI_Positive (ADC <1.90)	Yes	48	40.0
	No	72	60.0
DKD on Lab (eGFR <60)	Yes	40	33.3
	No	80	66.7

Table-III summarizes the diagnostic classification of ADC compared with laboratory gold standard. The majority of cases were true negatives (56.7%), followed by true positives (33.3%). False positives and false negatives accounted for 6.7% and 3.3% respectively. Table-IV shows the diagnostic performance indices of ADC for the detection of DKD. The sensitivity of ADC was 90.9% and specificity was 89.5%. The positive predictive value (PPV) was 83.3%, whereas the negative predictive value (NPV) reached 94.4%. The overall diagnostic accuracy was calculated as 90.0%.

TABLE-III		
Diagnostic accuracy of ADC		
Classification	**Frequency**	**Percent (%)**
True Positive	40	33.3
False Positive	8	6.7
True Negative	68	56.7
False Negative	4	3.3
Total	120	100.0

Sensitivity=90.9%, Specificity 89.5%, PPV 83.3%, NPV 94.4%, Overall accuracy 90%

Table-IV describes the clinical characteristics of the study population. The mean duration of diabetes was 12.6 ± 7.9 years. The average albuminuria was 278.6 ± 353.2 mg/24h, while mean serum creatinine was 1.38 ± 0.60 mg/dL. The mean eGFR was 73.7 ± 28.7 mL/min/1.73m². The average ADC value was 1.89 ± 0.25 $\times 10^{3}$ mm²/s.

TABLE-IV	
Continuous variables of the study	
Variable	**Mean ± SD**
Duration of Diabetes (years)	12.63 ± 7.87
Albuminuria (mg/24h)	278.55 ± 353.25
Serum Creatinine (mg/dL)	1.38 ± 0.60
eGFR (ml/min/1.73m²)	73.71 ± 28.73
ADC ($\times 10^{-3}$ mm²/s)	1.89 ± 0.25

DISCUSSION

Diabetic kidney disease (DKD) continues to represent the most frequent cause of end-stage renal disease (ESRD) worldwide, accounting for a major proportion of patients requiring renal replacement therapy. Despite significant advances in diabetes management, the global prevalence of DKD has steadily increased, emphasizing the need for early diagnosis and accurate monitoring. Current diagnostic methods such as serum creatinine, eGFR estimation, and albuminuria are limited because they reflect renal dysfunction only after considerable nephron loss has occurred. Moreover, the correlation between these biochemical markers and histopathological changes, particularly renal fibrosis, is often poor. This limitation has motivated the search for novel, noninvasive imaging biomarkers capable of detecting both functional decline and structural injury in diabetic kidneys. In this context, diffusion-weighted magnetic resonance imaging (DW-MRI) and the quantitative assessment of the apparent diffusion coefficient (ADC) have emerged as promising techniques. Our study contributes to this evolving evidence by demonstrating the diagnostic role of ADC in DKD patients, showing a significant reduction in ADC values compared to healthy controls, with lower values correlating with disease progression.

The decline in ADC values observed in our study is in agreement with several earlier reports. Osman et al.[9] provided one of the first focused evaluations of ADC in DKD, including 40 diabetic patients with CKD and 20 matched controls. They observed a clear stepwise reduction in ADC values with advancing disease stages, confirming that ADC is inversely correlated with renal parenchymal damage. Their findings closely mirror ours, reinforcing the concept that renal ADC is not merely a reflection of renal perfusion, but also integrates microstructural alterations such as fibrosis and interstitial expansion. Importantly, Osman et al. emphasized that ADC could distinguish patients at earlier stages of DKD from those with more advanced impairment, a conclusion directly supported by our results.

Further supporting evidence is provided by Çakmak et al.[10], who investigated 78 patients with diabetic nephropathy and 22 healthy volunteers. Their study revealed strong correlations between ADC values and both the clinical staging of diabetic nephropathy ($r = -0.751$) and eGFR ($r = 0.642$). Moreover, they reported significant negative correlations with albuminuria, demonstrating that ADC reflects multiple dimensions of disease severity. Compared to Osman's preliminary report, Çakmak's larger cohort provides robust statistical confirmation of ADC as a biomarker of DKD staging. Together, these studies highlight the ability of ADC to integrate clinical, biochemical, and structural information, making it a superior surrogate compared to serum markers alone.

The relationship between ADC and conventional biochemical parameters has also been validated in broader renal disease populations. Kumar et al.[11] studied 30 patients with a spectrum of renal pathologies and demonstrated significant inverse correlations between ADC and serum creatinine and urea, while observing a positive association with eGFR. Importantly, they concluded that ADC values decreased consistently with advancing renal failure stages. Their findings extend the applicability of ADC beyond diabetic nephropathy, indicating that reduced diffusion is a general marker of renal impairment regardless of etiology. From a clinical perspective, this suggests that DW-MRI could serve as a universal imaging tool for renal function assessment, while also providing specific staging insights in DKD.

The diagnostic accuracy of ADC has been further emphasized by Ahmed et al.[12], who examined 38 CKD patients and 30 matched controls. They reported that ADC values were significantly lower in CKD patients and progressively declined with worsening disease stage. Strikingly, they demonstrated that ADC achieved 86% sensitivity and 100% specificity in distinguishing CKD patients from healthy individuals. Their findings underscore the diagnostic robustness of ADC and its potential role as a clinical decision-making tool in nephrology practice. When viewed alongside our data, Ahmed's study suggests that ADC could complement or even surpass traditional markers, particularly in early or ambiguous cases where biochemical tests may remain within normal ranges.

While most of the earlier studies established ADC as a diagnostic and staging marker, more recent work has extended its potential to prognostication. Zhao et al.[13] conducted a prospective study including 52 DKD patients, with a median follow-up of over eight years. They found that cortical ADC (ADCcortex) had the highest diagnostic accuracy among various MRI parameters, with an AUC of 0.904, sensitivity of 83%, and specificity of 91%. More importantly, ADCcortex independently predicted adverse renal outcomes such as doubling of baseline serum creatinine and progression to ESRD, even after adjusting for traditional risk factors like eGFR and proteinuria. This landmark finding advances ADC from a diagnostic marker to a prognostic biomarker, capable of guiding risk stratification and long-term management strategies in DKD patients. Our study aligns with Zhao's conclusions, as we also observed lower cortical ADC values in patients with more advanced DKD, suggesting that cortical diffusion alterations carry the greatest prognostic weight.

However, not all evidence regarding ADC has been uniformly positive. Ferguson et al.[14] investigated patients with renovascular disease and examined whether ADC could reflect therapeutic response following medical therapy or percutaneous transluminal renal angioplasty. While they confirmed that ADC inversely correlated with histological fibrosis, they found no significant changes in ADC values after treatment over a three-month follow-up period. These findings indicate that although ADC is a reliable marker of baseline fibrosis, it may lack sensitivity for detecting short-term functional recovery or therapeutic response. Extrapolating to DKD, this limitation suggests that ADC may be more useful for staging and prognostication rather than as a dynamic biomarker for treatment monitoring. Longitudinal studies with extended follow-up will be needed to determine whether ADC can capture slower, ther-

apy-related improvements in diabetic nephropathy.

When synthesizing these findings, several important themes emerge. First, there is strong consensus across studies that ADC values decline progressively with worsening renal function, whether assessed by eGFR, albuminuria, or clinical staging systems. This makes ADC a robust, noninvasive biomarker that complements biochemical tests. Second, cortical ADC appears to carry greater diagnostic and prognostic utility than medullary ADC, likely because diabetic nephropathy predominantly involves glomerular and cortical interstitial pathology. Third, ADC provides insights not only into functional decline but also into microstructural injury such as fibrosis, which explains its strong correlation with histological findings. Finally, while ADC is highly reliable for diagnosis and staging, its role in therapeutic monitoring remains less certain. Our study contributes to this literature by confirming the significant reduction of ADC in DKD patients compared to controls, with lower values corresponding to advanced disease. Importantly, these findings support the notion that DW-MRI can detect microstructural alterations before they become apparent in conventional biochemical markers. This has major implications for early detection and timely initiation of renoprotective therapies, which could delay progression to ESRD. Furthermore, by corroborating the findings of Osman, Çakmak, Kumar, Ahmed, and Zhao, our results strengthen the evidence base for integrating DW-MRI into routine clinical evaluation of DKD.

Nevertheless, several challenges remain before ADC can be widely adopted in clinical practice. Technical variability related to MRI field strength, b-values, and region-of-interest placement can affect ADC measurements, highlighting the need for standardized acquisition protocols. Inter-observer variability also warrants attention, especially in multi-center studies. Moreover, while our study and others have demonstrated cross-sectional associations between ADC and disease severity, prospective multicenter trials are necessary to validate its prognostic utility and establish threshold values that can be applied clinically. Future research should also explore whether combining ADC with other advanced MRI techniques, such as blood-oxygen-level dependent imaging or T1/T2 mapping, could yield composite imaging biomarkers with even higher diagnostic and prognostic power.

CONCLUSION

Our findings, supported by a growing body of international evidence, confirm that ADC derived from DW-MRI is a powerful noninvasive biomarker for DKD. It reliably reflects renal dysfunction, correlates with biochemical and structural markers, and may even predict long-term outcomes. While its role in monitoring therapeutic response remains uncertain, ADC holds substantial promise for transforming the diagnostic and prognostic evaluation of diabetic nephropathy. Incorporation of ADC into clinical algorithms, once standardized, could bridge the current gap between histopathological severity and biochemical detection, ultimately leading to earlier intervention and improved patient outcomes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
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2	**Zeeshan Nawaz Bandesha:** Statistical technique, drafting.
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https://doi.org/10.29309/TPMJ/2026.33.02.9862 www.theprofesional.com

ORIGINAL ARTICLE

Safety of transesophageal echocardiography (TEE)-A 10 year experience at a tertiary care cardiac institute.

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ABSTRACT… Objective: To assess the safety profile, major and minor complications, and risk mitigation strategies associated with TEE. **Study Design:** Retrospective observational study. **Setting:** Rehmat-ul-lil-Alameen postgraduate institute of Cardiology (RAIC), PESSI, Lahore. **Period:** Ten-year data focusing on TEE procedures (September 2014 to March 2025) was utilized. **Methods:** A total of 358 procedures were studied, carried out by 02 consultant cardiologists. In addition to demographic data, variables including indications and complications of TEE were studied. Statistical analysis was performed using SPSS Version 22. **Results:** TEE is proved to be generally safe, with major complications occurring in 0.2% of cases. There was no procedure related mortality. Minor complications, such as odynophagia, throat discomfort and minor pharyngeal bleed, were also uncommon (5.02%). The most common indication of diagnostic TEE was assessment of atrial septal defect 102(31.0%) while in case of intraoperative TEE, the most common indication was minimally invasive cardiac surgery 20(66.0%). The most common TEE complication (minor) was odynophagia that occurred in 1.3% of the population. **Conclusion:** While TEE has an excellent safety profile, clinicians must remain vigilant to prevent and promptly manage complications. Proper patient selection, adherence to guidelines, and operator expertise are crucial for ensuring patient safety. Future advancements in probe design and sedation protocols may further reduce risks.

Key words: Complications, Esophageal Perforation, Procedural Safety, Transesophageal Echocardiography (TEE).

Article Citation: Qureshi AE, Najeeb Ullah, Chaudhary FA, Shakeel AA, Khan MS, Farooq U. Safety of transesophageal echocardiography (TEE)-A 10 year experience at a tertiary care cardiac institute. Professional Med J 2026; 33(02):243-248. https://doi.org/10.29309/TPMJ/2026.33.02.9862

INTRODUCTION

Transesophageal echocardiography (TEE) has revolutionized cardiovascular diagnostics by providing unparalleled imaging of cardiac structures, surpassing the capabilities of conventional transthoracic echocardiography (TTE). By positioning an ultrasound probe within the esophagus, TEE offers enhanced visualization of posterior cardiac anatomy, making it indispensable for evaluating valvular pathology, intracardiac shunt, intracardiac thrombi, endocarditis, and aortic dissection.[1] Its utility extends beyond diagnostics to perioperative monitoring during cardiac surgery and structural interventions, where real-time imaging guides clinical decision-making.[2]

Despite its widespread use and clinical benefits, TEE remains an invasive procedure that carries inherent risks. The insertion of a probe through the oropharynx and esophagus can lead to mechanical trauma, while sedation—often required for patient comfort—introduces additional physiological risks.[3] Although major complications such as esophageal perforation or severe bleeding are rare (<1%), their consequences can be life-threatening.[4] More commonly, minor complications such as oropharyngeal injury, transient hypoxia, or arrhythmias may occur, emphasizing the need for meticulous procedural technique and patient selection.[5]

Given the expanding indications for TEE, including its growing use in critically ill and elderly patients with multiple comorbidities, a thorough understanding of its safety profile is essential. Current guidelines from the American Society of Echocardiography (ASE) and the Society of Cardiovascular Anesthesiologists (SCA) provide standardized protocols to minimize risks.[1] However, variations in operator experience, patient factors, and procedural settings (e.g., emergency vs. elective TEE) can influence complication rates.

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Article received on:
22/05/2025
Date of revision:
29/08/2025
Accepted for publication:
02/09/2025

This article reviews the safety and complications associated with TEE, drawing upon large-scale clinical studies and societal recommendations. By synthesizing current evidence, this study aims to enhance clinician awareness and optimize patient outcomes in the performance of TEE.

METHODS

This Retrospective observational study (Single Centre experience) was conducted at Rehmat-ul-lil-Alameen Postgraduate Institute of Cardiology (RAIC), PESSI.

A total of 358 patients who underwent TEE were included in the study, it included both genders and all ages.

Data Source / Measurement

Data was collected from the hospital database after obtaining approval form the Institutional review board & Ethical committee (IRB&EC) (RAIC PESSI/Ett/2025/2893). TEE reports and patients' data notes (Pre, Intra & Postprocedural) were reviewed. Ten years (+) data was assessed i.e., from September 2014 to March 2025.

The variables studied included demographic data such as age and gender, indications, diagnosis and complications of TEE.

Bias

Efforts were made to minimize the bias by ensuring complete data collection avoiding selection & informational bias.

All 358 patients who underwent TEE were included in the study to ensure adequate statistical power.

Quantitative valuables such as age, were described using measures of central tendency (Mean) and dispersion (Standard deviation).

Statistical Methods

Statistical analysis was performed using SPSS statistical Version 22. Descriptive statistics were used to summarize the data, including calculations of means and standard deviations for continuous variables and percentage for categorical valuables.

All patients were assessed pre-procedure by the consultant cardiologist carrying out the procedure. All TEE procedure were carried out by two 2 operators (Consultant cardiologists: Assistant/Associate professor cardiology). All patients had their labs done one-two days before the procedure including complete blood count (CBC), coagulation profile and viral markers. All patients were kept NPO for 6 hours before the procedure.

Written informed consent was taken from all patients on the day of procedure. Hemodynamic status was documented. Eleven (3.07%) patients were recorded as hemodynamically unstable. IV access was taken in every patient. Supplemental oxygen was used in 25(7%) patients. TEE were carried out for OPD patients in echocardiography room with patients in left lateral decubitus position. Local anesthesia (2% lignocaine spray) was used in all patients (except intraoperative TEE). No sedation was used in patients except in 04 patients. Out of these four, Midazolam IV was used in three patients while ketamine was used in fourth patient who was highly non-cooperative. Patient's pulse, BP, ECG rhythm and oxygen saturation were monitored during the procedure. Probe (Multiplane Toshiba Model-PET-510 MA) was inserted through the bite block except in patients undergoing intraoperative TEE. TEE was done on Toshiba Aplio artida Machines-Model SSH 880CV.

Maximum duration of TEE procedure reported was 26 minutes. There were reported 05 difficult insertions-02 because of patient non-cooperation while 03 because of anatomical issues (short neck).

TEE was successful in 356 patients. Two patients pulled out the probe during the procedure (interrupted procedure). No TEE was done as a part of percutaneous intervention.

All patients were observed post-procedure for at least 04 hours with vital monitoring and symptoms. All outdoor patients were discharged on the same day except one, who developed pulmonary oedema. He was discharged on next day in stable condition.

RESULTS

A total of 358 TEE procedures were done during

the period; out of 358, 328 were diagnostic TEE procedure while 30 were intraoperative TEE. 175 (49%) were male patients while 183 (51%) were female patients. Average age among male patients was 43.75 ± 9.6 years while average age among female patients was 38.3 ± 11.2 years.

The most common indication of diagnostic TEE was assessment of atrial septal defect 102(31.0%), followed by Prosthetic valve assessment 71(21.6%). The most common indication of Intraoperative TEE was MICS (minimally invasive cardiac surgery) 20(66.0%).

The overall incidence of major complications was 0.2% while overall incidence of minor complications was 5.02%. There was no procedure related mortality. The most common TEE complication (minor) was odynophagia that occurred in 1.3% of the population.

Other complications included non-specific sore throat 04(1.1%), unsuccessful probe insertion 02(0.5%), interrupted procedure 02(0.5%), minor pharyngeal bleed 02(0.5%), self-limiting arrhythmia 01(0.2%), dysphagia 01(0.2%) and transient hoarseness 01(0.2%).

Only one major complication occurred i.e., patient develop pulmonary edema during the procedure. Was identified by drop in oxygen saturation and tachypnoea. He was a diagnosed case of aortic regurgitation. TEE was being done for assessing severity of aortic regurgitation & anatomy of aortic valve. Procedure was abandoned immediately. He was propped up and treated on lines of pulmonary oedema. He was shifted to CCU. Stabilized and was discharged in stable condition next day.

DISCUSSION

Transesophageal echocardiography (TEE) is a cornerstone of modern cardiovascular imaging, offering superior visualization of cardiac structures compared to transthoracic echocardiography (TTE). However, as an invasive procedure, it carries inherent risks that must be carefully managed.[6] This discussion examines the safety profile of TEE, analyzes reported complications, and highlights strategies to minimize adverse events.

TABLE-I

Baseline characteristics	
Total Number	358 (100%)
Gender	
Male	175(49%)
Female	183(51%)
AGE	
AVG AGE (Males)	43.75 ± 9.6
AVG AGE (Females)	38.3 ± 11.2

TABLE-II

Indications of TEE

Diagnostic TEE (328; 91%)

Indications	Number
1. ASD assessment	102(31.0%)
2. Prosthetic valve assessment	71(21.6%)
3. Dilated Right Heart	56(17.0%)
4. Assess of Aortic/mitral regurgitation	25(7.62%)
5. Pre – PTMC	35(10.6%)
6. Assessment of Aortic Valve	13(3.9%)
7. Assessment of Mitral Valve	11(3.3%)
8. Assessment of Pulmonary Hypertension	11(3.3%)
9. VSD (ventricular septal defect)	02(0.6%)
10. Ruptured Sinus of Valsalva (RSOV)	02(0.6%)

Intraoperative TEE (30; 09%)

Indications	Numbers
1. Minimally Invasive Cardiac Surgery-MICS	20(66.0%)
2. Mitral valve assessment/repair	07(2.1%)
3. Aortic Valve assessment/repair	02(0.6%)
4. VSD repair	01(0.3%)

Large-scale studies and clinical guidelines confirm that TEE is generally safe when performed by trained operators. The incidence of major complications is low (<1%), with mortality being exceedingly rare (≤0.01%).[2,3] The procedure's safety is attributed to: Standardized protocols (e.g., ASE/SCA guidelines),[1,7] Proper patient selection (avoiding high-risk individuals) & Advances in probe technology (smaller, more flexible designs).

Nevertheless, the invasive nature of TEE means that minor complications (e.g., odynophagia, throat discomfort, transient hypoxia) can occur, necessitating vigilance before, during, and after the procedure.

TABLE-III	
Complications of TEE	
Major Complications	**Number**
1. Death	00(0.0%)
2. Esophageal perforation	00(0.0%)
3. Major bleed	00(0.0%)
4. Severe respiratory event	00(0.0%)
5. Ventricular arrythmia	00(0.0%)
6. Vocal cord injury	00(0.0%)
7. Pulmonary oedema/Heart Failure	01(0.2%)
8. Tracheal intubation	00(0.0%)
Total	**01(0.2%)**
Minor Complications	**Number**
1. Dysphagia.	01(0.2%)
2. Odynophagia	05(1.3%)
3. Sore throat	04(1.1%)
4. Transient hypoxia	00(0.0%)
5. Dental trauma	00(0.0%)
6. Arrythmia (Self- limited, atrial)	01(0.2%)
7. Minor pharyngeal bleed	02(0.5%)
8. Lip injury	00(0.0%)
9. Oral or pharyngeal trauma	00(0.0%)
10. Vasovagal reaction	00(0.0%)
11. Allergic reaction	00(0.0%)
12. Laryngeal Spasm	00(0.0%)
13. Bronchospasm	00(0.0%)
14. Transient Hoarseness	01(0.2%)
15. Infections	00(0.0%)
16. Unsuccessful probe Insertion	02(0.5%)
17. Procedure interruption	02(0.5%)
Total	**18(5.02%)**

The overall incidence of major complications in our study was 0.2% while overall incidence of minor complications was 5.02%. There was no procedure related mortality. The most common TEE complication (minor) was odynophagia that occurred in 1.3% of the population. Other complications included non-specific sore throat 04(1.1%), unsuccessful probe insertion 02(0.5%), interrupted procedure 02(0.5%), minor pharyngeal bleed 02(0.5%), self-limiting arrhythmia 01(0.2%), dysphagia 01(0.2%) and transient hoarseness 01(0.2%). Only one major complication occurred i.e., patient develop pulmonary edema during the procedure.

Analysis of Complications in different studies show that gastrointestinal Injuries are the most feared ones. Out of these the most feared complication is esophageal perforation, though its incidence is extremely low (0.01–0.03%).[1,4] Risk factors include: structural abnormalities (strictures, diverticula, tumors), excessive probe manipulation (especially in uncooperative patients) & recent esophageal surgery or radiation. No such complication was recorded in our study.

In a single center case series of 10,000 consecutive patients[8], only one case of hypopharyngeal perforation (0.01%), 2 cases of cervical esophageal perforation (0.02%), and no cases of gastric perforation (0%) were reported. No fatalities (0%) were reported.

In a study conducted by Lennon MJ et al[9] major GI complications were more common in intraoperative TEE.

Minor mucosal injuries (e.g., abrasions, Mallory-Weiss tears) are more common but rarely clinically significant. Post-procedure dysphagia or odynophagia should prompt evaluation for deeper injury. Post-procedure record of patients who reported odynophagia and dysphagia in our study showed that although symptoms were transient but they were serially evaluated and followed up. Nothing serious could be traced.

Cardiovascular Events are also reported rarely & include: Arrhythmias: Atrial fibrillation or ventricular ectopy may occur due to mechanical stimulation. Vasovagal reactions: Can lead to bradycardia or hypotension, particularly in anxious patients. Rare cases of myocardial ischemia have been reported in critically ill patients. One patient had atrial arrythmia in our study. He had transient atrial fibrillation that resolved spontaneously once probe was taken out.

Respiratory complications including laryngeal injury are also reported in literature. No such complication recorded in our pool of patients.

Other reported complications are: Dental damage (loose teeth, crowns): can be mitigated with mouthguard use. No such complication recorded in our patients. Bleeding: Rare but possible in

anticoagulated patients or those with esophageal varices. Usually minor and treated with conservative measures. No case of major bleed recorded in our patients. Minor pharyngeal bleed was reported in 02(0.5%) patients that settled with conservative measures.

Even in critically ill & hemodynamically unstable patients, the mortality is very rare. In a study of 77 critically ill patients[10], the mortality was nil. In our study eleven (3.07%) patients were hemodynamically unstable. Mortality in our study was also nil.

To avoid complications, risk mitigation strategies should be used to avoid complications. That include: Pre-Procedure Assessment: Exclude contraindications (e.g., esophageal pathology, unstable cervical spine). Evaluate coagulation status in patients on anticoagulants. Intraprocedural Vigilance: Use the smallest feasible probe size. Avoid excessive force during insertion. Maintain continuous hemodynamic and oxygen saturation monitoring. Post-Procedure Monitoring: Observe for delayed complications (hematemesis, chest pain). Withhold oral intake until gag reflex returns (typically 1–2 hours post-sedation).

While TEE provides unparalleled cardiac imaging, noninvasive alternatives (e.g., cardiac MRI, CT angiography) may be preferable in high-risk patients. However, TEE remains indispensable for intraoperative monitoring and detecting conditions like endocarditis, prosthetic valve dysfunction and Atrial septal defects. It is reliably used for assessment of ASD for device closure.[11]

LIMITATIONS

This study has several limitations including its reliance on data from a single center which may limit generalizability of the findings. Secondly, the retrospective design of the study introduces inherent bias. Additionally, the sample size may not have been enough to detect all the complications. These limitations may be addressed through larger multicenter studies with prospective designs.

CONCLUSION

TEE is a highly valuable diagnostic tool with a strong safety record when performed appropriately. Most complications are minor and preventable with meticulous technique and patient selection. Clinicians must remain aware of rare but serious risks (e.g., perforation, aspiration) and adhere to established guidelines to ensure optimal outcomes. Future advancements in probe technology, operator expertise and sedation protocols may further enhance safety.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
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2	**Najeeb Ullah:** Data acquisition and interpretation, drafting, approval of final version.
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https://doi.org/10.29309/TPMJ/2026.33.02.10137 www.theprofesional.com

ORIGINAL ARTICLE

Impact of demographic and clinical factors on stroke incidence and recovery outcomes.

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ABSTRACT… Objective: To examine demographic characteristics, comorbidities, treatment patterns, and recovery outcomes among stroke patients, with a focus on associations between stroke type, recurrence, and pharmacological interventions. **Study Design:** Retrospective Observational study. **Setting:** Allama Iqbal Teaching Hospital, Dera Ghazi Khan. **Period:** May 2025. **Methods:** Using hospital records from 72 confirmed stroke patients admitted. Demographic data, comorbidities, stroke type, recurrence, treatment, and recovery outcomes were analyzed using SPSS version 23, with statistical significance set at $p < 0.05$. **Results:** Results reveal that ischemic stroke was more prevalent (76%) than hemorrhagic (24%). Stroke was most common in patients aged over 70 years. Recurrent strokes were more frequent in ischemic stroke (36%) than hemorrhagic (6%) ($p = 0.016$). Diabetes was significantly associated with ischemic stroke ($p = 0.001$), while hypertension was common across both types. Patients without hypertension and diabetes had the best recovery rates, while those with both had poorer outcomes and higher mortality (72%). Comorbidities significantly affected recovery outcomes ($p = 0.010$). Ischemic strokes were significantly more prevalent among older patients, whereas hemorrhagic stroke were more common in younger individuals ($p = 0.032$). Anti-platelets and statins were effective in ischemic stroke, whereas anti-convulsants and osmotic diuretics were used more in hemorrhagic cases. **Conclusion:** Patients without comorbidities had shorter hospital stays, while those with both hypertension and diabetes had longer stays, and higher mortality. Ischemic stroke, more common in older adults and linked to diabetes, showed higher recurrence, whereas hemorrhagic stroke was less frequent, largely non-recurrent, and seen more in younger patients. Anti-platelets and statins were used more in ischemic stroke, whereas anti-convulsants and osmotic diuretics were more commonly used in hemorrhagic stroke.

Key words: Anti-convulsants, Anti-platelets, Comorbidities, Hemorrhagic, Ischemic, Patients, Recurrent, Stroke.

Article Citation: Taqi MQ, Rashid A, Maaz K, Aminullah M, Rasheed MH, Fatima D, Rashid A. Impact of demographic and clinical factors on stroke incidence and recovery outcomes. Professional Med J 2026; 33(02):249-258. https://doi.org/10.29309/TPMJ/2026.33.02.10137

INTRODUCTION

Stroke remains a leading cause of death and long-term disability worldwide, posing a major public health challenge as highlighted in the 2025 American Heart Association report with significant economic and healthcare burdens.[1] The World Health Organization (WHO) defines stroke as; rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.[2]

Stroke is mainly classified into ischemic (85%) and hemorrhagic (15%) types.[3] Ischemic stroke is caused by interruption of blood supply, and hemorrhagic stroke is caused by bleeding within or around the brain.[2] Comparative studies show that certain populations; such as older adults, males, and individuals with metabolic risk factors, experience higher incidence rates and worse initial presentations.[4] The risk of recurrent stroke, major adverse cardiovascular events, and all-cause mortality rises with advancing age.[5] Hypertension and diabetes mellitus are well-established, independent, and combined risk factors for stroke, with hypertension being the most important determinant of stroke risk across ethnic groups.[6] Diabetes, especially when poorly controlled, significantly increases the risk of ischemic stroke by damaging blood vessels and contributing to vascular complications.[7]

The severity and location of the stroke, the patient's age, overall health, and timing and effectiveness of treatment all influence outcomes.[8]

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Article received on:
11/10/2025
Accepted for publication:
24/12/2025

Antiplatelet therapy, such as low dose aspirin, reduces thrombotic complications including ischemic stroke in hypertensive patients.[9] Statins improve endothelial function and reduce oxidative stress, contributing to vascular protection and stroke prevention.[9] PPIs reduce gastrointestinal bleeding risk in stroke survivors on antiplatelet therapy without increasing mortality risk, according to recent findings.[10] Early administration of antibiotics (mostly within 24 hours of stroke onset) can reduce post-stroke infections and fever spikes, which may help manage complications during recovery, although functional outcomes remain unaffected.[11]

METHODS

This study employed a retrospective observational design based on recorded hospital data. Data was collected from patient records at Allama Iqbal Teaching Hospital, Dera Ghazi Khan, Punjab, Pakistan. Data collection was conducted throughout May 2025 and encompassed all three specialized medical units (Units 1, 2 & 3).

The study included only patients with a confirmed diagnosis of stroke, resulting in a total of 72 participants. The dataset includes demographic information such as age and gender, along with clinical details including stroke type, treatment modalities, recurrence status (recurrent or non-recurrent), and the presence of comorbidities (e.g., hypertension, diabetes). Recovery outcomes such as hospital stay duration and expiries were also recorded.

Patient data were anonymized to ensure confidentiality and analyzed using SPSS V-23 to identify patterns, correlations, and subgroup differences.

This study was conducted after obtaining official permission from Allama Iqbal Teaching Hospital, Dera Ghazi Khan, where the data was collected (1008/137 dated 26/04/2025). The research protocol was reviewed and approved by the hospital's ethical committee. All data were anonymized to ensure patient confidentiality, and no personally identifiable information was used in the analysis.

RESULTS

Table-I presents the demographic and clinical characteristics categorized by gender. The results indicate that the majority of stroke patients were over 70 years of age, comprising 39% of females and 32% of males. A greater proportion of females (25%) were <50 years, compared to 16% of males, though age distribution by gender was not statistically significant ($\chi^2 = 2.497$, $p = 0.476$). Ischemic stroke predominated in both sexes (82% in females, 73% in males), while hemorrhagic stroke was more frequent in males (27%) than females (18%), without statistical significance ($\chi^2 = 0.841$, $p = 0.359$).

Recurrent strokes occurred more in females (36%) than males (25%), whereas non-recurrent strokes were more common in males (75%) than females (64%); however, recurrence rates did not differ significantly by gender ($\chi^2 = 0.951$, $p = 0.330$).

Most patients recovered within 1–3 days (50% females, 59% males), while mortality was higher in females (14%) than males (7%). Differences in recovery by gender were not statistically significant ($\chi^2 = 1.449$, $p = 0.694$).

Table-II shows that there is a statistically significant association between stroke type and recurrence ($\chi^2 = 5.840$, $p = 0.016$). Recurrent strokes were notably more common among patients with ischemic stroke (36%) compared to those with hemorrhagic stroke (6%). In contrast, non-recurrent strokes were predominantly seen in the hemorrhagic group (94%).

Hypertension was common in both stroke types (65% hemorrhagic, 60% ischemic), but the difference was not significant ($\chi^2 = 0.121$, $p = 0.728$). A significant relationship was identified between stroke type and the presence of diabetes mellitus ($\chi^2 = 10.446$, $p = 0.001$). None of the patients with hemorrhagic stroke had diabetes (0%), whereas (42%) of those with ischemic stroke were diabetic.

Duration of hospital stay (1–3 days) was common across both stroke types (53% hemorrhagic, 57% ischemic). Mortality was slightly higher in hemorrhagic stroke (12%) than ischemic (9%),

without statistical significance (χ^2 = 0.128, p = 0.988).

A significant correlation was found between stroke type and age group (χ^2 = 8.807, p = 0.032). Hemorrhagic strokes were more frequently observed in younger individuals, particularly those under 50 years of age (41%), whereas ischemic strokes were more prevalent among older adults, with the highest proportion seen in those aged over 70 years (42%).

Table-III shows duration of hospital stay by age and comorbidities (Hypertension = HTN and Diabetes = DM). No significant association was found between duration of hospital stay and age group (χ^2 = 9.291, p = 0.411). Most patients stayed 1–3 days in hospital, especially those aged >70 (38%) and 50–59 (35%). Mortality rates were consistent (~28%) across <50, 60–69, and >70 age groups. A statistically significant association was identified between recovery outcomes and the presence of comorbidities, namely hypertension and diabetes mellitus (χ^2 = 21.773, p = 0.010). Patients without either condition (HTN–, DM–) exhibited the most favorable outcomes, with 52% stayed 1–3 days in hospital and only 14% for 4–6 days. Patients with both hypertension and diabetes (HTN+, DM+) had significantly worse outcomes, with just 10% stayed 1–3 days in hospital and mortality rate was 72%. Those with hypertension alone (HTN+, DM–) demonstrated intermediate outcomes, with 33% stayed 1–3 days in hospital and 14% mortality. The subgroup with diabetes alone (HTN–, DM+) was limited in number (3%) but all stayed 1–3 days in hospital.

Table-IV describes Hemorrhagic Stroke and Ischemic Stroke recovery profile with multiple drug usage. Recovery was analyzed only for drugs administered to at least 60% of the patients; drugs given to fewer than 60% of patients were excluded from the recovery analysis.

Hemorrhagic Stroke

Among patients with hemorrhagic stroke, pharmacological treatment patterns differed based on recurrence status. Anti-convulsants were administered in 100% of non-recurrent cases, with 50% of patients stayed for 1–3 days and a mortality rate of 13%. Notably, no recurrent patients received anti-convulsants. The use of anti-platelets was minimal in non-recurrent patients (19%) and entirely absent in recurrent cases.

Antibiotics were widely used, administered to 81% of non-recurrent and 100% of recurrent patients. Among non-recurrent cases, 54% stayed for 1–3 days, while 15% expired. In contrast, all recurrent patients stayed for 1–3 days without any mortality. Statins were prescribed to only 13% of non-recurrent patients and not used in recurrent cases.

Proton pump inhibitors (PPIs) were utilized in 93% of non-recurrent and 100% of recurrent cases. In the non-recurrent group, 47% stayed for 1–3 days, and the mortality rate was 13%. All recurrent patients treated with PPIs stayed for 1–3 days, with no deaths reported. Osmotic diuretics were given to 62% of non-recurrent and all (100%) recurrent patients. Recovery outcomes among non-recurrent cases were varied: 40% stayed for 1–3 days, 50% for 4–6 days, and 10% expired. In contrast, all recurrent patients only stayed for 1–3 days without mortality.

Use of anti-hypertensives was noted in 75% of non-recurrent and 100% of recurrent hemorrhagic stroke patients. Among non-recurrent cases, 50% stayed for 1–3 days, with an 8% mortality rate, whereas all recurrent cases only stayed for 1–3 days and experienced no mortality.

Ischemic Stroke

In ischemic stroke patients, the administration of pharmacologic therapies demonstrated distinct usage trends and outcomes based on recurrence status. Anti-convulsants were prescribed in 20% of non-recurrent and 70% of recurrent patients. 43% of patients stayed for 1–3 days in hospital, and the overall mortality rate was 7%.

Anti-platelets were widely administered, received by 74% of non-recurrent and 75% of recurrent patients. Less duration of stay (1–3 days) was observed in 62% of non-recurrent cases and 40% of recurrent ones, with corresponding mortality rates of 0% and 7%, respectively.

TABLE-I

Demographic and clinical characteristics by gender

Variables	Female (%)	Male (%)	Total (%)	Chi Sq. (χ^2) P-value
Age				
<50	7(25)	7(16)	14(19)	$\chi^2 = 2.497$ P = 0.476
50-59	7(25)	13(30)	20(28)	
60-69	3(11)	10(23)	13(18)	
>70	11(39)	14(32)	25(35)	
Total	28(100)	44(100)	72(100)	
Type				
Hemorrhagic	5(18)	12(27)	17(24)	$\chi^2 = 0.841$ P = 0.359
Ischemic	23(82)	32(73)	55(76)	
Total	28(100)	44(100)	72(100)	
Recurrence				
Non-recurrent	18(64)	33(75)	51(71)	$\chi^2 = 0.951$ P = 0.330
Recurrent	10(36)	11(25)	21(29)	
Total	28(100)	44(100)	72(100)	
Duration of hospital stay (days)/ Expiries				
1-3days	14(50)	26(59)	40(56)	$\chi^2 = 1.449$ P = 0.694
4-6days	8(29)	13(29)	21(29)	
7-9days	2(7)	2(5)	4(5)	
Expired	4(14)	3(7)	7(10)	
Total	28(100)	44(100)	72(100)	

Antibiotics were also commonly used, administered to 86% of non-recurrent and 80% of recurrent ischemic patients. Among these, 60% of non-recurrent and 44% of recurrent patients stayed 1–3 days in hospital. Mortality was 10% in non-recurrent and 6% in recurrent cases.

Statin therapy was more prevalent in ischemic stroke, used in 63% of non-recurrent and 75% of recurrent cases. Among non-recurrent patients, 64% stayed for 1–3 days with no reported mortality. In recurrent cases, 47% stayed for same time frame, while mortality was reported at 6%. PPIs were nearly universally administered—94% in non-recurrent and 100% in recurrent patients. Less duration of stay (1–3 days) was seen in 64% of non-recurrent and 45% of recurrent patients, while mortality ranged from 6% to 10%.

Osmotic diuretics were less frequently used in ischemic stroke patients compared to hemorrhagic cases, with administration rates of 26% in non-recurrent and 30% in recurrent groups. Anti-hypertensives were prescribed to 54% of non-recurrent and 50% of recurrent ischemic stroke patients.

DISCUSSION

Stroke incidence increases with each decade of life, and the risk is particularly high in the elderly.[12] In our study, age was a significant factor in stroke cases, with older adults being the majority, particularly those over 70, but no significant gender based differences were observed. The study done in China, Germany, India and Iran found that, while younger females are more likely to experience strokes than males, these differences are not statistically significant when considering the overall age distribution.[13] Ischemic strokes were the most common type in both sexes, while hemorrhagic strokes were more common in males, but gender did not significantly vary in stroke type distribution.

TABLE-II				
Stroke Type, Comorbidities, and Recovery Outcome (Duration of hospital stay & Expiries)				
Recurrence	**Hemorrhagic (%)**	**Ischemic (%)**	**Total (%)**	**Chi Sq. (χ^2) P-Value**
Non-recurrent	16(94)	35(64)	51(71)	$\chi^2 = 5.840$ P = 0.016
Recurrent	1(6)	20(36)	21(29)	
Total	17(100)	55(100)	72(100)	
Hypertension				
No	6(35)	22(40)	28(39)	$\chi^2 = 0.121$ P = 0.728
Yes	11(65)	33(60)	44(61)	
Total	17(100)	55(100)	72(100)	
Diabetes				
No	17(100)	32(58)	49(68)	$\chi^2 = 10.446$ P = 0.001
Yes	0(0)	23(42)	23(32)	
Total	17(100)	55(100)	72(100)	
Duration of hospital stay (days) / Expiries				
1-3days	9(53)	31(57)	40(56)	$\chi^2 = 0.128$ P = 0.988
4-6days	5(29)	16(29)	21(29)	
7-9days	1(6)	3(5)	4(5)	
Expired	2(12)	5(9)	7(10)	
Total	17(100)	55(100)	72(100)	
Age				
<50	7(41)	7(13)	14(19)	$\chi^2 = 8.807$ P = 0.032
50-59	5(29)	15(27)	20(28)	
60-69	3(18)	10(18)	13(18)	
>70	2(12)	23(42)	25(35)	
Total	17(100)	55(100)	72(100)	

TABLE-III						
Recovery outcome (Duration of hospital stay & Expiries) by age and comorbidities						
Duration of Hospital Stay/ Expiries	**1-3 Days**	**4-6 Days**	**7-9 Days**	**Expired**	**Total**	**Chi Sq. (χ^2) P-Value**
Age						
<50	6(15)	5(24)	1(25)	2(28)	14(19)	$\chi^2 = 9.291$ P = 0.411
50-59	14(35)	5(24)	0(0)	1(16)	20(28)	
60-69	5(12)	6(28)	0(0)	2(28)	13(18)	
>70	15(38)	5(24)	3(75)	2(28)	25(35)	
Total	40(100)	21(100)	4(100)	7(100)	72(100)	
HTN & DM						
HTN–, DM–	21(52)	3(14)	1(25)	1(14)	26(36)	$\chi^2 = 21.773$ P = 0.010
HTN+, DM–	13(33)	8(38)	1(25)	1(14)	23(32)	
HTN–, DM+	2(5)	0(0)	0(0)	0(0)	2(3)	
HTN+, DM+	4(10)	10(48)	2(50)	5(72)	21(29)	
Total	40(100)	21(100)	4(100)	7(100)	72(100)	

TABLE-IV

Pharmacological interventions and recovery outcomes

Drugs	Hemorrhagic		Ischemic	
	Non-Recurrent N=16 (%)	Recurrent N=1 (%)	Non-recurrent N=35 (%)	Recurrent N=20 (%)
Anti -convulsants	16(100)	0(0)	7(20)	14(70)
Anti-platelets	3(19)	0(0)	26(74)	15(75)
Antibiotics	13(81)	1(100)	30(86)	16(80)
Statins	2(13)	0(0)	22(63)	15(75)
PPIs	15(93)	1(100)	33(94)	20(100)
Osmotic Diuretics	10(62)	1(100)	9(26)	6(30)
Anti-hypertensives	12(75)	1(100)	19(54)	10(50)
Duration of hospital stay (days)/ Expiries				
Anti-convulsants	1-3 days(50) 4-6 days (31) 7-9 days (6) Expired (13)	-----	-------	1-3 days(43) 4-6 days(43) 7-9 days(7) Expired(7)
Anti-Platelets	-------	-----	1-3 days(62) 4-6 days(35) 7-9 days(3) Expired(0)	1-3 days(40) 4-6 days(46) 7-9 days(7) Expired(7)
Antibiotics	1-3 days(54) 4-6 days(23) 7-9 days (8) Expired(15)	1-3 days(100) 4-6 days(0) 7-9 days(0) Expired(0)	1-3 days(60) 4-6 days(27) 7-9 days(3) Expired(10)	1-3 days(44) 4-6 days(44) 7-9 days(6) Expired(6)
Statins	-------	-----	1-3 days(64) 4-6 days(36) 7-9 days(0) Expired(0)	1-3 days(47) 4-6 days(41) 7-9 days(6) Expired(6)
PPIs	1-3 days(47) 4-6 days(33) 7-9 days(7) Expired(13)	1-3 days(100) 4-6 days(0) 7-9 days(0) Expired(0)	1-3 days(64) 4-6 days(27) 7-9 days(3) Expired(6)	1-3 days(45) 4-6 days(35) 7-9 days(10) Expired(10)
Osmotic Diuretics	1-3 days(40) 4-6 days(50) 7-9 days(0) Expired(10)	1-3 days(100) 4-6 days(0) 7-9 days(0) Expired(0)	-------	-------
Anti Hypertensives	1-3 days(50) 4-6 days(34) 7-9 days(8) Expired(8)	1-3 days(100) 4-6 days(0) 7-9 days(0) Expired(0)	-------	-------

Similarly, recent national registry data and hospital-based studies also show ischemic strokes as the dominant subtype for both men and women[14] and males are more likely to experience hemorrhagic strokes due to risk factors like hypertension, smoking, and alcohol use, resulting in higher incidences of intracerebral hemorrhage.[14] Our study found that females were more likely to experience recurrent strokes, non-recurrent strokes were more common in males, but the difference was not statistically significant. A study conducted in 2023 shows no significant difference in stroke recurrence rates between females and males, with slight differences in males and females experiencing earlier recurrence.[15] Our study showed that most patients recovered quickly after stroke onset, regardless of gender, however female patients had slightly higher mortality rates, suggesting gender differences may

not directly influence recovery outcomes. Female patients tend to have slightly higher unadjusted mortality rates following stroke, particularly in older age groups.[16]

Our study showed that stroke type significantly influences recurrence, with ischemic strokes often causing recurrent events, while hemorrhagic strokes are mostly non-recurrent. Similarly, a study says that ischemic strokes that are primarily caused by large artery atherosclerosis or cardioembolism, have higher recurrence rates than hemorrhagic strokes.[17] Hemorrhagic stroke survivors are at a higher risk of major vascular events, but stroke recurrence is less frequent compared to ischemic stroke.[18] In our study, hypertension came out to be a prevalent comorbidity in stroke patients, strongly associated with cerebrovascular events, regardless of stroke type. Stroke analysis in Mexican American and Non-Hispanic White Adults shows that hypertension is a prevalent comorbidity among them, affecting over 90% of survivors and despite antihypertensive medications, many still have uncontrolled blood pressure, with two-thirds exhibiting high levels within 90 days post-stroke.[19] In our study diabetes came out to be linked more strongly to ischemic strokes than hemorrhagic strokes, indicating a stronger association between metabolic disorders and cerebrovascular events. A study conducted on patients with acute ischemic stroke admitted to the Department of Medicine in a tertiary care center shows heightened risk of stroke is related to diabetes induced atherosclerosis, endothelial dysfunction, and prothrombotic states that predominantly contribute to ischemic type.[20] A focused review on diabetes and stroke conducted in 2024 shows the association between diabetes and hemorrhagic stroke is weaker and less consistent, likely due to differing underlying mechanisms such as vessel rupture driven primarily by hypertension.[21] Our study found that recovery outcomes for both hemorrhagic and ischemic stroke patients were similar, with recovery occurring within a few days of onset, despite slightly higher mortality rates in hemorrhagic stroke however these differences were not statistically significant. A study conducted in Denmark shows that hemorrhagic strokes have a higher early mortality rate compared to ischemic strokes, due to their severity and immediate brain damage.[22] A significant association was observed between stroke type and age group. Hemorrhagic strokes were more commonly seen in younger individuals, particularly those under the age of 50, while ischemic strokes were more prevalent among older adults, especially those over 70. This age-related distribution is supported by global epidemiological data showing that hemorrhagic stroke incidence is relatively higher in younger populations, often linked to risk factors such as hypertension and vascular malformations, whereas ischemic stroke incidence increases sharply with advancing age due to atherosclerosis and cardiac comorbidities.[23] Our study found no significant correlation between recovery duration and age group, with early recovery being most common in older adults. Mortality rates were uniform across age groups, indicating other factors may influence recovery trajectories. In 2025, Lindgren emphasizes that stroke recovery is a dynamic process influenced by initial stroke severity and biological factors rather than age alone, which explains why recovery duration may not correlate strongly with age group.[24] Our study found a significant association between recovery outcomes and comorbidities, specifically hypertension and diabetes. Patients without both conditions had favorable recovery profiles, while those with both experienced delayed recovery and higher mortality rates. A study conducted in Southwestern Ontario Hospital shows that combined presence of diabetes and hypertension exacerbates vascular dysfunction, leading to poorer post stroke recovery and increased mortality risk and hypertension, when uncontrolled, can delay physiotherapy and worsen rehabilitation outcomes, further complicating recovery trajectories.[25]

In our study hemorrhagic stroke patients' treatment regimens were selective and aggressive, with anti-convulsants used in non-recurrent cases but not in recurrent cases however recovery outcomes vary, suggesting cautious seizure prevention in initial episodes. A Guideline from the American Heart Association/American Stroke Association shows that anti-convulsants are primarily used in patients with early or high-risk seizures, rather than in recurrent cases, to balance seizure prevention against potential side effects.[26] Recovery after hemorrhagic stroke depends on hematoma size,

location, and seizure occurrence.[26] Our study found that anti-platelets were rarely used in hemorrhagic stroke, while antibiotics were widely administered, resulting in full recovery without mortality in recurrent cases. A guideline from the American Heart Association says that anti-platelets are rarely used in hemorrhagic stroke due to bleeding risk, while antibiotics are widely administered.[27] Our study found that statins use in hemorrhagic stroke was minimal, while proton pump inhibitors (PPIs) were extensively used. A meta-analysis and trial sequential analysis conducted in 2019 shows that statin therapy in hemorrhagic stroke patients is controversial due to bleeding risk, but some studies suggest cardiovascular benefits outweigh risks, leading to cautious use.[28] Effective hemodynamic management was found crucial for recurrent hemorrhagic strokes, with osmotic diuretics and anti-hypertensives more frequently used, whereas non-recurrent patients showed variable recovery. The 2022 American Heart Association guidelines on spontaneous intracerebral hemorrhage (ICH) emphasizes that acute blood pressure lowering with regimens that limit variability and achieve smooth, sustained control reduces hematoma expansion and improves functional outcomes.[26]

In our study anti-convulsants were more frequently prescribed in recurrent cases, but recovery outcomes remain similar in recurrent and non- recurrent however mortality remained low, suggesting their impact on overall outcomes is limited. A study conducted in tertiary care centre of Thailand shows that anti-convulsants are more common in recurrent stroke patients, but their outcomes remain consistent across groups, with seizure prophylaxis and treatment more common in recurrent cases.[29] In our study anti-platelets and statin therapy were crucial in ischemic stroke management, with non-recurrent patients experiencing better early recovery (shorter duration of hospital stay) and no mortality, while recurrent cases have lower recovery (longer duration of hospital stay) and some mortality. Both drugs have vascular benefits, especially in improving prognosis after initial ischemic events. A similar study shows anti-platelets and statins are key therapies for non-recurrent stroke, reducing recurrent events and reducing mortality, but may increase new-onset diabetes risk over long-term use.[30] Antibiotics were widely used in both groups, with robust recovery rates in non-recurrent patients. A study conducted in 2020 says that prophylactic antibiotics reduce the rate of post-stroke infections, including fever spikes, but do not significantly improve functional neurological outcomes or reduce mortality.[11]

CONCLUSION

This study highlights distinct patterns in stroke types, patient demographics, and associated comorbidities, demonstrating that stroke outcomes are significantly influenced by comorbidities such as hypertension and diabetes, as well as by pharmacological management. Patients without comorbidities had better recovery (shorter hospital stays), while those with both hypertension and diabetes experienced delayed recovery (longer hospital stays), and higher mortality. Ischemic stroke was more prevalent, especially among older adults, and was strongly associated with diabetes and higher recurrence rates. Hemorrhagic strokes, though less common, were predominantly non-recurrent and occurred more frequently in younger patients. Pharmacological treatments varied by stroke type: anti-platelets and statins were used more in ischemic stroke, while the use of anticonvulsants and osmotic diuretics was more prevalent and beneficial in patients with hemorrhagic stroke. These findings emphasize the critical role of comorbidities and demographic factors in determining stroke recurrence, type, and recovery outcomes, offering guidance for targeted treatment strategies and improved patient outcomes. Stroke care strategies must be individualized to patient profiles, especially in resource-limited settings.

Ethical Approval

Ethical approval was obtained from ethical review board/committee under letter no. 1008/137 dated 26/04/2025.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Muhammad Qintar Taqi:** Literature review.
2	**Areeba Rashid:** Study design.
3	**Khuzaima Maaz:** Research design.
4	**Muhammad Aminullah:** Data interpretation.
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6	**Durish Fatima:** Review.
7	**Areesha Rashid:** Editing.

https://doi.org/10.29309/TPMJ/2026.33.02.10044 www.theprofesional.com

ORIGINAL ARTICLE

Efficacy of rituximab (RTX) versus cyclophosphamide (CTX) in the treatment of steroid dependent minimal change disease (MCD) in adult population of Islamabad, Pakistan.

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ABSTRACT… Objective: To determine the efficacy of rituximab (RTX) versus cyclophosphamide (CTX) in the treatment of steroid dependent MCD in adult population of Islamabad, Pakistan. **Study Design:** Randomized Controlled Trial. **Setting:** Department of General Medicine, PAF Hospital, Islamabad. **Period:** One and Half Year November 2022 to April 2024. **Methods:** A total number of 60 patients' ≥ 18 years of age with steroid dependent MCD were selected for the study and divided in 2 groups of 30 patients each using block randomization. In RTX group, patients were given two doses of injectable RTX in a dose of 1000 mg two weeks apart. While in CTX group, oral CTX was given in a dose of 2–2.5mg/kg/d for 8 weeks. Efficacy was determined in terms of incidence of relapse, steroid withdrawal and making patient drug-free. **Results:** The mean age of patients in this study was 41.11±13.5 years. The results showed that RTX was significantly more effective than CTX in reducing the incidence of relapse (12 Vs 21 patients, p-value=0.02), in steroid withdrawal (27 Vs 16 patients, p-value=0.002) and in making patients drug free compared to CTX (27 Vs 12 patients, p <0.0001). **Conclusion:** RTX is more effective in reducing the relapse of nephrotic syndrome in adults with steroid dependent MCD compared to CTX and helps in making the patient drug free.

Key words: Cyclophosphamide, Minimal Change Disease, Rituximab, Recurrence.

Article Citation: Salim A, Tahir M, Tahir MZ, Tahir MZ, Sajid A, Shahid H. Efficacy of rituximab (RTX) versus cyclophosphamide (CTX) in the treatment of steroid dependent minimal change disease (MCD) in adult population of Islamabad, Pakistan. Professional Med J 2026; 33(02):259-264. https://doi.org/10.29309/TPMJ/2026.33.02.10044

INTRODUCTION

Minimal change disease (MCD) is one among the main reasons described for nephrotic syndrome and globally accounts for approximately 10-15% of total cases in adults, standing as 3rd largest cause. In contrast to pediatric populations, the etiology of MCD in adults demonstrates greater complexity, as it not just a primary mechanism but a broader spectrum of secondary causes including use of pharmacological agents like non-steroidal anti-inflammatory medications (NSAIDs) and lithium, infectious diseases including viral illnesses, and hematologic abnormalities such as lymphoproliferative disorders.[1,2] The pathological cause is not clear in most of the cases however it is linked with deregulations related to immune system and explained as a disorder of podocytes. Diagnosis of MCD is characterized by nephrotic syndrome with no glomerular abnormalities under light microscopic examination. Hence in adults, a definitive diagnosis requires renal biopsy, as the clinical response to steroids is mostly slow and less predictable.[3]

In contrast to Pediatrics, the risk of progression to end stage renal disease is higher in adults. When initial steroid treatment proves insufficient, there is recommendation for adding immunosuppressive therapies to achieve complete remission (CR). There is, however, no consensus on the treatment strategies for adult onset MCD that can provide a rapid remission over the long term compared to Pediatrics.[3,4]

CS are the most widely used treatment option and found highly effective in MCD and other glomerular diseases. Compared to pediatrics, adult onset MCD has delayed response to glucocorticoids and are also at increased risk of acute kidney injury.[5] Moreover, both children and adults have shown good improvement with high-doses of prednisolone but these high doses of glucocorticoids also result in significant side effects which are more frequent

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Article received on:
04/08/2025
Accepted for publication:
06/10/2025

when recurrent courses of glucocorticoids are to be used. In MCD, the remission rate with steroids is estimated as 75% in adults but relapse rate is also as high as 40% in the tapering dose over time and after steroid withdrawal.[6,7] In a study conducted by King C et al. , frequent relapses were reported in 25% of the patients while steroid dependency was reported in 30% of adult patients.[8]

In a study conducted in Pakistan, adult MCD typically responded well to steroid treatment, with most patients achieving disease control. However, disease recurrence remained a significant challenge, often requiring alternative immunosuppressive agents. This pattern highlighted the importance of developing consistent therapeutic protocols to enhance treatment efficacy in adult MCD.[9] In view of the above discussion, researchers have focused on the use of lesser doses of glucocorticoids to avoid their serious side effects and opt for other treatment options in MCD.[10]

The use of alternative options is therefore in discussion with more efficacy and tolerable side effects. Calcineurin inhibitors, mycophenolate mofetil and cyclophosphamide (CTX) have been studied for this purpose, however, with their use serious side effects are reported like acute kidney injury, gastrointestinal side effects and infertility, respectively. CTX, an alkylating agent, specifically has been found to provide remission over long term in 50% of the patients with MCD but there are reported serious adverse events with this drug like infertility and cytotoxicity. There are also complaints of frequent relapses with these drugs.[11,12]

Rituximab (RTX), a monoclonal antibody has also been used in paediatric patients with steroid dependent MCD. While some studies in pediatrics have shown that both the reduction and withdrawal of steroids was observed with RTX keeping the relapse rate lower but the incidence of relapse in adult onset MCD is relatively unclear.[13,14]

As discussed above the treatment strategies for adult with steroid dependent MCD are used without any clear recommendations and the use of immunosuppressive agents are uncertain in steroid resistant and frequently relapsing cases. The study was therefore planned to determine the efficacy of RTX versus CTX in the treatment of steroid dependent MCD in terms of incidence of relapse in adult population of Islamabad, Pakistan. The results of this study will help our clinicians to opt for evidence-based treatment plan for these patients.

METHODS

This Randomized controlled trial was conducted at the Department of General Medicine, PAF Hospital, Islamabad, Pakistan from November 2022 to April 2024, over a period of 18 months. Approval of conducting the study was received from the ethical committee of the hospital (4/10/22).

The sample size calculation was performed with a significance level (α\alpha$\alpha) of 5% (two-sided) and a statistical power of 90%. The expected percentages in the two populations were p_1=84.6% (patients becoming drug free in RTX group) and p_2 =37.5% (patients becoming drug free in CTX group). Based on these assumptions, the estimated sample size required for each group was 21 participants.[15]

A total of 60 patients' ≥ 18 years of age with steroid dependent MCD were included in the study through consecutive sampling. Patients were randomized into 2 groups of 30 patients each using block randomization to ensure balanced allocation of participants to each group.

Inclusion Criteria

Patients' ≥ 18 years of age with steroid dependent MCD who had previously received only CS and no other immunosuppressant were included in this study.

Diagnosis was confirmed by renal biopsy with normal light microscopy and fulfilling the criteria of nephrotic syndrome.[16]

Exclusion Criteria

Patients with secondary causes of MCD like cancers or infections, steroid dependence, frequent relapses and patients with focal segmental glomerulosclerosis.

Potential confounding factors included secondary causes of MCD, which were addressed through the

exclusion criteria. Block randomization was used to ensure balanced allocation and minimize potential confounding variables between groups.

In the RTX group, patients were given rituximab as two doses of 1000 mg two weeks apart, while in the CTX group, oral cyclophosphamide was given in a dose of 2-2.5mg/kg/d for 8 weeks. CS were allowed to be continued as subsequent therapy.

Primary outcome was set as overall incidence of relapse (Including disease progression, on-drug relapse and off-drug relapse), steroid withdrawal and patient being drug-free at the last follow up visit at the end of 15 months period.

A relapse during the tapering or within 2 weeks of discontinuation of steroid was declared as steroid dependence. Definition of steroid resistance, partial remission and complete remission was set as per the guidelines. After the initial response ≥2 relapses within 6-month period or ≥ 4 relapses within 12 months were declared as frequent relapses. In the CTX group, any progression of disease after 6 months was taken as non-response to treatment.[16]

Measurement of 24 hours urinary protein was done to quantify proteinuria. All the laboratory measurements were noted down at baseline, at any report of relapse and at final follow up visit.

Statistical analysis was performed using SPSS version 25.0, employing descriptive and inferential statistical methods. Continuous variables were presented as mean and standard deviation or median with interquartile range, depending on their distribution, which was assessed using the Shapiro-Wilk test. Categorical variables were presented in shape of frequencies and percentages. Group comparisons utilized independent t-tests for normally distributed continuous variables and Mann-Whitney U tests for non-normally distributed data. Categorical variables were analyzed using chi-square or Fisher's exact tests. A p-value <0.05 was considered statistically significant.

RESULTS

Age range in this study was 18-68 years with mean age of 41.11±13.5 years and male gender was dominant (55%) in overall study population. Details of clinical characteristics and laboratory investigations in both groups are shown in Table-I.

The achievement of primary outcomes at the final follow-up visit shows better efficacy in RTX group compared to CTX group in shape of less number of patients suffering from relapse, more patients able to have steroid withdrawal, and becoming drug free, as given in Table-II.

TABLE-I

Clinical Characteristics and Laboratory Investigations. n=60

Clinical & Lab. Findings		RTX Group (n=30)	CTX Group (n=30)
Hypertension n (%)		17 (56.55)	16(53.33)
Systolic BP mm HG(Mean±SD)		123±16	121.8±16.35
Diastolic BP mm Hg (Mean±SD)		79.86±9	80.53±9.76
Other Therapies	RAAS I n (%)	13 (43.33)	19 (63.33)
	Statins n (%)	11 (36.66)	16 (53.33)
	Furosemide n (%)	30 (100)	30 (100)
Previous Response on glucocorticoids	Complete Remission n (%)	25 (16.66)	27 (90)
	Partial Remission n (%)	5 (16.66)	3 (10)
Urine protein (g/day)		17.8±4.58	18.56±3.64
Serum Creatinine (mg/dl)		1.21±0.53	1.22±0.48

TABLE-II

Patient's outcome at the final visit n=60

Variables	RTX Group (n=30)	CTX Group (n=30)	Chi-Square Value	P-Value*
Relapse n (%)	12 (40)	21 (70)	5.46	0.02
Steroid withdrawal n (%)	27 (90)	16 (53.33)	9.93	0.002
Drug Free at completion of study n (%)	27 (90)	12 (40)	16.84	<0.0001

* McNemar Chi-Square test

DISCUSSION

The mean age in this study was 41.11±13.5 years. The male gender was in majority compared to females in overall study population (55% Vs 45% respectively). The results of primary outcomes of our study showed that the incidence of relapse was significantly lower in RTX group compared to CTX group (40% Vs 70% respectively, p-value =0.02).

A study by Ruggenenti P et al conducted in 2014 also reported a decreased number of relapses by (from 88 to 22) with RTX administration in one year period (P<0.001).[17] Munyentwali H et al. conducted a retrospective study in Nice, France, and analyzed 17 patients with steroid-dependent, frequently relapsing MCD. Over a mean follow-up period of 26.7 months, their findings demonstrated a significant reduction in annual relapse rates among patients treated with RTX group compared to the non-RTX group (20% versus 57%, respectively).[18] Janardan J in a clinical case report shared that an adult female patient of MCD who was initially non-responsive to steroid and then to CTX responded to two doses of RTX (500mg each) rapidly within 1 month. This remission was sustained over a long term follow up of up to 32 months period.[19] Heybeli et al. conducted a study in 2021 with 76 adult MCD patients and showed superior outcomes with RTX compared to CTX with fewer relapses (6 Vs 11 patients respectively), longer time to relapse (66 Vs 44 months respectively), and no disease progression in the RTX group compared to 3 cases in the CTX group.[15] In a prospective study conducted in India by Ramachandran R, 11 patients with steroid dependent/resistant MCD who were treated with RTX were in complete remission after 12 months.[20] A review by Gauckler P discussing the role of RTX in adult MCD shared that long term follow up proves a relapse free survival with RTX in adults with steroid dependent MCD.[21] In a recent study by Sun Y et al with 21 MCD patients, 90.48% achieved complete remission (median time: 4 weeks). RTX monotherapy showed 88.89% remission (3 weeks), RTX with low-dose glucocorticoids achieved 75% remission (4 weeks), while RTX with adequate-dose glucocorticoids demonstrated optimal results with 100% remission (3.5 weeks).[22]

The results of the study also revealed that significantly more number of patients had steroid withdrawal in RTX group compared to CTX group (90% Vs 53.33%, p-value=0.002). Similarly, significantly more number of patients were able to become drug free in group-A compared to Group-B (90% Vs 40%, p-value <0.0001). Similar results regarding steroid withdrawal were also reported in the studies conducted by Ruggenenti P et al. with statistically significant reduction in steroid dose in all patients including adults over 1 year period.[17] Munyentwali H et al. also reported that out of 11 patients, 9 successfully discontinued both steroids and immunosuppressants.[18] Discontinuation of steroid was also reported by Heybeli et al. in 92.3% patients in the RTX group while in 62.5% in CTX group. At the last follow up visit 84.6% of the patients in RTX group were drug free while this was observed in 37.5% patients in CTX group.[15]

In a study of 16 patients conducted by Bruchfeld A et al., MCD treated with a combination therapy of steroid and RTX, reported a complete remission in 13 patients, hence the tapering off or discontinuation of corticosteroid was possible. After a median of 44 months follow up relapse was reported in 7 patients while 4 patients responded to RTX re-administration.[23]

The findings of our study are aligned with those of previous researches discussed above for the treatment of adult patients with steroid dependent MCD and supports the evidence that RTX reduces the relapse rates and allows the steroid withdrawal. Treatment with RTX was also able to make these patients not only steroid free but also drug free.

The major limitation of this study is small number of patients and short follow up period. Future prospective studies with larger number of patients and longer follow up duration, therefore, will be helpful to suggest more evidence-based treatment strategies.

CONCLUSION

MCD in adults is a frequently relapsing disease despite the treatment strategy employed, including glucocorticoids and immunosuppressive agents. RTX is more effective in reducing the incidence of relapse in adults with steroid dependent MCD

compared to CTX and helps in making these patients drug free. The results of this study are useful and suggest evidence based treatment strategies for adult patients with steroid dependent MCD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Ayesha Salim:** Manuscript writing.
2	**Muhammad Tahir:** Critical review.
3	**Muhammad Zuhair Tahir:** Acquisition, analysis.
4	**Muhammad Zubair Tahir:** Design.
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6	**Hifza Shahid:** Interpretation of data.

https://doi.org/10.29309/TPMJ/2026.33.02.9183 www.theprofesional.com

ORIGINAL ARTICLE

Diagnostic accuracy of alpha-fetoprotein at various cut-off levels in hepatocellular carcinoma: A study in a tertiary health care centre, Peshawar.

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ABSTRACT… Objective: To evaluate the diagnostic accuracy of alpha-fetoprotein (AFP) at various cutoff levels in detecting hepatocellular carcinoma (HCC) and to determine the optimal AFP value for HCC diagnosis. **Study Design:** Cross-sectional study. **Setting:** Department of Interventional Radiology, Rehman Medial Institute. **Period:** May 2016 to Dec 2023. **Methods:** Utilising a dataset of 882 participants, among whom 707 were HCC positive and 175 HCC negative. The values obtained from the AFP measurements were classified into several ranges. Effectiveness of diagnostic test at various AFP cut-off points (10µg/L, 20µg/L, 100µg/L and 200µg/L) were calculated in terms of sensitivity, specificity and positive and negative predictive values. **Results:** The best sensitivity of 79.5% was obtained through the use of an AFP threshold of ≥10 ng/mL. However, this resulted in the true negative rate of 21.7%. The most sensitive cut-off value was ≥100 ng/mL for 84.2%, and the highest specificity and PPV was obtained in the cut-off at ≥200 ng/mL for 97.1% and 95.4%, respectively. This is because the AFP accuracy is not constant and varies from level, therefore, should be used in combination with other diagnostic tools. **Conclusion:** It was found that the diagnostic accuracy of AFP is different with different cut-off levels which make it appropriate for either screening or confirming diagnosis in different ways. The low cut-offs are suitable for screening, whereas the high cut-offs fit the purposes of diagnosis confirmation. Studying the correlations and combination of AFP with other diagnostic biomarkers and imaging modalities should be the direction of future studies for HCC diagnostic models.

Key words: Alpha-fetoprotein, Biomarkers, Diagnostic Accuracy, Hepatocellular Carcinoma.

Article Citation: Abdullah M, Khan AN, Umer US, Khan MK, Safi A. Diagnostic accuracy of alpha-fetoprotein at various cut-off levels in hepatocellular carcinoma: A study in a tertiary health care centre, Peshawar. Professional Med J 2026; 33(02):265-272. https://doi.org/10.29309/TPMJ/2026.33.02.9183

INTRODUCTION

HCC is the most common subtype of primary liver cancer, and it burdens comprehensive morbidity and mortality around the world.[1] The disease ranks fourth in the world for cancers and is one of the deadliest cancers for all patients with cancers.[2] HCC is not uniformly spread around the world; the highest incidences of HCC are found in countries with high prevalence of hepatitis B and C, such as Sub-Saharan Africa and East Asia.[3] Mostly, the reasons are associated with chronic liver diseases such as cirrhosis due to viral hepatitis, alcohol, or non-alcoholic fatty liver disease (NAFLD).[4] Despite the development of new technologies in medical sciences and clinic medicine, the outlook for HCC till the present moment remains rather grim mainly because of the gap between the time of diagnosis and the optimal moment for treatment and the complex organology of liver tissue.[5]

HCC is not easy to diagnose and there are many factors that contribute to it.[6] The first signs of HCC are often nonspecific and may not be manifested at all in early-stage disease, while the manifestation of symptoms most often occurs in the later stages of tumor progression, thereby complicating the treatment outcomes.[7] The existing diagnostic tools include imaging tests including ultra sound, CT scan, MRI scan, and liver biopsy.[8] However, it is essential to note some of the limitations of the above methods. Imaging procedures although are less invasive and can give complete image of the liver but can miss tiny nodules whereas liver biopsy, which is invasive and the gold standard, has complications including bleeding and can give a skewed picture if the biopsy sample is taken from an abnormal area of the liver.[9]

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Article received on:
20/02/2025
Accepted for publication:
27/08/2025

As a result, the identification of accurate, minimally invasive molecular signatures that would allow for quicker identification and assessment of HCC progression is imperative.[10] AFP is a glycoprotein generated by the fetal liver and has been found to be useful and investigated widely as a marker for HCC.[11] The abnormal levels of the factor AFP in adults can be a sign of liver malignancy, that is why this factor is important in using the diagnostics of HCC.[12] Nevertheless, the performance of AFP in its diagnostic ability has remained inconclusive because of the fluctuations of sensitivity and specificity found at the various cut-off points.[13] Even though AFP testing is easily done and inexpensive, the performance of AFP testing rises problems involving existence of False positive/False negative results that should be improved by finding the best cut-off values of diagnosing cancerous cells accurately. It is within this context that this research seeks to bridge the existing knowledge on the diagnostic efficiency of AFP at different cut-off points to optimise screening and management of HCC.[14] However, in fetal life, the role of AFP is similar to that of albumin because the protein is involved in the transportation of several substances such as metals, fatty acids and bilirubin.[11] It also has an immunosuppressive effect, whereby it is used to shield the fetus from the mother's immune system. Consequently, AFP levels decrease steadily and are generally undetectable in adults whose baby is otherwise healthy. It is, therefore, possible to infer that 'high' levels of AFP in adults can be associated with pathological conditions, especially those involving the liver.

AFP has been considered to be useful as a biomarker for HCC due to its higher level in most patients with this cancer.[11] The use of AFP in HCC diagnosis is well founded as hepatoma cells are known to produce this fetal protein which is not normally seen in adult livers.[15] Conventionally, AFP testing has been regarded as one of the most widely applied blood tests for patients with a probable liver cancer. Its role is important especially in the areas where Liver cancer is common and where application of advanced imaging techniques might not be readily available.[16] The advantage of using AFP as a biomarker is therefore based on the non-invasive approach, ability to measure it and the relatively cheap method of diagnosis compared to other modalities.

Even though AFP is known to be a reliable marker for various cancer types, the current literature is still inconclusive about the diagnostic performance of the test. It should be noted that AFP can be raised in conditions other than liver cancer such as chronic hepatitis and cirrhosis, acute hepatitis, and other liver diseases, leading to false positive results.[17] On the same note, not all HCC patients have problematic AFP levels and this often leads to false negative results. This shows that AFP is very sensitive and specific when used as a diagnostic marker but this is highly dependent on the upper and lower normal levels used in analysing the results. By using a low cut-off, the test has increased sensitivity but decreased specificity, while the high cut-off improves the specificity but has decreased sensitivity. These findings highlight the usefulness of AFP levels as a qualifier in specific situations and the importance of combining it with other tests.

The developments in HCC research in the last recent has also demonstrated that there is a possibility of adding some other biomarkers and imaging to improve the diagnosis rates of the disease besides use of AFP. This is because additional protein of AFP that has been modified by the deletion of gamma carboxy prothrombin or that has been bound with lens culinaris agglutinin is useful in increasing the specificity and sensitivity of the disease detection.[18] The current study seeks to replicate and extend earlier findings on the diagnostic psychometric properties of AFP when used at different cut-off values in a clinical setting and, thus, identify theoretical and practical enhancements for integrating it in screening for HCC.

METHODS

The present study utilizes a cross-sectional research design to determine the diagnostic likelihood of AFP at different cut points in HCC. This study was done in interventional radiology department of Reham Medical Institute after approval from ethical committee (RMI/RMI-REC/Article Approval/118/04-7-24), Peshawar form May 2016 to Dec 2023. The study sample comprises a total of 882 participants: 707 patients with confirmed

HCC, 175 patients without HCC. These patients were selected based on medical records from our HMIS (health Management information system) and PACS (Picture archiving and communication system). A total of 882 patients were enrolled in the study because they all had undergone AFP testing in the context of liver diseases. HCC diagnosis was made through typical imaging features on computed tomography (CT) and magnetic resonance imaging (MRI) with supporting tumor markers. In patients whose imaging features were inconclusive then ultrasound guided biopsy with histopathological analysis done. The conditions included non-malignant liver diseases in patients with non-HCC cancer being ruled out during follow-up tests. Moreover, serum concentrations of the AFP were determined by enzyme immunoassay, which is a reliable, sensitive and specific technique for assessment of AFP levels as used in this study. Furthermore, to evaluate the performance of the density of AFP at different cutoff points, different statistical measures like sensitivity that measures the ability of the density of AFP to identify actual HCC patients, specificity that measures the ability of the density of AFP to identify actual non-HCC patients, positive predictive value that estimates the probability of HCC in patients with a positive test result, negative predictive value that estimates the probability of no HCC in patients with a negative test.

These metrics were evaluated at four specific AFP cutoff levels: 10 nanograms per milliliter, 20 nanograms per milliliter, 100 nanograms per milliliter, 200 nanograms per milliliter. The conventional formulas were used to compute the sensitivity and specificity:

- Sensitivity = (True Positives) / (True Positives + False Negatives)
- Specificity = (True Negatives) / (True Negatives + False Positives)

While, the PPV and NPV were derived from the sensitivity, specificity, and the prevalence of HCC in the study population:

- PPV = (Sensitivity * Prevalence) / [(Sensitivity * Prevalence) + (1 - Specificity) * (1 - Prevalence)]
- NPV = [Specificity * (1 - Prevalence)] / [(Specificity * (1 - Prevalence)) + ((1 - Sensitivity) * Prevalence)]

We employed OpenAI's Chat GPT to help to improve the manuscript's coherence and clarity, within limitation of ethical standards. Lastly, the statistical investigations were performed with SPSS v27 software. For demographic data, the results were shown in frequency and percentage whereas for quantitative data, they used Mean and Standard Deviation. The diagnostic performance of each AFP cut-off level was also presented in tabular form, which displayed the true positive and true negative rates of each threshold depending on the preferred balance between sensitivity and specificity. This approach enables the development of a more elaborate recognition of AFP within the conceptualization of HCC and contribution in discovering the ideal cut-off points for a various setting.

RESULTS

AFP is a crucial biomarker in the diagnosis of HCC. This analysis is based on assessing the performance of AFP at different thresholds regarding the diagnosis of HCC and identification of the best AFP cut-off level for diagnosing it. From the dataset of 882 patients, 707 were diagnosed with HCC, and 175 were without HCC. The distribution of AFP levels among these patients is categorized into several ranges as depicted in the table 1 below.

TABLE-I

Distribution of AFP levels in diagnosis

AFP Level	Patients With HCC	Patients Without HCC
AFP < 10 ng/mL	145	137
AFP 11-20 ng/mL	51	9
AFP 21-40 ng/mL	52	9
AFP 41-100 ng/mL	67	5
AFP 101-400 ng/mL	102	8
AFP 401-2000 ng/mL	119	1
AFP > 2000 ng/mL	155	5

A sizeable subgroup of HCC patients even had AFP levels lower than 10 ng/mL, regarded as negative in the traditional sense. In total, only 145/707 of HCCs had AFP levels <10 ng/mL, which means that theoretically, about 20.5% of the assumed HCCs would not have been diagnosed when based only on AFP. At various cutoff points,

the diagnostic performance of AFP was assessed using the following metrics: sensitivity, specificity, (NPV), (PPV), and positive predictive value (NPV). 10 ng per millilitre, 20 ng per millilitre, 100 ng per millilitre, and 200 ng per millilitre are the cutoffs that were evaluated. AFP With a sensitivity of 79.5%, a threshold of 10 ng per millilitre can detect the majority of HCC patients. However, its low specificity (21.7%) indicates a high rate of false positives, making it less useful for definitive diagnosis without further confirmatory tests. While, AFP Cut-off of 20 ng/mL exhibits a moderate increase in specificity (43.4%) with a slight decrease in sensitivity (71.7%) suggests a better balance for screening purposes, but it still includes a considerable number of false positives. Similarly, AFP threshold of 100 ng/mL offers a much higher specificity (94.8%) and PPV (93.1%), indicating that patients with AFP levels above 100 ng/mL are very likely to have HCC. The sensitivity drops to 53.5%, indicating a higher risk of missing HCC cases with lower AFP levels. Lastly, AFP threshold of 200 ng/mL shows the highest specificity (97.1%) and PPV (95.4%) at this level make it highly reliable for confirming HCC diagnosis when AFP is elevated. However, the low sensitivity (39.0%) indicates that many HCC cases with AFP below 200 ng/mL would be missed. The result summary can be seen in the table 2 below;

TABLE-II

Evaluation of AFP cut off levels

AFP Level	AFP ≥ 10 ng/mL	AFP ≥ 20 ng/mL	AFP ≥ 100 ng/mL	AFP ≥ 200 ng/mL
Sensitivity	79.5%	71.7%	53.5%	39.0%
Specificity	21.7%	43.4%	94.8%	97.1%
PPV	68.5%	72.5%	93.1%	95.4%
NPV	30.9%	41.8%	61.3%	51.5%

In the context of other clinical factors such as status of Hepatitis B and C, HBV-positive patients showed higher AFP levels, aligning with the more aggressive tumor characteristics associated with HBV infection. Likewise, HCV-positive patients had a less pronounced correlation with elevated AFP levels, suggesting different mechanisms of AFP production in these infections. Furthermore, elevated bilirubin correlated with higher AFP levels, suggesting compromised liver function in more advanced HCC. While, lower serum albumin was associated with higher AFP levels, indicating poorer liver synthetic function in more aggressive HCC cases. In addition, elevated SGPT was often observed in HCC patients, reflecting liver cell damage and turnover. Moreover, higher Child-Pugh scores correlated with increased AFP levels, underscoring the link between liver cirrhosis severity and tumor aggressiveness. Similarly, as expected, higher ECOG scores correlated with a reduced survival rate, underscoring the role of general health status in HCC prognosis. Also, patients with high AFP levels had a very low life expectancy, showing that AFP is more of a prognostic marker.

In summary, the AFP cutoff for the diagnosis of HCC may also differ based on certain clinical contexts. However, lower screening levels (10–20 ng/mL) are applicable since they have a higher accuracy but at the same time have the disadvantage of possibly producing false positive results. While higher cutoffs (100–200 ng/mL) offer improved specificity and are more preferred in diagnosis than screening tests. Due to the rising number of patients with HCC and negative AFP levels, it should be noted that AFP cannot be relied on alone and should always be used in combination with other tests, such as imaging and biopsy, to enable accurate diagnosis and staging of HCC.

DISCUSSION

Our results on sensitivity and specificity of AFP at various cutoffs may be useful to understand the utility of this biomarker in HCC diagnosis. These findings are discussed in light of previous data indicating that AFP is a useful but not ideal serum biomarker of HCC. Variations in sensitivity and specificity coefficients of AFP reported by earlier workers are consistent with a relatively low discriminatory potential of this tumour marker when used singly. This study confirms these findings and highlights the concern that practice directions should be less black and white.

Our analysis displayed a sensitivity of 79.5% along with specificity of 21.7% in an AFP cutoff of 10 ng / mL, respectively. Although the rate of false positives is higher, AFP cutoffs with lower values provide higher sensitivity and are useful for screening,

according to Anwar et.al (2020).[19] The use of AFP in conjunction with other diagnostic instruments to improve accuracy was also noted.

Our sensitivity of 71.7% and specificity of 43.4% were achieved by adjusting the AFP cutoff to 20 ng / mL. Munir et.al (2021) found similar variation in AFP levels among Pakistani individuals, suggesting that moderate cutoffs may provide a more complete method for screening and diagnosis despite the risk of false positives.[20]

Our research found a rise in PPV (93.1 percent) and specificity (98.8 percent) in an AFP cutoff of 100 ng / mL along with a reduction in sensitivity (53.5 percent). This indicates that patients with higher than 100 ng / mL AFP are at increased risk for HCC. Khan et al. found similar associations between higher AFP levels and larger tumor sizes. (2022), which supports higher AFP cutoffs for more specific HCC diagnosis confirmation.[21]

We determined the highest PPV (95.4%) and specificity (97.1%) and lowest sensitivity (39%) at 200 ng / mL. Raised AFP levels have been described by Bajkani (2019) as a prognostic factor for HCC, especially in patients with chronic liver disease[22] Hence, our results suggest that high AFP cutoffs may be useful to confirm diagnoses and prognosis In more advanced cases.

Our study also identified a prognostic value for elevated AFP (> 200 ng / mL), which are associated with poorer survival. Shaikh et.al (2016) reported similar patterns, indicating that higher AFP levels are associated with higher mortality in HCC patients.[23] Bai et al. (2017) also explored the prognostic value of AFP levels, reporting that higher AFP levels at diagnosis are associated with worse pathological grades and poorer prognosis.[24]

In our study, intermediate AFP cutoffs (20-100 ng / mL) were found to be a good compromise between specificity and sensitivity that enhanced tumor detection without a high number of false positives. Sahbbir and others. both in 2019 and Laura et al. (2016) also found a correlation between HCC patients' AFP levels and tumor size and quantity, suggesting the utility of these intermediate cutoff levels for more precise tumor detection.[25,26]

Our study demonstrated that higher AFP levels are associated with more advanced disease stages and poorer liver function accompanied with elevated Child-Pugh scores and lower serum albumin. This supports the findings of Toader et al. (2019), who also noted elevated AFP levels in more aggressive tumor types, supporting AFP's significance as a marker of tumor aggressiveness and disease severity.[27]

Practical implications of the ROC curves representing the diagnostic reliability and accuracy of the test at different AFP thresholds are discussed. For example, AFP of 10 ng / mL may be sensitive but may not be appropriate for the distinction between normal and abnormal conditions due to its low specificity. This means patients may have to go through other processes that their conditions do not warrant and they become anxious as well. However in the very first round of triage where the aim is usually to identify as many HCC as possible, it can be useful, particularly for those in the community that are believed to be vulnerable to the illness. In contrast, at 200 ng / mL, its high specificity and positive predictive value establish the diagnosis of HCC.

The trade-off between the two factors when using different AFP cut-off levels should be considered. Cut offs of 10 ng / mL and 20 ng / mL are low for wishing high sensitivity to prevent HCC cases from being missed for confirmation at the cost of high specificity. Higher cut-offs such as 100 ng / mL or 200 ng / mL increase specificity, reducing false positive rates, and reducing sensitivity to possible true cases of HCC through consideration of client history and possible signs or symptoms, community prevalence rates, screening objectives rather than diagnostic goals. Lastly, because AFP is not as accurate as might be expected, its use in combination with other biomarkers or imaging studies may improve diagnostic outcome. Additionally, biomarkers such as des-gamma-carboxy prothrombin are as useful as imaging techniques such as ultrasound, CT or MRI, where an AFP level of 20 ng / mL together with features suggestive of altered imaging could improve diagnostic certainty without directly testing

with only this test.

Our research contributes to a global understanding of HCC epidemiology by revealing details about the diagnostic performance of AFP at different cutoffs and its pros and cons in different clinical settings. Toh et.al and Samant et al. (according to our results) claimed the value of biomarkers like AFP in the diagnosis & therapy of HCC.[28,29]

Gentile et.al (2017) found that greater combinations of AFP and additional markers improve diagnostic accuracy.[30] Hu et.al (2018) reported that neutrophil-to-lymphocyte ratio and AFP together confer additional diagnostic value[31] our results highlight the importance of combining AFP with other diagnostic modalities to increase accuracy and reliability when the study was limited to AFP.

We validate the combined use of AFP and imaging for accurate HCC diagnosis, and our data support this approach at higher AFP cutoffs where specificity is high, Abduljabbar (2023).[32]

Hanif et.al (2022) described the limitations of AFP as false positives and false negatives.[33] Our work underscores similar issues, with lower AFP cutoffs and the need for additional diagnostic methods to improve overall accuracy.

Finally Chang et.al. AFP measurement was promoted in cirrhosis patients' HCC surveillance, suggesting its utility for surveillance, especially at cutoff levels that compromise specificity / sensitivity.[34] This facilitates early detection and monitoring in high risk populations.

This study indicates that the diagnostic ability of AFP varies with different cut-off levels of AFP in HCC diagnosis. Low concentrations (10-20 ng / mL) provide high sensitivity and are used for first acting results with high rates of false-positives. Higher cut-off (100-200 ng / mL) provides greater specificity for diagnosis confirmation and miss of many HCC cases. These results indicate that current use of AFP as a screening tool is suitable when combined with imaging along with other biomarkers for better accuracy. The studies should involve the discovery of new biomarkers and better incorporation of newer diagnostic modalities to detect HCC earlier and to improve the survival of the patients. Clinicians should consider the trade off between sensitivity and specificity when using cut offs for AFP charting and adjust AFP threshold based on clinical context and patient characteristics.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Muhammad Abdullah:** Conception.
2	**Aman Nawaz Khan:** Design.
3	**Ummara Siddique Umer:** Acquisition of data.
4	**Muhammad Kamran Khan:** Analysis.
5	**Abdullah Safi:** Interpretation of data.

https://doi.org/10.29309/TPMJ/2026.33.02.8883 www.theprofesional.com

ORIGINAL ARTICLE

Frequency of fetomaternal complications among instrumental vaginal deliveries

Payal Davee[1], Falak Baloch[2], Pooja Seetlani[3], Zakir Ali[4]

ABSTRACT… Objective: To see the frequency of fetomaternal complications among women who have undergone instrumental vaginal deliveries. **Study Design:** Descriptive Cross-sectional study. **Setting:** Department of Gynaecology and Obstetrics Unit 2 in Civil Hospital Karachi. **Period:** 1st October 2020 to 30th March 2021. **Methods:** The sample size was calculated using OpenEpi version 3, which estimated a requirement of 94 participants with a 95% confidence interval and 5% confidence limit, based on a prevalence of 93.25%. Non-probability consecutive sampling was employed to recruit participants. **Results:** A total of 94 patients underwent instrumental vaginal deliveries. The average age of the patients was 25.98±4.52 years. The frequency of first-degree perineal tears was found to be 4.3% and second-degree perineal tears were also seen in 4.3% cases, while 3rd degree perineal tears were seen in 1.1% cases, and fourth degree tears were also found in 1.1% cases. The frequency of vaginal tears was 2.1% and cervical tears were seen in 3.2% cases. Retention of urine was observed in 2.1% of cases and postpartum haemorrhage was found in 4.3% cases. Paraurethral tears were observed in 1.1% cases, paravaginal hematoma and extension of episiotomy was observed in 0.3% and 10.6% respectively. As for the foetal complications, shoulder dystocia had occurred in 2.1%, cephalhematoma was seen in 3.2% babies and facial palsy in 1.1% however 17% babies were admitted to NICU. **Conclusion:** We conclude that Instrumental vaginal deliveries were found to be safer than caesarean section as they needed less expertise and had fewer chances of maternal morbidity. Forceps deliveries needed more skills and expertise to prevent maternal complications.

Key words: Cephalohematoma, Forceps Deliveries, Foetal Complications, Instrumental Vaginal Deliveries, Maternal Complication.

Article Citation: Davee P, Baloch F, Seetlani P, Ali Z. Frequency of fetomaternal complications among instrumental vaginal deliveries. Professional Med J 2026; 33(02):273-279. https://doi.org/10.29309/TPMJ/2026.33.02.8883

INTRODUCTION

Instrumental vaginal delivery refers to vaginal births that are associated with the assistance of forceps or a vacuum extractor.[1] In the United Kingdom, the rates of assisted vaginal delivery are around 10% to 15% and in the United States 4.5% while in India and Istanbul rates of 2.8% and 1.4% were seen.[2] The lowest rates of instrumental vaginal delivery (<5%) are observed in the Northeast, while the highest rates (20%-25%) are found in the South of the United States.[3] The overall complication rate is 17.3% (neonatal = 13.2%, maternal = 4.1%). The most common maternal complication was excessive bleeding after delivery (postpartum hemorrhage) (3.3%), which may be attributed to perineal tears, accounting for 62.5% of post-partum hemorrhage cases.[4] A study conducted in Pakistan in 2016 found that the most of the instrumental vaginal deliveries were carried out with the use of vacuum extraction. The incidence of instrumental vaginal births was 4.73%, with forceps delivery occurring in 6.75% of cases, while 93.25% of cases were delivered via vacuum extraction.[5] Maternal soft tissue trauma was more prevalent with forceps delivery compared to vacuum delivery.

Perineal tears of the first and second degree were noted in 4.25% of cases, while third- and fourth-degree perineal tears were seen in 0.75% cases. Vaginal and cervical tears were seen in (0.75%) cases. 0.75% of cases were complicated by retention of urine, while postpartum hemorrhage was found in 0.5% of cases. Paraurethral tears were observed in (0.25%) cases.[5] Fetal complications are more commonly associated with poor Apgar score at one minute, compared to the scores at five minutes.[5] In 98.25% of babies, the Apgar score at one minute was between 6 and 9, while in 1.75% of babies, it was between 2 and 5.[5]

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Article received on:
20/01/2025
Date of revision:
12/09/2025
Accepted for publication:
22/09/2025

The Apgar score at five minutes was between 8 and 9 in 93.25% of babies, and between 6 and 7 in 6.75% of babies.[5] Cephalhematoma was observed in 0.75% of babies, facial palsy in 1.5% babies, and 7.50% of babies were admitted to the neonatal unit.[5] A study done in Faisalabad in 2014 showed that shoulder dystocia occurs in 1.66% in forceps group 2.5% in vacuums group.[6] This finding correlates with results of research conducted by Caughey AB et al.[6,12,13]

The purpose of this study is to obtain insight into the scope of problem as there is very scanty data on this subject in our local population.[5] On extensive literature search only one study from Aga khan Hyderabad was done.[5] Moreover results of different studies have shown different results due to their different demographic features such as height, weight, so this is difficult to correlate our data with their data. So, to get further local evidence in this subject I have worked out to see the frequency of fetomaternal complications among instrumental vaginal deliveries. Results of this study will lead to reduction in maternal and fetal morbidity and mortality.

OBJECTIVE

To see the frequency of fetomaternal complications among instrumental vaginal delivery

METHODS

This descriptive cross-sectional study was conducted in the Department of Gynecology and Obstetrics, Unit 2, Civil Hospital Karachi, over a six-month period from 1st October 2020 to 30th March 2021. The sample size was calculated using OpenEpi version 3, which estimated a requirement of 94 participants with a 95% confidence interval and 5% confidence limit, based on a prevalence of 93.25%.[5] Non-probability consecutive sampling was employed to recruit participants.

Women aged 19–39 years who underwent instrumental vaginal deliveries, including vacuum or forceps-assisted deliveries, at a gestational age of over 34 weeks with a singleton pregnancy in cephalic presentation and longitudinal lie, and with parity one to three, were included in the study. Antenatal women with multiple pregnancies or preterm labor below 34 weeks of gestation were excluded, as these conditions are associated with higher fetomaternal complications.

The study was conducted following formal approval from the College of Physicians and Surgeons of Pakistan (Letter reference number: CPSP/REU/OBG-2018-183-8756) dated March 17, 2022. Data were collected from women meeting the inclusion criteria after obtaining informed consent. A pre-designed proforma was used to record maternal and fetal complications.

Maternal complications included perineal tears, defined as trauma to the perineal skin, muscles, and/or mucosa during vaginal childbirth, classified as first degree (skin and mucosa only), second degree (involving perineal muscles), third degree (involving the anal sphincter, assessed by digital rectal examination, and further subclassified as 3a <50% external sphincter, 3b >50% external sphincter, 3c internal sphincter involvement), and fourth degree (involving both sphincters and rectal mucosa). Cervical tears were diagnosed on speculum examination. Postpartum hemorrhage was defined as blood loss greater than 500 ml within 24 hours of delivery, measured by kidney tray and pad soakage. Paravaginal hematomas were diagnosed on vaginal, speculum, and rectal examination, supplemented by ultrasound, and categorized as supralevator (above levator ani, associated with cervical or fornix tears) or infralevator (below the broad ligament, around the vulva, perineum, or lower vagina).

Fetal complications included cephalohematoma (subperiosteal bleeding between skull and periosteum, assessed on scalp examination), scalp bruising (contusion due to rupture of subcutaneous vessels without breach of skin integrity), and shoulder dystocia, defined as failure to deliver the shoulders after head delivery despite gentle downward traction.

Data were processed and analyzed using IBM-SPSS (Version 22). Quantitative variables, including age, parity, and gestational age, were expressed as mean ± standard deviation (SD), while qualitative variables, including fetomaternal outcomes and types of instrumental vaginal deliveries, were presented

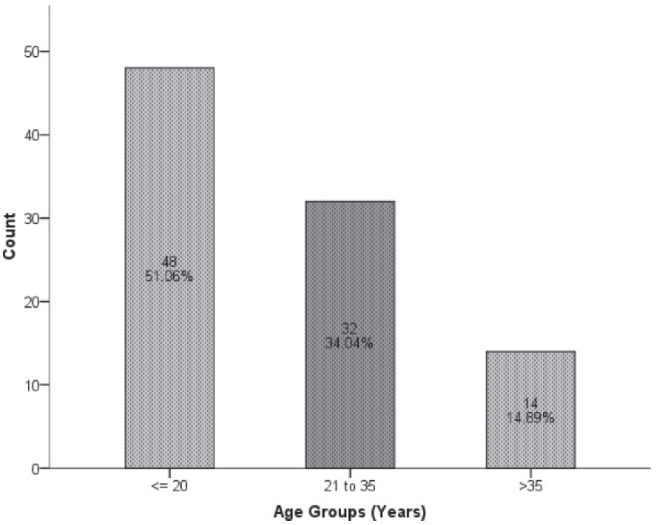
as frequencies and percentages. Potential effect modifiers such as age, parity, gestational age, and birth weight were managed through stratification. Post-stratification, the chi-square test and Fisher's exact test (for expected counts <5) were applied, with p-values <0.05 considered statistically significant.

RESULTS

A sum of 94 women who delivered via instrumental vaginal deliveries were included in the study. Most of the women 48 (51.06%) age were below and equal to 20 years, 32(34.04%) were 21-35 years old and 14(14.89%) were above 35 years old as shown in Figure-1.

FIGURE-1

The women age distribution (n=94)



The patients average age was 25.98±4.52 years. Mean gestational age was 36.83±1.31, and birth weight of the baby was 2.45±0.42 kg of baby as reported in Table-I.

Out of 94 instrument delivery, vacuum delivery was performed in 43(45.74%) cases and 51(54.26%) forceps as shown in Figure-2.

Extension of episiotomy was the most common maternal complication, occurring in ten patients (10.6%) among the 94 who underwent instrumental vaginal delivery. Para-vaginal hematoma was observed in five patients (5.3%), postpartum hemorrhage in four patients (4.3%), and cervical tears in three patients (3.2%). Vaginal tears and retention of urine were seen in two patients each (2.1%), while third- and fourth-degree tears and para-urethral tears occurred in one patient each (1.1%). First- and second-degree perineal tears were reported in four patients each (4.3%). Among the 94 neonates delivered via instrumental vaginal delivery, 16 infants (17%) required admission to the NICU. Cephalohematoma was observed in three neonates (3.2%), shoulder dystocia in two (2.1%), and both scalp bruising and facial palsy occurred in one neonate each (1.1%). The frequencies of fetal and maternal outcome complications among instrumental vaginal delivery are presented in figure 3 and 4 respectively.

TABLE-I

Patients demographic characteristics (n=94)

Variable	Mean 25.7	95% Confidence Interval		Standard Deviation
		Lower Bound	Upper Bound	
Age (years)	25.98	25.05	26.90	4.52
Gestational Age (weeks)	36.83	36.56	37.10	1.31
Parity	1.27	1.15	1.38	0.55
Fetal Weight (kg)	2.45	2.36	2.54	0.42

FIGURE-2

Instrumental vaginal delivery (n=94)

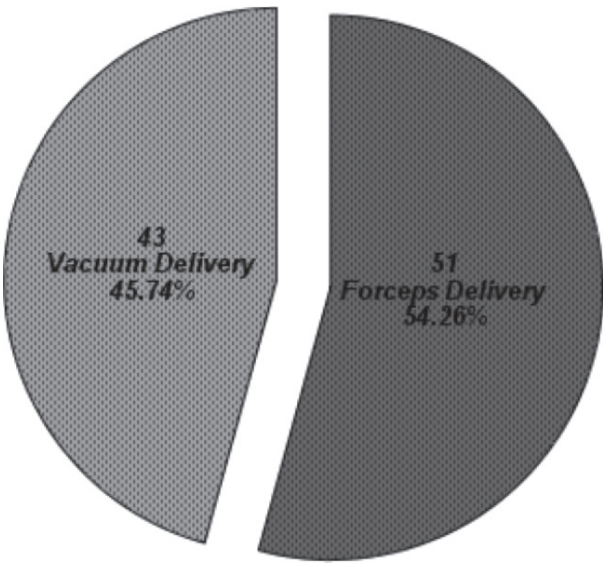


FIGURE-3

Frequency of maternal complications among instrumental vaginal delivery (n=94)

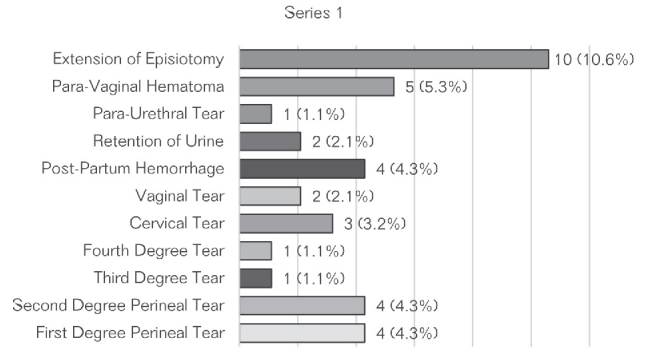
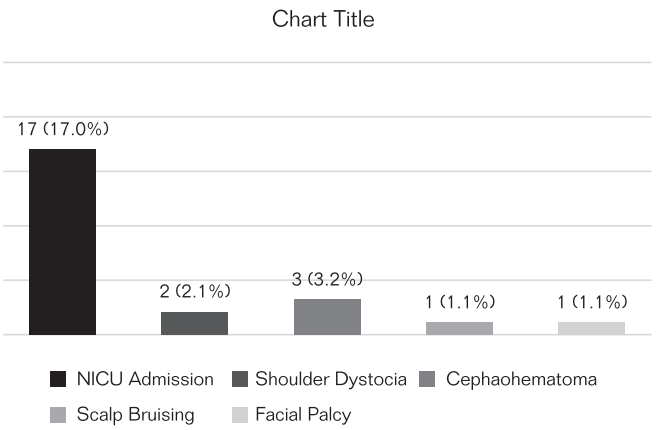


FIGURE-4

Frequency of fetal complications among instrumental vaginal delivery (n=94)



First- and second-degree perineal tears occurred in 4.3% of cases, while third- and fourth-degree perineal tears were observed in 1.1% cases. Vaginal and cervical tears seen in 2.1% and 3.2% cases. Urinary retention was observed in 2.1% cases and postpartum hemorrhage was found in 4.3% cases. Paraurethral tears were observed in 1.1% cases, paravaginal hematoma and extension of episiotomy was observed in 5.3% and 10.6% respectively (Figure-4). Fetal complications, shoulder dystocia occurred in 2.1% cephalhematoma was found in 3.2% babies and facial palsy in 1.1% however 17% babies were admitted to NICU. Stratification analysis was conducted and observed the rate of fetomaternal complications among age groups, gestational age, parity and birth weight as presented in 6 to 13 respectively. Rate of complications were not statistically significant among age groups, gestational age, parity and birth weight except NICU admission which was significantly high in low gestational age and low birth weight (<2.5kg) (p=0.0005).

DISCUSSION

Instrumental vaginal delivery involves the use of obstetric forceps or a vacuum extractor device to assist in the vaginal delivery of the fetus. Assisted vaginal deliveries are performed in cases of maternal or fetal conditions, or any event that may harm the mother or fetus, but can potentially be alleviated through intervention during the second stage of labor.[12,13] In developed countries, complications associated with assisted vaginal delivery are not very common, due to advancements in skills related to the administration of these procedures and the availability of adequate facilities and resources. However, in developing countries like Pakistan, both the mother and her newborn may experience varying degrees of morbidity and mortality as a result of instrumental delivery. Researchers reported that most of these problems can be avoided if early interventions are implemented.[14] While assisted vaginal delivery accounts for 1.5% of deliveries in some countries, the rate can be as high as 15% in others. The rates of instrumental vaginal delivery in the United Kingdom, range between 10% and 15%. The rates have remained relatively stable, although there has been a shift in the choice of instruments used.[15]

Few reported that forceps related fetal problems are seldom observed.[16] Fetal damage from vacuum-assisted delivery can range from minor to occasionally severe scalp injuries, including bruising, intracranial hemorrhage and subgaleal hematoma.[17] Maternal complications due to instrumental delivery can range from mild issues, such as vaginal and perineal lacerations, to more significant complications, including traumatic hemorrhage, bladder injury, and pelvic muscle damage.[18] To see the frequency of fetomaternal complications among instrumental vaginal delivery, total of 94 women, aged between19 to 39 years, delivered by instrumental vaginal deliveries were included in this study. In our study, most of the women 48(51.06%) age were below and equal to 20 years, 32(34.04%) were 21 to 35 years of age and 14(14.89%) were

above 35 years of age and the average patients age was 25.98±4.52 years. In a research study conducted in Chhattisgarh, India, the overall mean age was 23.81±3.6 years.[15] We found that out of 94 women, vacuum delivery was performed in 43 (45.74%) cases, while forceps was carried out in 51 (54.26%) cases, indicating that the most of the instrumental vaginal deliveries were conducted using obstetric forceps.

A similar rate of vacuum deliveries was observed in a study conducted at the Federal Teaching Hospital Abakaliki (FETHA)[19], but lower rates (1.7%) were reported in studies from Maiduguri and Lagos. The rate was reported as 3.1% in Benin City and 3.5% in Emug.[16,20] In developed countries, the preference for lower segment caesarean sections has resulted in a substantially lower rate of instrumental deliveries compared to developing countries. In our study, we found that primiparous mothers were approximately 3.5 times more likely to experience complications from instrumental deliveries compared to multiparous mothers. A possible explanation is that primigravid mothers are more likely to experience delays during the second stage of labor. Although the exact mechanism is not fully understood, primiparous women were found to have a higher risk for perineal injuries.[21] We observed in our study population, that the perineal tears were of same frequency in forceps and vacuum extraction i.e. 4.3% this observation is supported by other studies which showed that perineal damage had no difference between the two methods.[22,23]

Maternal morbidity associated with instrumental vaginal delivery included vaginal tears in 2.1%, cervical tears in 3.2%, and post-partum hemorrhage in 4.3% of cases. Para urethral tears were observed in 1.1% cases, paravaginal hematoma and extension of episiotomy was observed in 5.3% and 10.6% respectively. Weerasekera DS et al[24] also found that both vacuum and forceps deliveries are equally associated with cervical tears, perineal tears, and post-partum hemorrhage. Randomized clinical trials comparing forceps and vacuum, conducted by Fitzpatrick M, et al[25] found that extension of episiotomy and paravaginal hematoma were more common following forceps-assisted vaginal delivery. The study also identified vacuum as the preferred choice for assisted vaginal delivery. The Royal College of Obstetricians and Gynecologist (RCOG)[26] also recommends ventouse as the preferred instrument of choice for assisted vaginal delivery. Regarding rate of neonatal injuries related to instrumental vaginal deliveries we found, cephalohematoma has been more commonly associated with vacuum-assisted vaginal delivery compared to forceps delivery.[27,28]

In our cohort, the incidence of cephalhematoma was lower than previously reported (3.2% vs 15%)[29,30], which could be attributed to reporting bias. In majority of cases, cephalohematoma typically does not require treatment, although its reabsorption can lead to jaundice.[32,32] In our study, the incidence of shoulder dystocia was 2.1%, which is similar to the range reported in the literature (0.38-5.8 per 1000).[33] Some studies suggest that a birth weight greater than 4000g is independently associated with poor neonatal outcomes following instrumental vaginal deliveries.[31] However, in our study, the incidence of shoulder dystocia in instrumental vaginal deliveries was not influenced by birth weight. We found a significantly higher proportion of NICU admissions in instrumental deliveries, with a rate of 17%. The evidence on this matter is conflicting. Some studies conclude that neonates delivered via any surgical approach are at a higher risk of NICU admission[34], while others found that that forceps use was associated with higher rates of admissions of the newborns to the NICU compared to vacuum vaginal delivery.[35] Additionally, some studies argue that NICU admission should not be considered a predictor of newborn morbidity.[36]

However, we included NICU admission as a key variable in our study, as it leads to separation from the mother, which has been linked to challenges in breastfeeding. Murphy DG, et al[37] examined the effects of operative delivery in the second stage of labor on fetal morbidity and found that it was more commonly linked with the use of multiple instruments, increased manipulation, and greater operative experience.

CONCLUSION

In summary, instrumental deliveries appear safer than caesarean sections in terms of maternal

morbidity, though they require expertise to minimize risks, especially with forceps. While cesarean sections were linked to more maternal complications, instrumental deliveries carried higher risks of neonatal injury. Careful practice, timely interventions, and improved antenatal care can reduce these complications. Findings should be interpreted with caution due to the study's small sample size.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Falak Baloch:** Manuscript writing, Data collection.
2	**Payal Davee:** Final editing.
3	**Zakir Ali:** Data analysis.
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https://doi.org/10.29309/TPMJ/2026.33.02.9844 www.theprofesional.com

ORIGINAL ARTICLE

Obstacles and challenges encountered by undergraduate medical and dental students in pursuing research in a public sector university.

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ABSTRACT… Objective: To identify the common challenges obstructing undergraduate medical and dental students in pursuing research at Jinnah Sindh Medical University (JSMU), Karachi. **Study Design:** Cross-sectional survey. **Setting:** Jinnah Sindh Medical University. **Period:** October to December 2024. **Methods:** Study was conducted among 322 undergraduate medical and dental students from Sindh Medical College (SMC) and Sindh Institute of Oral Health Sciences (SIOHS). Data were collected through a structured questionnaire after informed consent. Descriptive statistics and chi-square tests were performed using SPSS v26. **Results:** Of the 322 participants, 64.9% were females and 27% had a GPA of 4.0. While most students (83.5%) expressed interest in research and 95.3% acknowledged its importance, only 55.6% had ever participated in a project, and just 15.8% had published their work. The most frequently reported barriers were lack of research skills (65.2%) and difficulty in selecting a topic (52.8%). No significant associations were observed between demographic variables and reported barriers. **Conclusion:** Despite positive attitudes toward research, undergraduate medical and dental students at JSMU face substantial challenges, particularly inadequate research skills and difficulties in topic selection. Universities should strengthen structured mentorship programs, provide research training workshops, and allocate institutional funding to foster a sustainable research culture in undergraduate education.

Key words: Dental, Goals, Medical, Mentoring, Motivation, Research Design, Students.

Article Citation: Shah H, Rizvi M, Irshad M, Ayoub D, Urooj I, Lakhani K. Obstacles and challenges encountered by undergraduate medical and dental students in pursuing research in a public sector university. Professional Med J 2026; 33(02):280-286. https://doi.org/10.29309/TPMJ/2026.33.02.9844

INTRODUCTION

Scientific research is a systematic study characterized by its approach to problem-solving such as evaluating the issue and is the catalyst in a community for its development and gauge of its growth.[1,2] There is a growing focus on scientific research across both under developed and developed nations as research in biomedical field can improve the outcome of care provided.[2] The importance of research is highlighted by the fact that the world's top seven science-producing nations are also the leading countries in terms of research facilities, whereas underdeveloped nations lag behind due to limited research opportunities and infrastructure.[3] According to a survey of 2007, established high income countries had 3655.8 researchers per meg individuals while just 580.3 in under developing countries.[4]

Research plays a vital role in the health care services by contributing in terms of advancement of medical equipment and development of new medicines and diagnostic tests. Previously published data supports the importance of conducting research during undergraduate medical education in securing a position in highly competitive residency programs.[5,6] Furthermore, studies have also shown that exposure to research and related activities early in their academics encourages them to choose academics as career.[7]

The initial step toward organizing research activities is gaining an accurate understanding of the available capabilities and facilities, as well as assessing the strengths and weaknesses of research plans. Recognizing shortcomings and identification of awareness of the quality and degree of achievement of research goals are among essential tools for research decision-makers. A significant indicators of the growth and development of the societies is the technological prowess and scientific research capacity, both of which may encounter

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Article received on:
16/05/2025
Date of revision:
18/09/2025
Accepted for publication:
22/09/2025

obstacles originating from economic, social, and cultural factors, which could potentially impede the progress.[8] Largely, most of the obstacles in pursuing medical researches experienced by students are known, that creates a demand for further study.[9] To resolve this shortcoming, it is essential to foster some characteristics during their academic journey including learner driven learning, problem solving skills, critical thinking, adapting the teaching approach to prioritize treatment planning and integrating research into the curriculum is of particular importance.[10,11]

Most of the medical students judged research as nerve-racking and complicated, they have just a little bit knowledge about any kind of medical research and very low-priority of practice according to a lot of reported studies.[12,13] In medical colleges, undergraduate participation in research is hindered by the inadequate assistance and guidance from the medical and dental school, economic challenges, intense workload, technique problems, disinterest and lack of knowledge, vast curriculum, lack of time and limited exposure to research methodology.[2,14-16] These challenges appear to be more prominent in developing nations.[15] When these students get into their post-graduation, their proficiency in writing protocols or proposals may not meet expectations.[2] In addition, not all students are native English speakers, so they face many problems in the process writing article.[17]

As universities constitute the primary scientific backbone of societies, it is the duty of the universities to undertake a significant portion of research endeavors. The responsibility within universities falls on both students and faculty members. Unfortunately, research findings indicate that many faculty members in developing countries allocate most of their time to educational activities. Hence the dearth of time for research activities.[1]

The majority of students expressed positive perception regarding three items; medical research's promotion of critical thinking, its potential to enhance career prospects, and enhancing knowledge. Additionally, as students' GPA increased, their perception of medical research improved. Among the identified barriers to participation by students from health sciences, "lack of allotted time for research" emerged as the most predominant barrier (80.3%) followed by "limited exposure and opportunities" (79.9%), "a lack of training and support" (78.3%), and a "lack of mentoring and guidance" (76.6%) according to research conducted in American University of Beirut.[18]

As the students have an important part in the development of a nation through their research and by conducting the medical research so it is necessary for medical students to know everything about the medical research so they can achieve the goal in their field as they will be the future's star.[17,18] Medical and dental students play an essential role in the advancement of healthcare through research. Despite this importance, there exists a notable gap regarding the obstacles and challenges that prevent them from actively participating in medical research. This study will help identify the knowledge gap that exists in the local context in the literature about the potential obstacles and challenges in pursuing medical research.

METHODS

A Cross-sectional study was completed at Jinnah Sindh Medical University (JSMU), Sindh Medical College (SMC) and Sindh Institute of Oral Health Sciences (SIOHS) Karachi, Pakistan from October 2024 to December 2024 after the approval of IRB of Jinnah Sindh Medical University (JSMU/IRB/2024/893 approved on 4th September 2024) and was conducted in accordance with the Declaration of Helsinki. The sample size was calculated by taking total number of undergraduate medical and dental student at JSMU (SMC and SIOHS) 1950 and maintaining a margin of error of 5% and a confidence level of 95%, a sample size of 322 is calculated using the reputable online calculator Open Epi.[19] Inclusion criteria was all undergraduate medical (1st, 2nd, 3rd, 4th and 5th year) and dental students (1st, 2nd, 3rand 4th year) of JSMU (SMC and SIOHS), regardless of whether they have previous experience in pursuing research from both genders were included. The teaching and non-teaching medical and dental faculty, non-consenting participants and house officers, residents and interns were excluded. Non-probability convenience sampling technique was utilized for data collection.

Data was using a modified self-administered, structured questionnaire. The questionnaire consisted of closed-ended questions divided into three sections. The first section of the questionnaire comprised of demographic information like age, sex, academic year, discipline (medical or dental) and GPA etc. The second section of the questionnaire comprised of attitude of students towards pursuing research. The last part will consist of obstacles and challenges in pursuing medical research experienced by undergraduate students. Likert scale was used for the second and third sections of the questionnaire. Further, the questionnaire pilot tested on 10 participants yielding good face validity and 0.7 Crohn Bach`s Alpha was also good.

The questionnaire was distributed among the students of JSMU (SMC and SIOHS) after obtaining consent from them. Researchers distributed a hard copy of questionnaire among participants before a lecture in which they were informed about the aims and objectives of the study and how to fill the questionnaire after signing the consent. Data was entered and analyzed using SPSS v26.0 (IBM Corp, Armonk, NY, USA). and incomplete forms were removed as part of protocol. Personal information was coded, and raw data remained with the principal investigator.

RESULTS

The descriptive analysis of the participants (n = 322) provides insights into their demographic and academic characteristics. The age distribution shows that most participants were between 20 to 22 years old, with 22.7% (n = 73) being 21 years old, followed by 22.0% (n = 71) aged 20 years. The age range extended from 18 to 25 years, with only 0.9% (n = 3) of participants being 25 years old. In terms of gender, most participants were females, accounting for 64.9% (n = 209), while males made up 35.1% (n = 113). Regarding the academic institute, the majority (84.5%, n = 272) were from SMC, with only 15.5% (n = 50) from SIOHS.

The academic year distribution was relatively balanced, with the highest proportion of participants in the 4th year (21.4%, n = 69) and the lowest in the 5th year (16.8%, n = 54). For GPA/cGPA, a significant proportion of participants (27%, n = 87) had a GPA of 4.0. Other notable GPA ranges included 3.50, held by 7.5% (n = 24), and 3.70, reported by 6.5% (n = 21). The participants with GPAs between 2.0-2.9 were minimal, making up only 0.3% (n = 1). Overall, most of the sample exhibited strong academic performance. The final data was checked for normalcy before applying statistical tests, and it showed deviation from the "normal".

In Table-I summarizes students' attitudes toward research based on their responses. Chi-square test was used; $p<0.05$ was considered statistically significant. Data were analyzed using SPSS v26.0 (IBM Corp, Armonk, NY, USA).Overall, students showed strong interest in and recognition of research's importance, but participation and success in research activities are lower, indicating a need for more support and opportunities.

Table-II The data presents student experiences regarding research across two institutes (SIOHS and SMC) with a total of 322 responses. Chi-square test was used; $p<0.05$ was considered statistically significant. The responses Strongly agreed and agreed are summarized as "agree" and strongly disagree and disagree as "disagree" to simplify the data. The Pearson chi-square value was non-significant for all the items. Only 2 items showed more than 50% responses of the participants from both colleges having 2 similar problems that is lacking in research skill (SIOHS=38, SMC=171) and selecting topic for research (SIOHS=30, SMC=140).

DISCUSSION

The current study provides valuable insights into the demographic and academic characteristics of medical and dental students and their attitudes toward research. The descriptive analysis reveals that most of the participants were between 20 and 22 years old, with a significant proportion being female (64.9%). Additionally, the academic performance of the sample was generally strong, with a notable number of students achieving a GPA of 4.0. However, despite their academic success, the findings show that students face several barriers when it comes to research participation.

TABLE-I

Attitudes of students regarding Research

S No.	Item	Response	
		Yes	No
1	Do you have an interest in doing research?	269	53
2	Do you think undergraduate students should take part in research?	286	36
3	Do you believe in the importance of medical research?	307	15
4	Have you ever attended a research session?	188	134
5	Have you ever participated in any research?	179	143
6	Did you publish it?	51	271
7	Did you get awarded for your research?	11	311
8	Do you have a plan to continue research after graduation?	258	64

TABLE-II

Responses of Student's regarding their Experience from Both Institutes.

Item	Response N=322	SIOHS	SMC	Pearson-Chi Square
I lack interest in pursuing research	Agree Disagree	16(4.96%) 21(6.52%)	73(22.6%) 86(26.7%)	.613
I lack opportunities to conduct research	Agree Disagree	20(6.2%) 16(4.96%)	109(33.8%) 105(32.6%)	.263
I lack knowledge/skill in conducting research	Agree Disagree	38(11.8%) 0(0%)	171(53.1%) 0(0%)	0.627
I have lack of time due to overburden of studies	Agree Disagree	20(6.2%) 11(3.4%)	86(26.7%) 120(37.3%)	0.151
I am bit short of finance	Agree Disagree	20(6.2%) 13(4%)	154(47.8%) 47(14.6%)	.114
I have lack of mentoring	Agree Disagree	20(6.2%) 13(4%)	154(47.8%) 47(14.6%)	0.298
I find it difficult to choose topic	Agree Disagree	30(9.3%) 9(2.79%)	140(43.5%) 57(17.7%)	0.343
I find it difficult to write a proposal	Agree Disagree	23(7.14%) 11(3.4%)	107(%) 92(28.6%)	0.381
I find it difficult to get ethical permission	Agree Disagree	14(4.34%) 20(6.2%)	81(25.1%) 99(30.7%)	0.500
I find it difficult to collect data	Agree Disagree	17(5.3%) 18(5.6%)	116(36%) 94(29%)	0.685
I find it difficult to analyze data	Agree Disagree	23(7.1%) 10(3.1%)	101(31.4%) 87(27%)	0.424
There is inaccessibility to relevant medical & other electronic databases	Agree Disagree	20(6.2%) 18(5.59%)	115(35.7%) 85(26.4%)	0.779
There is inefficient faculty staff to deliver necessary knowledge & skills in the institute	Agree Disagree	19(5.9%) 20(6.2%)	187(58%) 59(18.3%)	0.065
I am awarded for my work	Agree Disagree	4(1.24%) 31(9.6%)	26(8.1%) 140(32.3%)	0.641

*Value significant up to the level of 0.05, "Value significant up to the level of 0.001.

One of the most prominent barriers identified in this study is a "lack of research skills", which was reported by a majority of participants (SIOHS=38, SMC=171). This finding aligns with previous studies, such as Chellaiyan et al. and Soe et al.(72.1% of Malaysian students) , where inadequate knowledge and skills were highlighted as significant obstacles.[4,5] Similarly, Dadipoor et al. in 2019 reported that students in Iran also struggled with insufficient research skills, suggesting this is a widespread issue that transcends regional boundaries.[1]

Another key issue identified in both studies is the "challenge of time management".[4,5] In our study, students cited academic responsibilities as a major obstacle to engaging in research, consistent with the findings of Dadipoor et al., Soe et al., and Ibrahim et al.[1,4,7] Time constraints are consistently reported as a significant barrier across multiple regions, from Egypt to Malaysia. This highlights the need for better time management training and institutional support to enable students to balance their academic workloads with research activities.

The "lack of mentorship" also emerged as a crucial barrier in this study. Students from both SIOHS and SMC indicated that insufficient guidance from experienced researchers hindered their ability to participate in research. This is consistent with findings from El Achi et al., who reported that the absence of proper mentoring significantly limited students' research engagement.[10] Similar findings were observed in studies conducted by Turk et al.and Alhabib et al., suggesting that mentorship is a critical factor in enabling students to succeed in research.[3,8]

In addition to skill-related and mentorship barriers, "organizational constraints" were reported by the participants. Students indicated that difficulties in accessing research resources, such as databases and institutional support, were major obstacles. This issue is not unique to this study, as Assar et al. and Safdari et al. also identified organizational barriers as significant challenges for students and faculty alike.[2,6] Addressing these infrastructural issues is essential for promoting student involvement in research across institutions.

While most students acknowledged the importance of research, the study revealed a "lack of enthusiasm" among some participants, with a portion expressing disinterest in pursuing research. This finding is in line with Alhabib et al., where 14.7% of students were not involved in research due to lack of interest.[8] However, the literature also suggests that fostering a positive attitude towards research, as seen in the studies by Turk et al. and El Achi et al., can significantly enhance student participation.[3,10]

Finally, "incentives and motivators" such as career prospects and academic benefits were identified as key drivers for research participation in both this and previous studies. Alhabib et al. found that career advancement, particularly residency admission, was a strong motivator for students to engage in research, which was also supported by the current study's findings. The findings illustrate the importance of trained faculty with designated time for conducting research and funds allocation by the institute to support the researchers. Adding them as weighted part of the curriculum is another strategy that was recently done by Pakistan Medical and Dental Council, research is added as longitudinal theme in both medical and dental curriculum which is assessed by theory paper and publication of the research.[20] Since, importance of research in recent years have remarkably increased in all fields of life sciences hence, more efforts should be made to support students to have the relevant knowledge and skills.

CONCLUSION

This study identified the common challenges that obstruct undergraduate medical and dental students at JSMU from pursuing research. While students recognize the importance of research and express strong interest in engaging with it, their participation is hindered by limited skills, inadequate mentorship, and difficulties in selecting suitable topics. These barriers are consistent with global trends, indicating that challenges in undergraduate research are not unique to Pakistan. Addressing these obstacles requires universities to integrate structured research training into the curriculum, establish dedicated mentorship systems, and ensure access to resources and funding. Such institutional support

is essential for fostering a research-oriented culture and preparing future healthcare professionals to actively contribute to evidence-based practice and academic scholarship.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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1	**Hina Shah:** Designing of study, data analysis, manuscript writing.
2	**Mohsin Rizvi:** Basic idea, writing.
3	**Marium Irshad:** Manuscript draft.
4	**Dua Ayoub:** Drafting of tables.
5	**Ifra Urooj:** Questionnair.
6	**Karina Lakhani:** Data collection.

https://doi.org/10.29309/TPMJ/2026.33.02.9820 www.theprofesional.com

ORIGINAL ARTICLE

Smartphone use and its relationship with addiction, depression, and anxiety among undergraduate medical students in Nawabshah, Pakistan: A cross-sectional study.

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ABSTRACT… Objective: 1. To investigate smartphone use and severity of addiction, anxiety and depression. 2. To find out the relationship between smartphone use with addiction, anxiety and depression. **Study Design:** Cross-sectional study. **Setting:** At MBBS and Allied (DPT, Pharmaceutical Sciences, Public Health & Nursing) Departments of Peoples University of Health Sciences for Women, Shaheed Benazirabad, Pakistan. **Period:** from August 2023 to January 2024. **Methods:** Among undergraduate medical students aged 18 to 25 the study's sample size was 350, and a multistage random sampling technique was used to select the participants from the Peoples University of Medical and Health Sciences for Women. After approval by the institution, data were collected from the medical students using validated tools, including smartphone addiction (SAS scale), depression (PHQ-9), and anxiety (GAD-7). The data were analyzed using SPSS software version 25. A chi-square test was used to identify the association between smartphone usage and addiction, depression, and anxiety, and a p-value of <0.05 was considered statistically significant. **Results:** The findings revealed that half the students (49.7%) spent more than 6 hours per day on their mobile screens. (49.1%) of medical students reported having a high prevalence of smartphone addiction, (48.6%) reported having moderate to severe depression, and (55.8%) reported having moderate to severe anxiety. Addiction, depression, and anxiety scores were higher among the excessive smartphone use group than in the low smartphone users. A statistically positive association was found between smartphone usage and the addiction level, depression level, and anxiety level scores. **Conclusion:** This study highlights the overdependence on smartphones among medical students and the positive association between smartphone usage and mental health outcomes like addiction, anxiety and depression among PUMHSW medical students in Pakistan. Excessive screen time can impact students' academic performance, sleep quality, and eating behaviors.

Key words: Anxiety, Depression, Medical Students, Smartphone Usage, Smartphone Addiction, Undergraduate.

Article Citation: Mirbahar I, Saleem A, Anis F, Fatima H, Arshad U, Khalil S. Smartphone use and its relationship with addiction, depression, and anxiety among undergraduate medical students in Nawabshah, Pakistan: A cross-sectional study. Professional Med J 2026; 33(02):287-294. https://doi.org/10.29309/TPMJ/2026.33.02.9820

INTRODUCTION

Electronic devices have become ubiquitous in today's world, with smartphones being the most commonly used electronic items among college students and younger generations.[1] These devices facilitate various functions, such as making calls, taking pictures, playing media, browsing the web, and sending emails.[2] In Pakistan, there are over 185.62 million smartphone users, according to newly released statistics, while the global smartphone user count has surpassed 7.10 billion. However, there is currently no demographic information available regarding the prevalence of smartphone addiction in Pakistan or around the world.[3]

Students at universities can stay up-to-date on the latest innovations in communications technology and stay within reach of their friends and family through their smartphones.[4] Digital technologies have revolutionized the lives of youth and students, providing access to education, communication, and social interaction. Technology has created new educational and personal development possibilities by providing easier access to educational materials and enabling real-time collaboration with peers and teachers.[5] On the other hand, problematic smartphone use is recognized as a significant issue, especially among younger generations. Smartphone addiction influences their thoughts, behavior, habits, feelings, and overall well-being.

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Article received on:
30/04/2025
Date of revision:
03/09/2025
Accepted for publication:
04/09/2025

Addiction symptoms appear in many forms, including obsession, intolerance, loss of control, mood swings, and disinterest in other activities.[6] Its problematic use which in turn contributes to social isolation, reduced self-confidence, and increased mental health issues like depression and anxiety.[7] Academic engagement, headaches, neck pain, exhaustion, sleep disturbances, memory loss, and hearing loss are all negatively impacted.[8] Furthermore, there has been a noticeable rise in the occurrence of insomnia, a frequently encountered sleep disorder characterized by challenges in either falling asleep or maintaining sleep.[9]

Globally, it is believed that 27% and 34% of medical student's experience anxiety and depression.[10,11] The percentage of Asian medical students who were addicted to their smartphones was 41.93%.[12] Compared to the entire population, medical students are more likely to suffer from mental health issues.[10,11]

370 medical students between the ages of 16 and 41 participated in a cross-sectional survey between July and October 2020. According to the findings, 79% of students use their smartphones excessively, 78% of them experience depressed symptoms, and 69% experience anxiety symptoms. Additionally, there is a correlation between anxiety-related symptoms and smartphone misuse.[13] Another cross-sectional study involving 600 participants was carried out in India to evaluate the effect of smartphones on the mental health of undergraduate medical students. According to the findings, 42% of the participants used a screen for 4–6 hours every day on average. About 15.6% of people with mild depression, 16% of people with moderate depression, and 11.6% of people with really severe depression, respectively, exhibited symptoms.[14]

According to a study, 60% of Pakistani young people reported having a smartphone dependency. This is due to students' overreliance on smart screens for studying and a lack of understanding of their harmful effects. Awareness sessions have a positive impact on students' use of mobile phones, according to a cohort study done on students in Pakistan.[15] A systematic survey has determined a strong correlation between cellphone reliance and the severity of feelings of depression and anxiety.[16]

A recent study using a sample of 436 students from public and private universities in Bahawalpur, Pakistan, aimed to determine the prevalence of stress, anxiety, and nomophobia among university students. The study's findings show that 56.2% of students felt uneasy not having a constant connection to their smartphones, and those who suffered from that also reported feelings of anxiousness and nervousness, which made them uncomfortable among other people.[17] More evidence confirms the findings that smartphone reliance is associated with depression or anxiety symptoms, as those people with depression excessively use their mobile phones to reduce their symptoms because they have insufficient solutions for coping with their symptoms.[18] This cross-sectional study aimed to investigate the relationship between smartphone usage with addiction, depression, and anxiety among medical students at PUMHSW, Nawabshah, Pakistan. By concentrating on this group, we intend to advance knowledge about the possible negative consequences of smartphone use on psychological well-being and possibly provide guidance for interventions.

METHODS

This descriptive cross-sectional study was conducted among undergraduate female students at the Peoples University of Medical & Health Sciences for women Shaheed Benazirabad from August 2023 to January 2024.

The sample size 325 calculated by using formula $n = X^2.NP\ (1 – p) \div d^2\ (N – 1) + X^2\ P\ (1 – p)$ at a 95% confidence interval with a 5% margin of error, and the 44.7% prevalence of excessive smartphone use was calculated from the previous study in South India.[19] To further minimize the margin of error, the sample size was increased to 350. (X = 1.96, P = 0.447, (1-p) = 0.553, N = 2240, d = 0.05). The students were selected randomly using a multi-stage sampling technique (Stratified and systematic random sampling). This sample was proportionally allocated: (MBBS) = 182, (BSPH) = 39, (Pharm-D) = 39, (DPT) = 49, and (BSN) = 41.

Inclusion criteria were students using smart phone

aged 18-25 years from different departments of PUMHSW (MBBS, DPT, Pharm-D, BSN and Public health). Exclusion criteria were Smartphone users aged below 18 and above 25, Students apart from PUMHS SBA, students having Pre-existing psychiatrist problem (diagnosed) and who are on substance abuse and Participants who are having recent major traumatic life event.

The data collection was performed using a self-administered composed of five main sections: demographics, smartphone usage, SAS scale, PHQ-9 depression scale, and GAD-7 scale for anxiety. To assess the validity of the questionnaire, a pilot study was conducted among 30 university students which indicated that the questionnaire had good reliability and validity. Informed written consent of participants was obtained before involving them in the study. The participants were informed about the purpose, method of collection, benefits, and risks of the study. They were assured of the maintenance of privacy and confidentiality throughout the data collection, analysis, and dissemination of the research. This study was performed after the permission of Institutional Ethical Review Board (PUMHS/SBA/CHS/588/05(21-1-23).

Data analysis was carried out using the software SPSS (Statistical Package for the Social Sciences) for Windows version 25.0. Descriptive statistics were performed to report the analysis of the data presented as frequencies, percentages, mean, and standard deviation. The chi-square test was employed to determine the association between smartphone usage with the addiction, depression, and anxiety. A p-value of < 0.05 indicated a statistically significant relationship. Categories of smartphone usage duration was measured as: Low usage (0-2 hours), Moderate usage (3-5 hours), High usage (6 or >6 hours).

RESULTS

Out of the 350 students, 172 (49.1%) were between 20 and 22 years old, whereas 138 (39.4%) were aged 23 to 25, and those less than 20 years old were 40 (11.4%). The majority of the students from the MBBS department were 181 (51.7%); Pharm-d and BSPH students were 39 (11.1%); DPT students were 50 (14.3%); and BSN students were 41 (11.7%), respectively. First-year and 3rd-year students were 21.4%; however, 21.1% in the 4th year, 20.9% in the 2nd year, and 15.1% in the 5th year. (Table-I)

TABLE-I

Demographic characteristics of respondents (n=350)

Demographics		Frequency (%)
Age of Respondents	Less than 20 years	40 (11.4)
	20 to 22 years	172 (49.1)
	23 to 25 years	138 (39.4)
Mean ± SD		21.86±1.887
Department	MBBS	181 (51.7)
	DPT	50 (14.3)
	Pharm-D	39 (11.1)
	BSPH	39 (11.1)
	BSN	41 (11.7)
Year of Study	1st Year	75 (21.4)
	2nd Year	73 (20.9)
	3rd Year	75 (21.4)
	4th Year	74 (21.1)
	5th Year	53 (15.1)

Figure-1 shows the level of depression among medical students. Out of the total, 8.0% of participants have experienced severe depression, 46.6% have mild depression, 40.6% have moderate depression, and 4.9% have no depression. The mean and standard deviation of depression were 9.80 ± 5.87.

FIGURE-1

Level of Depression among medical students

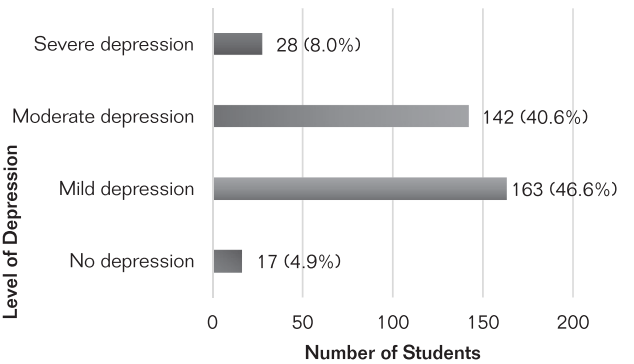

Table-II represents that for a total of 350 participants, the students spent their time on mobile screens for more than 6 hours per day (49.7%), while 48.9% used them for 3 to 5 hours per day, and a few students (1.4%) spent less than 2 hours. 48.3% of participants checked their mobile phones occasionally, whereas 12.6% rarely checked. Most students never checked their smartphones while sleeping (77.4%); however, 22.6% of students occasionally checked their screens. The total scoring of smartphone usage was 59.4% of participants who moderately used their smart screens, 39.1% highly used their phones, and 1.4% limited use.

TABLE-II

Smartphone usage

Smartphone usage		Participants, n=350 n(%)
Duration of mobile phone usage per day	0-2 hour	5 (1.4)
	3-5 hour	171 (48.9)
	6 or >6 hour	174 (49.7)
Frequency of mobile phone checking	Rarely	44 (12.6)
	Occasionally	169 (48.3)
	Frequently	137 (39.1)
Checking mobile phone in between sleep	Rarely or Never	271 (77.4)
	Occasionally	79 (22.6)
	Frequently	0 (0.0)
Total scoring of Smartphone usage	Mild	5 (1.4)
	Moderate	208 (59.4)
	High	137 (39.1)
Mean ± SD	2.38 ± 0.514	

Table-III shows the level of addiction, depression, and anxiety among medical students. Out of the total, 49.1% of participants have exhibited high addiction, 45.4% moderate addiction, and 4.3% very high addiction levels. Similarly, 8.0% of participants have experienced severe depression, 46.6% have mild depression, 40.6% have moderate depression, and 4.9% have no depression. Furthermore, 46.9% of medical students experienced a moderate level of anxiety and 8.9% severe anxiety.

Table-IV represents the distribution of smartphone usage with addiction, depression, and anxiety levels. Out of the total of 350 undergraduate students, among moderate smart phone users 142 (89.3%) were having moderate addiction, 130 (79.8%) had mild depression and 105 (84.7%) had mild anxiety (p-value <0.05). Among high smart phone usage 106 (61.6%) had high addiction, 82 (57.7%) had moderate depression and 92 (56.1%) had moderate anxiety (p-value <0.05).

TABLE-III

Level, mean and standard deviation: smartphone addiction, depression and anxiety (n=350)

Variable	n (%)
Low addiction	4 (1.1%)
Moderate addiction	159 (45.4%)
High addiction	172 (49.1%)
Very high addiction	15 (4.3%)
No depression	17 (4.9%)
Mild depression	163 (46.6%)
Moderate depression	142 (40.6%)
Severe depression	28 (8.0%)
No anxiety	31 (8.9%)
Mild anxiety	124 (35.4%)
Moderate anxiety	164 (46.9%)
Severe anxiety	31 (8.9%)

DISCUSSION

The present study demonstrated to explore the relationship between smartphone usage and the level of addiction, depression, and anxiety among undergraduate medical students in Nawabshah, PUMHSW. Our study findings revealed that 49.1% of the participants were 20–22 years old, and their mean age was 21.86±1.887. Majority of the undergraduate students 49.7% used their mobile phones for >6 hours per day, and 48.9% used them for 3-5 hours.The study findings are aligned with research done in Switzerland, which revealed the duration of smartphone use was 5.6 hours per day.[20] In contrast to earlier data, research conducted in the United Kingdom showed a lower screen time use of 3.1 hours per day.[21]

The findings revealed that 45.4% were at a moderate level of addiction, 49.1% of medical students reported high smartphone addiction, and 4.3% experienced very high addiction, means almost all of the students showed addiction.

TABLE-IV

Related Frequency between Smartphone usage with smartphone addiction, depression and anxiety

Total scoring of variables	Smartphone Usage			P-Value
	Limited	Moderate	High	
	n (%)	n (%)	n (%)	
Smartphone Addiction				
Low addiction	4 (100%)	0 (0.0%)	0 (0.0%)	
Moderate addiction	1 (0.6%)	142 (89.3%)	16 (10.1%)	
High addiction	0 (0.0%)	66 (38.4%)	106 (61.6%)	<0.001*
Very high addiction	0 (0.0%)	0 (0.0%)	15 (100%)	
Total	5 (1.4%)	208 (59.4%)	137 (39.1%)	
Depression				
No depression	0 (0.0%)	16 (94.1%)	1 (5.9%)	
Mild depression	4 (2.5%)	130 (79.8%)	29 (17.8%)	
Moderate depression	1 (0.7%)	59 (41.5%)	82 (57.7%)	<0.001*
Severe depression	0 (0.0%)	3 (10.7%)	25 (89.3%)	
Total	5 (1.4%)	208 (59.4%)	137 (39.1%)	
Anxiety				
No anxiety	0 (0.0%)	31 (100%)	0 (0.0%)	
Mild anxiety	4 (3.2%)	105 (84.7%)	15 (12.1%)	
Moderate anxiety	1 (0.6%)	71 (43.3%)	92 (56.1%)	<0.001*
Severe anxiety	0 (0.0%)	1 (3.2%)	30 (96.8%)	
Total	5 (1.4%)	208 (59.4%)	137 (39.1%)	

These prevalence rates are higher compared to those of Bangladeshi university students, who were at 86.9%[22]; nursing students in Karachi, Pakistan, at 69.39%[23]; medical students in India, at 52.7%[24]; and young adults in Brazil, where it was found that 35% aged 18 to 25 had smartphone addiction.[25] According to the study findings, a substantial portion of high smartphone users (61.6%) demonstrated a high level of addiction. In contrast, all cases of severe addiction were documented among participants categorized as high smartphone users. Meanwhile, the majority of moderate smartphone users (89.3%) experienced a moderate level of addiction. The P-value <0.001 highlights a significant association between smartphone usage and level of addiction. The findings of this study are consistent with the previous study showing that excessive smartphone use can lead to smartphone addiction, which has a negative effect on mental health among undergraduate university students.[6] A study was conducted in Sudan and in this study 67.6% exhibited only in high levels of smartphone addiction which is higher than our finding of high smart phone addiction.[26] Other studies reported that smartscreen use can result in modifications related to lifestyle factors that can cause irregular dietary behaviors.[27] Constant access to social media, academic materials, and gaming platforms are the fundamental causes of smartphone addiction. These factors support compulsive behaviour's, which in turn contribute to the development of the addiction. Students often rely on smartphones as a coping mechanism for stress, which inadvertently contributes to addiction.

Depression was also prevalent in medical students, who suffered from moderate to severe depression were 48.6%. The prevalence of depression in this study is higher than that of a study conducted in Uganda in 2023 that was 16.73% using a comparable measurement.[28] The prevalence of depression and anxiety symptoms among the medical students was 57.5 which is higher than our findings.[29] According to the investigation, out of 137 students who used

smartphones high reported having moderate levels of depressive symptoms in 82, while 208 who were using smart screens moderately they had moderate depression in 59. Additionally, severe depression was found individuals who were using high smartphone. The study found a significant correlation (p-value <0.01) between high levels of depression and excessive smartphone use. Individuals who experience loneliness often use their phones more, struggle with personal issues and struggle with performance, and feel disconnected from others surrounding them as a result of their increasing smartphone use.[30,31] Several studies showed that excessive smart screen use was correlated with decreased quality of sleep among medical students, as we observed in our study also, which can lead to an impact on their academic performance, according to the findings of other research that revealed comparable findings at the same time.[19,32] A study conducted in Saudi Arabia presents findings that are inconsistent with the results of our research.[33]

In accordance with the findings, 55.8% of medical students exhibited moderate to severe anxiety. A similar prevalence of anxiety, 59.5%, was found among Saudi medical students.[34] Additionally, 96.8% of high smartphone users were experiencing severe anxiety symptoms, although 56.1% of high screen users reported having moderate anxiety symptoms. The related frequency is statistically significant between smartphone usage and anxiety (p-value <0.01). These results are consistent with the previous findings that showed excessive smartphone use can lead to social anxiety.[34,35] According to a systematic review of 23 peer-reviewed publications, using smartphones excessively is significantly associated with anxiety and depressive symptoms.[16] Prior research suggests that people with high levels of anxiety may favor social communication that helps them to manage and avoid undesirable aspects of their behavior or appearance. Because of this, people could use their phones excessively to avoid social situations, which has detrimental effects for social communication.[36] Additionally, a study revealed the overuse of smartphones leads to disruptive behavioral issues and concentration deficits, inhibits students from attending education and employment, affects academic progress, and diminishes the amount of time spent on real-life connections with others.[37] Loneliness also corresponds to several adverse mental and physical outcomes, such as anxiety, depression, obesity, and heart disease.[33]

This study has some limitations. Firstly, the cross-sectional design prevents establishing a causal link between smartphone usage and mental health effects. In addition, drawing a sample from just one university and only girl students limits our ability to generalize the findings to all medical students in Pakistan. Moreover, not analyzing specific usage behaviors, such as the duration of internet or gaming activities, restricts our capacity for deeper analysis. Additionally, failing to consider factors associated with excessive screen time impacts the results.

CONCLUSION

The results of the current study provide significant associations among the excessive use of smartphones with moderate to high level of addiction, depression, and anxiety. Furthermore, the study highlights the need of maintaining adequate control over social media use and its adverse consequences, such as depression and anxiety disorder.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Imran Mirbahar:** Conceptualization of project.
2	**Anum Saleem:** Statistical analysis.
3	**Fiza Anis:** Data collection.
4	**Hasnat Fatima:** Manuscript writing.
5	**Ujala Arshad:** Data collection.
6	**Saqiba Khalil:** Literature search, revision.

https://doi.org/10.29309/TPMJ/2026.33.02.10021 www.theprofesional.com

ORIGINAL ARTICLE

Prevalence of pes planus and pes cavus and its association with risk of fall, activities of daily living and muscular discomfort among school teachers of Hayatabad, Peshawar. A cross sectional study.

Aqsa Khan[1], Seema Gul[2]

ABSTRACT… Objective: To determine the prevalence of pes planus and pes cavus and its association with risk of fall, activities of daily living and muscular discomfort. **Study Design:** Multi-center Cross-sectional study. **Setting:** Hayatabad Public and Private Schools. **Period:** August 2024 to January 2025. **Methods:** This was multi-center cross-sectional study; conducted on school teachers of Hayatabad, Peshawar. Total 113 school teachers (mean age 29.42± 6.07) were included in the study through convenience sampling technique. Demographic details were obtained from all the study participants. Navicular drop test was used to assess arch of the foot. Risk of fall and activities of daily living were assessed using Efficacy Scale International and Foot and Ankle Ability Measure respectively. Cornell Musculoskeletal Discomfort Questionnaire is used for muscular discomfort. Data was analyzed using Statistical Package for Social Sciences (SPSS) version 25. **Results:** The sample in this study consisted of 47.8% male and 52.2% female school teachers. The results of this study showed that pes planus is slightly more prevalent (19.16%) than pes cavus (16.93%). The baseline variables like gender, age and Body Mass Index (BMI) and functional outcomes like risk of fall and activities of daily living were strongly associated with type of foot ($p<0.05$). **Conclusion:** This study found that foot arch deviations, such as pes planus and pes cavus, are highly prevalent and show strong associations with age, gender, and BMI. These deviations also have a significant impact on functional outcomes.

Key words: Activities of Daily Living, Flat Foot, High Arch Foot, Muscular Discomfort, Pes Planus, Pes Cavus, Risk of Fall.

Article Citation: Khan A, Gul S. Prevalence of pes planus and pes cavus and its association with risk of fall, activities of daily living and muscular discomfort among school teachers of Hayatabad, Peshawar. A cross sectional study. Professional Med J 2026; 33(02):295-299. https://doi.org/10.29309/TPMJ/2026.33.02.10021

INTRODUCTION

The human foot is a complex structure of bones, ligaments, muscles, and tendons that supports body weight and enables balance, shock absorption, propulsion, and movement adaptability.[1] The foot arches are vital for maintaining stability and efficient gait, and any alteration can lead to foot stress and lower-limb musculoskeletal complications.[2] Pes planus, marked by a depressed medial longitudinal arch, everted hind foot, and abducted/dorsiflexed midfoot, causes excessive pronation, altered lower-limb mechanics, and poor load distribution; often resulting in pain, stiffness, gait changes, reduced activity, and fatigue.[3] On other hand pes cavus, characterized by an abnormally elevated medial arch may progressively impair function, balance, and footwear tolerance.[4] Foot disorders affect 61–79% of young individuals.[5] Advancement in age poses a higher prevalence of abnormal medial arch structure and related foot pain.[6]

In healthy individuals, abnormal foot architecture has been shown to adversely affect skilled motor performance and elevate the likelihood of injuries.[7] Foot pain is reported as the most common complaint among American population. It is strongly linked to functional disabilities, such as limitations in activities of daily living, reduced social participation, higher medical expenditures, and increased absenteeism from work.[8] Furthermore inconsistent evidence is available regarding the association of risk of fall with foot architecture with some studies reporting a significant relationship while others show no clear link.[9] The lack of standardized treatment protocols and the considerable variation in therapeutic approaches pose a major challenge in managing pes planus and pes cavus.

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Article received on:
05/08/2025
Date of revision:
05/11/2025
Accepted for publication:
05/11/2025

This variability contributes to suboptimal treatment outcomes like functional mobility and quality of life.[10]

Although the existing literature acknowledges their prevalence and potential to impact physical function, there is a notable lack of research exploring their association with risk of falls, activities of daily living (ADLs), and musculoskeletal discomfort; particularly in adult working populations. This study addresses a significant gap by focusing specifically on school teachers and examining the associations between foot arch types and key functional risk factors, including fall risk, daily activity limitations, and musculoskeletal discomfort. The findings aim to contribute to early identification and prevention strategies in occupational health settings.

METHODS

This was a multi-center cross sectional study conducted on school teachers of Hayatabad, Peshawar. The approval was obtained from the Review Board of Khyber Medical University (DIR/KMU-ASRB/PP/IPMR/003104). The study duration was 6 months from (from August 2024 to January 2025). The sample size was calculated using the Openepi online sample size calculator (97% confidence level, and a 5% margin of error). Data was collected from 3 public schools and 3 private schools of Hayatabad. A total of 313 teachers were initially screened for eligibility. Following the application of the inclusion criteria, 113 school teachers (both male and female), aged 18–50 years, were selected and recruited into the study through a convenience sampling technique. Participants were excluded from the study if they have (1) history of any neurological condition, such as Meniere's disease or vestibular disease (2) any form of muscle atrophy or dystrophy, (3) BMI over 30, (4) diagnosis of any abnormality or surgery of the lower limbs (5) use of medications that can potentially produce symptoms of dizziness or imbalance (6) individuals with normal foot arches. After fulfilling the eligibility criteria, written informed consent was obtained from all participants for inclusion in the study and for the use of their data in publications, ensuring anonymity. A detailed information sheet was provided to each participant, and any questions related to the study were addressed satisfactorily.

Demographic details were obtained from all the participants. A detailed evaluation of foot was conducted for each patient. To classify participants into pes cavus and pes planus category "navicular drop test" was performed. Navicular drop is a reliable test for assessing foot arch (ICC= 0.82 - 0.89).[11] illustration of the test is given in the Appendix I. Functional outcomes included risk of fall assessment and activities of daily living.

To assess the risk of fall among participants; "Fall Efficacy Scale International" was used. This tool evaluates concern about fear of falling. It is a valid, reliable, and easy-to-understand tool for measuring fear of fall; suitable for use across different cultures. A higher score indicates poor outcome showing high concern about falling.[12]

Foot and Ankle Ability Measure (FAAM-ADL) was used for assessing activities of daily living. Previous studies have reported that FAAM has high correlation with the function (r = 0.87, 95% confidence interval [CI] 0.81-0.91) and pain component (r = 0.75, 95% CI 0.65-0.83). A higher score on FAAM suggests better functional status.[13]

Muscular discomfort was measured using Cornell Musculoskeletal Discomfort Questionnaire; it is a valid and reliable instrument for the exploration of musculoskeletal discomfort. The higher score suggests high degree of discomfort.[14,15]

Data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 25. Mean and standard deviation were calculated for continuous variables such as age. Categorical variables, including age groups, BMI, Navicular Drop Test results, and the Foot and Ankle Ability Measure categories, were presented using frequency tables. The Chi-square test and cross-tabulation were applied to assess the association between variables. A p-value ≤ 0.001 was considered statistically significant.

RESULTS

The mean age of the sample was 29.42 ± 6.07 years, comprising 47.8% male and 52.2% female school teachers. The majority of participants (58.4%) had a normal BMI, while 31% were classified as

overweight. Based on the Navicular Drop Test, 53.1% of the participants exhibited pes planus, whereas 46.9% had pes cavus. (See Table-I) The prevalence of pes planus was (19.16%); slightly higher than prevalence of pes cavus (16.93%).

TABLE-I

Characteristics of study population

Parameters	Categories	Frequency	%
Age	Young Adult (18-25)	26	23.0
	Early Adult (26-30)	43	38.1
	Adult (31-35)	33	29.2
	Middle Aged Adults (41-45)	11	9.7
Gender	Male	54	47.8
	Female	59	52.2
BMI	Underweight	12	10.6
	Normal weight	66	58.4
	Over weight	35	31.0
Navicular Test	Pes planus	60	53.1
	pes cavus	53	46.9
Foot & Ankle Ability Measure	Moderate difficulty	41	36.3
	Slight difficulty	47	41.6
	No difficulty at all	25	22.1
Risk of fall	Fairly concerned	66	58.4
	Somewhat concerned	47	41.6

Based on chi square test, it was determined that structure of foot is strongly associated with individual's age, gender, BMI, foot &ankle ability and risk of fall ($p < 0.05$). See Table-II

Statistically significant association was observed between foot architecture and reports of discomfort across lower extremities on Cornell Musculoskeletal Discomfort Questionnaire ($p<0.05$). See Figure-1(a, b).

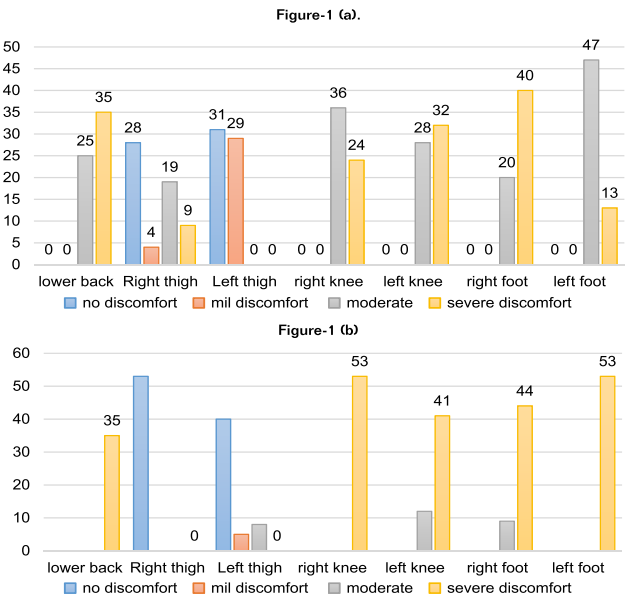
TABLE-II

Foot architecture in relation to Age, Gender, BMI and Functional outcomes

Variable	Categories	Structure of Foot		P- Value
		Pes Planus	Pes Cavus	
Age	Young Adult	10	16	0.005
	Early Adult	19	24	
	Adult	22	11	
	Middle Aged Adults	9	2	
Gender	Male	6	53	0.001
	Female	54	0	
BMI	Underweight	12	0	0.001
	Normal weight	48	18	
	Over weight	0	35	
Foot & Ankle Ability	Moderate difficulty	0	41	0.001
	Slight difficulty	37	10	
	No difficulty at all	23	2	
Risk of fall	Fairly concerned	50	16	0.001
	Somewhat concerned	10	37	

FIGURE-1

Showing reports of discomfort felt across lower extremities by participants with (a) Pes Planus and (b) Pes Cavus.



DISCUSSION

The findings of this study suggest that foot arch deviations, such as pes planus and pes cavus, are highly prevalent across all the categories of ages and affects both male and female. This study showed a strong association of foot architecture with body mass index. These deviations significantly impact on functional outcomes like activities of daily living and risk of fall.

In our study sample we observed that the prevalence of pes planus (19.16%) is higher than pes cavus (16.93%). On the basis of navicular drop test, no female had pes cavus architecture of foot; all the females presented a pes planus deformity. On other hand, among males only 10.16% were diagnosed with pes planus and 89.83% presented pes cavus deformity. Shah et al. conducted a study, in which he reported 26% of subjects had pes planus and 54% had pes cavus. This high number could be due to the fact that his population had a higher percentage of male 72.0%.[15] This pattern is also confirmed by our study that pes cavus was more prevalent in male population.

Troiano et al. reported that younger age is a significant risk factor for the presence of flat feet (pes planus), suggesting that the condition is more prevalent in early life stages. These findings are consistent with the results of our study, which demonstrated a marked reduction in the incidence of pes planus among individuals older than 40 years. This age-related decline may reflect developmental and structural changes in the foot arch over time, or possibly an adaptive response due to long-term mechanical loading and musculoskeletal maturation. Our findings reinforce the idea that age plays a crucial role in the prevalence and progression of pes planus.[16]

Hajirezaei et al published a study in 2017. The study population comprised 260 female students from Mazandaran University. According to the results, no significant relationship was found between body mass index (BMI) and the presence of flat feet or high arched foot.[17] Contrary to that, the findings of our study show a substantial and significant correlation between the type of foot and BMI. We observed that among overweight individuals; 60% showed pes cavus and zero reports of pes planus and 40% showed normal foot arches. Pes planus was more common in normal weight and underweight individuals 25.3% and 18.18% respectively.

A strong association between foot posture and lower extremity pain was reported by Riskowski et al; he reported that participants with planus structure had higher odds of knee and ankle pain while participants with cavus foot had higher risk of ankle pain.[18] This prediction is confirmed by our study where 66 to 78% participants with pes planus reported moderate to severe type of pain & discomfort in their feet; followed by 40 to 60% pes planus reporting knee pain. A sharp spike (41 to 58%) in the complaint of lower back pain and discomfort is observed in our study as well. Among pes cavus individuals; 100% reports of foot and knee pain was recorded in our study.

In our study, 50% individuals with either pes planus or cavus showed fair concern of balance related to risk of fall. These findings are supported in a study by Sahan et al; in which he objectively compared lower extremity dominance, subtalar angle, balance, fall risk, and performance in young adults with and without pes planus. Significant differences were found in subtalar angles and jump test performance ($p < 0.05$), with reduced values in the pes planus group.[9]

Lopez et al conducted a case control study in 498 participants. Based on the self-reported data on foot health-related quality of life, it was concluded that significant difference exits between cases and controls for foot health, general health and physical activity.[5] These findings align with the results of our study: which determined that functional outcomes like activities of daily living are strongly associated with architecture of foot. Thus concluding that foot pathologies have a negative impact on quality of life.

LIMITATIONS & RECOMMENDATION

This study was a multi-center cross-sectional study that was conducted in specific region of Peshawar; thus the sample may not be a true representation of the entire population of Peshawar. A larger sample size and random inclusion of participants from all regions of Peshawar may produce more

generalizable results.

CONCLUSION

This study found that foot arch deviations, such as pes planus and pes cavus, are highly prevalent and show strong associations with age, gender, and BMI. These deviations also have a significant impact on functional outcomes.

Ethics Approval and Consent to Participate

Ethical approval for the study was granted by the Review Board of Khyber Medical University (DIR/KMU-ASRB/PP/IPMR/003104).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Aqsa Khan:** Data collection, data entry.
2	**Seema Gul:** Manuscript writing, data analysis, proof read.

https://doi.org/10.29309/TPMJ/2026.33.02.10018 www.theprofesional.com

ORIGINAL ARTICLE

Molecular basis of beta thalassaemia intermedia in Pakistan.

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ABSTRACT… Objective: To investigate the primary β-globin gene mutations and their association with secondary genetic modifiers—Xmn-1 polymorphism and BCL11A variant—in patients diagnosed with β-thalassemia intermedia in Pakistan. **Study Design:** Descriptive Cross-sectional study. **Setting:** Fauji Foundation Hospital, Islamabad. **Period:** June 2021 to January 2022. **Methods:** Seventy patients with β-TI were enrolled. DNA was extracted using the Chelex method, and molecular analysis was performed using PCR-RFLP and ARMS-PCR to detect BCL11A (rs11886868) and Xmn-1 polymorphisms, respectively. Statistical analysis was carried out using SPSS version 17. **Results:** The most frequent primary mutations included Cd-15 (14.3%), IVSI-5 (11.4%), and Fr 8-9 (12.9%). Xmn-1 and BCL11A polymorphisms were identified in 37.1% and 71.4% of patients, respectively. Statistically significant associations were found between certain primary mutations (e.g., IVSI-5 and IVSI-5/cap +1) and both secondary modifiers ($p < 0.001$ and $p = 0.005$, respectively). Dual modifier presence was observed in 26% of patients. **Conclusion:** This study reveals considerable molecular diversity in β-thalassemia intermedia in Pakistan. The significant association between specific β-globin mutations and secondary genetic modifiers highlights the complex genotype-phenotype interplay. These findings underscore the need for larger, multi-centric genetic studies to enhance predictive accuracy for clinical management and personalized therapy in thalassemia.

Key words: HBF, Secondary Modifiers, Thalassaemia Intermedia.

Article Citation: Nasreen F, Shaikh A, Rehan M, Iqbal F, Irshad Z, Noureen A. Molecular basis of beta thalassaemia intermedia in Pakistan. Professional Med J 2026; 33(02):300-306. https://doi.org/10.29309/TPMJ/2026.33.02.10018

INTRODUCTION

Thalassemia syndrome is the commonest autosomal recessive genetic disorder which is caused due to mutations that resulted in reduction of (β°) or (β+) production of β-globin chains of hemoglobin, a combination of two alpha and two beta globin chains (α2 & β2) required for formation of HbA. There is great molecular heterogeneity having more than 300 different molecular defects.[1] It's a global health problem most commonly affecting Asia, Mediterranean regions and Middle East.[2] The severity of the condition is determined by the type and existence of mutations in either one allele (thalassemia minor) or both alleles (thalassemia major as β-thalassemia).

Patients diagnosed having Beta Thalassemia Major require regular blood transfusions for their survival. Recurrent transfusions bring these patients at great risk for heart problems or liver cirrhosis, and iron overload frequently results in death at age 30 or younger.[3] Thalassemia intermedia is a clinical condition with less severity which is also called as non-transfusion dependent thalassemia (NTDT) and ranges in intensity from transfusion-dependent patients to symptomatic carriers.[4]

Pakistan has a total population of about 225,633,392 (225 million). Both the federal and provincial governments govern Pakistan's healthcare delivery system. In Pakistan, around 5000 children are diagnosed with β-thal major (β-TM), and the prevalence of β-thalassemia (β-thal) trait ranges from 5.0 to 7.0%.[5] Based on inequality between the α/β-globin chain production, thalassemia syndrome are broadly classified as minor, major and intermedia.[3] In β-thalassaemia intermedia combination of different genetic defects leads variable clinical manifestations few combinations are compound heterozygotes of β- and α-thalassemia gene and β+/β+ compound heterozygotes.[4]

Beside β globin chain deficiency imbalance between level of α and gamma (γ) globin chain, co-inheritance

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Article received on:
04/08/2025
Date of revision:
25/09/2025
Accepted for publication:
15/10/2025

of α thalassemia or various genetic factors can also lead to phenotypic variability in thalassemic patients. These genetic factors which influence the phenotype of β thalassemia are known as "Genetic Modifiers". The "primary modifier" signifies the varying expression of β thalassemia alleles resulting in phenotypic variation. Whereas secondary modifiers are genetic factors comprised of Co inheritance of alpha (α) globin gene copy or which augment fetal hemoglobin (Hb F) production. Tertiary modifiers are genetic factors which do not have any bearing directly on the globin chain balance but influence the clinical phenotype.[5]

Xmn1 polymorphism is one of the most important secondary modifier.[6] A major challenge faced in most under resourced countries in effective management of β-thalassemia intermedia is the early identification of the phenotype of patients.[7] Predicting phenotypic variability from several genotypic variants in patients with thalassemia has advanced globally.[8]

Although, different studies at international level have emphasized the incidence of different genetic mutations but scarcity in literature have been observed at national level in this context. Our goal in this investigation is to determine the molecular underpinnings of beta thalassemia intermedia, with a focus on the interplay between primary beta globin gene mutations and secondary genetic modifiers.

METHODS

Descriptive cross-sectional study was carried out at the Fauji Foundation Hospital Islamabad. Seventy individuals with a diagnosis of thalassemia intermedia were included in this study. The Fauji Foundation Hospital's ethical review committee granted ethical approval (Ref No.975/RC/FFH/RWP). The study took place between June 2021 and January 2022. Patients with a diagnosis of beta thalassemia intermedia are eligible to apply. Both sexes and all ages were represented. Exclusion criteria: beta thalassemia intermedia was the only thalassemia type that was not included. Five milliliters of venous blood were drawn in an EDTA (Ethylene Diamine Tetra Acetic Acid) container following the acquisition of informed consent and a thorough medical history from each patient. The Chelex method was used to extract deoxyribonucleic acid (DNA). PCR was performed. BCL11A polymorphism: The PCR-RFLP technique was used to identify the single nucleotide polymorphism of rs11886868 in the BCL11A gene (T→C).

The primers 5'-TTTGGTGCTACCCTGAAAGAC-3' and 5'-ACTCAACAGTAGCAGAATGAAAGAG-3 were used to the amplification of a 548 bp fragment. After five minutes of incubation at 37°C, the 548-bp product was digested using the MboII restriction enzyme, and the fragments were separated on 6% polyacrylamide gels. The MboII restriction site is present in the C allele but absent in the T allele. Two 470 bp and 70 bp segments of the C allele were found.Xmn-1 Polymorphism: The Amplification Refractory Mutation System (ARMS) approach was used to accomplish the Xmn-1 polymorphism.

The primers listed below were utilized:Xmn-I-Normal5'-TGCAAATATCTGTCTGAAAC-GATCXmn-I-Mutant5'-TGCAAATATCTGTCT-GAAACGATT Xmn-I-Common5'-CCCATGGC-GTCTGGACTAGA 25 μl reaction mixture comprising 5 pM of each primer, 0.5 units of Taq polymerase (Thermo Fisher Scientific, USA), 30 μM of each dNTP (Thermo Fisher Scientific, USA), 10 mM Tris HCl (pH 8.3), 50 mM KCL, 1.5 mM MgCl2, 100 mg/ml gelatin (Sigma, UK), and 0.3-0.5 μg of genomic DNA was used when performing the PCR for ARMS. Macrogen (Korea) manufactured the primers. The Gene Amp 9700 (ABI, USA) automated DNA thermal cycler was utilized for thermal cycling.

Each of the 25 cycles in the regimen included one minute of denaturation at 94°C, one minute of primer annealing at 65°C, and one and a half minutes of DNA extension at 72°C. The extension reaction was extended for an additional three minutes in the last cycle. For testing, Mini Poly Acrylamide Gels (PAGE) were used. Analysis of statistics: SPSS version 17 was utilized to analyze the data. For qualitative variables such as patient gender and secondary modifiers, frequency and percentages were evaluated. For quantitative variables such as the patient's age, the mean and standard deviation were calculated.

RESULTS

TABLE-I

Baseline characteristics of studied patients (N=70)

Characteristics		n	%
Age Group	<5 years	9	12.9
	5 - 10 years	23	32.9
	11 - 15 years	15	21.4
	16 - 20 years	8	11.4
	21 - 25 years	9	12.9
	>25 years	6	8.6
	Mean (±SD)	13.2	±8.0
Gender	Male	32	45.7
	Female	38	54.3
Age at diagnosis (years)	<5 years	43	61.4
	5 - 10 years	16	22.9
	11 - 15 years	6	8.6
	16 - 20 years	5	7.1
	Median (Range)	4	1 – 25

Table-I reports the baseline characteristics of studied patients, in the present study among seventy patients mean age was 13.2 (SD=±8.0) years, Age group less than five years were (12.9%), from 5 - 10 years were (32.9%), from 11 - 15 years were (21.4%), from 16 - 20 years were (11.4%),from 21 - 25 years were (12.9%), and aged >25 years were (8.6%), Male were (45.7%), Female were (54.3%), patients with age at diagnosis less than 5 years were (61.4%), from 5 - 10 years were (22.9%), from 11 - 15 years were (8.6%), from 16 - 20 years were (7.1%), median age of diagnosis was 4 years with range from 1 – 25 years.

FIGURE-1

Molecular basis of beta globin gene mutations in thalassemia intermedia phenotype

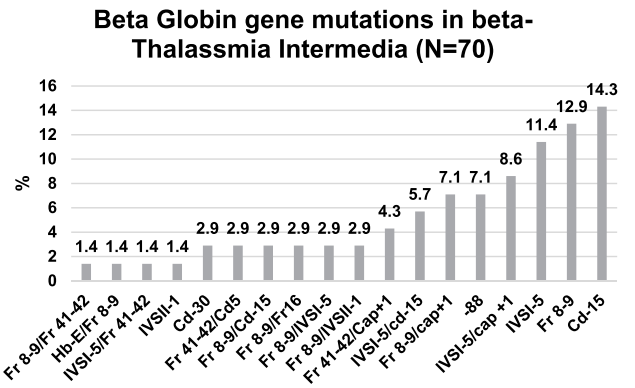

Figure-1 reports the frequency of primary mutations among beta thalassmia intermedia patients, -88 were (7.1%), Cd-15 were (14.3%), Cd-30 were (2.9%), Fr 41-42/Cap+1 were (4.3%), Fr 41-42/Cd5 were (2.9%),Fr 8-9 were (12.9%), Fr 8-9/cap+1 were (7.1%), Fr 8-9/Cd-15 were (2.9%), Fr 8-9/Fr 41-42 were (1.4%),Fr 8-9/Fr16 were (2.9%),Fr 8-9/IVSI-5 were (2.9%), Fr 8-9/IVSII-1 were (2.9%), Hb-E/Fr 8-9 were (1.4%), IVSI-5 were (11.4%), IVSI-5/cap +1 were (8.6%), IVSI-5/cd-15 were (5.7%), IVSI-5/Fr 41-42 were (1.4%), IVSII-1 were (1.4%), and Undetermined were (5.7%) cases.

FIGURE-2

Secondary Modifiers in beta-Thalassmia Intermedia

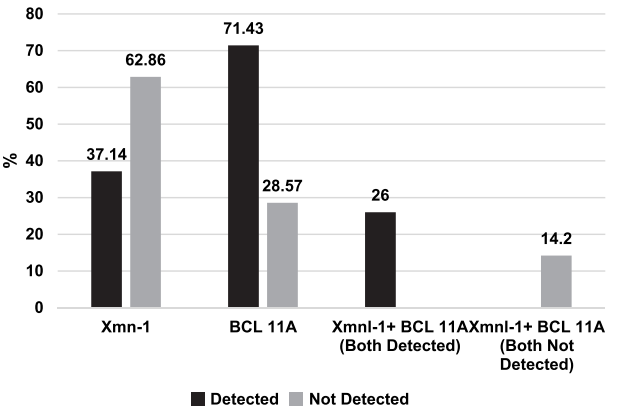

Figure-2 reports the frequency of secondary modifiers in beta Thalassemia Intermedia, results showed among 70 patients 26(37.14%) Xmn-1 and 50(71.43%) BCL 11A were detected, among 18(26%) cases both Xmn-1 and BCL 11A were detected whereas among 8(14.2%) none of the modifier was detected.

Table-II reports the association of primary mutation with Xmn-1, results showed in Xmn-1 detected cases in primary mutations Fr 41-42/Cd5 were (7.7%), Fr 8-9/cap+1 were (7.7%), Fr 8-9/Fr16 were (7.7%), Fr 8-9/IVSII-1 were (7.7%), Hb-E/Fr 8-9 were (3.8%), IVSI-5 were (30.8%), IVSI-5/cap +1 were (15.4%), IVSI-5/Fr 41-42 were (3.8%), IVSII-1 were (3.8%), and Undetermined were (11.5%). Fishers exact test did give significant association of Xmn-1 detected cases with primary mutations (p<0.001)

TABLE-II

Association of primary mutation with XMN-1

Primary Mutation	Xmn-1				P-Value
	Detected		Not Detected		
	n	%	n	%	
-88	0	0.0	5	11.4	
Cd-15	0	0.0	10	22.7	
Cd-30	0	0.0	2	4.5	
Fr 41-42/Cap+1	0	0.0	3	6.8	
Fr 41-42/Cd5	2	7.7	0	0.0	
Fr 8-9	0	0.0	9	20.5	
Fr 8-9/cap+1	2	7.7	3	6.8	
Fr 8-9/Cd-15	0	0.0	2	4.5	
Fr 8-9/Fr 41-42	0	0.0	1	2.3	
Fr 8-9/Fr16	2	7.7	0	0.0	<0.001*
Fr 8-9/IVSI-5	0	0.0	2	4.5	
Fr 8-9/IVSII-1	2	7.7	0	0.0	
Hb-E/Fr 8-9	1	3.8	0	0.0	
IVSI-5	8	30.8	0	0.0	
IVSI-5/cap +1	4	15.4	2	4.5	
IVSI-5/cd-15	0	0.0	4	9.1	
IVSI-5/Fr 41-42	1	3.8	0	0.0	
IVSII-1	1	3.8	0	0.0	
Undetermined	3	11.5	1	2.3	

*p<0.05 was considered statistically significant using Fishers Exact test

TABLE-III

Association of primary mutation with BCL 11A

Primary Mutation	BCL 11A				P-Value
	Detected		Not Detected		
	n	%	n	%	
-88	4	8.0	1	5.0	
Cd-15	8	16.0	2	10.0	
Cd-30	2	4.0	0	0.0	
Fr 41-42/Cap+1	2	4.0	1	5.0	
Fr 41-42/Cd5	0	0.0	2	10.0	
Fr 8-9	5	10.0	4	20.0	
Fr 8-9/cap+1	2	4.0	3	15	
Fr 8-9/Cd-15	2	4.0	0	0.0	
Fr 8-9/Fr 41-42	0	0.0	1	5.0	
Fr 8-9/Fr16	0	0.0	2	10.0	0.005*
Fr 8-9/IVSI-5	2	4.0	0	0.0	
Fr 8-9/IVSII-1	0	0.0	2	10.0	
Hb-E/Fr 8-9	1	2.0	0	0.0	
IVSI-5	8	16.0	0	0.0	
IVSI-5/cap +1	6	12.0	0	0.0	
IVSI-5/cd-15	4	8.0	0	0.0	
IVSI-5/Fr 41-42	1	2.0	0	0.0	
IVSII-1	1	2.0	0	0.0	
Undetermined	2	4.0	2	10.0	

*p<0.05 was considered statistically significant using Fishers Exact test

Table-III reports the association of primary mutation with detected cases of BCL 11A, results showed among detected cases of BCL 11A in primary mutation -88 were (8%), Cd-15 were (16%), Cd-30 were (4%), Fr 41-42/Cap+1 were (4%), Fr 8-9 were (10%),Fr 8-9/cap+1 were (4%), Fr 8-9/Cd-15 were (4%), Fr 8-9/IVSI-5 were (4%), Hb-E/Fr 8-9 were (2%), IVSI-5 were (16%), IVSI-5/cap +1 were (12%), IVSI-5/cd-15 were (8%), IVSI-5/Fr 41-42 were (2%), IVSII-1 were (2%) and Undetermined were (4%). The association between these two was considered statistically significant with p=0.005 was obtained using Fisher's Exact test.

DISCUSSION

β-thalassemia intermedia comprised of genetically and phenotypically heterogeneous clinical conditions with severity ranges from mild-to-moderate anemia and variability in transfusion requirement.[9] Primary determinant of clinical severity of Thalassemia intermedia is β-globin gene mutation. However, clinical heterogeneity is also dependent on many genetic modifiers that modulates the level of globin chain imbalances, and therefore, the degree of ineffective erythropoiesis.[10,11]

Severity of illness of B-Thalassemia syndrome is also affected by improvement in α-globin chain to β-globin chain balance, either by the production of β-like globin or by reducing the production of α-globin genes. It has been discovered that co-inheritance of the α-thalassemia trait (-α/αα, --/αα, -α/-α) improves the clinical symptoms of β-thalassemia and, in rare instances, eliminates the requirement for lifelong transfusions in thalassemia.[12,13] Genetic modifiers improve clinical symptoms by increasing the production of the γ-globin chain, which protects against the harmful effects of an excess α-globin gene.[13,14]

Numerous genome editing techniques, which have been widely used in recent decades, have been shown to either reactivate HbF[15] or fix mutations that cause thalassemia. Among them, certain DNA double-strand breaks (DSBs) are produced by three generations of programmable nucleases: zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and CRISPR-associated nuclease Cas9 (CRISPR-Cas).[16] Clinical

trials are showing encouraging outcomes from advanced gene therapies that aim to reactivate HbF in autologous HSPCs by ex vivo CRISPR/Cas9 gene-editing targeting the erythroid enhancer region of BCL11A.[17]

Current research findings not only reflect the frequency of primary mutations and secondary modifiers present in thalassemia intermedia in Pakistan but it signifies the association of primary mutations with secondary modifiers. There are currently no research available worldwide that offer statistics regarding the relationship between primary and secondary modifiers. The age range in our study was 3–30 years old, with a mean age of 13.2 ± 8.0 years. The majority of the 23 patients (32.9%) were in the 5–10 age range. Thirty-two (45.7%) and thirty-eight (54.3%) of the 70 thalassemia intermedia cases were male.

In a mutational analysis conducted by Hariharan et. al commonest mutation found was IVS 1–5, mutation experienced in both the β-thalassemia homozygous group (TM: 32%, TI: 28%). Other mutations including codons 8/9, 619 bp deletion IVS 1-1, codon 15 and codons 41/42 considered for 82.5% of molecular lesions (TM: 44.5%, TI: 38%).[18] It is in contrast to our study in which commonest mutation found was Cd-15 (14.3%). Other mutations found were -88 (7.1%), Cd-30 (2.9%), Fr 41-42/Cap+1 (4.3%), Fr 41-42/Cd5 (2.9%), Fr 8-9 (12.9%), Fr 8-9/cap+1 (7.1%), Fr 8-9/Cd-15 (2.9%), Fr 8-9/ Fr 41-42 (1.4%), Fr 8-9/Fr16 (2.9%), Fr 8-9/IVSI-5 (2.9%), Fr 8-9/IVSII-1 were (2.9%), Hb-E/Fr 8-9 were (1.4%), IVSI-5 were (11.4%), IVSI-5/cap +1 were (8.6%), IVSI-5/cd-15 (5.7%), IVSI-5/Fr 41-42 (1.4%), IVSII-1 (1.4%), and Undetermined were (5.7%) cases.

Study conducted by Hassan et al showed that commonest mutations were Cap +1, Fr 8-9, IVS1-5 and del 619, respectively which were identified as homozygosity and compound heterozygous mutations. It is also in contrast to our study according to which most common primary mutation is Cd-15.[19] This difference may be due different sample size and different sample population.

In our study mutational analysis was performed only in thalassemia intermedia patients whereas the study conducted by Priya Hariharan included patients of thalassemia major as well as of sickle cell anemia. Also in study by Hariharan[18], the homozygosity for the mutant T allele T/T, Xmn I+/+] was found to be substantially greater in TI (44.0%) than in TM (28.0%) in the β-thalassemia homozygous group (P: 0.01). Whereas in our study frequency of secondary modifiers Xmn-1 in beta Thalassemia Intermedia found out to be 37.14%.[18]

In a study conducted in District Bannu total 250 patients of beta thalassemia intermedia were checked by ARMSPCR for six B-thalassemia mutations.

Results of study revealed that frame shift codons (FSC) 8/9, the most common mutation. Other mutations found to be Codons 41/42, IVS-I-5 and FSC 5 having frequencies of 42%, 26%, 19% and 13% respectively. However, this study could not report codon 15 & IVS-I- which was found to be the most common mutation according to our study.[20]

83.3% of β-thalassemia intermedia patients were heterozygous for the XmnI polymorphism, according to an Egyptian study. These patients with a single T allele of XmnI had milder disease, a delayed diagnosis, and higher HbF levels than patients who were negative for the XmnI polymorphism.[21] Whereas in our study secondary mutations Xmnl-I Homozygous were (10%), Heterozygous were (25.7%).[24]

A research in northern Iran found that 86% of people had Xmn1 gene polymorphism, either at one locus (-/+, 21%) or both loci (+/+, 65%).[22] The frequency of Xmn1 gene polymorphism in the southeast of Iran was 62%, according to another Iranian study by Miri-Moghaddam et al.[23] This may be because patients from different countries and even different regions within the same countries have varied geographical distributions of the Xmn1 polymorphism.

In our study it has been found that primary mutations highly associated with Xmn-1 polymorphism are IVSI-5 (30.8%), IVSI-5/cap +1 (15.4%), whereas association of other primary mutations was low with Xmn-1 polymorphism. These mutations are Fr

41-42/Cd5 (7.7%), Fr 8-9/cap+1 (7.7%), Fr 8-9/Fr16 (7.7%), Fr 8-9/IVSII-1 (7.7%), Hb-E/Fr 8-9 (3.8%), IVSI-5/Fr 41-42 (3.8%), IVSII-1 (3.8%), and Undetermined (11.5%).

In our study Primary mutations which are highly associated with BCL 11 A are IVSI-5 (16%), Cd-15 (16%) and IVSI-5/cap +1 (12%). Whereas other primary mutations associated with BCL 11 A were found to be Cd-30 (4%), Fr 41-42/Cap+1 (4%), Fr 8-9 (10%),Fr 8-9/cap+1 (4%), Fr 8-9/Cd-15 (4%), Fr 8-9/IVSI-5 (4%), Hb-E/Fr 8-9 (2%), IVSI-5/cd-15(8%), IVSI-5/Fr 41-42 (2%), IVSII-1(2%) and Undetermined were (4%).

Our findings indicate that certain primary mutations, particularly IVSI-5 and its combinations, show a relatively higher association with both Xmn-1 polymorphism and BCL11A variants, suggesting a potential modifying effect on clinical phenotype. However, the overall distribution of secondary modifiers across other mutations appears scattered and inconsistent. This variability, alongside the notable proportion of undetermined cases, highlights the complexity of genotype-modifier interactions and suggests that additional genetic or epigenetic factors may be involved. The limited dataset underscores the need for larger cohort studies and functional analyses to better elucidate the role of secondary modifiers in modulating disease severity, especially in compound heterozygotes or less common mutation profiles.

CONCLUSION

In summary, while our current understanding of the interplay between the primary mutation and potential secondary modifiers remains limited, the available evidence highlights the complexity of genotype-phenotype relationships. The scarcity of comprehensive data underscores the need for larger, well-characterized cohorts and integrative approaches that combine genetic, epigenetic, and environmental factors. Future studies are essential to unravel the modifying effects that may influence disease presentation and progression, ultimately guiding more precise diagnostic and therapeutic strategies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Fariha Nasreen:** Literature search, Conceptualization of study.
2	**Asma Shaikh:** Literature search.
3	**Madeeha Rehan:** Data collection.
4	**Fatima Iqbal:** Data analysis.
5	**Zareen Irshad:** Proof reading.
6	**Aqsa Noureen:** Literature search.

https://doi.org/10.29309/TPMJ/2026.33.02.9885 www.theprofesional.com

ORIGINAL ARTICLE

Capillary electrophoresis-based screening for haemoglobinopathies in Sindh and Balochistan, Pakistan: A cross-sectional study.

Kanwal Shafiq[1], Munazza Rashid[2], Intezar Hussain[3], Hafiza Sidra[4]

ABSTRACT… Objective: To assess the frequency and spectrum of haemoglobinopathies in Sindh and Balochistan using the Sebia Capillarys 3 Octa capillary electrophoresis system, and evaluate its diagnostic utility in routine clinical practice. **Study Design:** Descriptive Cross-sectional study. **Setting:** Department of Hematology, Chughtai Laboratory, Karachi, Pakistan. **Period:** June 2023 to June 2024. **Methods:** A total of 1,340 patients referred for hemoglobinopathy screening were included using consecutive non-probability sampling. Capillary electrophoresis (CE) was performed using the Sebia Capillarys 3 Octa system to detect hemoglobin variants and quantify HbA2. A cut-off value of HbA2 >3.5% was used to identify β-thalassemia trait. Complete blood counts and peripheral smears were also evaluated. Patients with recent transfusions or incomplete data were excluded. **Results:** Out of 1,340 patients, 344 (25.7%) were diagnosed with haemoglobinopathies. β-thalassemia trait was most frequent (59.9%), followed by elevated HbF cases (13.9%). Females comprised 61.7% of the study population, with the 18–35 years age group most affected. Karachi reported the highest number of cases. CE showed high analytical performance in identifying common and rare hemoglobin variants. **Conclusion:** CE using the Sebia Capillarys 3 Octa system is a reliable and efficient tool for hemoglobinopathy screening. The high prevalence of β-thalassemia trait highlights the need for regional screening and prevention strategies.

Key words: Capillary Electrophoresis, Electrophoresis, Haemoglobinopathies, Thalassemia.

Article Citation: Shafiq K, Rashid M, Hussain I, Sidra H. Capillary electrophoresis-based screening for haemoglobinopathies in Sindh and Balochistan, Pakistan: A cross-sectional study. Professional Med J 2026; 33(02):307-313. https://doi.org/10.29309/TPMJ/2026.33.02.9885

INTRODUCTION

Inherited hemoglobin disorders, including hemoglobinopathies and thalassemias, are among the most common autosomal recessive conditions worldwide. These disorders can be broadly categorized into structural (qualitative) defects such as hemoglobin S, C, D, and E and quantitative (regulatory) abnormalities, which result in reduced or imbalanced globin chain production, as seen in α- and β-thalassemias.[1] Globally, approximately 7% of the population carries abnormal hemoglobin genes, with over 300,000 infants born each year with severe forms of these disorders.[2] Effective screening and prevention programs have been shown to significantly reduce the disease burden, yet such initiatives remain limited in many low- and middle-income countries.[3,4]

In Pakistan, the burden of hemoglobinopathies is particularly high, largely due to the prevalence of consanguineous marriages, which increase the likelihood of inheriting these autosomal recessive conditions.[5,6] Previous regional studies report β-thalassemia trait carrier rates ranging from 5% to over 9%, with even higher prevalence in some areas.[7,8]

Accurate laboratory diagnosis is essential for effective management and prevention. Conventional method such as gel electrophoresis, isoelectric focusing (IEF), and high-performance liquid chromatography (HPLC) have been widely used for hemoglobinopathy screening, though each comes with limitations in terms of resolution and efficiency.[4,9,10] Capillary electrophoresis (CE) has emerged as a highly effective alternative, offering superior resolution, automation, and reproducibility, particularly for quantifying HbA2 and HbF and detecting compound heterozygous states.[1,11-14]

Sebia's Capillarys 3 Octa system is an advanced CE based platform designed for the high-throughput and precise analysis of hemoglobin variants.

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Article received on:
03/06/2025
Date of revision:
28/07/2025
Accepted for publication:
05/08/2025

This system is widely recognized for its analytical accuracy, automation, and ability to deliver consistent, reproducible separation of hemoglobin fractions. These characteristics make it particularly well-suited for the detection and characterization of both common and rare hemoglobinopathies in clinical diagnostic settings. Despite the growing global adoption of CE, there is a paucity of regional data evaluating its utility within diverse populations in Pakistan. Therefore, its application in large-scale screening and diagnosis of hemoglobin disorders in this setting warrants further exploration.[7,13,14]

This study aims to assess the frequency and spectrum of hemoglobinopathies in the coastal provinces of Sindh and Balochistan, using CE as the diagnostic modality. The goal is to evaluate the utility of CE in routine diagnostic settings and to contribute updated regional epidemiological data to support informed public health strategies.

METHODS

This descriptive cross-sectional study included 1,340 patients referred for hemoglobin disorder screening between June 2023 and June 2024 at the Department of Hematology, Chughtai Laboratory, Karachi, Pakistan. The laboratory serves as a reference center, receiving samples from multiple collection units.

Ethical approval was obtained from the Institutional Review Board (IRB) under letter number CIP/IRB/1189. Patients of all ages and both sexes referred for hemoglobinopathy screening were enrolled using consecutive non-probability sampling. Individuals who had received a blood transfusion within the last three months or had incomplete laboratory data were excluded.

Complete blood counts (CBCs) were performed using the Sysmex XN-1000 and Mindray BC-6200 analyzers. Peripheral blood smears were stained with Leishman's stain, and red cell morphology was assessed for hypochromia, anisocytosis, microcytosis, macrocytosis, and polychromasia using standard criteria.

Hemoglobin electrophoresis was performed using the Sebia Capillarys 3 Octa system, which employs capillary zone electrophoresis through eight parallel quartz capillaries to separate hemoglobin fractions based on electrical charge in free solution. Whole blood samples were analyzed directly using the system's cap-piercing technology. Electropherograms were evaluated for hemoglobin variants (e.g., HbS, HbC, HbE), and HbA2 quantification. A cut-off value of HbA2 > 3.5% was used for the diagnosis of β-thalassemia trait. Key performance metrics included peak resolution, coefficient of variation (CV) for HbA2 measurements, and concordance with reference diagnoses.

RESULTS

As per the inclusion criteria, a total of 1340 patients were enrolled in the study. Of the 1,340 patients, 344 (25.7%) were diagnosed with haemogobinopathies while the rest harboured a normal pattern (n=996; 74.3%). The distribution of the various hemoglobinopathies reported in the present study are displayed in Figure-1. The most frequent hemoglobinopathy observed in the current study was β-thalassemia trait (n=206/344; 59.9%) followed by cases with of high fetal hemoglobin (HbF), (n=48/344; 13.9%). These were patients with a history of blood transfusions, who showed elevated HbF levels and morphological findings suggestive of thalassemia syndrome. These patients were advised to repeat hemoglobin electrophoresis after three months. Single cases of compound heterozygous for HbE/β-Thalassemia, compound heterozygous for HbC/β-Thalassemia, and compound heterozygous for HbS/D-Thalassemia were reported in the present study (Figure-1). The present study had a female predominance (n=827; 61.7%). Based on gender, in the most common hemoglobinopathy i.e. β-thalassemia trait, more than half of the patients were females (55.8%; n=115/206) (Figure-2). Figure-2 illustrates the gender-wise distribution of various hemoglobinopathies observed in the study population. Overall, a female predominance was noted, with females accounting for 61.7% of the total participants (n=827). When evaluating the most frequently diagnosed hemoglobinopathy, β-thalassemia trait, a similar gender trend was observed. Out of the 206 individuals diagnosed with β-thalassemia trait, 55.8% (n=115) were female, indicating a slightly higher prevalence among

females compared to males.

Based on age, the most frequent age group was 18-35 years (n=585) followed by 0.02 -10.0 years (n=462). With hemoglobinpathies as a focus of study, β-thalassemia trait was the most frequent group in which majority of the patients fell in 18.0 years -35 years age group (n=102/206; 49.5%) (Table-I). Regionally, the predominance of hemoglobinopathies was observed in Karachi (n=169) followed by Quetta (n=61) (Table-II). The median (IQR) values of the electrophoresis for different hemoglobin variants are shown in Table-III.

FIGURE-1

Overall frequency of various haemoglobinopathies

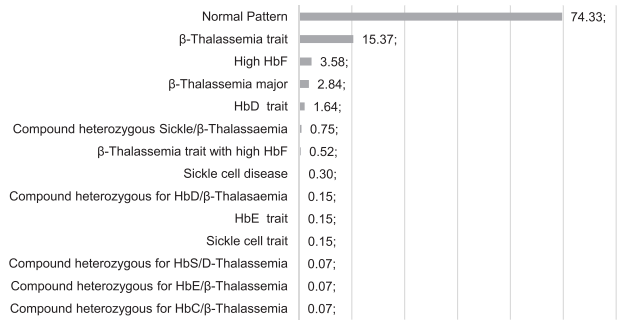
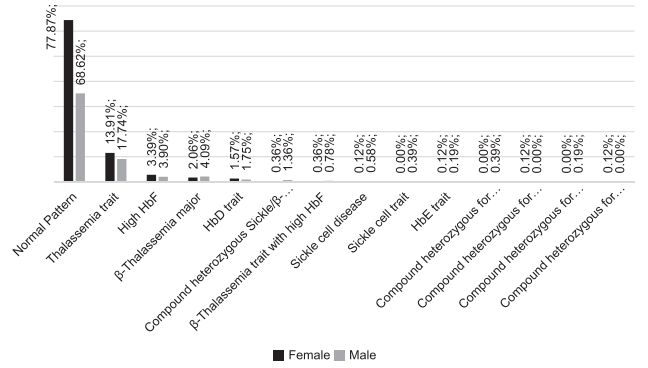


FIGURE-2

Gender distribution for various haemoglobinopathies



DISCUSSION

This cross-sectional study conducted at Chughtai Laboratory, Karachi, provides important insights into the prevalence and spectrum of hemoglobinopathies in the provinces of Sindh and Balochistan. Among the 1,340 individuals screened, hemoglobinopathies were identified in 25.7% (n=344) of cases. These findings are consistent with previous research, such as Waheed et al. (2012), who reported a 28.4% frequency of hemoglobinopathies in Islamabad, reinforcing the significant public health impact of β-thalassemia in Pakistan.[15]

Haemoglobin disorders are a major global health concern, affecting 71% of 229 countries, which together account for 89% of the world's births. Each year, over 330,000 infants are born with severe hemoglobinopathies (83% with sickle cell disorders and 17% with thalassaemias), contributing to approximately 3.4% of deaths in children under five; globally, about 7% of pregnant women carry β-thalassaemia, α^0-thalassaemia, or hemoglobin variants S, C, D Punjab, or E, and more than 1% of couples are at genetic risk. Integrating hemoglobinopathy screening and genetic counseling into routine healthcare systems is therefore essential to identify at-risk couples and reduce disease incidence through informed reproductive decisions. In Pakistan, the burden is compounded by the high rate of consanguineous marriages, which increases the inheritance of autosomal recessive traits.[6,16]

In the present study, the most prevalent hemoglobinopathy was β-thalassemia trait (59.9%), followed by cases with elevated fetal hemoglobin (HbF) levels (13.9%). Recent studies from urban centers such as Rawalpindi and Islamabad have reported similarly high prevalence rates. One study found hemoglobinopathies in 37.8% of 600 individuals, with β-thalassemia trait (47.1%) and β-thalassemia major (23.3%) as the most common forms. Another study involving 5,961 participants identified hemoglobinopathies in 11.9% of cases, with β-thalassemia trait again being the most frequent (9.5%). These findings underscore the significant burden of hemoglobinopathies in urban populations and highlight the urgent need for comprehensive screening programs and preventive strategies.[17,18] These results reflect a considerable burden in urban centers and emphasize the need for comprehensive screening and preventive measures.

A study from Peshawar detected hemoglobinopathies in 42.2% of 263 samples, with β-thalassemia minor (32.7%) and major (8.4%) as the most frequent.

TABLE-I

Age wise distribution of haemoglobinopathies

Haemoglobinopathies	Frequency	Age (years)						
		0.02-10.0 (n=462)	11.0-17.0 (n=138)	18.0-35.0 (n=585)	36.0-50.0 (n=118)	51.0-65.0 (n=25)	66.0-80.0 (n=10)	81.0-95.0 (n=2)
Normal Pattern, n (%)	996	323 (69.9)	105 (76.1)	458 (78.3)	84 (71.8)	16 (64.0)	9 (90.0)	1 (50.0)
β-Thalassemia trait, n (%)	206	44 (9.5)	21 (15.2)	102 (17.4)	28 (23.7)	9 (36.0)	1 (10.0)	1 (50.0)
High HbF, n (%)	48	40 (8.7)	2 (1.4)	6 (1.6)	-	-	-	-
β-Thalassemia major, n (%)	38	37 (8.0)	1 (0.7)	-	-	-	-	-
HbD trait, n (%)	22	5 (1.1)	4 (2.9)	11 (1.9)	2 (1.7)	-	-	-
Compound heterozygous Sickle/β-Thalassaemia, n (%)	10	4 (0.9)	2 (1.4)	3 (0.5)	1 (0.8)	-	-	-
β-Thalassemia trait with high HbF, n (%)	7	7 (1.5)	-	-	-	-	-	-
Sickle cell disease, n (%)	4	-	2 (1.4)	2 (0.3)	-	-	-	-
Sickle cell trait, n (%)	2	-	1 (0.7)	-	1 (0.8)	-	-	-
HbE trait, n (%)	2	1 (0.2)	-	-	1 (0.9)	-	-	-
Compound heterozygous for HbD/β-Thalasaemia, n (%)	2	-	-	2 (0.3)	-	-	-	-
Compound heterozygous for HbE/β-Thalassemia, n (%)	1	1 (0.2)	-	-	-	-	-	-
Compound heterozygous for HbC/β-Thalassemia, n (%)	1	-	-	-	1 (0.2)	-	-	-
Compound heterozygous for HbS/D-Thalassemia, n (%)	1	-	-	1 (0.2)	-	-	-	-

TABLE-II

Regional distribution of haemoglobinopathies

Haemoglobinopathies	Frequency	KHI (n=920)	HDD (n=92)	Sindh (Besides KR & HDD) (n=165)	QTA (n=122)	Balochistan Besides QTA (n=41)
Normal Pattern, n (%)	996	751 (81.6)	64 (69.6)	101 (61.2)	61 (50.0)	19 (46.3)
β-Thalassemia trait, n (%)	206	122 (13.3)	11 (12.0)	26 (15.8)	34 (27.9)	13 (31.7)
High HbF, n (%)	48	12 (1.3)	9 (9.8)	18 (10.9)	6 (4.9)	3 (7.3)
β-Thalassemia major, n (%)	38	12 (1.3)	3 (3.3)	15 (9.1)	3 (2.5)	5 (12.2)
HbD trait, n (%)	22	14 (1.5)	1 (1.1)	3 (1.8)	3 (2.5)	1 (2.4)
Compound heterozygous Sickle/β-Thalassaemia, n (%)	10	2 (0.2)	1 (1.1)	-	7 (5.7)	-
β-Thalassemia trait with high HbF, n (%)	7	4 (0.4)	2 (2.2)	1 (0.6)	-	-
Sickle cell disease, n (%)	4	-	1 (1.1)	-	3 (2.5)	-
Sickle cell trait, n (%)	2	1 (0.1)	-	-	1 (0.8)	-
HbE trait, n (%)	2	-	-	1 (0.6)	1 (0.8)	-
Compound heterozygous for HbD/β-Thalasaemia, n (%)	2	-	-	-	2 (1.6)	-
Compound heterozygous for HbE/β-Thalassemia, n (%)	1	1 (0.1)	-	-	-	-
Compound heterozygous for HbC/β-Thalassemia, n (%)	1	-	-	-	1 (0.8)	-
Compound heterozygous for HbS/D-Thalassemia, n (%)	1	1 (0.1)	-	-	-	-

KHI: Karachi; HDD: Hyderabad; QTA: Quetta

TABLE-III

Haemoglobin electrophoresis results in various haemoglobinopathies

Haemoglobinopathy	N	HbA%	HbA2 %	HbF %	HbS %	HbD %	HbS/D %	HbE %	HbH %	HbC %
Normal Pattern, Median (IQR)	996	97.7 (97.4-98.0)	2.3 (2.0-2.5)	1.7 (1.0-2.7)	-	-	-	-	-	
β-Thalassemia trait, Median (IQR)	206	94.6 (93.9-95.0)	5.2 (4.8-5.6)	2.1 (1.5-3.3)	-	-	-	-	-	
High HbF, Median (IQR)	48	70.8 (47.5-89.5)	2.8 (2.1-3.3)	27.2 (8.6-50.1)	-	-	-	-	-	
β-Thalassemia major, Median (IQR)	38	4.7 (3-13.4)	2.4 (1.9-3.2)	97.0 (93.8-98.0)	-	-	-	-	-	
HbD trait, Median (IQR)	22	61.6 (59.3-65.2)	2.9 (2.5-3.1)	1.5 (0.43-2.3)	-	35.4 (32.1-37.4)	-	-	-	
Compound heterozygous Sickle/β-Thalassaemia, Median (IQR)	10	3.0 (3.0-3.0)	4.0 (3.8-4.6)	32.7 (26.2-38.6)	63.6 (57.4-69.3)	-	-	-	-	
β-Thalassemia trait with high HbF, Median (IQR)	7	84.7 (79.5-86.4)	4.2 (1.4-5.4)	9.8 (7.8-16.3)	-	-	-	-	-	
Sickle cell disease, Median (IQR)	4	-	1.6 (1.2-2.3)	21.3 (14.1–28.8)	77.3 (69.9–83.6)	-	-	-	-	
Sickle cell trait, Median (IQR)	2	62.0 (60.0-64.0)	2.8	-	35.2 (33.2-37.2)	-	-	-	-	
HbE trait, Median (IQR)	2	70.2 (68.1-72.3)	1.75 (0.8-2.7)	-	-	-	-	28 (25-31.0)	-	
Compound heterozygous for HbD/β-Thalasaemia, Median (IQR)	2	-	6.6 (6.4-6.8)	2.0 (1.0-3.0)	-	91.4 (90.6-92.2-)	-	-	-	
Compound heterozygous for HbE/β-Thalassemia, Median (IQR)	1	7	27.2	-	-	-	65.8	-	-	
Compound heterozygous for HbC/β-Thalassemia, Median (IQR)	1	-	6.1	1.6	-	-	-		-	92.3
Compound heterozygous for HbS/D-Thalassemia, Median (IQR)	1		3.1	3.7	-	-	93.2	-	-	

The study also reported a 37.3% association with consanguinity, underscoring the role of intra-family marriages in the transmission of these disorders. Such findings highlight the importance of family-based screening programs to reduce both the medical and financial impact on affected populations.[19]

A retrospective analysis conducted at Indus Hospital and Health Network in Karachi, using the ADAMS A1C HA-8180T analyzer, reported a hemoglobinopathy prevalence of 14.5% among 2,422 patients. The β-thalassemia trait was again the most common, accounting for 6.4% of cases.[20]

Another study from a tertiary care hospital utilizing HPLC on 3,289 samples revealed hemoglobinopathies in 21.5% of individuals.

Thalassemia minor was the most prevalent (19.6%), followed by HbD trait (1.3%), HbS trait (0.36%), and HbE trait (0.21%). No cases of HbC were reported. The mean age of patients with thalassemia minor was 24 ± 14.7 years, highlighting the asymptomatic nature of many carriers.[21]

Data from District Dera Ismail Khan pointed to notable ethnic differences in hemoglobinopathy prevalence. The Baloch, Mehsud, and Marwat tribes exhibited higher rates of β-thalassemia, while the sickle cell gene was more frequent in the Sherani, Bhatni, and Ustrana communities. These findings underscore the necessity of implementing targeted community-based screening, genetic counseling, and public education programs. In our study, most hemoglobinopathy cases were reported from Karachi, likely due to its ethnically diverse population.[22]

A comparative study at the Armed Forces Institute of Pathology, Rawalpindi, evaluated 90 newly diagnosed cases using both HPLC and CE. The study found β-thalassemia trait to be the most common (55.6%), while HbD homozygosity was the least frequent (1.1%). Notably, CE outperformed HPLC in detecting hemoglobin variants such as HbD Iran and HbE, affirming its diagnostic advantage.[23]

This study is limited by its exclusion of recently transfused patients, lack of genetic confirmation, and single-center design, which may affect the generalizability and completeness of the findings.

CONCLUSION

This study highlights the substantial burden and diverse spectrum of haemoglobinopathies in the coastal provinces of Sindh and Balochistan, with β-thalassemia trait emerging as the most frequently diagnosed variant. The demographic distribution indicates a higher prevalence among young adults and females, particularly in urban centers like Karachi. CE demonstrated high diagnostic accuracy, effectively identifying both common and rare haemoglobin variants, and offers a practical, high-throughput solution for routine clinical use. These findings emphasize the need for region wide screening initiatives, early diagnostic interventions, and public awareness programs. Future studies integrating genetic analysis and multi-center collaboration are essential to deepen our understanding and to inform national strategies for the prevention and control of haemoglobin disorders in Pakistan.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Kanwal Shafiq:** Analysis, manuscript formatting.
2	**Munazza Rashid:** Interpreted the data.
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4	**Hafiza Sidra:** Data entry.

https://doi.org/10.29309/TPMJ/2026.33.02.10037 www.theprofesional.com

ORIGINAL ARTICLE

Significance of New Index Matos and Carvalho Index in differentiation of iron deficiency anemia and beta thalassemia trait.

Noorulain Fareed[1], Saba Aman[2], Muhammad Younus Jamal Siddiqi[3], Shazia Kousar[4], Ghulam Fatima[5]

ABSTRACT… Objective: To assess the value of the Matos and Carvalho index (MCI) in detecting beta thalassemia traits in patients with microcytic hypochromic anemia. **Study Design:** Retrospective study. **Setting:** Department of Hematology, CHK Central Laboratory Dr Ruth KM Pfau Civil Hospital Karachi, Pakistan. **Period:** 1st July to 31st December 2022. **Methods:** All newly diagnosed cases of iron deficiency and Beta Thalassemia trait were included. 297 patients with an age range of 1–60 years were evaluated. We calculated 4 discrimination indices in all patients with hemoglobin (Hb) values of <10 g/dL. The patient groups were evaluated according to red blood count; the Mentzer index (MI); the Srivastava index (SI) and Matos and Carvalho index (MCI). In this study complete blood counts for red cell indices were processed on a Hematology analyzer (XN-1000), HPLC was done on Arkray HA-8108T and serum ferritin was done on a chemistry analyzer (COBAS 501). **Results:** 297 patients were included in the present study with hypochromic, microcytic anemia for beta thalassemia trait (BTT) and iron deficiency anemia (IDA). HPLC detected 141 patients with BTT, while 156 were diagnosed with IDA. The average age of Patients with BTT was 14.5 years, whereas the average age of IDA patients was 20.6 years. The Mentzer index correctly identified patients at 64.6%, followed by MCI and SI at 63.2%, 62.2%, and 55.2%, respectively. **Conclusion:** The Matos & Carvalho Index offers an easy and accessible way to enhance thalassemia detection and iron deficiency anemia by the simple test of CBC at the frontline. In this study Srivastava index (SI) demonstrated the most robust reliability levels when distinguishing between beta thalassemia trait and Iron deficiency anemia. However, the absence of red cell indices and methods that possess 100% specificity, efficacy, and sensitivity hinders the differentiation of BTT from other hypochromic microcytic anemia.

Key words: Anaemia, Beta Thalassemia Trait, Ferritin, HPLC, Microcytic, Matos and Carvalho Index.

Article Citation: Fareed N, Aman S, Siddiqi MYJ, Kousar S, Fatima G. Significance of New Index Matos and Carvalho Index in differentiation of iron deficiency anemia and beta thalassemia trait. Professional Med J 2026; 33(02):314-319. https://doi.org/10.29309/TPMJ/2026.33.02.10037

INTRODUCTION

Thalassemia was first described by Dr. Thomas Cooley in the pediatric population of Mediterranean region almost a century ago.[1] most of the thalassemia major patients have severe anemia in the initial 2 years of life and without treatment and transfusion, they have shortened life expectancy.[2]

According to literature 5%–7% cases reported in the population of the world, which has carrier state of beta thalassemia. . It involves genetic Hb variations in the thalassemia.[3]

According to reported literature around 800 million cases of anemia, major cases of anemia are secondary to iron deficiency anemia or thalassemia carrier state. World Health Organization (WHO) estimated that iron deficiency anemia can cause 273,000 deaths, and developing countries are majorly affected around 97%.[4]

In a developing country like Pakistan, this hemoglobin disorder can cause burden on the health care system because of regular and frequent blood transfusions and treatment of complications such as iron overload are quite costly, mostly affected persons and their family cannot afford the treatment.[5]

Pakistan is one of those countries with the highest thalassemia burden.[6] According to safe blood transfusion authority, about 2.7 million blood collections are made in Pakistan annually, around one fourth blood products are used for the treatment of thalassemia.[7] This is quite a large figure of blood transfusions for a developing country like Pakistan.

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Article received on:
18/08/2025
Date of revision:
24/10/2025
Accepted for publication:
30/10/2025

The most common causes of microcytic, hypochromic anaemia are iron deficiency anemia (IDA) and beta thalassemia trait (BTT), especially in the pediatric population.[8]

In the Southeast Asia, the Mediterranean region, middle east and central Africa, around 50% of the population having thalassemia trait.[9]

Thalassemia carriers can be discovered in people with no obvious signs and symptoms. To confirm the diagnosis of thalassemia trait, we need specialized tests such as hemoglobin electrophoresis or high-performance liquid chromatography (HPLC). In the patients who present with hypochromic, microcytic picture on CBC, serum iron profile and HPLC should be done for exact diagnosis. Diagnosis of the Beta thalassemia trait (TT) is usually confirmed by hemoglobin electrophoresis or HPLC method with elevated HbA2 levels (>3.5%).

In previous studies, several red cell indices parameters were found to be useful to simplify the difference between iron deficiency anemia and thalassemia carrier state-based complete blood count parameter analysis. The formula developed by Green & King [MCV2) × RDW]/(Hb × 100) where MCV means corpuscular volume, RDW is RBC distribution width and Hb is hemoglobin} is a useful formula according to some studies. The major disadvantage is that in the formula the RDW has to be calculated which is not mentioned in CBC analysis reports. In addition, the current indexes that have been recorded in literature lack the biology molecular studies to diagnose thalassemia. This analysis is essential to confirm the diagnosis and exclude concurrent diseases. A novel modified index, called the Matos and Carvalho index (MCI)[10] has been reported in recent studies. This index utilizes the RBC count and mean corpuscular hemoglobin concentration (MCHC) parameters. The formula MCI is = (1.91 × RBC) + (0.44 × MCHC). Through the analysis of the ROC curve> MCI has demonstrated a discriminative cut-off value of 23.85 to distinguish between Iron Deficiency Anemia (IDA) and Beta Thalassemia (BTT). Patients with an index value less than 23.85 are categorized as having Iron Deficiency Anemia, while those with an index value greater than 23.85 are identified as carriers of Thalassemia. This research aims to assess the significance of a new index capable of distinguishing between Iron Deficiency Anemia and carriers of Thalassemia. This will be accomplished with simple red cell indices provided by all automatic hematology analyzers.

METHODS

This retrospective cross sectional study was conducted in the Hematology Department CHK Central Laboratory Dr Ruth KM Pfau Civil Hospital Karachi from 1st July to 31st December 2022.

Ethical approval was obtained from the Institutional Review Board (IRB-2953/DUHS/EXEMPTION/2023/134). CBC, serum ferritin levels, Hb A2 and detection of Hb H inclusion bodies were done to confirm the diagnosis. All newly identified cases of beta thalassemia trait and iron deficiency anemia were included based on serum ferritin and CBC results. In samples obtained in our laboratory, a complete blood count was performed on an XN 1000 analyser, followed by a ferritin analysis on a COBAS and HPLC by Arkray ADAMs HA-8108T was used.

Over 6 months, 297 patients with confirmed microcytic anaemias were included with non-probability sampling in the study. 156 patients were diagnosed with iron deficiency anemia based on low hemoglobin, low MCV and MCH levels and low serum ferritin levels. 141 patients were diagnosed with beta-thalassemia trait based on low Hb and MCV levels, normal serum ferritin and elevated levels of Hb A2 (>3.5%).

Patients were classified as having BTT if their HbA2 level was greater than 3.5% or IDA if their blood ferritin level was less than 10 ng/ml.

In this research article, five discrimination indices were calculated and used for evaluation. These indices included specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), and Youden's index. The values for each discrimination index were analyzed and compared to the ones reported in the previous research reports. Specifically, the Mentzer index (MI), the Srivastava Index (SI), the Matos & Carvalho index (MCI), and

the red blood cell (RBC) count were analyzed. The data were presented as the mean ± standard deviation. Data analysis was performed using the SPSS version 24.0 program. A P-value of < 0.05 was considered statistically significant.

RESULTS

Two hundred nine seven patients of microcytic, hypochromic anemia were enrolled and on the screening of these cases, they diagnosed iron deficiency anemia (IDA) and beta thalassemia trait (BTT). 141 were diagnosed with BTT using HPLC, while 156 were diagnosed with IDA based on low ferritin levels. It was observed that patients with BTT had a mean age of 14.5 years, whereas patients with IDA had a mean age of 20.6 years.

In the Table-I red cell indices formula mentioned, were applied to distinguish between IDA and BTT in our study, such as RBC count, Mentzer index (MI), Matos & Carvalho (MCI), and Srivastava index (SI).

In this study, the mean and ranges of complete blood count (CBC) parameters were calculated in the present study. The comparison of discrimination indices for both study groups are shown in Table-II.

In our study, the most reliable index for identifying the IDA and BTT patients at a rate of 64.6%, followed by RBC count, MCI, and SI at rates of 63.2%, 62.2%, and 55.2%, respectively, which is shown in Table-II.

Sensitivity, specificity, positive predictive value, negative predictive value, and Youden's index of each discrimination index mentioned in Table-III. The most sensitive index for BTT was the Srivastava index (SI) with sensitivity, specificity and Youden's index of 70.9%, 77.8% and 48.1% respectively, followed by the Mentzer index (MI), RBC count and Matos & Carvalho index (MCI). The MCI index showed great sensitivity and specificity for iron deficiency anemia cases (98%) & (92.1%) respectively, followed by MI, RBC count and SI index.

The mean Matos & Carvalho Index (MCI) was 24.3 in patients with BTT and 21.4 in those with IDA, with a notable P-value of 0.001.

TABLE-I

Different RBC indices and mathematical formulas used to differentiate between -TT and IDA

Hematological Index	Formula
Mentzer index (MI)	MCV/RBC
MCI	(1.91×RBC) +(0.44×MCHC)
Srivastava Index (SI)	MCH/RBC

TABLE-II

Results obtained from each discrimination index.

Indices (Cut off)	IDA (156)	BTT (141)	Correctly Diagnosed Subjects	Correctly Diagnosed (%)
MCI				
IDA <23.85	153	109	185	62.2
TT >23.85	03	32		
Mentzer				
IDA >13	120	69	192	64.6
TT <13	36	72		
SI				
IDA >4.4	64	41	164	55.2
TT <4.4	92	100		
RBC count				
IDA <5.0	116	69	188	63.2
TT >5.0	40	72		

DISCUSSION

Several studies have established different indices or formulas based on red blood cell (RBC) indices that can be utilized for the differentiation of iron deficiency anaemia (IDA) from beta thalassemia trait (BTT). The differentiation between these two conditions of microcytic anemia remains a challenge for physicians or hematologists because correct diagnosis is needed for the management and prevention of the disease.

In the present study, a new index (MCI) was used to validate in the screening of IDA and BTT as reported in the previous study by Matos. Our research suggests that MCI may not serve as the most reliable indicator for physicians in detecting beta thalassemia traits.

TABLE-III

Sensitivity, specificity, positive predictive value, negative predictive value, and Youden's index of each discrimination index

Index	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Efficiency	Youden's indices
RBCx10^12/L						
IDA	74.3	84.9	82.2	77.9	79.8	59.2
TT	51	75	46.1	79.3	68.7	26.9
MI						
IDA	76.9	87	85.1	79.6	82	64
TT	51	75	46.1	79.3	68.7	26.9
MCI						
IDA	98	92.1	92.7	97.9	95	90
TT	22.7	68.1	20.5	70.8	56	-9.2
SI						
IDA	41	64.6	45.3	60.5	54.8	5.6
TT	70.9	77.8	64	82.7	75.3	48.1

No red cell index or formula offers complete sensitivity, specificity, and efficacy (100.0%) in distinguishing BTT from IDA. The diversity of thalassemia mutations significantly influences these variations.

The RBC count emerges as a readily accessible and straightforward method for BTT detection. Through comprehensive statistical analysis to effectively distinguish between IDA and thalassemia traits. Advanced or special investigations such as High-performance liquid chromatography (HPLC) may not be available or affordable in healthcare facilities, especially in developing countries.

The Physician must know these indexes that can help in the differentiation between BTT and IDA. In this study, we aimed to identify more effective RBC indices and formulas that are more suitable for our specific circumstances in comparison to previous studies. The accuracy rate of correctly identifying patients' MCI values was found to be 62.2%, which is noticeably lower than the 99.6% reported in Matos et al.'s study.[11] It is important to acknowledge the limitation of using the MCI index as a screening test for BTT; this constraint was previously mentioned in Hoffmann's study. Hoffmann proposed that the utilization of the MCI index may be more appropriate following additional justification based on the patient population.[12]

According to the data available in our study, the Srivastava index, exhibited a higher value than MCI in identifying patients with β-thalassemia trait (BTT). This index also demonstrated the highest Youden's index of 48.1% in accurately distinguishing between the β-thalassemia trait (BTT) and iron deficiency anemia (IDA). The calculation of the Mentzer index correctly diagnosed 64.6% of patients with microcytic anemia, which is comparable to findings from other studies.[13-14]

This formula exhibited a substantial level of sensitivity and specificity. Moreover, the MCI demonstrated a high positive predictive value (PPV) of 92.7%, which indicates its suitability as a screening tool in clinical practice. Notably, the MCI displayed a high sensitivity of 90% in detecting IDA. Given that sensitivity signifies the proportion of individuals correctly identified with the iron deficiency, the MCI's high sensitivity in detecting IDA suggests that it is a valuable tool for identifying the iron deficiency cases.

Ebrahim reported that cell differential counters help in the diagnosis process by enabling easy determination of RBC count.

Another study in the Indonesian population especially Surabaya also showed that the Matos and Carvalho Index has a low performance in discriminating BTT and IDA. Subjects used in the study were aged 3-17 years with different hematological profiles than the adult population (> 12 years) used in this study. Some hematological profiles in children tend to have lower values than adults affecting the study results.[15]

In our study, the RBC count and MI index showed more sensitivity for iron deficiency cases than BTT. RBC count and MI index showed sensitivity for IDA 74.3% and 76% respectively.

Previous studies, such as Fakher et al study (82%), Vehapoglu et al. study (65.3%), and George et al study (63.4%), have reported RBC indices with high Youden's indices.[16-18] This is supported by

the hematological profile between populations in Iran and Indonesia which both have higher average RBC values. In addition to the Matos and Carvalho indices, other indices in this study have also been shown to produce varying results compared to previous studies within sample populations globally or within the same geographical region.[19]

The spectrum of mutations could be the potential as a contributing factor to the differences in study outcomes, given the prevalence of thalassemia mutations in the global population, including Indonesia. This has been demonstrated in studies on the spectrum of beta-thalassemia mutations in Central Java and West Java.[20-22]

CONCLUSION

Our study suggests that MCI may not be the most reliable indicator for physicians to detect BTT. No single red cell index or formula offers complete sensitivity, specificity, and efficacy (100.0%) in distinguishing beta thalassemia traits from other forms of hypochromic microcytic anemia. The diversity of thalassemia mutations significantly influences these variations.

LIMITATIONS

The results of this study are biased as only selected samples were tested using conventional methods. Moreover, the high incidence of iron deficiency anemia in the population and the study cohort is another limiting factor that could be a reason for the underdiagnosis of beta thalassemia trait.

ACKNOWLEDGEMENT

We thank Miss Ariba, Mr. Rehan and Mr. Fayyaz for contributing to this study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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https://doi.org/10.29309/TPMJ/2026.33.02.10203 www.theprofesional.com

ORIGINAL ARTICLE

A comparison of pain-reducing effectiveness using laparoscopic-guided transverse abdominal plane block and port site infiltration in laparoscopic cholecystectomy: A randomized controlled trial.

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ABSTRACT… Objective: To compare the effectiveness, in terms of pain score and additional analgesia requirement, using laparoscopic-guided transverse abdominis plane block in comparison to port site infiltration in laparoscopic cholecystectomy. **Study Design:** Randomized Control Trial. **Setting:** Surgical Unit 2, Jinnah Hospital, Lahore. **Period:** Jan 2022 to Dec 2022 **Methods:** Included 92 patients (46 in each group) undergoing elective laparoscopic cholecystectomy Group A patients received a laparoscopic TA plane block with 40 ml 0.25% bupivacaine, 20 ml in each subcostal region, while group B received 40 ml 0.25% bupivacaine, 10 ml in each port site. The outcomes were assessed at 1st, 4th, 12th, and 24 hours post-operatively. **Results:** In Group A versus B patients, the mean age was 43.30+10.875 versus 44.22+8.894 years, the mean score at 1 hour was 3.26+0.953 vs 4.09+0.725, at 4 hours was 4.17+0.877 vs 4.87+1.046, at 12 hours was 4.52+0.983 vs 5.35+ 0.822 and at 24 hours 4.52+1.110 vs 5.52+ 1.516, respectively. In Group A vs B, rescue analgesia at 1st, 4th, 12th, and 24 hours was required in 8.7%, 26.1%, 43.5% & 52.1% versus 30.4%, 65.2%, 82.6% & 82.6%, respectively ($p<0.05$ at all intervals). **Conclusion:** The laparoscopic-guided transverse abdominal plane block is considerably superior to port site infiltration in terms of pain score and additional analgesia requirement.

Key words: Laparoscopic-guided TAP Block, Laparoscopic Cholecystectomy, Postoperative Pain.

Article Citation: Ali K, Nasim T, Sattar Z, Ahmad F, Hassnain S, Zohaib F. A comparison of pain-reducing effectiveness using laparoscopic-guided transverse abdominal plane block and port site infiltration in laparoscopic cholecystectomy: A randomized controlled trial. Professional Med J 2026; 33(02):320-325. https://doi.org/10.29309/TPMJ/2026.33.02.10203

INTRODUCTION

Gallstones were discovered in Egyptian mummies and have been known since antiquity.[1] Gallstone disease (GD) impacts 10–15% of Western adults, with females and the elderly being the most affected.[2] Each year, between one and four percent of individuals with gallstones become symptomatic and may require surgical intervention. Acute cholecystitis, cholangitis, obstructive jaundice, and acute pancreatitis can all be life-threatening if left untreated.[3]

In comparison to standard open cholecystectomy, laparoscopic cholecystectomy is associated with less post-operative discomfort, less painkiller usage, a quicker recovery period, and a reduction in hospital stay. Despite this, the intensity of postoperative abdominal and shoulder pain remains high, preventing cholecystectomy via laparoscopy from being performed on the same day in a significant proportion of patients.[4] Various therapy approaches and tactics have been developed and deployed throughout the years to address the problem of untreated post-operative pain.[5] One of these treatments is wound infiltration, which is used in conjunction with another regimen of analgesia. The effects of a peripherally administered local anesthetic, such as bupivacaine, might differ depending on the application site, such as instilling intraperitoneally, infiltration at the port and trocar site, and infiltration in the viscera.[5] A blind 'double pop' technique was used in 2001 to provide local anesthetics into the fascial plane.[6] TAP block with ultrasound guidance was first introduced in 2007, and while it is a better alternative to blind infiltration, it is still dependent on the operator.[7] Later, long-acting local anesthetics such as bupivacaine were used with laparoscopy-guided fascial infiltration.[8] GI surgeons have used the laparoscopically inserted TA plane (LTAP) block with comparable results to the ultrasound-guided TA plane (UTAP) block technique[9], especially in colorectal surgery and

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Article received on:
19/11/2025
Date of revision:
15/12/2025
Accepted for publication:
21/01/2026

laparoscopic cholecystectomies.[10] A recent meta-analysis claims that in patients who underwent a surgical intervention that was invasive minimally (such as laparoscopic abdominal procedures), LTAP was found to be a safe and superior intervention than local wound analgesia in terms of early control of pain, consumption of opioids, and satisfaction of patients.[11] Because laparoscopic techniques have advanced significantly, several doctors have recently started using TAP block and comparing it to port site infiltration to determine whether the block is better; nonetheless, the results are still unclear.[12]

OBJECTIVE

The objective of the research was to assess the effectiveness of port site infiltration against the laparoscopic-guided transverse abdominis plane block in laparoscopic cholecystectomy.

METHODS

It was a randomized control trial conducted at Surgical Unit 2, Jinnah Hospital, Lahore. A sample size of 92 patients (46 patients in each group) was taken by using a 95% confidence level, 80% power of test, and by taking mean VAS pain score after laparoscopic cholecystectomy with infiltration of local anesthesia in transverse abdominis plane and with infiltration of local anesthesia at port sites as 1.82±0.42 and 2.12±0.58 respectively.[12]

$$n = \frac{2\sigma^2(z_{1-\alpha/2} + z_{1-\beta})^2}{(\mu_1 - \mu_2)^2}$$

$Z_{1-\alpha/2}$= 95% = 1.95
$Z_{1-\beta}$= 80% = 0.80
μ_1 = Mean of population 1 = 2.12
μ_2 = Mean of population 2 = 1.82
$2\sigma^2 = 2(0.50^2)$

Following ethical committee permission (48/02/03/2021/52 ERB/11-03-21) at the hospital and patient informed consent, a randomized trial was carried out on 92 patients who had a laparoscopic cholecystectomy. Patients were admitted from the OPD. Group A had a laparoscopic-guided transverse abdominis plane block with 40 ml of 0.25% bupivacaine, 20 ml in each subcostal area, while group B received 40 ml of 0.25% bupivacaine, 10 ml in each port site. The patients were assigned to groups A and B by using a computerized random number table.

Inclusion Criteria

Recruitment was through non-probability purposive sampling with patients of the age group 18-65 years of either gender, including patients undergoing elective laparoscopic cholecystectomy for chronic cholecystitis / symptomatic gallstones.

Exclusion Criteria

Patients with a history of bleeding disorders, emphysematous or empyema gallbladders, mucocele, acute pancreatitis, acute cholecystitis, or prior abdominal surgery; a history of allergy to local anesthesia; with abdominal wall infection on examination; patients in whom laparoscopic procedures get converted to an open procedure; and with hepatobiliary malignancy diagnosed on ultrasound were excluded.

General Anesthesia was given to all the patients on a regimen that included induction with propofol 2 mg/kg and nalbuphine 6 mg, and for intubation, 0.5 mg/kg atracurium was given. Anesthesia was maintained with volatile isoflurane 1-2 MAC in oxygen and air (FiO_2 0.5). Standard monitoring included three leads: ECG, monitoring of blood pressure non-invasively, pulse oximetry (SpO_2), and temperature charting; the patient received intervention according to the group assignment.

A total of 40 ml of bupivacaine 0.25% was bilaterally injected. This created a bulge inferior to the Transversus Abdominus muscles, away from the Inferior Oblique muscle. While patients in group B had 40 ml of 0.25% bupivacaine and 10 ml on each site in subcutaneous tissue.

TAP block can be easily carried out laparoscopically by a surgeon. Under the guidance of a laparoscope, at the level of the midaxillary line, a Braun Stimuplex A needle is passed midway between the costal margins and the iliac crest. The needle is further advanced between the internal oblique and transversus abdominus muscle. Local anesthesia is injected, and a bulge would be appreciated laparoscopically. This procedure is performed on the opposite site as well.

Following surgery, all patients received 30 mg of intravenous ketorolac every eight hours and 1 g of paracetamol every eight hours. All individuals with visual analogue pain ratings of 4 or higher received additional analgesia with intravenous nalbuphine. This study's main objective was to assess pain score and additional analgesia requirement, which was calculated by the visual analogue score at the 1st, 4th, 12th & 24th hours post-operatively. All the data was collected through a pre-designed proforma.

Total postoperative nalbuphine requirement was noted in the first 24 hours. Nalbuphine was provided by the nursing staff, who were blinded by the study. When the VAS score was above 4, 10 mg of nalbuphine every 8 hours was used. A maximum of 3 doses was given in the first 24 hours.

Data were analyzed using SPSS v25.0. Quantitative variables such as age and pain scores were expressed as mean ± SD, while qualitative variables such as gender were expressed as frequencies and percentages. An independent sample t-test was used to compare pain scores between groups, and a chi-square test for categorical outcomes. To adjust for potential confounding factors (age, gender), multivariable linear regression (for pain scores) and logistic regression (for additional analgesia requirement) were applied. A p-value ≤0.05 was considered statistically significant.

RESULTS

Among 46 patients of Group A, 17.4% were males and 82.6% were females. Similarly among 46 patients of Group B, 21.7% were males and 78.3% were females.

Among 46 Group A (TAP Block) patients, 43.5% were up to 40 years old and 56.5% were above 40 years old. The mean age of the patients was 43.30+10.875 years.

Among 46 patients of Group B (Port Site Infiltration), 34.8% were up to 40 years old and 65.2% were above 40 years old. The mean age of the patients in this group was 44.22+8.894 years. (Table-I)

In Group A, 91.3%, 73.9%, 43.5%, and 47.8% patients had 1-4 pain score (analgesia not required) and 8.7%, 26.1%, 43.5% and 52.1% patients had >4 pain score (analgesia required) while the mean score of patients was 3.26+ 0.953, 4.17+ 0.877, 4.52+ 0.983 and 4.52+ 1.110 at one, four, twelve, and twenty-four hours, respectively.

Likewise in Group B, 69.6%, 34.8%, 17.4%, and 17.4% patients had 1-4 pain score (analgesia not required) and 30.4%, 65.2%, 82.6% and 82.6% patients had >4 pain score (analgesia required) while the mean score of patients was 4.09+ 0.725, 4.87+ 1.046, 5.35+ 0.822 and 5.52+ 1.516 at at one, four, twelve, and twenty-four hours, respectively. (Table-II)

TABLE-I

Comparison of age between both groups

Age	Group A TAP Block		Group B Port Site Infiltration	
	Frequency	Percentage	Frequency	Percentage
<40 years	20	43.5	16	34.8
>40 years	26	56.5	30	65.2
Total	46	100.0	46	100.0
Mean+SD	43.30+10.875		44.22+8.894	

In Group A, 8.7%, 26.1%, 43.5% & 52.1% of patients required analgesia, while 91.3%, 73.9%, 43.5% & 47.8% did not require analgesia at one, four, twelve, and twenty-four hours, respectively.

Whereas in Group B, 30.4%, 65.2%, 82.6% & 82.6% of patients required analgesia, while 69.6%, 34.8%, 17.4% & 17.4% did not require analgesia at one, four, twelve, and twenty-four hours, respectively. (Figure-1)

FIGURE-1

Comparison of Need for Analgesia between Both Groups

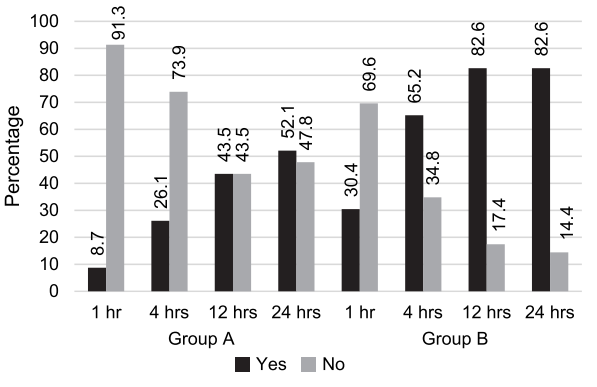

TABLE-II

Comparison of pain score between both groups

Pain Score	Group A TAP Block				Group B Port Site Infiltration			
	1 hr	4 hrs	12 hrs	24 hrs	1 hr	4 hrs	12 hrs	24 hrs
0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
1-4	42 (91.3%)	34 (73.9%)	20 (43.5%)	22 (47.8%)	32 (69.6%)	16 (34.8%)	8 (17.4%)	8 (17.4%)
>4	4 (8.7%)	12 (26.1%)	26 (43.5%)	24 (52.1%)	14 (30.4%)	30 (65.2%)	38 (82.6%)	38 (82.6%)
Total	46 (100%)	46 (100%)	46 (100%)	46 (100%)	46 (100%)	46 (100%)	46 (100%)	46 (100%)
Mean+SD	3.26+ 0.953	4.17+ 0.877	4.52+ 0.983	4.52+ 1.110	4.09+ 0.725	4.87+ 1.046	5.35+ 0.822	5.52+ 1.516

TABLE-III

Comparisons of different durations of pain score and need for analgesia

		t	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
						Lower	Upper
Age	Equal variances assumed	-.441	.660	-.913	2.071	-5.028	3.202
	Equal variances not assumed	-.441	.660	-.913	2.071	-5.030	3.204
Gender	Equal variances assumed	.521	.604	.043	.084	-.122	.209
	Equal variances not assumed	.521	.604	.043	.084	-.122	.209
Pain score (1 hour)	Equal variances assumed	-4.679	.000	-.826	.177	-1.177	-.475
	Equal variances not assumed	-4.679	.000	-.826	.177	-1.177	-.475
Pain score (4 hour)	Equal variances assumed	-3.457	.001	-.696	.201	-1.095	-.296
	Equal variances not assumed	-3.457	.001	-.696	.201	-1.096	-.296
Pain score (12 hour)	Equal variances assumed	-4.372	.000	-.826	.189	-1.201	-.451
	Equal variances not assumed	-4.372	.000	-.826	.189	-1.202	-.451
Pain score (24 hour)	Equal variances assumed	-3.609	.001	-1.000	.277	-1.551	-.449
	Equal variances not assumed	-3.609	.001	-1.000	.277	-1.551	-.449
Need for analgesia (1 hour)	Equal variances assumed	2.703	.008	.217	.080	.058	.377
	Equal variances not assumed	2.703	.009	.217	.080	.057	.378
Need for analgesia (4 hour)	Equal variances assumed	4.052	.000	.391	.097	.199	.583
	Equal variances not assumed	4.052	.000	.391	.097	.199	.583
Need for analgesia (12 hour)	Equal variances assumed	2.804	.006	.261	.093	.076	.446
	Equal variances not assumed	2.804	.006	.261	.093	.076	.446
Need for analgesia (24 hour)	Equal variances assumed	3.256	.002	.304	.093	.119	.490
	Equal variances not assumed	3.256	.002	.304	.093	.118	.490

Table-III exhibits that when the t-test was applied in both groups, significant results (P<0.05) were found regarding pain score at 1st, 4th, 12th & 24 hours and the need for analgesia at 1st, 4th, 12th & 24 hours while age and gender showed insignificant results (P>0.05).

DISCUSSION

Laparoscopic cholecystectomy is mostly accepted as a standard technique to treat benign gallbladder disease. For GD, laparoscopic cholecystectomy has become the treatment of choice and is linked with decreased post-operative pain, less analgesic consumption, reduced recovery period, and less hospital stay when compared with conventional procedures.

This study was carried out to compare the outcome of TAP block under the guidance of laparoscopy versus infiltration at the port site in individuals who

underwent laparoscopic cholecystectomy. Our study indicated that more than half of the patients in both groups were above 40 years. The mean age of the patients in the TAP block was 43.30+10.875 years, while in port site infiltration, it was 44.22+8.894 years. Virtually, the findings of our research are similar to a study performed by a study done in 2021, which asserted that the patient's mean age in the TAP block was 39.54±3.23 years, while in port site infiltration was 38.48.2±2.55 years.[13]

Among the general population, the major risk factor of gallstone development is gender, and it is believed that gallstones are more prevalent among females than males. The findings of our study also confirmed that 82.6% of patients in the TAP block and 78.3% of patients in port site infiltration were females.

During the study, the severity of pain was evaluated by VAS, and it was found that patients in the TAP block group had a lower pain score than patients in the port site infiltration group. Patients in the TAP block had mean scores of 3.26+ 0.953, 4.17+ 0.877, 4.52+ 0.983, and 4.52+ 1.110, while patients in the post-site infiltration had mean scores of 4.09+ 0.725, 4.87+ 1.046, 5.35+ 0.822, and 5.52+ 1.516 at 1, 4, 12, and 24 hours, respectively, which shows the better efficacy of the TAP block. A study in 2020 also confirmed that the TAP block is better than port site infiltration.[15] They reported that patients in the TAP block had mean scores of 1.38+0.23, 2.12+0.54, 2.01+0.87, 2.65+1.53, and 1.56+0.56, while patients in post-site infiltration had mean scores of 3.83+0.76, 3.45+0.30, 3.67+1.20, 2.14+1.11, and 1.69+0.79 at 3, 6, 12, 24, and 48 hours, respectively. A study done by Vindal and associates (2021) demonstrated that median VAS at 3rd, 6th, and 24th hours, at discharge, and one week after surgery were lower in the TAP block group than the port site infiltration group.[16] They further elucidated that the TAP block reduced the pain severity after surgery, helped in early discharge from the hospital and quick recovery, and enhanced patient satisfaction. However, a study undertaken by Siriwardana and collaborators (2019) indicated that laparoscopic-guided TAP block does not offer extra pain relief or better outcomes.[17] But a study carried out by Grape and teammates (2021) confirmed that TAP block offers better analgesia as compared to port site infiltration among patients experiencing LC.[18]

It was found during the study that patients in TAP block required less analgesic than port site infiltration. In TAP block, 8.7%, 26.1%, 43.5% and 52.1% patients, but in port site infiltration, 30.4%, 65.2%, 82.6% & 82.6% of patients required analgesia at 1st, 4th, 12th & 24 hours, respectively. Similar results were reported in a study done by Majeed et al. who also asserted that patients in TAP block required less analgesia, 15.6% of patients in TAP block while 28.6% of patients in post-site infiltration required analgesia.[19]

A study done by Grape and teammates (2021) also indicated that patients in TAP block required less analgesia than patients in port site infiltration.[18] Goel and coworkers (2021) reported in their study that TAP block notably reduced 24-hour overall analgesia consumption by 3.85 mg as compared to port site infiltration.[6]

Since this study only included a small sample size and was carried out only in one place, more research is required on a larger level to confirm the effectiveness of the laparoscopic-guided transverse abdominal plane block.

CONCLUSION

Laparoscopic-guided TAP block is better than infiltration in terms of pain score at the port site and additional analgesia requirement. This study would help us in the future for better postoperative pain management, early discharge of patients, less analgesic consumption, and fewer side effects like PONV (postoperative nausea and vomiting). This study provided local evidence that would help implement this anesthetic technique in laparoscopic cholecystectomy.

Ethical Consideration

The Institutional & Ethical Review Board of Jinnah Hospital provided the IRB. (48/02/03/2021/52 ERB/11-03-21)

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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https://doi.org/10.29309/TPMJ/2026.33.02.9840 www.theprofesional.com

ORIGINAL ARTICLE

Role of erector spinae plane block versus paravertebral block in postoperative pain management of mastectomy.

Noor Fatima[1], Naseem Ahmed[2], Komal Mumtaz[3], Khalid Mahmood[4]

ABSTRACT… Objective: To determine the role of erector spinae plane block versus paravertebral block by finding the time to need the first rescue analgesia in postoperative pain management of Mastectomy. **Study Design:** Randomized Controlled Trial. **Setting:** Department of Anesthesia, Fauji Foundation Hospital Rawalpindi. **Period:** October 2024 to March 2025. **Methods:** A total of 220 females (aged 18-65 years) undergoing unilateral modified radical mastectomy with axillary dissection were randomly assigned (1:1) to receive either erector spinae plane block (Group ESPB) or paravertebral block (Group PVB). Under ultrasound guidance at T4-T5, patients in Group ESPB received 20-25mL of 0.25%-0.375% bupivacaine with epinephrine into the erector spinae plane, while patients in Group PVB received the same solution injected into the paravertebral space at multiple levels. The primary outcome was time to first rescue analgesia (triggered at pain score ≥4 on Visual analogue scale 0-10). Secondary outcomes included 24-hour total rescue analgesia consumption, pain scores at 8, 12, and 24 hours. A p-value <0.05, established the statistical significance. **Results:** The results of primary outcomes established no significant difference between the Group ESPB and Group PVB in terms of time to need first recue analgesia (5.95±0.63 hours Vs 6.11±0.66 hours respectively, p=0.07). Total morphine consumption was comparable between the two groups (7.1±1.61 mg vs. 7.05 ± 1.64 mg, p=0.82). Higher pain scores was observed at 8 hours in the ESPB group compared to Group PVB (6.1 ± 0.88 vs. 5.83 ± 0.78, p=0.02), with no differences at 12 and 24h. **Conclusion:** Both techniques showed similar time to first rescue analgesia after mastectomy and total morphine use during 24 hours. Paravertebral block provided better early pain control at 8h; analgesia was, however, comparable beyond 12h.

Key words: Analgesia, Erector Spinae Muscles, Mastectomy, Nerve Block, Paravertebral Block.

Article Citation: Fatima N, Ahmed N, Mumtaz K, Mahmood K. Role of erector spinae plane block versus paravertebral block in postoperative pain management of mastectomy. Professional Med J 2026; 33(02):326-331. https://doi.org/10.29309/TPMJ/2026.33.02.9840

INTRODUCTION

Breast cancer (BC) is among the common types of malignancies reported in women, as approximately 24.5% of total cancer in females at global level are caused by BC. The severity of the situation can be assessed by the data from year 2020 that showed an estimated global figure of BC to be 2.3 which claimed the lives of over 685,000 individuals.[1,2]

Mastectomy is a primary surgical intervention for these cases performed in 37 to 40% women with BC and serve as a life-saving procedure. Patients, however, experience some serious post-treatment problems related to social, psychological, and sexual well-being. The surgical procedure may cause treatment related side effects, like post-operative pain (POP), lymphedema, and mastectomy scars.[3]

One of the most serious sides effect faced by 50% of these women undergoing mastectomy is the post mastectomy pain syndrome (PMPS) documented after 20 to 68% of mastectomy procedures. Inadequate pain management, reported to lead chronic postoperative pain in 25–60% of cases. Reported symptoms related to this complication include numbness, pressure, and burning sensations, primarily affecting the axilla, pectoral and lateral thoracic areas, and upper legs. Pain arises from inflammation due to tissue damage, while neuropathic pain results from the disruption of the 2nd to 6th intercostal nerves (typically T2-T6). Consequently, this leads to prolonged hospital stays and an increase in postsurgical hospital admissions, causing significant distress.[4,5] Management of POP following mastectomy therefore presents a significant challenge to the health care professionals to ensure a reduced opioid consumption, facilitate early mobilization and enhancing patient comfort.[6]

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Article received on:
22/05/2025
Accepted for publication:
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Use of regional anesthesia techniques have gained prominence as key components of multimodal analgesic approaches during recent years as these are found to reduce these post-surgical concerns in BC. Among these techniques, the Paravertebral Block (PVB) has long been taken as the gold standard, while the Erector Spinae Plane block (ESPB) in newer alternative with promising results reported in some studies.[7]

In PVB, local anesthetic was administered near the thoracic vertebrae at the point where spinal nerves exit through the intervertebral foramina. The technique offered effective unilateral analgesia by blocking the spinal nerves' dorsal and ventral rami, along with the sympathetic chain. PVB has shown excellent efficacy in controlling PMPS, with the advantages of reduced opioid consumption, lower pain scores, and faster recovery following mastectomy. PVB is, however, technically challenging to perform, requires significant expertise, and carries risks of some serious complications including pneumothorax, vascular puncture, and epidural or intrathecal spread of local anesthetic.[8]

The ESPB a relatively novel approach, firstly mentioned in 2016, is an interfascial plane technique hypothesized to work through diffusion of local anesthetic to the spinal nerves' dorsal and ventral rami. In this technique, local anesthetic is deposited deep to the erector spinae muscle group, superficial to the transverse processes of the vertebrae, which results in widespread cranio-caudal diffusion of the anesthetic, providing both visceral and somatic analgesia. The benefits of ESPB include its easier administration under ultrasound guidance, lower risk of complications, and effective analgesia after mastectomy. It also offers opioid-sparing effects and reduces the chances of systemic side effects found with commonly used techniques.[9,10]

Recent comparative studies have yielded varying results regarding efficacy of PVB and ESPB, where some researchers suggest near-equivalent analgesic efficacy, while other studies indicate superior pain control with PVB. On one hand, the technical simplicity of ESPB makes it an attractive option, particularly in settings with limited resources or expertise. On the other hand, the more established track record regarding efficacy, targeted nerve blockade and potentially consistent dermatomal coverage continue to supports its use as a primary approach in mastectomy procedures.[9] Hence, the relative efficacy of ESPB versus PVB in POP management remains an area of active investigation. This study was therefore aimed to compare the analgesic efficacy of ESPB and PVB after mastectomy evaluated in terms of time to first request for analgesia. The outcomes of our work will be help to find the comparison of this POP in our local population to help the clinicians in making evidence based decisions.

METHODS

This randomized controlled trial was conducted at the department of Anesthesia, Fauji Foundation Hospital Rawalpindi from October 2024 to March 2025 over a period of 6 months after getting approval from the ethical review committee of the hospital (No.713/ERC/FFH/RWP.0/8/25).

Sample size was calculated as per following assumptions:
α=5% (two-sided), power: 90%.
m_1 (mean time to first rescue analgesia with PVB) = 6.35 + 0.42 hours
m_2 (mean time to first rescue analgesia with ESPB) = 6.5 + 0.60 hours.[11]
The estimated sample size n_1 = 107, n_2=107.
We however selected a total of 220 patients with 110 patients in each group.

A total of 220 females aged 18-65 years with American Society of Anesthesiologists (ASA) physical status I or II, scheduled for unilateral modified radical mastectomy (MRM) with axillary dissection under general anesthesia were included in this study through consecutive sampling.

Exclusion criteria comprised of patient suffering from coagulopathy, liver or renal failure, or serious respiratory or cardiac conditions. Women with severe obesity (BMI >35 kg/m^2) which can complicate regional blocks and hinder anesthetic diffusion were also excluded. Additionally, patients with local infection at the injection site, with anatomical abnormalities (such as spine or chest wall deformities), allergy to local anesthetics, chronic

pain syndromes, psychiatric conditions affecting pain assessment, were also part of exclusion criteria.

All women gave their informed consent prior to inclusion in the study.

These 220 women were randomly allocated in a 1:1 ratio to be managed by either by ESPB (Group ESPB) or by PVB (Group PVB) using a computer-generated randomization.

All the base line demographics and medical history related to this surgical procedure was collected.

All the patients received standardized general anesthesia with a premedication including midazolam (0.02–0.03 mg/kg) and fentanyl (2 µg/kg) for anxiolysis and analgesia. Propofol (2 mg/kg) was used to induce anesthesia in order to make endotracheal intubation easier. Maintenance was achieved with sevoflurane in an oxygen-air mixture, with fentanyl boluses (1 µg/kg) as per need. Standard intraoperative monitoring was ensured during the procedure.

In the ESPB group, patients were positioned laterally keeping surgical side uppermost. A high-frequency ultra-sonographic probe was positioned in a parasagittal plane at the T4–T5 transverse process, approximately 3 cm lateral to the spinous process. A 22-gauge needle under sterile conditions, was advanced in-plane to reach the erector spinae muscle plane. A 20–25 mL of local anesthetic (0.25%–0.375% bupivacaine) with epinephrine was injected while elevating the erector spinae muscle from the surface of the transverse process.

In the PVB group, a high-frequency ultrasound probe was placed lateral to the T4–T5 transverse process to identify the paravertebral space. With an in-plane method, a 22-gauge needle was advanced until the tip approached the space. Placement was confirmed with negative aspiration and pleural movement, and 20–25 mL of local anesthetic (0.25%–0.375% bupivacaine) was then administered with epinephrine, injected at multiple levels.

Tracheal extubation was performed after meeting the extubation criteria. All the patients received paracetamol (Intravenous 1 g) every 6 hours.

POP was assessed on the Visual analog scale VAS 0-10. (Where zero meant, no pain and 10 meant, worst imaginable pain pain). POP was assessed on arrival at the post-anesthesia care unit and then at 2, 4, 6, 8, 12, 18 and 24 hours after surgery.

Rescue analgesia (Intravenous morphine 1 gm) was administered by nursing staff promptly when requested by the patients for breakthrough pain (pain score ≥4 on VAS) while ensuring a minimum interval of 10 minutes between doses. All analgesic requests and administrations were noted and documented including time of first request and dose administered.

The primary outcome set for the study was the time to need the first rescue analgesia (asked by the patients when pain score ≥4 as on VAS). The secondary outcomes included total dose of rescue analgesia required during first 24 hours, pain scores (at 8, 12 and 24 hours). Additionally, we also compared the incidence of complications during first 24 hours postoperatively (Including postoperative nausea and vomiting (PONV) and any adverse effects associated with the administered drugs or procedural techniques, such as pneumothorax or local anesthetic toxicity).
SPSS version 26 was used for data analysis. Continuous variables including (e.g. time to first rescue analgesia and total morphine dose) were expressed as mean ± standard deviation or median (interquartile range) based on normality as assessed by Shapiro-Wilk test. Categorical variables (e.g., PONV incidence) were presented as frequencies and percentages. Comparison between the groups was made using independent t-tests or Mann-Whitney U tests for continues variables while independent t-tests or Mann-Whitney U tests were employed for categorical variables. A p-value <0.05, established the statistical significance for all these comparisons.

RESULTS

The mean age of women in this study was 51.53±6.7 years (ranging from 36 to 64 Years). The group wise demographics and clinical features are shown in Table-I.

TABLE-I			
Demographic details and clinical features n= 220			
Demographics and Clinical Features		**Group ESPB**	**Group PVB**
Age (Mean±SD) years		50.74±6.76	52.32±6.5
Marital status n (%)	Married n (%)	105 (95.5)	107 (97.3)
	Unmarried n (%)	5 (4.5)	3 (2.7)
ASA	I n (%)	58 (52.7)	51 (46.4)
	II n (%)	52 (47.3)	59 (53.6)
BMI (Mean±SD) Kg/m^2		27.45±3.73	26.98±3.7
Duration of surgery (Mean±SD) minutes		126.32±13.75	130.5±13.02

The results of primary outcomes of the study showed no significant difference between the Group ESPB and Group PVB in terms of time to need first recue analgesia (p=0.07). Among the secondary outcomes, total morphine consumption was also comparable between the two groups (p=0.82), while the results showed higher pain scores on VAS at 8 hours in the Group ESPB compared to Group PVB (p=0.02). No difference in pain score was, however, observed at 12 hours and 24 hours as shown in Table-II.

TABLE-II			
Comparison of the efficacy between ESPB and PVB n= 220			
Outcomes Variables	**Group ESPB**	**Group PVB**	**P-Value**
Primary Outcomes			
Time to first rescue analgesia (Mean±SD) hours	5.95±0.63	6.11±0.66	0.07
Secondary Outcomes			
Total morphine consumption (mg) (Mean±SD)	7.1±1.61	7.05±1.64	0.82
Pain score at 8 hours on VAS (Mean±SD)	6.1±0.88	5.83±0.78	0.02
Pain score at 12 hours on VAS (Mean±SD)	5.54±0.60	5.46±0.60	0.32
Pain score at 24 hours on VAS (Mean±SD)	3.46±0.71	3.42±0.75	0.69

Post-operative complication between the two groups were also recorded, where the incidence of PONV were comparable (p=0.35). No cases of pneumothorax, block failure, or local anesthetic toxicity were observed in either group as shown in Table-III.

TABLE-III			
Incidence of complications n= 220			
Incidence of Post-operative Complications	**Group ESPB (n=110)**	**Group PVB (n=110)**	**P-Value**
PONV n (%)	5 (4.5)	9 (8.2)	0.35
Pneumothorax n (%)	0 (0)	0 (0)	N/A
Block failure n (%)	0 (0)	0 (0)	N/A
Local Anesthetic Toxicity	0 (0)	0 (0)	N/A

DISCUSSION

The results of primary outcomes showed no statistically significant difference between the Group ESPB and Group PVB in terms of time to need first recue analgesia (5.95±0.63 hours Vs 6.11±0.66 hours respectively, p=0.07). Among the secondary outcomes, total morphine consumption was also comparable between the two groups (7.1±1.61 mg vs. 7.05 ± 1.64 mg, p=0.82). Higher pain scores was observed at 8 hours in the ESPB group compared to Group PVB (6.1 ± 0.88 vs. 5.83 ± 0.78, p=0.02), with no differences at 12 and 24h. Comparison of the incidence of complication between the two groups showed that the incidence of PONV (4.5% vs. 8.2%, p=0.35), were comparable and no cases of pneumothorax, block failure, or local anesthetic toxicity were observed in either group. Our findings contribute to the ongoing debate regarding the comparative efficacy of these two techniques for POP management after mastectomy which share mixed results in the medical literature.

The comparison between PVB and ESPB was made by El Ghamry MR and Amer AF in 70 women undergoing mastectomy. Results showed comparable time for the need of first analgesia (p= 0.075), 24-hour morphine use (P=0.32), pain scores, and complications. The study concluded that PVB

and ESPB are equally effective for post-mastectomy pain control and opioid-sparing without significant differences in safety or efficacy.[11] Similar to El Ghamry, Gürkan et al. found comparable efficacy between the two techniques, with some differences in temporal pain control patterns. Gürkan Y et al. compared the postoperative analgesic effects of ESPB and PVB in breast surgery. Both ESP and PVB significantly reduced 24-hour morphine consumption compared to the control ($p < 0.001$), with no difference between ESP and PVB ($p > 0.05$). PVB showed lower pain scores at 1st and 6th hours ($p = 0.018$, $p = 0.027$), while the ESPB has lower risk of complications compared to PVB.[12]

Amr SA et al. studied the efficacy of ESPB, PVB and control group in acute and chronic pain in post-mastectomy women. Time to need for first analgesia dose (morphine) was significantly lower in the ESPB compared to the PVB (8.13 ± 1.75 Vs. 10.64 ± 1.8 hours respectively, p=0.03). Similarly more morphine was consumed in the ESPB group compared to the PVB group (8.17 ±1.7 Vs. 5.7±1.9 mg respectively, $p < 0.001$). The mean pain score on VAS was also higher in the ESPB group compared PVB group at 12 and 24 hours after surgery (p=0.02 and p=0.01 respectively). PVB hence proved to be more effective in the acute pain management. However, both techniques were equally effective over chronic pain relief at 1, 3 and 6 month time.[13]

Contradictory to the findings of comparable efficacy, some previous research found superior results with ESPB compared to PVB in POP management. A study by Eldemrdash AM and Abdelzaam E-SM. compared ESPB and PVB for postoperative analgesia after radical mastectomy. ESB provided longer analgesia (416 ± 68 min vs. 371 ± 67 min), lower morphine requirement (4 ± 2 mg vs. 6 ± 2 mg), and fewer complications than PVB. Conclusively, ESB was narrated to be more effective, safer, and technically easier than PVB for managing POP.[14]

Premachandra A et al. compared ESPB and PVB for preventing acute POP in BC surgery. Among 94 matched patients, morphine use was significantly higher with ESPB (74.5%) than TPVB (41.5%), showing a 33% difference ($p < 0.001$). While ESPB had no complications, PVB proved more effective in reducing the postoperative opioid need during early hours after surgery.[15]

Despite these individual studies showing variable results, a comprehensive systematic review conducted by Weng WT et al. provides important perspective on the overall body of evidence. This meta-analysis also aligns with our findings, demonstrating that ESPB and PVB provide comparable analgesic efficacy for breast surgery with no statistical difference between ESPB and PVB in opioid consumption, pain scores, or side effects. Despite moderate heterogeneity, results confirm ESPB as a viable alternative to PVB, offering equivalent POP relief without increased complications, supporting their interchangeable use in clinical practice.[16]

The limitations of this study include the short duration of follow-up, which did not assess long-term pain outcomes. Future studies with longer follow up time will add up in this useful data regarding POP in women undergoing mastectomy.

CONCLUSION

Both ESPB and PVB offer effective POP control following mastectomy in terms of first rescue analgesia needed and the total morphine consumption. However, PVB demonstrated superior analgesia during early hours, indicating deeper sensory blockade. With these similar efficacy results, ESPB remains advantageous due to its technical ease, which make it suitable in resource-limited settings. The study underscores the individualized technique selection based on patient needs and clinical context.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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https://doi.org/10.29309/TPMJ/2026.33.02.10013 www.theprofesional.com

ORIGINAL ARTICLE

Comparison of effectiveness of pediatric caudal block with ultrasound guidance versus landmark technique.

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ABSTRACT… Objective: To compare the efficacy of ultrasound guidance versus landmark technique for performing caudal block in children undergoing infraumbilical surgery. **Study Design:** Non Randomized Controlled Trial. **Setting:** Institute of Child Health and Children Hospital, Faisalabad. **Period:** January 2025 – April 2025. **Methods:** After institutional ethical approval, 240 children aged 2 to 10 years were randomly assigned to two equal groups: Group USG (ultrasound-guided) and Group LM (landmark technique). Caudal block was administered under general anesthesia in both groups. Primary outcome was success on first attempt; secondary outcomes included performance time, incidence of tachycardia (defined as ≥10% rise in heart rate during skin incision), and number of needle punctures. Data were analyzed using SPSS version 23. **Results:** No significant difference was found between the groups in terms of age, weight, and gender. The USG group showed a significantly higher success rate on the first attempt (95% vs. 70.83%, p = 0.000) and a lower incidence of tachycardia (10% vs. 32%, p = 0.000). However, time taken was significantly longer in the USG group (110.88 ± 16.11 sec vs. 63.62 ± 13.10 sec, p = 0.000). **Conclusion:** Ultrasound guidance significantly increases the success rate of pediatric caudal block compared to landmark technique, although it requires more time to perform.

Key words: Caudal Block, Landmark Technique, Pediatric Anesthesia, Sacral Hiatus, Ultrasound Guidance.

Article Citation: Malik S, Askri MR, Maqbool S, Manzoor W, Fatima S, Talal H. Comparison of effectiveness of pediatric caudal block with ultrasound guidance versus landmark technique. Professional Med J 2026; 33(02):332-335. https://doi.org/10.29309/TPMJ/2026.33.02.10013

INTRODUCTION

Painful stimuli from surgery evoke significant stress responses in pediatric patients, which can result in complications such as tachycardia, hypertension, and delayed recovery.[1] Caudal block is a popular and effective regional anesthetic technique in children, often used in infraumbilical surgeries to provide both intraoperative and postoperative analgesia.[2] Its use minimizes the requirement for systemic opioids and inhalational anesthetics, leading to fewer side effects like nausea, ileus, and respiratory depression.[3]

Despite its popularity, the landmark (LM) technique for caudal block relies heavily on palpation of anatomical structures such as sacral hiatus and cornu, which may vary significantly in pediatric populations.[4] In certain cases, especially in infants and young children, identifying these structures accurately becomes challenging due to immature bone development and soft tissue coverage. These variations may lead to multiple punctures, failed blocks, or inadvertent injury.[5]

Ultrasound guidance (USG) has emerged as a safer and more accurate technique for performing regional blocks, including caudal block.[6] It allows real-time visualization of anatomical structures, verification of needle position, and monitoring of local anesthetic spread.[7] This technique is non-invasive, easily teachable, and avoids radiation exposure unlike fluoroscopy.[8]

Multiple international studies have demonstrated that ultrasound-guided caudal blocks improve accuracy and safety, reduce failure rates, and increase patient comfort.[9] However, data from Pakistani pediatric populations remain sparse. Limited local studies have addressed whether the use of ultrasound truly confers a measurable clinical advantage over conventional landmark-based methods.[10]

This study was designed to compare the effectiveness of ultrasound-guided versus landmark-guided caudal blocks in children undergoing infraumbilical surgeries.

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Article received on:
04/08/2025
Accepted for publication:
15/10/2025

By quantifying block success rate, performance time, and hemodynamic response, we aim to validate the use of ultrasound as a superior alternative in pediatric anesthesia practice.

METHODS

This study was a non-randomized controlled trial conducted at the Institute of Child Health and Children Hospital, Faisalabad, from January 2025 to April 2025. Ethical Approval: Approved by the Institutional Ethical Review Committee (Ref#: 31/CH & ICH/FSD; Date: 07/01/2025).

A total of 240 children aged 2 to 10 years, scheduled for elective infraumbilical surgeries under general anesthesia, were enrolled after obtaining written informed consent from parents or guardians. Patients were divided into two equal groups based on the technique used for caudal block: Group USG (ultrasound-guided) and Group LM (landmark technique).

Inclusion Criteria

- Children aged 2–10 years
- ASA Physical Status I or II
- Undergoing elective infraumbilical surgeries under general anesthesia

Exclusion Criteria

- Age below 2 or above 10 years
- ASA III or IV
- Emergency surgery
- Coagulopathy
- Spinal deformity or infection at injection site
- Allergy to local anesthetics

All patients received general anesthesia with sevoflurane (6–8%) via facemask followed by IV access and airway secured with an I-gel or LMA. Standard monitoring (SpO_2, ECG, NIBP) was applied throughout. In Group LM (Landmark technique), the sacral hiatus was palpated and a 22G hypodermic needle was inserted. After confirming negative aspiration for blood or CSF, 1 mL/kg of 0.125% bupivacaine was injected slowly. In Group USG (Ultrasound-guided technique), the sacral hiatus was identified using a high-frequency linear ultrasound probe. The needle was advanced in-plane under real-time ultrasound guidance, and the same dose of bupivacaine was administered after confirming correct spread in the caudal canal. A waiting period of 10 minutes was allowed post-injection before surgical incision.

First-attempt success rate (defined as successful caudal block with no blood, CSF, resistance, or subcutaneous swelling) were our primary outcomes whereas Incidence of tachycardia (≥10% increase in HR during skin incision), Performance time (in seconds), Number of needle punctures were secondary outcomes.

Data were analyzed using SPSS version 23. Continuous variables were expressed as mean ± standard deviation and compared using Student's t-test. Categorical variables were analyzed using Chi-square test. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 240 children meeting the inclusion criteria were enrolled in this study and divided equally into two groups: Group USG (ultrasound-guided) and Group LM (landmark technique). Both groups were comparable in baseline characteristics, including age, gender, and weight. The mean age in the ultrasound group was 5.52 ± 2.16 years, while in the landmark group, it was 5.45 ± 2.08 years (p = 0.76). Mean body weight in Group USG was 16.83 ± 4.21 kg and in Group LM was 16.54 ± 3.98 kg (p = 0.54). There was no statistically significant difference between the groups in terms of gender distribution, with males representing 60% of Group USG and 57.5% of Group LM (p = 0.69).

TABLE-I

Demographic characteristics

Parameter	Group USG (n=120)	Group LM (n=120)	P-Value
Age (years)	5.52 ± 2.16	5.45 ± 2.08	0.76
Weight (kg)	16.83 ± 4.21	16.54 ± 3.98	0.54
Male (%)	72 (60%)	69 (57.5%)	0.69
Female (%)	48 (40%)	51 (42.5%)	0.69

Age and weight were compared using the independent samples t-test. Gender distribution was analyzed using the Chi-square test.

The clinical performance of caudal blocks varied significantly between the two groups. First-attempt success was achieved in 114 patients (95%) in the ultrasound-guided group, compared to only 85 patients (70.83%) in the landmark group ($p < 0.001$). This indicates a significantly higher reliability and precision with ultrasound guidance.

The mean performance time, defined as the interval from positioning the patient to successful administration of local anesthetic, was considerably longer in Group USG (110.88 ± 16.11 seconds) as compared to Group LM (63.62 ± 13.10 seconds), with a p-value of <0.001. Though the USG technique required more time, its improved accuracy and lower complication rates were evident.

A marked difference was also observed in hemodynamic responses. In Group USG, only 10% of children developed tachycardia (≥10% rise in heart rate during incision), whereas in Group LM, 32% exhibited this sympathetic response ($p < 0.001$), indicating less effective analgesia in the landmark group.

TABLE-II

Clinical outcomes

Outcome	Group USG (n=120)	Group LM (n=120)	P-Value
First-attempt success (%)	114 (95%)	85 (70.83%)	<0.001
Performance time (sec)	110.88 ± 16.11	63.62 ± 13.10	<0.001
Tachycardia during incision (%)	12 (10%)	38 (32%)	<0.001

First-attempt success and tachycardia were compared using the Chi-square test. Performance time was analyzed using the independent samples t-test.

DISCUSSION

The findings of this study underscore the clinical superiority of ultrasound-guided caudal blocks over the traditional landmark technique in pediatric patients. Our results show that ultrasound guidance significantly improves first-attempt success rates and reduces the incidence of tachycardia during surgical incision — a proxy for intraoperative pain. These outcomes are critical in pediatric anesthesia, where minimizing both procedural trauma and physiological stress is paramount.

The increased success rate of 95% in the ultrasound group aligns with several international studies reporting high efficacy when real-time imaging is used to guide needle placement.[6] This is likely due to enhanced visualization of anatomical landmarks, which is especially useful in children whose sacral anatomy can vary due to age-related differences in ossification.[4] Conversely, the 70.83% success rate in the landmark group reflects the common challenge of blind insertion, as palpation may be difficult in obese, anxious, or very young children.[5]

One important trade-off noted in this study was the longer performance time associated with ultrasound guidance. This increase, while statistically significant, is not clinically alarming, particularly given the safety and accuracy benefits. Other studies support this observation, noting that with experience and frequent use, the ultrasound-guided technique becomes more efficient over time.[7]

The significantly lower incidence of tachycardia in Group USG (10% vs. 32%) further emphasizes the effectiveness of this approach. Tachycardia during surgical incision typically reflects an inadequate block or incomplete analgesia, which was more common in the landmark group. This finding is consistent with prior research demonstrating better spread of anesthetic and block confirmation when ultrasound is used.[8,9]

The ultrasound technique also minimizes risks such as intravascular injection, dural puncture, and multiple needle attempts — complications that, while rare, can have serious consequences in pediatric patients. This study did not encounter these adverse events, likely due to the skill level of the anesthesiologists involved and the small sample size.

The non-randomized design of the study is a limitation, as it may introduce selection bias. However, both groups were well matched in demographics and baseline characteristics. Also, the same volume and concentration of local anesthetic were used, and

experienced providers carried out all procedures, which helped standardize interventions.

This research contributes valuable data from a local pediatric population, addressing the existing gap in region-specific evidence. While international studies support the role of ultrasound in improving regional block techniques, this study reinforces its application in resource-limited settings, demonstrating that it is not only feasible but also highly beneficial.

CONCLUSION

In conclusion, ultrasound guidance significantly improves the efficacy and safety profile of pediatric caudal blocks compared to the landmark technique. While it requires additional time and equipment, the benefits — including higher success rates, better intraoperative stability, and reduced procedural discomfort — make it a superior choice for infraumbilical surgeries in children. Based on these results, ultrasound-guided caudal blocks should be encouraged as a standard of care in pediatric anesthesia, particularly when expertise and resources allow.

Future studies should aim to further validate these findings across diverse surgical types, age groups, and clinical environments. Randomized multicenter trials may provide stronger evidence and help formulate guidelines for routine use of ultrasound in pediatric regional anesthesia.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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https://doi.org/10.29309/TPMJ/2026.33.02.7567 www.theprofesional.com

ORIGINAL ARTICLE

Incidence of keratopathy in vernal catarrh.

Muhammad Firdous[1], Qamar Farooq[2], Aftab ur Rehman[3]

ABSTRACT… Objective: To identify the severity and types of corneal complication of vernal catarrh and the extent of visual impairment caused by them. **Study Design:** Cross-sectional study. **Setting:** Margalla Hospital Taxila Cantt. **Period:** March 2021 to May 2022. **Methods:** The study included all vernal catarrh cases with informed consent. Slit lamp inspection allowed for the exclusion of patients from the study. The majority of the diagnosis was made based on the history and lab tests. Slit lamp examination and corneal fluorescein staining were carried out in each case. The variables were noted and statistical analysis was performed on them. Inclusion Criteria: All patients between age of 5-20years of VKC were included. Exclusion Criteria: Patients who were difficult to examine on slit lamp or did not agree to informed consent were excluded. **Results:** The most frequent corneal complication was superficial punctate keratitis (45%). Cases with corneal plaques (8%) and shield ulcers (14% each) had more severe visual impairment. Also observed was a strong association with keratoconus (15%). Hydrops (6%), pseudogentoxon (3%) and corneal opacification (9% each) were also found. **Conclusion:** In VKC, corneal complications are frequent, potentially dangerous, and can impair vision.

Key words: Allergic Conjunctivitis, Vernal Keratoconjunctivitis (VKC) Vernal Catarrh.

Article Citation: Firdous M, Farooq Q, Aftab ur Rehman. Incidence of keratopathy in vernal catarrh. Professional Med J 2026; 33(02):336-340. https://doi.org/10.29309/TPMJ/2026.33.02.7567

INTRODUCTION

Vernal catarrh (VKC) is a seasonal exacerbation-prone recurrent bilateral allergic inflammation of the conjunctiva and cornea. It is a bilateral disorder in which both IgE- and cell mediated immune mechanism play an important role.[1] Within minutes of exposure to an allergen, it can manifest as an acute type 1 immediate hypersensitivity reaction. When airborne antigen is released in the tear film, it travels to the conjunctiva where immunoglobulin E (IGE) binds to the mast cell surface, causing histamine to be released. Patients with the condition may be allergic to a wide range of things, including airborne allergens like pollen, mites, mold, and animal dander. With a self-limiting course, VKC mostly affects young boys between the ages of 5 and 20. Around puberty, it starts to go away, and it rarely returns after age 25.

The primary cause of visual morbidity is disease-related corneal complications. A study done on 82 subjects with VKC has shown that twenty six (31.7%) of 82 subjects had complications with keratopathy. Keratopathy is more frequent in palpebral disease. A study done on 290 eyes with VKC shows corneal scarring in 59 (20.3%) eyes, Keratoconus in 17 (5.9%) eyes, shield ulcer in 09 (3.1%) eyes while 07 (2.4%) eyes had corneal neovascularization.[2] Eosinophil derived proteins, such as eosinophil cationic protein (ECP) and eosinophil derived major basic protein (EMBP), are the cause of this vernal keratopathy. It is cytotoxic to the corneal epithelium and prevents protein synthesis and migration of the epithelium. Both serum and tears have higher concentrations of them.[3]

Vernal keratopathy has an impact on many aspects of a patient's daily life, particularly on children's academic pursuits. Determining the corneal complications of vernal catarrh and researching its impact on visual acuity were the goals of our study. It was decided to conduct a thorough investigation into the corneal complications of VKC. Early detection of these subtle corneal changes is vital to help arrest these changes in the early stages before developing further complications.

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Article received on:
06/05/2023
Date of revision:
01/12/2025
Accepted for publication:
17/12/2025

These changes can be measured accurately by corneal topography, making it the gold standard in the screening of keratoconus and other corneal ectasias.[4]

To find disease-related corneal complications, a test was run, which included fluorescein staining of the cornea.

METHODS

At Margalla Hospital in Taxila Cantt, we carried out this cross-sectional study after approval from local ethical committee (Dated: 03-04-2023). The study included a total of 100 cases of VKC with corneal involvement. From March 2021 to May 2022, these patients were seen at the Ophthalmic OPD.

Our patients' names, ages, genders, addresses, length of illness, any seasonal variations, medical history, and personal or family history of any allergic disorder were all included in a thorough proforma that was created for the study. Itching, redness, watering, photophobia, a feeling of a foreign body, blurred vision, and conjunctival discharge were listed as the complaints that were present. The different types of corneal signs include opacification keratoconus acute hydrops, corneal plaque, shield ulcer, superficial punctate keratitis, and pseudogentoxon. The history and clinical examination served as the primary foundation for the diagnosis. To find corneal complications of the disease, a Snellen chart was used after checking visual acuity (VA) with a through slit lamp examination (including fluorescein staining of the cornea). Clinically, the Munson sign and the oil droplet sign by ophthalmoscope were used to identify keratoconus. Keratoscope confirmation of subtle cases. The disease's conjunctival symptoms were also noted.

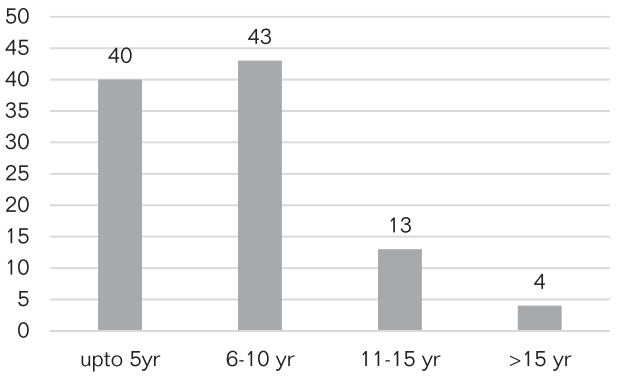
All patients with VKC and corneal involvement who agreed to participate in the study met our inclusion criteria. Patients who refused informed consent were also excluded, as were those who were challenging to examine with a slit lamp. As needed, medical and surgical care was given.

RESULTS

In our study, we included 100 cases of VKC with varying degrees of corneal involvement. Our patients were split 90 percent male and 10 percent female. 34 cases (34%) were in the age range of 11 to 20 years, while 61 (61%) cases were up to 10 years old. Five (05%) of the people were older than 20. Figure-1 displays the age of the disease's onset. None started before the age of 20, and the earliest one started was 28 months old. Twenty (20%) and twelve (12%) people had been in pain for more than ten years.

FIGURE-1

Age of disease onset.



The majority of the patients were from lower socioeconomic classes, and Table-I below lists their monthly family income. 83% of our patients resided in slums, 5% did so in upscale neighborhoods, and 70% presented with no symptoms. Table-II gives a description of their frequency 20% of patients had a perennial course, while 8% had a history of seasonal recurrence.

TABLE-I

Monthly family income of patients

Monthly Income in Rs.	No of Patients
< 200	15 (15)
2000-5000	64 (64)
5001-10000	13 (13)
>10000	08 (8)

Total no. of patient = 100; value in parentheses are percentages.

While 73% of cases had no history of such conditions, 27% of cases had associated monocular allergic diseases. 84% of patients had no family

history of monocular allergy, compared to 16% of patients who did.

In 22% of cases, pseudooptosis was present, and 19% of cases had blepharitis of varying severity. In our study, palpebral VKC accounted for 56% of all cases. Only 4% of patients had the limbic type of VKC, and 40% of patients had the mixed type.

TABLE-II

Types of symptoms of patients

Type of Symptom	No of Patients
Itching	100 (100)
Redness	97 (97)
Watering	88 (88)
Photophobia	95 (95)
Foreign body sensation	52 (52)
Defective vision	48 (48)
Discharge	68 (68)

48% of patients had upper palpebral papillary hypertrophy, 24% had enlarged papillae, and 18% had a cobblestone appearance. Cobblestones and enormous papillae were present in 10%. In Table-III, the severity and different kinds of corneal complications are listed.

TABLE-III

Showing corneal signs / complications.

Corneal Signs	No of Patients
Superficial punctate keratitis	45 (45)
Keratoconus	10 (10)
Shield ulcer	14 (14)
Corneal opacification	9 (9)
Plaque	8 (8)
Acute corneal hydrops	3 (3)
Pseudogentoxon	3 (3)

Total no. of patients= 100; value in parenthesis are percentage.

The ranges of visual acuity measured were 6/6 to 6/12, 6/18 to 6/36, 6/60 to CF 3 m, and CF less than 3 m. Corneal involvement was the primary cause of vision loss. Only 75% of patients can have their visual acuity accurately recorded. In the remaining cases, this was brought on by the patient's lack of cooperation or extreme distress.VA record of the worse affected eye is show in Table-IV.

TABLE-IV

Showing visual acuity in the worse affected eye.

Visual Acuity	No. of Patients
6/6—6/12	31 (31)
6/18---6/36	24 (24)
6/60---CF 3m	5 (5)
<CF 3m	15 (15)
Could not be recorded	25 (25)

Total No. of patients= 100; values in parenthesis are percentage.

DISCUSSION

VKC is a bilateral recurrent condition characterized by photophobia, itching, watering, and redness. VKC is one of the several disorders in the spectrum of allergic conjunctivitis, which also includes perennial allergic conjunctivitis, seasonal allergic conjunctivitis, atopic keratoconjunctivitis, vernal keratoconjunctivitis, and giant papillary conjunctivitis.[5] It affects people all over the world and is more prevalent in young men who have an individual or family history of atopy. Nagrale et al16 also observed a higher prevalence of VKC in males, with 82.5% of affected individuals being male, while the incidence in females was 17.5%.

In the current study, 100 cases of VKC with corneal complications were included. Male predominance in this disease is confirmed by the 90 cases that were male. Others have noted a male predominance similar to this one.

In our study, 61% of participants were under the age of 10—the same age as that reported both domestically and abroad.

The majority of the study participants were underprivileged and belonged to a lower socioeconomic class. Eighty percent of our patients had large families, lived in slums, and had low socioeconomic status. This could be because some environmental allergens are constantly being exposed to VKC patients. Poor nutrition, unsanitary living conditions, and extreme poverty may all be causes of this illness. The inability to maintain

good medication adherence, which is required to treat and prevent corneal complications of the disease, is another explanation for this. The poor socioeconomic standing of our patients may be an indicator of the same for our society as a whole.

16% of patients' families and 27% of patients had histories of allergies. 39% of the patients, according to Khan et al, had a personal or family history of allergies. 20% of patients had a perennial course, while 80% had a seasonal variation. This finding concurs with Khan and contradicts Bonini al, who favored the persistent nature of the illness.

Despite the fact that VKC has long been associated with allergies. Environmental conditions play a significant role in the development and severity of keratopathy in VKC. VKC often occurs on a seasonal basis, with a peak incidence over late spring and summer, although there may be mild perennial symptoms.[6] The immunopathogenesis of VKC is multifactorial. VKC is not only IgE mediate reaction via mast cell release but also activated eosinophils are thought to play a significant role and these can be shown consistently in conjunctival scrapings; However mononuclear cells and neutrophils are also present in VKC patients.CD4 T-helper-2 driven type IV hypersensitivity with immunomodulators such as IL-4, IL-5, and bFGF also plays an important role in VKC patients.[7]

In 45% of these cases, superficial punctate keratitis was present. Patients' levels of photophobia were associated with this frequent corneal complication in varying degrees. VKC is of more concern due to its vision threatening complications like, keratoconus, corneal scarring, refractive errors, shield ulcers and treatment related complications like steroid induced glaucoma.[8] A comparatively high 5% of our cases—keratoconus—were reported. In a different Japanese study, 40% of patients with keratoconus had a history of allergies. Numerous authors have supported the relationship between VKC, atopy, and keratoconus. Early visual disability is more common in children with VKC and keratoconus than with keratoconus alone. Corneal hydrops is more frequent in keratoconus eyes with concurrent VKC than in eyes without VKC, and it may be a sign of keratoconus. The high incidence of keratoconus in this study can be used to explain the high percentage of acute hydrops (3%) found there. Shield ulcers and corneal plaques are severe vernal keratopathy manifestations in children. They endanger children's vision because of their propensity for corneal scarring and amblyopia. The risk of bacterial or fungal keratitis is higher in these patients. Shield ulcers and corneal plaques were present in 14% and 8% of our cases, respectively. Acute hydrops, corneal plaques, or healed shield ulcers may have caused nine percent of corneal opacities.

VKC is a severe form of ocular allergy that can cause permanent cosmetic or visual defects, usually as a result of the disease's or its treatment's steroid-induced corneal complications.

In our study, shield ulcers, plaques, keratoconus, acute hydrops, and corneal opacities were the primary causes of vision loss. Patients with pseudogentoxone and superficial punctate keratitis were not significantly more visually impaired.

Medical therapy is typically used as the first line of treatment and frequently entails injecting steroids into the supratarsal region as well as mast cell stabilizers and topical steroids. Surgical intervention is indicated when a case is unresponsive to medical therapy and when an ulcer is severely crusted and has inflammatory deposits at the base. These could include amniotic membrane transplantation, contact lenses, superficial keratectomy, or excimer laser phototherapeutic keratectomy with or without bandages.[9]

CONCLUSION

In the practice of ophthalmology, VKC is of more concern due to involvement of cornea and its complications like, shield ulcers, superficial corneal scarring, keratoconus, astigmatism, mechanical ptosis. vernal keratopathy is a fairly common presentation. More young men than women are impacted. As a result of vernal catarrh, superficial punctate keratitis was discovered to be the most frequent corneal complication. Keratoconus, shield ulcers, corneal plaques, and acute hydrops were the main causes of vision loss. Vernal keratopathy may be brought on by poverty, overcrowding, and unsanitary living conditions. Early diagnosis, effective

management, and regular follow-up are crucial to mitigate the risk of long-term visual impairment. The findings underscore the importance of awareness and education among healthcare providers and caregivers regarding the potential severity of VKC and the necessity for timely intervention.[10]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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https://doi.org/10.29309/TPMJ/2026.33.02.9952 www.theprofesional.com

ORIGINAL ARTICLE

Comparison of glyceryl trinitrate (GTN) 0.2% with lateral anal sphincterotomy in the management of chronic anal fissure.

Farhan Tahir[1], Amin Warraich[2], Mudassar Rasool[3], Rashid Ehsan Randhawa[4], Hafsa Ijaz[5], Imran Amin[6]

ABSTRACT… Objective: To compare GTN ointment with lateral anal sphincterotomy. **Study Design:** Randomized Control Trial. **Setting:** Department of Surgery, Gujranwala Medical College and Teaching Hospital, Gujranwala. **Period:** September 2021 to January 2023. **Methods:** Sixty (60) patients with age 20 to 60 were included in the study. These were equally distributed randomly into two groups. 1st group underwent lateral anal sphincterotomy and second group receive 0.2% GTN for chronic anal fissure. All these patients were assessed 6 weeks after the start of treatment and were on the basis of control of symptoms per rectum bleed, constipation and pain around perianal region. **Results:** A total of 60 patients were enrolled and evenly divided into two groups. After 6 weeks of treatment, 90% of patients in the lateral sphincterotomy group achieved complete healing, compared to 50% in the GTN ointment group. Post-treatment perianal pain persisted in only 10% of the surgical group versus 50% in the GTN group. Similarly, per rectal bleeding and constipation were significantly lower in the sphincterotomy group (6.7% each) compared to the GTN group (30% and 46.7%, respectively). The differences between groups were statistically significant ($p < 0.05$) across all outcome variables. **Conclusion:** Lateral anal sphincterotomy is significantly more effective than 0.2% glyceryl trinitrate ointment in the treatment of chronic anal fissure. It provides higher healing rates and better symptomatic relief with minimal residual symptoms. Therefore, it should be considered the treatment of choice, especially in patients who do not respond adequately to conservative management.

Key words: Chronic Anal Fissure, Constipation, Lateral Anal Sphincterotomy, Per Rectal Bleeding.

Article Citation: Tahir F, Warraich, A, Rasool M, Randhawa RE, Ijaz H, Amin I. Comparison of glyceryl trinitrate (GTN) 0.2% with lateral anal sphincterotomy in the management of chronic anal fissure. Professional Med J 2026; 33(02):341-345. https://doi.org/10.29309/TPMJ/2026.33.02.9952

INTRODUCTION

Fissure in ano is very painful condition of the perianal region because of tear in the perianal area of skin.[1] The presentation mostly is pain at perianal area during and after passing stool with most of the times bright red colored bleeding along the surface of stool.[2] It is a very common perianal problem in which all age groups are involved but mostly seen in the younger and middle age group people with almost equal incidence in both male and female gender.[3] Around 90% perianal fissure occur at posterior mid line. Many times it heal spontaneously but in some patients enter into a complexity of perianal pain, constipation, injury due to fecal matter and spasm of sphincter.[4]

The pathophysiology of perianal fissure clearly fully understood, however, hypertonicity of internal anal sphincter and decrease blood supply and oxygen supply of anterior and posterior skin of perianal region have been seen to be cause.[5] As far as treatment option for conservative management, GTN (glyceryl trinitrate) ointment was the first line modality this relaxes the internal anal sphincter. This option was cost effective in this modern time of surgical management.[6] Option of surgery was considered when the conservative management which includes laxative, stool softeners and GTN, fail. This treatment option is invasive with post operative pain, but very effective. On the other hand, topical option of treatment took more time for the recovery of fissure and also results in headache. Ladies normally suffer for long time as they didn't opt surgical management due to social dilemma.[7,8]

Clinical evidence clearly leans in favor of lateral anal sphincterotomy when compared to glyceryl trinitrate ointment. Patients undergoing surgical treatment tend to experience more consistent and faster healing, with quicker relief from pain

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Article received on:
07/07/2025
Accepted for publication:
18/09/2025

and fewer instances of the condition returning over time.[9] In contrast, those treated with GTN ointment often face delayed symptom relief and a higher likelihood of the fissure recurring after initial improvement.[10] Additionally, the topical treatment is frequently associated with bothersome side effects, such as persistent headaches, which can discourage patients from continuing its use. While GTN may be considered a first-line, non-invasive option—particularly for individuals hesitant about surgery—its overall effectiveness is limited when weighed against the durable results offered by surgical intervention.[11]

This study aims to compare these two primary treatment modalities—GTN 0.2% ointment and lateral anal sphincterotomy—based on their clinical outcomes, recurrence rates, side effect profiles, and overall efficacy in managing chronic anal fissure. By analyzing healing outcomes and patient responses from both treatment arms, the study provides practical insights into the optimal management of this debilitating condition. Ultimately, the findings highlight the need for tailored treatment strategies, considering the patient's preference, symptom severity, and likelihood of adherence, while acknowledging that LAS remains the gold standard for long-term resolution.

METHODS

This randomized controlled trial was designed to evaluate and compare the effectiveness of lateral anal sphincterotomy and 0.2% glyceryl trinitrate (GTN) ointment in the management of chronic anal fissure. It was conducted at the Department of Surgery, Gujranwala Medical College and Teaching Hospital, over a period extending from September 2021 to January 2023 after the approval from the Institutional Review Board (Letter No: No.Admn.192/GMC, Dated: 29/07/2021 in the name of Dr. Farhan Tahir).

A total of sixty patients, ranging in age from 20 to 60 years and presenting with symptoms consistent with chronic anal fissure for more than eight weeks, were randomly divided into two equal groups. One group underwent lateral anal sphincterotomy, while the other received topical application of 0.2% GTN ointment. Both male and female patients were included regardless of gender distribution.

Patients were evaluated based on the presence of perianal pain, rectal bleeding, and constipation prior to and after treatment. Follow-up assessments were performed six weeks after the initiation of treatment to monitor symptom resolution and treatment response. The primary outcome measured was healing of the fissure, while secondary outcomes included persistence or improvement of associated symptoms. Patients with acute fissures, underlying anorectal conditions such as inflammatory bowel disease, rectal polyps, or malignancy, as well as those outside the specified age range, were excluded from the study. Data collected during the study were analyzed using SPSS and Microsoft Excel to determine treatment efficacy and compare clinical outcomes between the two therapeutic approaches.

RESULTS

Gender wise in the 1st group (lateral sphincterotomy) male patients were (60%) and female patients were (40%) while in group II (0.2% GTN CREAM) male patients were (47%) and female patients were (53%). Most of patients were between 20 to 40 years age group.

Per rectal bleeding, pain around perianal region and constipation were main features in both the groups. In the 1st group (lateral sphincterotomy) after 6 weeks treatment 90% healed completely only 10% patients have mild perianal pain which persist, around 7% with per rectal bleeding and around 7% with constipation In group II (0.2% GTN CREAM): 50 % patients were completely healed and another 50% healed with mild perianal pain and pruritus, 30% with per rectal bleeding and around 47% with constipation. (p-value = 0.0019) There is a statistically significant difference in residual perianal pain. (p-value = 0.0008) Pain is significantly lower in the surgery group. And there is a statistically significant difference in complete healing between the two groups. Lateral sphincterotomy is significantly more effective than GTN 0.2% cream. Post-treatment bleeding is significantly less in the sphincterotomy group compared to GTN group. (p-value = 0.0176)

TABLE-I

Baseline demographic and clinical features of patients in both groups

Variable	Category	Group I: Lateral Sphincterotomy	Group II: 0.2% GTN Cream
Gender	Male	18 (60.0%)	14 (46.7%)
	Female	12 (40.0%)	16 (53.3%)
Age (Years)	20–30	9 (30.0%)	10 (33.3%)
	31–40	10 (33.3%)	11 (36.7%)
	41–50	7 (23.3%)	6 (20.0%)
	51–60	4 (13.3%)	3 (10.0%)
Pain Around Perianal Region	Yes	25 (83.3%)	26 (86.7%)
	No	5 (16.7%)	4 (13.3%)
Per Rectal Bleeding	Yes	13 (43.3%)	12 (40.0%)
	No	17 (56.7%)	18 (60.0%)
Constipation	Yes	21 (70.0%)	20 (66.7%)
	No	9 (30.0%)	10 (33.3%)

TABLE-II

Clinical symptoms at 6-week follow-up

Symptom	Group I: Lateral Sphincterotomy	Group II: 0.2% GTN Cream
Pain (perianal region)	3 (10.0%)	15 (50.0%)
Per Rectal Bleeding	2 (6.67%)	9 (30.0%)
Constipation	2 (6.67%)	14 (46.7%)

DISCUSSION

Although, there are many options of treatment are known for chronic anal fissure but all these options are very time consuming and bothersome for the patient. Therefore, surgical management which is lateral internal sphincterotomy is the safest and most effective mode of treatment. After 6 weeks follow up of patient's surgery has a great chance around 90% of quick recovery from symptoms with no any major complication and result in quick postoperative relief of constipation problem along with the quick release of defecation discomfort which is as compare to GTN cream 50% recovery from pain and other symptoms.

In our study after 6 weeks almost all the patients after surgery has healed fissure and in other group around 50% has healed fissure. This present study has results comparable to the study done by Siddique et al. In which there was 28 out of 33 (84.85%) patients after surgical treatment and 11 out of 31 (35.48%) patients after medical treatment with GTN ointment ($p<0.001$) had complete healing at the end of six weeks.[12]

Our study results were non-comparable to the results of the study done by Mishra et al., on 40 patients with chronic anal fissure in which there were out of 20 patients 18 have healed with medical treatment 0.2% GTN ointment and out of 20 patients 17 have healed with lateral internal sphincterotomy surgery at the end of 6th weeks of treatment.[13]

The Consultants know the efficacy and advantage of surgery but still give preference to medical treatment for chronic fissure in ano which is very bothersome and time taking for the patients. The surgical procedure which is lateral anal sphincterotomy should be the first option by the surgeons for treatment of chronic anal fissure.[14] This approach is cost effective. Chronic fissure in ano has high prevalence of around 1 out of 350 individuals. Patients even with the pain and bleeding often ignore it and don't go for proper treatment which result in compromise of their daily activities, discomfort and complications like anemia. Till now, many medical options are in practice including of GTN (glyceryl trinitrate) 0.2%, which is very useful as local applicant specially for acute anal fissure which results in increase blood flow by dilating the vessels, relaxes the sphincter and relaxes the anal canal for defecation.[15]

Anal Fissure is also very common in children and is one of the cause of Per rectal bleeding, low fibre diet and decrease water intake are two most important factors leading to Fissure in ano. This is a metabolic disease need patient's education about good diet, increase water intake and also to educate people that don't overlook the symptoms of anal fissure and consult doctor immediately and get themselves examined. All need is good awareness and nothing else.

CONCLUSION

Chronic anal fissure, is a disease of both the genders equally effected. Although, many treatment options are available but all are time consuming and with high recurrence rate and are not cost effective. Therefore, the safe and most effective option of treatment is lateral anal sphincterotomy. This method has a great chance around 96% of quick recovery from symptoms with no any major complication and result in quick postoperative

relief of constipation problem along with the quick release of defecation discomfort. Doctors knows the advantage of surgery but still use conservative options for chronic anal fissure. The surgical option must be the first and absolute option for chronic anal fissure treatment. This will save both time and money

RECOMMENDATIONS BASED ON STUDY RESULTS

Based on the findings of this randomized controlled trial, lateral anal sphincterotomy should be considered the first-line treatment for patients suffering from chronic anal fissure, especially those with persistent symptoms and poor response to conservative measures. The procedure demonstrated a significantly higher rate of complete healing (90%) compared to 0.2% glyceryl trinitrate (GTN) ointment (50%), along with a markedly lower incidence of residual symptoms such as perianal pain, rectal bleeding, and constipation. These outcomes support the superior efficacy, faster symptom resolution, and better overall patient outcomes with surgical management. Therefore, clinicians should prioritize sphincterotomy in treatment algorithms, while reserving GTN ointment for patients who are unwilling or unfit for surgery.

LIMITATIONS OF THE STUDY

Despite its valuable findings, the study has several limitations. Firstly, the sample size was relatively small (n=60), which may limit the generalizability of the results to the broader population. Secondly, the short follow-up duration of 6 weeks does not allow assessment of long-term outcomes, such as recurrence rates or late complications like incontinence. Thirdly, blinding was not mentioned, which may introduce observer or performance bias. Moreover, patient compliance and side effects from GTN ointment, such as headache, were not evaluated or documented, which could have impacted treatment adherence and outcomes. Lastly, the study was conducted at a single center, which may limit external validity. Future research with larger, multi-center trials and longer follow-up periods is recommended.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
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2	**Amin Warraich:** Data collection.
3	**Mudassar Rasool:** Data analysis.
4	**Rashid Ehsan Randhawa:** Discussion writing.
5	**Hafsa Ijaz:** Review of manuscript.
6	**Imran Amin:** Data analysis.

https://doi.org/10.29309/TPMJ/2026.33.02.9504 www.theprofesional.com

ORIGINAL ARTICLE

Influence of pneumoperitoneum pressures in laparoscopic cholecystectomy: A clinical trial.

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ABSTRACT… Objective: To compare the severity of postoperative abdominal pain between high (12mmHg) vs low (8mmHg) pressure pneumoperitoneum in patients undergoing elective laparoscopic cholecystectomy. **Study Design:** Prospective, Randomized, Double-blinded Controlled Trial. **Setting:** Surgical Unit of Pir Abdul Qadir Shah Jeelani Institute of Medical Sciences in Pakistan. **Period:** Six Months, from 1st May to 30th November 2024. **Methods:** Was carried out involving patients undergoing laparoscopic cholecystectomy (LC) with ethical approval obtained beforehand. Sixty patients participated and were randomly allocated to two groups in equal numbers. Group A underwent LC using high-pressure pneumoperitoneum (12–14 mmHg), whereas Group B had the procedure performed under low-pressure pneumoperitoneum (8–10 mmHg). The level of postoperative pain was assessed using the Visual Analogue Scale (VAS) 24 hours after surgery. **Results:** The mean age of Group A was 41 ± 9.96 years, and Group B was 38 ± 10.09 years. Group A included 18 (60%) males and 12 (40%) females, whereas Group B had 20 (67%) males and 10 (33%) females. At 24 hours postoperatively, 22 (73%) patients in Group A experienced mild pain, while 8 (27%) reported moderate-to-severe pain. In Group B, 26 (87%) patients had mild pain, whereas only 4 (13%) experienced moderate-to-severe pain. **Conclusion:** The article concludes that lower pneumoperitoneum pressures used during laparoscopic cholecystectomy reduced post-operative pain in comparison to when higher pressures were used without compromising the operative visibility. Future studies require larger sample size studies to address further the concerns for surgical visibility, operative duration, while also assessing the outcomes.

Key words: Laparoscopic Cholecystectomy, Pneumoperitoneum Pressure, Postoperative Pain, Randomized Controlled Trial, Visual Analogue Scale.

Article Citation: Moosa S, Raza H, Ahmed B, Umar M, Akram M, Tahir A. Influence of pneumoperitoneum pressures in laparoscopic cholecystectomy: A clinical trial. Professional Med J 2026; 33(02):346-351. https://doi.org/10.29309/TPMJ/2026.33.02.9504

INTRODUCTION

Gallstone disease is the commonest disease affecting the biliary tract, often requiring surgical intervention. Since its introduction in 1882, cholecystectomy has remained the definitive treatment, with Laparoscopic cholecystectomy gaining prominence due to its minimally invasive nature, which translates to several patient benefits.[1] These include reduced postoperative pain, abbreviated hospital stays, and quicker recovery periods, making it a preferred surgical option for gallbladder-related conditions.[2]

A crucial aspect of LC is the creation of a pneumoperitoneum, which provides adequate visualization of the surgical field by insufflating carbon dioxide (CO_2) into the peritoneal cavity. In clinical practice, 12-14mmhg pressure is used, which raises concerns for adverse effects such as increased post-operative pain, altered hemodynamics, and reduced pulmonary compliance, these adverse effects can be avoided with the use of 8-9mmHg pressure techniques.[3] Scientific literature also supports with evidence that lower pressures maintain adequate surgical exposure but help reduce post-operative pain, and improve patient outcomes.[4]

Despite the benefits, some surgeons raise concerns that reduced pressures may prolong operative time and increase technical difficulties and may also be not feasible in maintaining sufficient work space for safe dissection.[5] Concerning the aforementioned debate, this study aimed to compare the influence of different pneumoperitoneum pressures (Low vs high) on postoperative pain in patients undergoing elective Laparoscopic Cholecystectomy, for contributing to the surgical protocols for better patient care and comfort.

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Article received on:
21/03/2025
Accepted for publication:
30/05/2025

METHODS

Study Design and Setting

This randomized controlled trial was conducted at the Department of Surgery, Pir Abdul Qadir Shah Jeelani Institute of Medical Sciences, Pakistan, after approval from ethical committee (Reference No: 24/08 Dated: 08/04/2024) as a prospective study, all patients admitted during the six-month enrollment period (1st May to 30th November 2024) were assessed for eligibility. Recruitment ceased once 60 eligible patients were selected.

Patient Selection

Patients were assigned into two equal groups of 30 each by randomization. Patients having age above 18 years, with either gender having symptomatic gallstones, who were planned for elective LC, having ASA Grade I or II were included in this study. However, patients with acute cholecystitis, cholangitis, or gallbladder malignancy, and those having severe comorbidities (ASA Grade III or above), Pregnant female, and those changed to open cholecystectomy were excluded to participate in this study. In the study, two groups underwent laparoscopic cholecystectomy under different conditions: Group A, serving as the control group, underwent the procedure at the typical pneumoperitoneum pressure of 12–14 mmHg, whereas Group B, designated as the intervention group, experienced the surgery with a reduced pneumoperitoneum pressure set at 8–10 mmHg.

Randomization and Blinding

A convenient sample of 60 participants was selected and randomly assigned into two equal groups (30 per arm) using a computer-generated randomization list. Allocation followed a pre-set list, with each study arm color-coded for randomization, data entry, and analysis. Concealment was maintained through sequentially numbered sealed envelopes. While the surgeon was aware of the group assignment, all participants, postoperative pain assessors, and data analysts remained blinded to the pneumoperitoneum pressure used.

Intervention and Technique

In this study, patients in the intervention group underwent laparoscopic cholecystectomy using low-pressure pneumoperitoneum, where the gas insufflation pressure was maintained at 8–10 mmHg. In contrast, the control group underwent the procedure with standard-pressure pneumoperitoneum, set between 12–14 mmHg. This distinction allowed for a comparative analysis of outcomes based on pressure levels. At the start of surgery, initial insufflation was set to 8 mmHg for the low-pressure group and 12 mmHg for the standard-pressure group. Pressure adjustments were made at two points upon the surgeon's request. Trocars were introduced on pressure allocated by each group. Pain ratings were made using the short 11-point (0-10) pain scale, assessed per patient at 24 hours post-operatively. All procedures were performed by experienced surgeons under general anesthesia and followed a standardized, stepwise technique: A standard four-port technique was used with the following trocar positions: The creation of pneumoperitoneum was achieved through carbon dioxide (CO_2) insufflation using an open technique. This involved making an infra-umbilical incision and inserting a 10 mm trocar at the umbilical site.

Additional trocars were placed at specific positions: a 10 mm trocar at the sub-xiphisternum, a 5 mm trocar at the medial subcostal region, and another 5 mm trocar at the lateral subcostal region. These precise placements ensured proper access for the laparoscopic procedure. To minimize diaphragm expansion, all trocars were inserted during exhalation.

The critical view of safety technique was employed to dissect the cystic duct and cystic artery, which were subsequently clipped and divided. The gallbladder was carefully dissected and extracted through the umbilical port. Pneumoperitoneum pressures were maintained at 12–14 mmHg for Group A (standard pressure) and 8–10 mmHg for Group B (low pressure). Finally, all port sites were closed using absorbable sutures to ensure proper wound healing. The peri-operative preparation and postoperative protocol for the patients is detailed elsewhere.[1]

Outcomes

The primary outcome was the postoperative pain score at 24 hours. Postoperative pain was assessed using the Visual Analogue Scale at 24

hours after surgery. VAS scores were divided into specific categories to assess pain intensity. A score of 0–4 mm represented no pain, while mild pain was categorized as 5–44 mm. Scores ranging from 45–74 mm indicated moderate pain, and severe pain corresponded to scores between 75–100 mm. This classification provides a clear framework for evaluating postoperative discomfort levels in patients. Pain score was recorded by a blinded observer who was unaware of the pneumoperitoneum pressure used during surgery.

Statistical Analysis

SPSS version 24.0 was used to analyze the data. Continuous variables, including age, BMI, and pain scores, were reported as mean ± standard deviation (SD) and analyzed using a t-test for comparison. Categorical variables, such as gender, ASA grade, and pain severity, were expressed as percentages and evaluated using the chi-square test. Statistical significance was defined as a p-value of less than 0.05.

RESULTS

The mean age was 41 years in Group A (SD ± 9.96), while 38 years in Group B (SD ± 10.09). In terms of gender distribution, Group A included 18 males (60%) and 12 females (40%), whereas Group B included 20 males (67%) and 10 females (33%), shown in Table-I.

Most patients in both groups had a BMI between 25–30 kg/m^2. Specifically, 67% of Group A and 70% of Group B fell within this range. The remaining patients had a BMI of 31–33 kg/m^2. ASA Grade I patients were slightly more common in Group B (63%) compared to Group A (57%), shown in Table-I.

Postoperative pain at 24 hours was assessed using the VAS. In Group A, 22 patients (73%) reported mild pain, while 8 patients (27%) experienced moderate to severe pain. In contrast, in Group B, 26 patients (87%) had mild pain, and only 4 patients (13%) experienced moderate to severe pain. The pain score was significantly lower in Group B (35 mm ± 10.39) compared to Group A (63 mm ± 15.43), shown in Table-II.

A chi-square test for assessment of the differences in postoperative pain was applied, with a p-value of 0.1967, suggesting a trend favoring low-pressure pneumoperitoneum in reducing postoperative pain, though not reaching statistical significance.

TABLE-I

Demographics.

Variable	Group A (High Pressure)	Group B (Low Pressure)	P-Value
Age (Mean ± SD, years)	41 ± 9.96	38 ± 10.09	-
Gender	Male: 18 (60%) Female: 12 (40%)	Male: 20 (67%) Female: 10 (33%)	0.62
BMI (kg/m^2)	25–30: 20 (67%) 31–33: 10 (33%)	25–30: 21 (70%) 31–33: 9 (30%)	0.78
ASA Grade	Grade I: 17 (57%) Grade II: 13 (43%)	Grade I: 19 (63%) Grade II: 11 (37%)	0.65

In both age groups (18–30 years versus 31–60 years), mild pain was more prevalent in Group B than Group A. A greater percentage of males and females in Group B reported mild pain compared to Group A. Within the group of patients whose BMI falls between 25 and 30 kg/m^2, mild pain was reported in 18 patients from Group B versus 15 patients in Group A, shown in Table-II.

The results indicate that low (8mmhg) pressure pneumoperitoneum reduced postoperative pain compared to high (12mmhg) pressure pneumoperitoneum without compromising the surgical visibility. Since, the results were not statistically significant, however, the trend suggests that lower pressures are contributory to better postoperative comfort.

DISCUSSION

This study evaluated the impact on postoperative pain in patients undergoing elective laparoscopic cholecystectomy by using high vs low pressure pneumoperitoneum. The findings indicate that low (8 mmhg) pressure pneumoperitoneum is linked to lower postoperative pain at 24 hours compared to high-pressure pneumoperitoneum. Specifically, a greater proportion of patients in the low (8 mmHg) pressure group reported mild pain (87%) in comparison to the high (12mmHg) pressure group (73%).

TABLE-II

Postoperative pain scores and stratification by age, gender, BMI, and ASA Grade.

Variable	Group A (High Pressure)	Group B (Low Pressure)	P-Value
Overall Pain Score (VAS at 24h)	Mild (VAS 5–44): 22 (73%) Moderate-Severe (VAS 45–100): 8 (27%)	Mild (VAS 5–44): 26 (87%) Moderate-Severe (VAS 45–100): 4 (13%)	0.19
Pain Stratification by Age			
18–30 years	Mild: 9 (69%) Moderate-Severe: 4 (31%)	Mild: 11 (85%) Moderate-Severe: 2 (15%)	0.25
31–60 years	Mild: 13 (76%) Moderate-Severe: 4 (24%)	Mild: 15 (88%) Moderate-Severe: 2 (12%)	0.3
Pain Stratification by Gender			
Male	Mild: 12 (67%) Moderate-Severe: 6 (33%)	Mild: 15 (75%) Moderate-Severe: 5 (25%)	0.4
Female	Mild: 10 (83%) Moderate-Severe: 2 (17%)	Mild: 11 (90%) Moderate-Severe: 1 (10%)	0.5
Pain Stratification by BMI			
BMI 25–30 kg/m²	Mild: 15 (75%) Moderate-Severe: 5 (25%)	Mild: 18 (86%) Moderate-Severe: 3 (14%)	0.35
BMI 31–33 kg/m²	Mild: 7 (70%) Moderate-Severe: 3 (30%)	Mild: 8 (80%) Moderate-Severe: 2 (20%)	0.45
Pain Stratification by ASA Grade			
ASA Grade I	Mild: 12 (71%) Moderate-Severe: 5 (29%)	Mild: 14 (84%) Moderate-Severe: 3 (16%)	0.28
ASA Grade II	Mild: 10 (77%) Moderate-Severe: 3 (23%)	Mild: 12 (89%) Moderate-Severe: 2 (11%)	0.32

Moreover, moderate to severe pain was less common in the low (8mmHg) pressure group (13%) than in the high (12mmHg) pressure group (27%). However, the difference was not found statistically significant ($p = 0.19$).

Although the trend suggests a potential benefit of the low (8mmhg) pressure approach in reducing postoperative pain, larger patient sample studies are needed to confirm statistical significance.

The results of this study align with previous research suggesting that lower insufflation pressures lead to reduced postoperative pain. Low-pressure pneumoperitoneum minimizes peritoneal stretch, decreases irritation of the diaphragm, and reduces CO_2 retention, all of which contribute to lower pain levels.[6] Several studies have reported similar findings, with patients in low-pressure groups experiencing less pain in the immediate postoperative period.[6,7,8] However, conflicting evidence exists in the literature, with some studies raising concerns about whether lower pressure compromises surgical exposure.[7] Limited intra-abdominal working space may increase the complexity of dissection, potentially leading to prolonged operative time or higher conversion rates to open surgery.[9] While these concerns remain theoretical in many cases, they highlight an important balance between patient comfort and the technical demands of the procedure. Our study did not assess operative duration or surgical field clarity, and further research is needed to explore these factors.

The reduction in postoperative pain observed with low-pressure pneumoperitoneum can be attributed to several physiological mechanisms, such as lowered activation of the visceral pain receptors by decreasing mechanical stretch on the peritoneum, which also reduces irritation of the phrenic nerve and the diaphragm, contributing to lowering referred pain on the shoulders which is common after laparoscopic surgeries. Lower Pressures also help lowering CO2 absorption in the blood that contributed to decrease hypercapnia associated side effects i.e., reduced inflammatory response

and discomfort in the peritoneal cavity.[6,10] Despite these benefits, concerns regarding adequate surgical exposure and the feasibility of maintaining low pressures throughout the procedure must be addressed in future studies.

The strengths of this study include sample randomization, which reduces selection bias, and the use of the VAS for pain measurement. Additionally, blinded observer assessed the postoperative pain which also reduces the bias for reporting pain. This study has some limitations that it included a small sample size of 60 patients which may have limit the ability to detect statistical significant difference, even when the trend in the literature is evident towards reduced reporting of pain. Furthermore, the study assessed postoperative pain up to 24 hours without reporting the operative time and visibility. Other postoperative variables such as potential complications and need for additional analgesic were not assessed for the article. Another limitation is that this article is conducted at single center which can reduce impact of the findings to the broader population and various surgical settings.

Future studies should include larger multicenter patient samples focusing on additional postoperative variables such as analgesic requirements and operative time. Worldwide, laparoscopic cholecystectomy being the most performed surgery, optimizing pneumoperitoneum settings to enhance patient comfort while maintaining surgical efficiency remains a critical area of ongoing research.

CONCLUSION

The article concludes that lower pneumoperitoneum pressures used during laparoscopic cholecystectomy reduced post-operative pain in comparison to when higher pressures were used. Lower pressures contributed to better patient comfort which can serve as an effective strategy for surgery. This study had short follow-up and small sample size, so, larger sample size studies to address the concerns for operative duration, while also assessing the outcomes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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https://doi.org/10.29309/TPMJ/2026.33.02.10070 www.theprofesional.com

ORIGINAL ARTICLE

Comparison of bipolar "button" plasma vaporization of the prostate versus bipolar transurethral resection in saline for benign prostate obstruction.

Zain Yasin Butt[1], Muhammad Irfan[2], Muhammad Shafi Ghouri[3], Athar Mahmood[4], Muhammad Asif Raza[5], Rao Nouman Ali[6]

ABSTRACT… Objective: To determine the differences in outcomes when bipolar button plasma vaporization is used to manage benign prostatic obstruction, compared to bipolar transurethral resection. **Study Design:** Randomized Controlled Trial. **Setting:** Department of Urology & Renal Transplant, DHQ Teaching Hospital, Gujranwala. **Period:** 9-6-2023 to 10-12-2023. **Methods:** To participate, 62 patients were selected and then randomized by simple random sampling into two groups. Group A received gamma knife BPVP and group B had the procedure known as Transurethral Resection of the Prostate (TURP). Patients stayed in post-surgical wards after the operation until they were allowed to go home. We noted how many days the patients were hospitalized, the time spent using irrigation and if they had a catheter. We also measured the amount of blood lost and how severe the lower urinary tract symptoms were. SPSS version 25 was used to look at the data. **Results:** The average patient age in group-I was 58.59±4.59 years and 57.67±4.61 years in group-II. BPVP patients had improvements in many perioperative outcomes, with less time for surgery (45.5 versus 69.8 mins), irrigation (9.96 versus 12.87 hours), catheterization (2.83 days versus 4.96 days), hospital length of stay (3.32 days versus 5.96 days) and lower blood loss (109.38 mL compared to TURP's 197.25 mL) ($p < 0.05$). Overall and when grouped by age and how long symptoms had lasted, IPSS scores showed no significant differences between the groups ($p > 0.05$). **Conclusion:** Initial findings indicate that BPVP is comparatively safer than TURP, extremely efficient, associated with reduced perioperative bleeding, and resulting in a shorter hospital stay.

Key words: Button Plasma Vaporization for Bipolar, Benign Prostatic Obstruction, Resection of Prostate Using Bipolar Technology.

Article Citation: Butt ZY, Irfan M, Ghouri MS, Mahmood A, Raza MA, Ali RN. Comparison of bipolar "button" plasma vaporization of the prostate versus bipolar transurethral resection in saline for benign prostate obstruction. Professional Med J 2026; 33(02):352-357. https://doi.org/10.29309/TPMJ/2026.33.02.10070

INTRODUCTION

Benign prostatic obstruction, often called benign prostatic hyperplasia, occurs when the prostate enlarges and causes problems and changes in the urinary tract.[1] It is estimated that one third of men at least 50 years old experience a worsening of their quality of life because of BPH. BPH can be seen under a microscope in almost all men older than 85 years. More than 14 million men in America are thought to have symptoms of BPH.[2] Throughout the world, it's estimated that 30 million men are troubled by BPH symptoms. In BPH, the prostate grows in size without becoming cancerous. Some symptoms are frequent urination, difficulty starting to urinate, a weak flow, an inability to urinate and loss of control over urinating. Sometimes, complications may be urinary tract infections, bladder stones or persistent kidney problems.[3,4]

The course of BPO in an individual is fundamentally uncertain. The symptoms and objective measurements of urethral obstruction may last without substantial alterations for a prolonged duration, and in certain instances, they may even exhibit amelioration over time in roughly one-third of males. Over a span of 3.5 years, a significant majority of men (73%) with moderate benign prostatic blockage did not encounter a deterioration in their urine symptoms.[5] A number of interventions have been developed and implemented in clinical practice to address the associated morbidity of symptomatic BPO.

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Article received on:
08/09/2025
Accepted for publication:
19/11/2025

Various minimally invasive surgical procedures obviously have advantages over traditional surgery when it comes to treating this group of men and, possibly, can promote the efficacy of surgical intervention.

On the other hand, however, there is no sufficient long-term evidence regarding the effectiveness and potential side effects of these new methods vs. Bipolar transurethral resection of the prostate TURP.[6] Current research repeatedly demonstrates that both Monopolar Transurethral Resection of the Prostate (TURP) and open surgery are still associated with significant health concerns. Moreover, the emergence of innovative endoscopic therapies has led to a constant questioning of these old approaches. Bipolar plasma vaporization of the prostate (BPVP) is considered a safe and preferable alternative to TURP.[7] Rationale of this study is to compare the outcome of BPVP versus bipolar TURP, in saline. Literature showed that BPVP is better method to resolve BPO as compared to Bipolar TURP. But it is not in practice in public sector settings due to non-availability of local evidence. So, through this study we want to get local evidence that BPVP is safer and more effective method for BPO than bipolar TURP. This will help to improve our practice and in future we will implement the BPVP as first management protocol for patients of BPO instead of bipolar TURP.

METHODS

A Randomized Controlled Trial was conducted at Department of Urology & Renal transplant, DHQ Teaching Hospital, Gujranwala from 9-6-2023 to 10-12-2023 after approval from ethical review committee (Admin R.C No. 3149, 02/01/22). Sample size of 62 cases; 31 cases in each group were calculated with 95% confidence level, 80% power of study and taking magnitude of mean hospital stay i.e. 1±2.1 days with BPVP and 3±3.3 days with standard technique for management of BPO [8] using simple random sampling technique. Patients of age between 50 to 65 years presenting with BPO. BPO is defined as a noncancerous enlargement of the prostate gland that lasts for a duration beyond six months. The ultrasonographic assessment determined the dimensions of prostate and found no evidence of malignant cells on cytology. Nevertheless, the patient is encountering difficulty in urinating. Patients with known previous prostatic or urethral surgery (on medical record) neurogenic bladder, prostate cancer, significant high PSA (>14 ng/dl) and hard or nodular prostate, negative Transrectal Ultrasound (TRUS) of prostate or responded to medical therapy were excluded.

A total of 62 patients who met the selection criteria were enrolled. Each patient provided informed consent. The demographic information, including the individual's name, age, address, and duration of symptoms, was recorded. The patients were allocated into two groups using a random lottery procedure. BPVP was conducted in group A. Bipolar TURP was performed in group B. A solitary surgical team conducted all surgeries with the support of a researcher. General anesthesia was used for all surgical procedures. The duration of the operation was recorded in hours, starting from the time when anesthetic was fully provided until its completion. Blood Loss was assessed in ml of blood in suction drain and soaked gauze (1g=1ml). After undergoing surgery, patients were transferred to post-surgical wards and remained there until they were discharged. The patient will be released from the hospital once the drain is removed and they indicate a pain level below 3 on a vocal rating pain scale that ranges from 0 to 10. The length of the hospitalization period was recorded. The study also recorded the total duration of irrigation, catheterization, blood loss, and lower urinary tract symptoms (LUTS score). Irrigation time was assessed post-operatively as the time required to irrigate the resected prostate in terms of hours. Catheterization Time was entailed quantifying the duration required for catheter insertion. LUTS symptoms were compared according to the International Prostate Scoring System (IPSS) 24 hours following the operation. The catheter will be removed whenever the discharge reduces to below 20 milliliters per day. All data was entered and analyzed in SPSS version 25.0. Both groups were compared for mean outcome by using independent sample t-test. P-value < 0.05 was taken as significant.

RESULTS

The mean age of patients in group-I was 58.59 years (±4.59) and the mean age of those in group-II was

57.67 (±4.61). The typical duration of symptoms for group-I was 8.29±1.10, as were they for group-II at 8.32±1.24 as showed in Table-I

TABLE-I

Baseline characteristics of patients in both groups

	Group-I	Group-II
n	31	31
Age of the Patients	58.58 ± 4.59	57.67 ± 4.61
Duration of Symptoms	8.29 ± 1.1	8.32 ± 1.24

Table-II shows the International Prostate Symptom Score (IPSS) comparison for LUTS in subjects with BPVP and those with TURP, grouped by how long their symptoms had been present and their age. The average for the IPSS was slightly lower with BPVP (8.032 ± 3.7281) than the average with TURP (8.774 ± 3.0409); yet, the difference was not significant (p = 0.39). There was no significant difference in the International Prostate Symptom Score (IPSS) by age group (50–55, 56–61 and 62–67 years) between the Montelukast and Verapamil groups. Results from analysis by duration (7 to 8 years and 9 to 10 years) of symptoms also did not find any differences in IPSS scores between patients in the BPVP and TURP groups (p = 0.72, p = 0.49, respectively).

Table-III looks at important outcomes of care following surgery for both the BPVP and TURP approaches. Several parameters indicated that the BPVP procedure could result in positives. Patients who received BPVP had significantly shorter operating times on average (45.51 ± 14.29 minutes) than those who had TURP (69.83 ± 32.08 minutes, p = 0.0004). BPVP plants also needed less irrigation, spending 9.96 ± 2.9 hours under water vs. 12.87 ± 5.0 hours for the control group, p = 0.007. Catheterization time was much shorter for BPVP (2.83 ± 0.82 days) than for TURP (4.96 ± 1.49 days, p < 0.0001).

The mean hospital stay was shorter in the BPVP group (3.32 ± 1.93 days) than in the TURP group (5.96 ± 1.44 days; p < 0.0001). The BPVP group had less estimated blood loss (109.38 ± 33.04 mL) than the TURP group (197.25 ± 77.74 mL, p < 0.0001). Although the IPSS for LUTS was a little lower in the BPVP group (8.03 ± 3.73) than in the TURP group (8.77 ± 3.04), this difference was not considered significant (p = 0.395).

DISCUSSION

Recent studies indicate that about 75% of men will have BPH by the age of 70. [9] The TURP remains the prevailing method for managing BPO. Nevertheless, numerous difficulties were documented in relation to this surgery.[10] Laser treatment and transurethral microwave therapy have made it difficult for TURP to help those with symptoms of BPO. This technique removes obstructive tissue using laser energy, not thermal or electrical radiation which is used in other treatments.

TABLE-II

Comparison of IPSS for LUTS between BPVP and TURP groups

Stratification	Group	n	Mean	SD	t-value	P-Value
Overall	BPVP	31	8.032	3.7281	0.86	0.39
	TURP	31	8.774	3.0409		
Age 50–55	BPVP	7	7.714	3.8173	0.24	0.81
	TURP	11	8.091	2.8445		
Age 56–61	BPVP	14	6.571	3.5239	1.45	0.15
	TURP	12	8.500	3.1766		
Age 62–67	BPVP	10	10.300	3.0930	0.12	0.91
	TURP	8	10.125	3.0443		
Duration 7–8 years	BPVP	19	7.263	3.1241	0.35	0.72
	TURP	17	7.647	3.3716		
Duration 9–10 years	BPVP	12	9.250	4.3927	0.69	0.49
	TURP	14	10.143	1.9158		

TABLE-III			
Comparison of outcome in both groups			
	BPVP	**TURP**	**P-Value**
n	31	31	
Time of Operation	45.51 ± 14.29	69.83 ± 32.08	0.0004
Irrigation Time	9.96 ± 2.9	12.87 ± 5.0	0.007
Catheterization Time	2.83 ± 0.82	4.96 ± 1.49	<0.0001
Hospital stay	3.32 ± 1.93	5.96 ± 1.44	<0.0001
Blood Loss	109.38 ± 33.04	197.25 ± 77.74	<0.0001
IPSS For LUTS	8.03 ± 3.73	8.77 ± 3.04	0.395

Light from the laser passes into the adenomatous tissue in the prostate and vaporizes it so the tissue does not burn. There is a thin layer of clotted tissue that forms too which helps control the bleeding.[11] Now, we are looking at these treatments and weighing them against TURP based on their effectiveness, the problems patients may experience, their length of hospital stay and their expense. The plasma kinetic system was begun by performing transurethral vaporization of the prostate with water instead of steam. The plasma corona that appears on a spherical electrode from the UES-40 bipolar high-frequency generator is the basis for BPVP. Applying plasma vaporization leaves a gentle seal on the problem area, stopping bleeding. Because bleeding was handled well, the surgeon had an excellent view of everything during the procedure.[12-13]

The study conducted by El-Hawy et al., in 2021 found that postoperative outcomes were significantly better in cases where BPVP was used compared to classic TURP. The researchers reported that BPVP improved operative visibility, reduced capsular perforation, decreased operative time, and resulted in faster and more complete tissue removal, which is consistent with findings from previous studies.[14] However, our investigation yielded contrasting results compared to the aforementioned study. In our study, we did not observe any notable disparity in the average values of BPVP and TURB, since the p-value did not reach statistical significance. The p-value is 0.39. Samir et al. also found that bipolar TURP resulted in less intraoperative bleeding and a shorter irrigation time, with statistical significance ($P < 0.001$).[15] These findings are consistent with multiple meta-analysis studies that have demonstrated that PVP utilizing laser energy and BPVP resulted in significantly reduced durations of catheterization and hospitalization compared to monopolar TURP.[16]

The rationale behind shorter postoperative hospitalization after BPVP is that it promotes correct haemostasias, reduces blood loss and hemorrhagic episodes, and subsequently decreases morbidities.[17] Patients who underwent TURP required a longer duration of irrigation postoperatively. Our study found that the irrigation for TURP was twice as long as that for BPVP, which aligns with these findings. In the study conducted by Castellani et al. in 2021, did a study comparing the effectiveness of the BPVP and standard TURP procedures for treating BPO. The study identified a marked distinction between the two methods with regards to the average operating time, the duration of catheterization, the length of irrigation, and the length of hospital stay. Data was reported in average values, and the following p-values were assigned to each variable: (53min vs. 62min 0.004), (2days vs. 3days, 0.03), (15hours vs. 26hours, 0.0001), (1days vs. 3days, 0.0001), respectively.[18] In our investigation, the average operating duration in the BPVP group was 45.51±14.29, which is shorter than the study mentioned before. The mean values of BPVP and TURP in our investigation did not show any significant difference, which aligns with the findings of the previously described study.[19]

The report indicates that the average duration of catheterization for the TURP group was significantly longer than that of the BPVP group (115.2 vs. 23.8). These findings align with our study, where we observed a longer duration for the TURP group

compared to the BPVP group (4.96 vs. 2.83). Additionally, the report highlights a significant decrease in IPSS (International Prostate Symptom Score) for the BPVP group (24.2–5.0) compared to the TURP group (18.8–7.2).[20] The results of our investigation differ from these findings. In our study, we did not see a significant difference in the IPSS score between the BPVP group and the TURP group (8.03 vs 8.77). Additionally, the p-value was not statistically significant (p-value=0.39). According to the earlier study performed by Habib, et al. in 2022, the duration of operation was also markedly shorter for BPVP in comparison with TURP – 39.0 ± 15.5 min and 69.3 ± 24.8 min, correspondingly.

The same has been observed concerning the length of catheter use – 4.1 ± 4.1 and 6.8 ± 6.8 days for the first and the second groups, respectively. The quantity of blood loss was notably reduced in the first group in comparison to the second group (64.7 ± 103.8 ml vs. 254.7 ± 325.4 ml, P = 0.040). The duration of hospitalization was shorter in the first group as compared to the second group (8.7 ± 1.0 days vs. 11.7 ± 1.5 days, P = 0.000). The first group had a lower IPSS score compared to the second group (4.2 ± 8.0 vs. 9.3 ± 3.7, P = 0.049).[21] To summarize, BPVP with a "button-type" electrode is a highly efficient and low-risk endoscopic treatment for BPH. It has a high success rate and is well-received by patients during follow-up. However, when comparing BPVP with "button-type" electrode to its predecessor PKVP, bipolar TURP, and standard TURP, it shown a considerable improvement in short-term effectiveness. The new approach can be supported by credible evidence of substantial enhancements in catheterization duration, hospital stay, complications rate, and follow-up metrics such as IPSS, HRQL, and Qmax.[22] Karakose et al., suggested that BPVP may be used for cardiac pacemaker and bleeding disorder patients since there is no return current needed in this surgery and hence, minimizes the risks of burns and problems with pacemakers.[5]

Sinha et al. compared TURP to laser treatment used for men with BPO. They explained that a laser procedure allows people to be discharged from the hospital sooner (0.7 days) than other treatments, yet the laser requires patients to be followed for a longer period of time. Due to the small group, single-center approach and little time for follow-up, the results cannot be generalized to everyone. Further studies with bigger groups and a longer follow-up are necessary to test if BPVP works well and safely over a long period, as compared to TURP. Further research should also explore patient-reported outcomes and cost-effectiveness to support broader implementation in public healthcare settings.

CONCLUSION

The data suggests that BPVP is safer, just as effective as TURP, linked to less perioperative bleeding and allows for a shorter hospital stay than TURP. For appropriate cases, we propose that BPVP should be the first type of surgery used for BPO patients.

ACKNOWLEDGEMENT

The authors would like to acknowledge the Medical Affairs Department of Getz Pharma for their technical support and assistance in the publication process.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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https://doi.org/10.29309/TPMJ/2026.33.02.10200 www.theprofesional.com

ORIGINAL ARTICLE

Comparison of Fistulotomy versus Use of 1% silver nitrate in terms of post-operative pain in low-lying perianal fistula.

Ali Iqbal[1], Muhammad Yaqoob[2], Shahbaz Ahmad[3]

ABSTRACT… Objective: To compare the average postoperative pain in patients who received fistulotomy and those who received 1 percent silver nitrate to treat low-lying perianal fistulas. **Study Design:** Randomized Controlled Trial. **Setting:** Department of Surgery, Allied Hospital II (DHQ Hospital), Faisalabad. **Period:** 25th February to 25th August 2025. **Methods:** The qualified patients were randomly allocated into two groups. Group A was done under general anesthesia and had fistulotomy, and Group B was done with 1% of silver nitrate to be applied following curettage of the fistula tract. Visual Analog Scale (VAS) was used to evaluate postoperative pain at 12 weeks, and all analysed data were recorded on an organised proforma. **Results:** Group B (1% silver nitrate) had significantly lower mean pain scores (VAS: 3.37 ± 1.09) than Group A (fistulotomy) did (VAS: 4.30 ± 1.80, p = 0.019) at 12 weeks. Silver nitrate treatment was especially beneficial to younger patients, males, and those who did not have comorbidities. **Conclusion:** The study concludes that 1% silver nitrate is a less invasive and effective alternative to fistulotomy for the treatment of low-lying perianal fistulas, significantly reducing postoperative pain and promoting better recovery.

Key words: Fistulotomy, Minimally Invasive Treatment, Perianal Fistula, Postoperative Pain, Silver Nitrate.

Article Citation: Iqbal A, Yaqoob M, Ahmad S. Comparison of Fistulotomy versus Use of 1% silver nitrate in terms of post-operative pain in low-lying perianal fistula. Professional Med J 2026; 33(02):358-363. https://doi.org/10.29309/TPMJ/2026.33.02.10200

INTRODUCTION

A fistula in ano is a chronic aberrant communication that extends from the anorectal lumen to an external orifice on the skin of the buttock or perineum. It is typically partially coated by granulation tissue. There are two types of anal fistulas: non-specific and specific. Fistulae can be caused by a number of diseases, including actinomycosis, Crohn's disease, cancer, ulcerative colitis, and tuberculosis. Simple inter-sphincteric, low trans-sphincteric, and complex—high trans-sphincteric, supra-sphincteric, and extra-sphincteric—are the three types of fistulae.[1] Most non-specific perianal fistulas develop after a cryptoglandular abscess drains.[2] Tunnels between the epidermis, anal canal, and rectal mucosa can result from any inflammatory condition. The incomplete repair of these tunnels largely causes fistula development. Many times, perianal fistulas are severe and resistant to conservative therapies. High rates of recurrence, frequent operations, damage to external sphincters, and disruption of quality of life continue to be significant barriers to effective therapy.[3]

Surgery, which was often thought to be the sole therapeutic option, is linked to recurrence, repeated surgery, and, in rare instances, incontinence, which lowers quality of life and does not necessarily lead to full recovery. The two procedures that are typically chosen for this surgery are fistulectomy and fistulotomy. The fistulous tract is opened during a fistulotomy, leaving behind tiny, epithelialized lesions that may speed up the healing process.[4-5] Surgical treatment does, however, come with difficulties. Numerous alternative options for treatment have been discussed. The granulation and epithelialized tissue that border the fistula tract can be ablated with the aid of silver nitrate solution, a chemical agent with cauterizing and corrosive qualities. It promotes the production of scar tissue and the eventual closure of the fistulous tract. Furthermore, the fluid contains antibacterial qualities that lower the microbial burden and aid in anal fistula repair.

A study reported mean postoperative pain after 12 weeks of fistulotomy as 4.49 ± 1.53[6], while another study reported 3.3 ± 1.21 after 1% silver nitrate treatment.[7]

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Article received on:
19/09/2025
Accepted for publication:
28/11/2025

There are conflicting results for the management of perianal fistula.

Recent evidence has also revealed that treatment choice is not only effective in the postoperative pain but also has a significant impact on the wound healing period, repetition rates, in addition to being simple, cheap, and associated with a low pain profile compared to surgical procedures. Moreover, the procedure does not require any division of the sphincter, thereby minimizing the chances of postoperative incontinence, a frequent complication of fistulotomy.[8-9]

Moreover, research has proposed silver nitrate to enhance healing by a process of coagulation of proteins and sclerosis of tissues that results in the sealing of the fistulous tract by causing fibrosis, which is contrary to fistulotomy, whereby secondary intention is required to accelerate the healing process and cause more pain after surgery.[10] Thus, it is important to test the outcome of pain management in patients who underwent fistulotomy and 1% silver nitrate to create a management plan that would reduce the morbidity, improve the recovery, and increase the quality of life of a patient. Therefore, the study aimed to compare the mean postoperative pain in patients undergoing fistulotomy versus those treated with 1% silver nitrate for low-lying perianal fistulas.

METHODS

This randomized controlled trial was conducted in the Department of Surgery, Allied Hospital II (DHQ Hospital), Faisalabad from 25th February to 25th August 2025 after obtaining approval from the Hospital Ethical Review Committee (No. ERC/FMU/2024-25/126). The sample size was determined using the WHO sample size calculator, keeping the level of significance at 5% and the power of the test at 80%. The anticipated mean in the fistulotomy group was 4.49 ± 1.53[6], while in the silver nitrate group it was 3.31 ± 1.21.[7] The sample size was calculated to be 60 patients, and 30 patients in the group. The sampling of patients was done using a non-probability consecutive sampling method. Both men and women aged between 18 and 50 years who reported low-lying perianal fistula were included in the study. Patients who had earlier undergone surgery to excise fistula, those with complex high rectal fistula (two or more external openings), and those with secondary causes of fistula, including cancer, tuberculosis, or actinomycosis, were not included.

All patients were pre-enrolled using a written informed consent. Each participant was captured on demographic and clinical information. The patients were randomly assigned to two groups according to a computer-generated table of numbers. Group A was treated with fistulotomy, and Group B was treated with 1% silver nitrate. Fistulotomy was an elective procedure done under general anesthesia by a consultant surgeon who had three years of post-fellowship experience. The epithelial lining of the tract in the silver nitrate group was curetted with the plastic end of the cannula until the bleeding appeared. This was followed by flushing 11 ml of 1% solution of silver nitrate, and it was removed gradually as the cannula was withdrawn. To ensure that the skin around the external opening was not exposed to spillage, gauze was placed around the external opening. Visual Analog Scale (VAS) was used in measuring pain, with a range of 0-10, at a 12-week follow-up. SPSS version 25 was used to analyse the data. The quantitative characteristics like age, duration of symptoms (purulent discharge), and the VAS score were given in the form of mean and standard deviation. The gender and comorbidities (hypertension, diabetes mellitus, and cardiac disease) and the type of fistula were specified as frequencies and percentages. The independent sample t-test was used to compare the pain scores of the two groups. Stratification was done, and an independent sample t-test was applied, taking a p-value of 0.05 as significant.

RESULTS

Table-I demonstrates that the baseline demographic and clinical characteristics of both groups were similar, which means that the patient groups were successfully randomized. The age range of the majority of patients in the two groups was 1835 years of age, with a slightly higher mean age of 35.40 4.67 years in the silver nitrate group and 34.07 4.58 years in the fistulotomy group. Both groups were dominated by males, with 60 percent and 56.7 percent, respectively.

The majority of patients in both groups had a brief period of the symptoms (1-2 months), 76.7% in Group A and 73.3% in Group B, with mean durations of the same (1.90 ±0.76 vs. 1.97 ±0.73 months). In the comorbidities, there were more cases of hypertension (30% in each group), and diabetes mellitus was marginally higher (26.7%) in the silver nitrate group than in the fistulotomy group (16.7%). There were 4 cardiac disease patients (13.3) in the fistulotomy group and 0 patients in the silver nitrate group. Approximately 4043 percent of patients in both groups had no comorbidities. In terms of fistula type, the intersphincteric variant was predominant (70% in Group A vs. 73.3% in Group B), followed by transsphincteric fistulas.

Table-II compares postoperative pain scores between the two treatment groups and across various subgroups. The overall mean VAS pain score was significantly lower in the 1% silver nitrate group (3.37 ± 1.09) compared to the fistulotomy group (4.30 ± 1.80) (p = 0.019), indicating that silver nitrate treatment was more effective in reducing postoperative pain. When analyzed by age, patients aged 18–35 years in the silver nitrate group reported significantly less pain than those in the same age range in the fistulotomy group (p = 0.03), whereas no significant difference was observed among those aged 36–50 years. Similarly, male patients experienced significantly lower pain in the silver nitrate group (p = 0.015), while the difference among females was not statistically significant.

Patients with a shorter symptom duration (1–2 months) showed a significant reduction in pain with silver nitrate (p = 0.004), suggesting better efficacy in early-stage cases. Among comorbidities, diabetic patients and those without comorbidities reported notably lower pain levels with silver nitrate (p = 0.002 and p = 0.033, respectively). However, no significant difference was found among hypertensive or cardiac patients. Although pain scores were lower in the silver nitrate group for both intersphincteric and transsphincteric fistulas, these differences did not reach statistical significance (p = 0.089 and p = 0.090, respectively).

DISCUSSION

The treatment of low-lying perianal fistulas has been a clinical challenge because they are recurrent, chronic, and have a severe effect on the quality of life of the patient. Two treatment modalities were checked in the current study: fistulotomy and application of 1 per cent silver nitrate based on the postoperative pain.

TABLE-I

Demographic and clinical characteristics of patients (n = 60)

Characteristics	Categories	Group A (Fistulotomy) n=30 (%)	Group B (1% Silver Nitrate) n=30 (%)	Mean ± SD (Group A)	Mean ± SD (Group B)
Age (years)	18–35	19 (63.3%)	15 (50.0%)	34.07 ± 4.58	35.40 ± 4.67
	36–50	11 (36.7%)	15 (50.0%)		
Gender	Male	18 (60.0%)	17 (56.7%)		
	Female	12 (40.0%)	13 (43.3%)		
Duration of Symptoms (months)	1–2	23 (76.7%)	22 (73.3%)	1.90 ± 0.76	1.97 ± 0.73
	>2	7 (23.3%)	8 (26.7%)		
Comorbidities	Cardiac Disease	4 (13.3%)	0 (0%)		
	Hypertension	9 (30.0%)	9 (30.0%)		
	Diabetes Mellitus	5 (16.7%)	8 (26.7%)		
	None	12 (40.0%)	13 (43.3%)		
Type of Fistula	Intersphincteric	21 (70.0%)	22 (73.3%)		
	Transsphincteric	9 (30.0%)	8 (26.7%)		

TABLE-II

Comparison of Mean Postoperative Pain Scores (VAS) and associations (n = 60)

Variable	Subgroup	Group A Mean ± SD	Group B Mean ± SD	P-Value	Significance
Overall Pain (VAS)		4.30 ± 1.80	3.37 ± 1.09	0.019	Significant
Age (years)	18–35	4.77 ± 2.04	3.43 ± 1.16	0.03	Significant
	36–50	3.47 ± 0.81	3.31 ± 1.08	0.68	NS
Gender	Male	4.61 ± 2.00	3.16 ± 1.21	0.015	Significant
	Female	3.83 ± 1.38	3.64 ± 0.91	0.693	NS
Duration of Symptoms (months)	1–2	4.64 ± 1.61	3.35 ± 1.21	0.004	Significant
	>2	3.16 ± 2.02	3.41 ± 0.76	0.754	NS
Comorbidities	Cardiac	3.55±0.89	-		
	Hypertension	3.25 ± 1.81	3.29 ± 1.44	0.956	NS
	Diabetes Mellitus	5.26 ± 1.45	3.12 ± 0.47	0.002	Significant
	None	4.93 ± 1.79	3.58 ± 1.15	0.033	Significant
Type of Fistula	Intersphincteric	4.23 ± 1.90	3.39 ± 1.23	0.089	NS
	Transsphincteric	4.45 ± 1.62	3.32 ± 0.69	0.09	NS

The results showed that the mean scores of pain in patients who received 1 percent silver nitrate were lower at 12 weeks than the means in patients who received fistulotomy. These findings are in line with the mounting evidence that has been in favor of a minimally invasive, sphincter-preserving solution in minimizing postoperative morbidity and improving the post-surgery outcome.

Fistulotomy has long been considered the standard surgical procedure for simple, low-lying perianal fistulas because of high rates of healing and tolerable recurrence rates. According to Quinn et al. (2025) and Kadiyan et al. (2023), fistulotomy is an effective procedure that provides good elimination of the tract and a low chance of recurrence and incontinence in case it is done properly. However, it can still be associated with much postoperative pain, prolonged healing of the wound, and secondary infection.[11-12] Similar findings were also advised by Choudhury et al., who have stated that despite the fact that fistulotomy has a shorter recovery period than fistulectomy, the pain after the surgery is a significant issue that affects patient satisfaction and adherence to the treatment.[13]

The current study's results are consistent with previously reported literature that suggests chemical cauterization with 1% silver nitrate can still achieve good results with less pain and morbidity. Silver nitrate works by inducing protein coagulation and sclerosis, successfully necrosing epithelialized fistulous tracts while inciting fibrosis and closure. Attaallah et al. (2014) and Demirel et al. (2013) described the actual chemical ablation of granulation tissue in conjunction with decreasing bacterial load to trigger obliteration of the tract without affecting the sphincters.[14,15] Another noteworthy observation was made by Placer-Galan et al. (2019) and Iqbal et al. (2019), who noted significant improvements in pain and healing, ranging from 44% healing to 76% healing, depending on case selection and complexity of the tract.[16,17]

In the current trial, the statistically significant reduction in pain scores (VAS: 3.37 ± 1.09 vs. 4.30 ± 1.80; p = 0.019) highlights the analgesic benefit of chemical cauterization compared to surgical excision. The long-term findings of Attaallah et al. (2021), who reported minimal discomfort and long-lasting symptom relief after multiple outpatient chemical ablation sessions, are similar to these outcomes.[18] Another study found that the postoperative pain for fistulotomy was 1.55 ± 0.79.[19] The lack of extensive tissue dissection, the minimal amount of wound exposure, and the natural antimicrobial properties of

silver nitrate, which lessen the risk of infection and inflammation, may all contribute to the decreased postoperative pain.[20]

The subgroup analysis of the study also indicated that younger patients, males, and those who did not have comorbidities had a greater reduction in pain with silver nitrate. This trend is similar to previous findings that reported patient age, immunity, and systemic conditions like diabetes have an effect on wound healing and postoperative recovery. Yang et al. (2025) further stressed the fact that pain management is a major area of intervention in the context of maximizing patient comfort and adherence levels during the healing process. The use of silver nitrate is an inexpensive outpatient method where the patient does not need to be admitted to the hospital or undergo anesthesia, which is especially advantageous in the patient population with cardiovascular or metabolic comorbidities.[21]

In a broader scope, the present evidence adds to the trend of switching to the sphincter-sparing or least invasive practices in the management of fissures. There have been studies on the use of novel adjuncts like fibrin glue, seton, laser closure, and non-thermal plasma with mixed success rates and cost-effectiveness. An et al. (2024) and Lopez-Callejas et al. (2024) discovered that such advanced methods are effective in complex or recurrent fistulas, and most of them may need specific equipment and skills, which are unavailable in low-resource scenarios; however, silver nitrate is a simple, cheap, and repeatable method that can be promoted into general surgery.[22-23]

One of the strongest points of the research is its randomized controlled design that reduces the selection bias and enhances the validity of intergroup comparisons. The objective measurement of the postoperative discomfort is the assessment of the pain at a fixed interval of 12 weeks using the Visual Analog Scale (VAS). Moreover, effective modifiers like age, comorbidities, and duration of symptoms should be controlled to increase the reliability of subgroup analyses.

The study had limitations. First, the sample (n = 60) was very small, and thus, this could affect generalization. Second, the short-term follow-up (12 weeks) does not permit the assessment of the long-term recurrence and complete fistula healing as the most important indicators of the treatment outcomes. Third, the experience of postoperative pain is subjective, and differences in individual minimal threshold of pain or analgesics could have confounded the results. In addition to that, the researchers have only used one tertiary care facility, and this has diminished the external validity. The future needs to verify these results with multicenter research with larger cohorts, longer follow-up, and patient-reported quality-of-life outcomes to simplify treatment regimens.

These results have a great effect on clinical practice. Silver nitrate is an outpatient, less invasive form of therapy that minimizes postoperative pain and accelerates recovery. It will be of greatest benefit to patients who have increased surgical risks, including those with comorbid conditions like diabetes or those who place premiums on convenience and comfort. It is, however, limited by its low success rate in challenging cases and the occasional need to have multiple sessions of therapy. The use of silver nitrate can be supplemented and its efficacy enhanced together with other less invasive methods, such as fibrin glue or biologic dressing.

CONCLUSION

We concluded that 1% silver nitrate is a less invasive and effective alternative to fistulotomy for managing low-lying perianal fistulas, significantly reducing postoperative pain with a favorable safety profile. Further studies with larger cohorts and extended follow-up are warranted to validate these findings and refine treatment strategies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
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2	**Muhammad Yaqoob:** Proof reading, data analysis.
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https://doi.org/10.29309/TPMJ/2026.33.02.9973 www.theprofesional.com

ORIGINAL ARTICLE

Frequency of diplopia in zygomatic maxillary complex fractures in patients presenting to Ayub Teaching Hospital Abbottabad.

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ABSTRACT… Objective: To find out the incidence of diplopia in ZMC fracture patients reporting to the trauma center and maxillofacial outpatient department. **Study Design:** Cross Sectional study. **Setting:** Department of Trauma Center and Maxillofacial Outpatient, Ayub Teaching Hospital (ATH), Abbottabad. **Period:** December 2024 to May 2025. **Methods:** A total of 113 patients between the ages of 18–60 years with radiologically proven ZMC fractures were recruited using non-probability consecutive sampling. Data regarding age, gender, etiology of trauma, fracture pattern (unilateral/bilateral), and presence/direction of diplopia was obtained on a structured proforma. Diplopia was evaluated clinically by history and nine-gaze examination. Data were analyzed using SPSS version 22. Chi-square test was employed to evaluate associations, with $p < 0.05$ being statistically significant. **Results:** Of the 113 patients, diplopia occurred in 32.74% (n = 37). Horizontal diplopia was the most frequent (54.87%), followed by vertical (32.74%) and oblique (12.39%). Both-sided ZMC fractures were strongly related to diplopia (52.17%) than single-sided fractures (27.78%) ($p = 0.026$). No significant association was found with age, gender, cause of trauma, or direction of diplopia gaze. **Conclusion:** Diplopia is a relatively frequent ZMC fracture complication, especially in the case of bilateral trauma. Early detection can support ophthalmic referral and improved functional results.

Key words: Diplopia, Facial Trauma, Fracture Pattern, Orbital Injury, Zygomatic Maxillary Complex.

Article Citation: Saleem A, Alam K, Khan MM, Aziz B, Jannat-ul-Mawa, Qadir S. Frequency of diplopia in zygomatic maxillary complex fractures in patients presenting to Ayub Teaching Hospital Abbottabad. Professional Med J 2026; 33(02):364-368. https://doi.org/10.29309/TPMJ/2026.33.02.9973

INTRODUCTION

The Zygomatic bone is a strong buttress of lateral portion of middle third of facial skeleton lying between Zygomatic process of frontal bone and maxilla, and articulates with frontal, temporal, sphenoid and maxilla.[1] Zygomatic maxillary complex (ZMC) fractures are lateral midface fractures and second most common in facial region after nasal fractures.[2] The prominent convex shape of zygomatic bone makes it vulnerable to traumatic injury and the signs and symptoms exhibited by zygomatic maxillary complex fractures include flattening of cheek, swelling, paresthesia, limited mouth opening and difficulty in chewing.[3] The etiology of ZMC fractures include road traffic accident, assaults, falls and sports injuries.[4]

Panneerselvam et al. reported ZMC fractures accounting for 13%–40% of all facial fractures in cases of facial trauma, frequently resulting in functional deficits such as diplopia.[5]Shabbir et al. revealed a 25.9% occurrence of diplopia[6], whereas Khattak et al. observed a slightly elevated percentage of 28.9% in a tertiary care facility.[7] Likewise, Javed et al. reported diplopia in 26% of cases of ZMC fractures.[8] In a larger case series, Yamsani et al. had 22% of patients with visual disturbances.[9] Kambalimath et al. highlighted the importance of fracture severity in ocular complications, reporting that diplopia occurred in 31.5% of patients with complex ZMC fractures, particularly those involving the orbital floor and rim.[10]

Although a number of regional and global studies have published the incidence of diplopia among patients with ZMC fractures, most were postoperative series or did not employ standardized clinical examination in each direction of gaze. In addition, little localized data are available from northern parts of Pakistan, specifically Khyber Pakhtunkhwa (KPK), where trauma patterns and access to care may impact diagnosis and presentation.

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Article received on:
15/07/2025
Accepted for publication:
03/10/2025

The aim of the present study was to find out the incidence of diplopia in ZMC fracture patients reporting to the trauma center and maxillofacial outpatient department of Ayub Teaching Hospital, Abbottabad, and to assess its association with demographic and clinical factors such as age, gender, etiology, mechanism of trauma, and gaze of diplopia. This will assist in the direction of early diagnosis, referral, and management plans for ocular complications after mid-facial trauma.

METHODS

This was a cross-sectional study conducted at the Trauma Center and Maxillofacial Outpatient Department of Ayub Teaching Hospital (ATH), Abbottabad from December 2024 to May 2025. A sample size of 113 patients was calculated using the WHO sample size calculator, based on the following confidence level of 95%, absolute precision: 7% and expected frequency of diplopia in ZMC fractures of 17.4% (Khattak et al).Non-probability consecutive sampling was employed to recruit participants who met the inclusion criteria during the study period.

Inclusion Criteria

Patients aged between 18 and 60 years, both male and female genders, and with either unilateral or bilateral ZMC fractures confirmed radiographically.

Exclusion Criteria

Patients with non-displaced ZMC fractures, with pre-existing orbital pathologies and who declined to provide informed consent were excluded from the study.

Patients fulfilling the inclusion criteria were enrolled from the Department of Oral and Maxillofacial Surgery at ATH, Abbottabad, after obtaining ethical approval from the institutional review board (IRB) vide letter (Approval Code/Ref.No.RC-EA-2024/030) Written informed consent was taken from all participants after explaining the purpose and procedures of the study. Confidentiality and anonymity of data were maintained throughout the research process.

Demographic data, including age, gender, place of residence, educational level, and monthly income, were recorded using a structured data collection proforma. A thorough clinical assessment was conducted, including extraoral and intraoral examination, visual acuity testing, and evaluation for diplopia in all nine gaze positions (primary, left, right, up, down, up-left, up-right, down-left, down-right).

The diagnosis of ZMC fracture was confirmed through computed tomography (CT) scans of the face. Radiological findings were interpreted by a fellow of CPSP with a minimum of five years of clinical experience to ensure diagnostic accuracy. All data regarding the type and cause of trauma, pattern of fracture (unilateral or bilateral), presence and direction of diplopia (horizontal, vertical, or oblique), and other clinical findings were collected by the principal investigator.

Diplopiadefined as double vision of a single object observed in any of the horizontal, vertical, or oblique gazes, assessed clinically by history and physical examination. Zygomatic Maxillary Complex (ZMC) fracturedefined radiologically as a fracture involving one or more of the zygomatic arch, inferior orbital rim, anterior/posterior walls of the maxillary sinus, lateral orbital rim, frontozygomatic suture, and/or zygomaticomaxillary suture.

Data were analyzed using statistical package for social sciences (SPSS) version 22. Quantitative variables such as age were summarized as mean ± standard deviation or median (interquartile range), depending on the normality of distribution (assessed using the Shapiro-Wilk test). Categorical variables including gender, cause of trauma, trauma pattern, presence of diplopia, and direction of diplopia were presented as frequencies and percentages.

To assess associations between diplopia and demographic or clinical variables, stratification was performed based on age and gender to control for potential effect modifiers. Post-stratification comparisons were made using the Chi-square test or Fisher's exact test. A p-value < 0.05 was considered statistically significant.

RESULTS

113 patients with Zygomatic Maxillary Complex (ZMC) fractures were made part of the study. Majority of the patients (51.33%) belonged to the age group of 18–40 years, whereas 48.67%

belonged to 41–65 years of age. The sample had 56.64% males and 43.36% females.

Concerning the reason for trauma, Road Traffic Accidents (RTA) was the leading cause, with 61.95% of cases, followed by falls (23.89%) and assault (14.16%). The majority of patients (79.65%) had unilateral fractures of the ZMC, and 20.35% had bilateral fractures.

The total prevalence of diplopia among the study population was 32.74% (n = 37). Of the cases, horizontal diplopia occurred the most (54.87%), followed by vertical (32.74%), and oblique (12.39%) diplopia as shown in Table-I.

On bivariate analysis (Table-II), pattern of trauma was significantly correlated with diplopia presence (p = 0.026), with bilateral fractures presenting higher diplopia frequency (52.17%) than unilateral fractures (27.78%). The other variables like age, gender, reason of trauma, and direction of diplopia gaze did not present statistically significant association with diplopia presence (p > 0.05).

DISCUSSION

The purpose of this study was to establish the frequency and clinical presentation of diplopia in patients attending a tertiary care hospital with zygomatic maxillary complex (ZMC) fractures. Out of 113 patients, the overall prevalence of diplopia was 32.74%, and most frequently encountered was horizontal diplopia (54.87%). A significant association was found between the trauma pattern and presence of diplopia (p = 0.026), where bilateral fractures significantly contributed to the incidence of diplopia.

Table-I

Distribution of demographic and clinical variables among patients with zygomatic maxillary complex fractures (n=113)

Variables	Categories	n (%)
Age	18-40	58 (51.33%)
	41-65	55 (48.67%)
Gender	Male	64 (56.64%)
	Female	49 (43.36%)
Reason of Trauma	Road Traffic Accident	70 (61.95%)
	Fall	27 (23.89%)
	Assault	16 (14.16%)
Pattern of Trauma	Unilateral	90 (79.65%)
	Bilateral	23 (20.35%)
Presence of Diplopia	Yes	37 (32.74%)
	No	76 (67.26%)
Gaze of Diplopia	Horizontal	62 (54.87%)
	Vertical	37 (32.74%)
	Oblique	14 (12.39%)

TABLE-II

Association of demographic and clinical variables with presence of diplopia (n = 113)

Variables	Categories	Diplopia Presence		P-Value
		Yes	No	
Age	18-40	17 (29.31%)	41 (70.69%)	0.425
	41-65	20 (36.36%)	35 (63.64%)	
Gender	Male	23(35.94%)	41 (64.06%)	0.408
	Female	14 (28.57%)	35 (71.43%)	
Reason of Trauma	Road Traffic Accident	19 (27.14%)	51 (72.86%)	0.184
	Fall	10 (37.04%)	17 (62.96%)	
	Assault	8 (50%)	8 (50%)	
Pattern of Trauma	Unilateral	25 (27.78%)	65 (72.22%)	0.026
	Bilateral	12 (52.17%)	11 (47.83%)	
Gaze of diplopia	Horizontal	19 (30.65%)	43 (69.35%)	0.375
	Vertical	15 (40.54%)	22 (59.46%)	
	Oblique	3 (21.43%)	11 (78.57%)	

The incidence of diplopia in this research was relatively greater than in earlier study reports in comparable regional and global studies. For example, Starch-Jensen et al. reported that the incidence of diplopia was 29% in cases of ZMC fractures[11] and Rahman et al. reported a 17.4% rate of diplopia among ZMC fracture cases in Pakistan[12], a rate significantly lower than the 32.74% rate found in the present study's sample population. Likewise, Giudice et al. in a European population reported diplopia in about 21.2% of ZMC fracture patients who needed surgical management.[13] This difference may be due to differences in the severity of fractures, study inclusion criteria, or more sensitive diagnostic examinations in our study, e.g., diplopia testing in all nine directions of gaze. Additionally, Hashemi and Avval also conducted studies in an Iranian population that also documented 19% of cases with diplopia, pointing to variability in the prevalence as reported in different geographic and clinical environments.[14] Conversely, Siniscalchi et al. highlighted the value of orthoptic assessments and concluded that a majority of diplopia cases remain undiagnosed without extensive gaze analysis[15], perhaps explaining the greater prevalence in our report.

The prevalence of horizontal diplopia (54.87%) was greater than vertical (32.74%) and oblique (12.39%), which is in agreement with the literature. For example, Salma et al. described 56.2% horizontal diplopia due to medial and inferior rectus muscle involvement, which is the usual presentation in orbital floor and wall trauma with ZMC fracture.[16] Vertical diplopia represented 31.2%, while oblique diplopia was the least frequent at 12.5% as indicated in their results which aligns closely to our findings of 32.74% and 12.39%, respectively. This anatomical basis is consistent with our findings, particularly with bilateral fractures where there is a higher chance of orbital floor and wall violation. The significant association observed between bilateral ZMC fractures and presence of diplopia ($p = 0.026$) in our study is also supported by the results of Rizvi et al. and Manlove & Bailey, both of which reported greater ocular severity in complex bilateral fractures following increased bony displacement and muscle entrapment risk.[17,18] In addition, Obuekwe et al. also found that road traffic accidents were the most common reason for ZMC fractures, a finding corroborated in the present study with 61.95% of cases resulting from RTAs.[19]

Although age, gender, and trauma cause were not significantly associated with diplopia in the current analysis, this concurs with Javed et al. reporting no significant demographic associations.[20] Nevertheless, subtle variations in trauma biomechanics or in reporting bias may affect statistical results between studies. Generally, the general consensus of trends reinforces the validity of our results as well as highlighting the specific characteristics of our environment, for instance, greater severity of injury or late clinical presentation.

LIMITATIONS

This research contributes useful epidemiological information to the paucity of regional literature regarding ocular sequelae of ZMC fractures. However, a few limitations in this study were present. Firstly, it was a single-center tertiary care center study, so it may not be generalizable to other patient populations or care settings, particularly rural or resource-poor locations. Secondly, the cross-sectional study design limits the capacity to determine improvement or resolution of diplopia over time since follow-up data were not obtained to track long-term outcomes or healing after treatment. Furthermore, diplopia was assessed clinically without the implementation of advancedorthoptic instruments like Hess charts or synoptophore, which could have improved diagnostic accuracy, particularly in borderline or inconspicuous cases. Observer bias is also possible as clinical examination and history-taking were done by a single investigator without blinding, which could have affected the detection and classification of diplopia. Finally, though computed tomography (CT) scans were employed for radiographic verification of the fractures, the extent of entrapment of muscle or injury to soft tissue was not measured quantitatively, which might also have explained the occurrence and extent of diplopia.

CONCLUSION

The incidence of diplopia in ZMC fracture patients presenting at Ayub Teaching Hospital was significantly high at 32.74%, with the most frequent type being

horizontal diplopia. Bilateral fractures were found to be strongly correlated with an increased incidence of diplopia. These findings support the need for early and thorough ocular examinations in cases of ZMC trauma, in order to achieve an early diagnosis and prevent long-term sequelae.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Ammara Saleem:** Data collection, Literature review
2	**Khurshid Alam:** Data analysis, write up.
3	**Muhammad Masood Khan:** Data analysis, literature review.
4	**Bakhtawer Aziz:** Data collection.
5	**Jannat-ul-Mawa:** Literature review.
6	**Sidra Qadir:** Data analysis.

https://doi.org/10.29309/TPMJ/2026.33.02.10327 www.theprofesional.com

ORIGINAL ARTICLE

Globe salvage in Group D and Group E Retinoblastoma after Intra-arterial chemotherapy (IAC).

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ABSTRACT… Objective: To evaluate the effectiveness of IAC in Group D and E retinoblastoma, with a specific focus on globe salvage, in a tertiary care center in Pakistan. **Study Design:** Retrospective study. **Setting:** Lahore General Hospital, Lahore. **Period:** 20th June 2025 to 20th August 2025. **Methods:** In which patients with group D and E retinoblastoma were included. Demographic and clinical data were retrieved from ophthalmology department of Lahore General Hospital. Patients received six cycles of intravenous chemotherapy followed by IAC. Up to four IAC sessions were administered. Tumor regression was assessed one-month post-IAC, and globe salvage was defined by sustained stability over six months. **Results:** There were 55 eyes of 55 patients. Mean age was 20.96±14.03 months. Twenty-nine eyes had group D and 26 had group E retinoblastoma. Tumor regression was noted in most of both groups, with no significant difference. Globe salvage with vision was observed more frequently in Group D (44.8%) compared to Group E (19.2%). Enucleation and loss of visual function were more common in Group E. Ischemic toxicity was rare, signifying the relative safety of IAC. **Conclusion:** Intra-arterial chemotherapy is an effective globe-sparing treatment for retinoblastoma, achieving high rates of tumor regression and globe salvage, even in advanced disease stages.

Key words: Chemotherapy, Etoposide, Melphalan, Ophthalmic Artery, Retinoblastoma, Vincristine.

Article Citation: Saleemi KB, Malik TG, Khalid I, Ali MH, Khalid H, Abdul Fatir C, Farqaleet M, Shahid M. Globe salvage in Group D and Group E Retinoblastoma after Intra-arterial chemotherapy (IAC). Professional Med J 2026; 33(03):369-373.
https://doi.org/10.29309/TPMJ/2026.33.02.10327

INTRODUCTION

Over the years, possibilities for treating retinoblastoma (RB) have improved significantly. Intravenous chemotherapy (IVC) and, if necessary, adjuvants, have formed the backbone of treatment for the past two decades.[1] As Reese-Ellsworth (RE) classification system was based on radiotherapy for intraocular retinoblastoma, it has mostly been replaced with International Classification of Retinoblastoma (ICRB) for managing this disease.[2] Based on this classification group E tumors require enucleation while groups A through C have shown considerable success after chemotherapy.[3] Since the advent of IVC, several centers have stopped using external beam radiation (EBRT) as their primary treatment for group D eyes and the eye globe salvage rate has improved.[4] However, globe salvage still remains a challenge in cases where only IVC is used. Recently, intra-arterial chemotherapy (IAC) has been adopted as a first-line therapy for group D tumors.[5] It has the advantage of higher concentration of chemotherapy drugs reaching the tumor, with negligible systemic side effects when compared with systemic IVC. It is effective in tumor control and eye salvage in cases of advanced and refractory RB. By achieving higher concentration in the target tumor, IAC has shown improved outcome in group D and E retinoblastoma. With these added benefits, IAC has emerged as the first-line management option in selected cases, and in developed countries the 5-year survival rate has reached 99% as the patients present with early disease.[6] However, in the developing countries, varying results are seen in terms of survival, vision saving and globe salvage especially in group D and E, retinoblastoma. In one study, globe salvage was achieved in 5 out of 6 eyes of group D and 3 out of 5 eyes of group E patients, after IAC.[7] The results were preliminary as the sample size was very small and all groups of RB were included.

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Article received on:
03/11/2025
Accepted for publication:
10/01/2026

We planned this study in a larger sample size and focusing on the group D and E retinoblastoma.

The objectives of the study were to determine the frequency of globe salvage and compare the results of group D and group E retinoblastoma after IAC.

METHODS

It was a retrospective study which included all the patients who presented to Lahore General Hospital, which is a tertiary care center in Punjab after approval from the hospital ethical review committee Ref. No. (OSP-IRB/003-2025), medical records of retinoblastoma patients were retrieved from 2018 to 2024. Patients who underwent IAC in group D and E were selected. Globe salvage was defined as regression in terms of no active tumor vascularization, no hemorrhage, along with decrease in tumor size, increase in calcification and increase in scarring, and remaining stable on monthly examination under anesthesia for 6 months. A total of 55 records qualified the inclusion criteria which was defined as patients of either gender, age less than or equal to 5 years with diagnosed group D or group E retinoblastoma. Patients with retrolaminar tumor invasion, extraocular tumor extension and metastatic disease were excluded.

The demographic details (name, age, gender, group D or E) were recorded on a self-designed proforma. Data regarding history and examination was collected. Number of IVC and IAC sessions were recorded. Primary IVC consisted of six cycles of intravenous vincristine, etoposide, and carboplatin (VEC) every 3 weeks, followed by one cycle of IAC. The second IAC was given if needed (maximum of 4 injections were given). A micro-catheter was guided through the femoral artery to the ophthalmic artery in the treated eye. The melphalan was delivered directly into the artery. The dosage was determined by the child's age: 3mg for under 2 years old, 4mg for 2-3 years old, and 5mg for over 3 years old. Examination under anesthesia was conducted after one month following IAC to look for signs of regression. Patients showing complete regression in terms of no active tumor vascularization, no hemorrhage, along with decrease in tumor size, increase in calcification and increase in scarring were kept on one monthly follow up and the globe was considered salvaged if stable for 12 months.

The collected data was entered into and analyzed through SPSS version 26.0. Mean+SD was calculated for quantitative variables like age. Frequencies and percentages were calculated for gender and outcome in each group. Frequency of globe salvage was determined in group D and group E and was compared using chi square test. Data was stratified for age, gender, and post stratification chi square test was applied to see the effect of these effect- modifiers on the outcome. P value of <0.05 was considered statistically significant.

RESULTS

Fifty-five eyes of 55 patients were included. Only one eye of patients with bilateral disease was included. Mean age of patients was 20.96 ± 14.03 months including 63.6% males and 36.3% females. Twenty-nine eyes had group D and 26 had group E retinoblastoma, classified according to ICRB. Tumor regression was noted in most of both groups, with no significant difference (Table-I). Globe salvage with vision was observed more frequently in Group D (44.8%) compared to Group E (19.2%), though this difference was not statistically significant. Enucleation and loss of visual function were more common in Group E, consistent with disease severity. Ischemic toxicity was rare, signifying the relative safety of IAC in experienced hands. Figures-1, 2 and 3 show three different cases with group D and E retinoblastoma.

FIGURE-1

Group D tumor pre and post intra-arterial chemotherapy

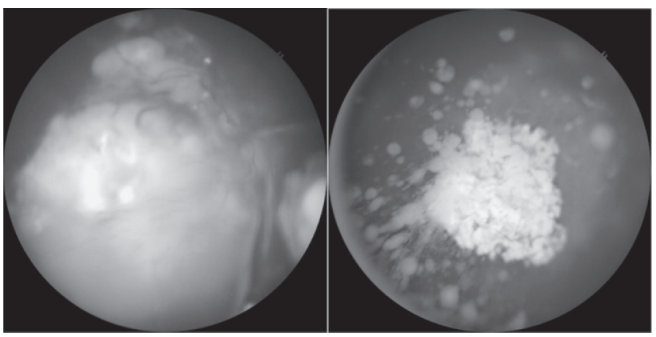


TABLE-I

Details of tumor response to intra-arterial chemotherapy in group D and E.

Variables		ICRB Group				P-Value
		D		E		
		Number	%age	Number	%age	
Side of eye	Left	12	41.4	15	57.7	0.227
	Right	17	58.6	11	42.3	
Procedure IAC	Single injection	4	13.8	4	15.4	
	2 to 4 injections	25	86.2	22	84.6	
	Tumor regression	22	75.9	17	65.4	0.867
	No regression	5	17.2	8	30.8	
	No follow up data	2	6.9	1	3.8	
Outcome	Globe salvaged with some vision	13	44.8	5	19.2	0.951
	Globe salvaged but no vision	7	24.1	10	38.5	
	Enucleation	5	17.2	8	30.8	
	Lost to follow up	4	13.8	3	11.5	
Ischemic chorioretinal toxicity	Lost to follow up	4	13.8	3	11.5	.0.556
	Present	0	0.0	1	3.8	
	Not seen	25	86.2	22	84.6	

FIGURE-2

Group E tumor pre and post intra-arterial chemotherapy

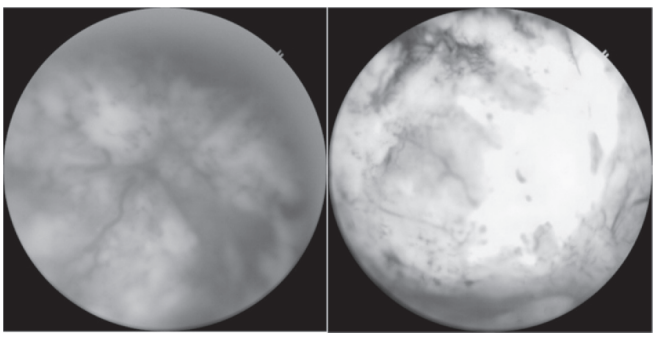
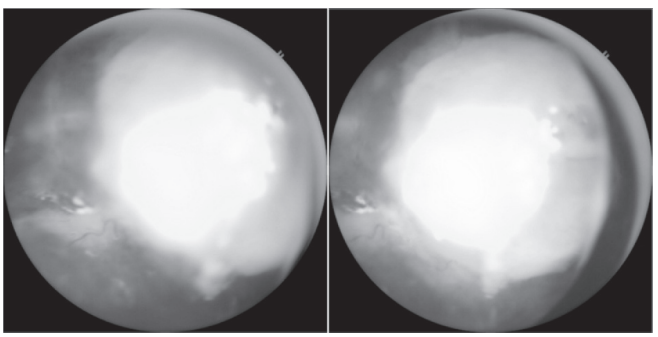


FIGURE-3

Group D tumor pre and post intra-arterial chemotherapy showing no response and was enucleated



DISCUSSION

Our results showed that globe salvage with some vision was observed more frequently in Group D (44.8%) compared to Group E (19.2%), though this difference was not statistically significant. None of the patients reported mortality although a total of 7 patients out of 55 (12.7%) lost to follow up.

Retinoblastoma is a rare tumor of the eye and the data from the low- and middle-income countries is scarce.[8] Due to the high mortality associated with the condition, previously the focus was on saving the life of the patient. Over the last couple of decades, globe salvage and preservation of vision has been widely considered. Present-day globe-sparing treatments for RB include chemotherapy, radiotherapy, thermotherapy, cryotherapy, and laser photocoagulation.[9] Chemotherapy may be administered through various routes, including intravenous, intravitreal, and intra-arterial delivery.[9] Over 26 countries have adopted intra-arterial chemotherapy as part of the treatment approach for retinoblastoma.[10] Since IAC is delivered locally, it helps prevent the adverse effects typically associated with systemic chemotherapy.[11] Prior to the advent of intra-arterial chemotherapy (IAC),

nearly 80% of patients with advanced retinoblastoma required enucleation to prevent the risk of central nervous system invasion and hematogenous dissemination.[12,13]

The effectiveness of IAC in preserving the eye has been well-established through various studies. According to a meta-analysis, globe salvage rates with IAC were 35% for groups D and E, and 63.3% for Groups A to C.[14] In our study the globe salvage rate was 68.9% and 57.7% for group D and E respectively. However, our follow up was only for one year.

In this study, initial tumor regression following IAC was achieved in both D and E groups. These findings support the growing body of evidence suggesting that IAC is an effective primary treatment modality for advanced intraocular RB. The globe salvage rate with preserved vision was comparable in both groups—44.8% in group D and 19.2% in Group E. Additionally, the enucleation rates were relatively low (17.2% in Group D and 30.8% in Group E). However, the rates could have been different if the patients follow up record was more than one year.

Complications such as ischemic chorioretinal toxicity were rare. Only one case (3.8%) in group E experienced such toxicity, and no cases were reported in group D. This suggests a favorable safety profile for IAC.

In an early report, Abramson et al. found that intra-arterial chemotherapy successfully prevented enucleation in 7 out of 9 eyes.[15] Peterson et al. examined 17 eyes diagnosed with Group D retinoblastoma that had not responded to systemic chemotherapy and were subsequently treated with IAC, resulting in globe salvage in 13 cases (76%).[16] Eyes that eventually required enucleation typically showed widespread recurrence of subretinal or vitreous seeding. Gunduz et al. identified that the primary causes of treatment failure after chemo-reduction were subretinal seeding, vitreous seeding, and the presence of subretinal fluid, features that are frequently associated with Group D retinoblastoma.[17]

Intra-arterial chemotherapy (IAC), when used in combination with intravenous chemotherapy (IVC) and focal therapies, has been shown to be an effective treatment strategy for advanced retinoblastoma.[18,19] Studies also indicate that IAC contributes not only to tumor regression but may also play a role in reducing the risk of metastasis.[20]

Limitations of this study include retrospective design, limited follow up and a notable proportion of patients who were lost to follow-up (13.8% in Group D and 11.5% in Group E), which may affect the accuracy of outcome assessments, particularly regarding long-term visual and globe salvage rates. The study did not include genetic and molecular data and vision was examined only subjectively.

CONCLUSION

Intra-arterial chemotherapy demonstrates high effectiveness in achieving globe salvage, even in advanced retinoblastoma, with minimal complications, reinforcing its role as a key globe-sparing treatment option.

ACKNOWLEDGEMENTS

The authors would like to thank the medical and nursing staff involved in the care of the patients included in this study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Khuda Bukhsh Saleemi:** Design, data collection.
2	**Tayyaba Gul Malik:** Methods, design.
3	**Iqra Khalid:** Data collection.
4	**Mian Hassan Ali:** Literature review.
5	**Hina Khalid:** Data entry.
6	**Chaudhary Abdul Fatir:** Data analysis.
7	**Muhammad Farqaleet:** Interpretation.
8	**Muhammad Shahid:** Critical intervention.

https://doi.org/10.29309/TPMJ/2026.33.02.10088 www.theprofesional.com

CASE REPORT

A case of concomitant iron and folate deficiency in a 26-year-old female with beta thalassemia minor.

Muhammad Irtza Tanveer[1], Saima Mansoor Bugvi[2], Sadaf Farzand[3], Areeba Manzoor[4], Ambereen Anwar[5]

ABSTRACT… We are reporting a known case of a 26-year-old lady with beta thalassemia minor (also called as beta thalassemia trait) who developed severe anemia due to co-existing iron and folate deficiency. The patient showed hypochromic microcytic anemia with markedly reduced mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), along with biochemical features of iron depletion and folate deficiency. The baseline laboratory evaluations showed low values of Hb, serum iron, serum ferritin and transferrin saturation, along with increased TIBC. The patient was treated with intravenous ferrous sulfate (200 mg per week for 4 weeks), oral ferrous sulfate (14 mg/day for 10 weeks), oral folic acid (5 mg daily for 10 weeks), and intramuscular methycobalamine (500 mcg for 7 doses on alternate days). By the end of the 10th week patient showed a significant improvement in haematological and biochemical parameters. This case highlights the need for screening and treating the nutritional deficiencies in patients with beta thalassemia minor to prevent the worsening of anemia.

Key words: Beta Thalassemia, Folate Deficiency, Iron Deficiency.

Article Citation: Tanveer MI, Bugvi SM, Farzand S, Manzoor A, Anwar A. A case of concomitant iron and folate deficiency in a 26-year-old female with beta thalassemia minor. Professional Med J 2026; 33(02):374-376. https://doi.org/10.29309/TPMJ/2026.33.02.10088

INTRODUCTION

Beta thalassemia minor is a heterozygous carrier state of beta-globin gene mutation, characterized by reduced beta-globin chain synthesis, microcytosis, and mild anemia. Most carriers remain asymptomatic; however, anemia worsens when concomitant nutritional deficiencies, particularly iron or folate deficiency, occur. Iron deficiency is common in females of reproductive age group due to menstrual blood loss.[1] Beta thalassemia minor females are also at risk of developing iron deficiency particularly in their reproductive years. There are studies showing that iron deficiency and beta thalassemia minor coexists and around 33% of the beta thalassemia minor patients are at risk of developing iron deficiency.[2] Folate deficiency may also develop in hemolytic states such as thalassemia due to increased erythropoietic activity.[3] The coexistence of these deficiencies in thalassemia carrier patients complicates diagnosis and management because microcytosis is a feature common in both conditions, but their therapeutic approaches differ.

DISCUSSION

A 26-year-old married female with a known diagnosis of beta thalassemia minor and mother of a beta thalassemia major girl presented in our Out-patient Department with history of generalized weakness, exertional fatigue, and numbness in her hands and feet for three months. She had no history of overt bleeding, chronic illness, or recent infections. Menstrual cycles were regular with moderate flow. On examination, she was pale but hemodynamically stable. There was no sign of icterus, lymphadenopathy, or organomegaly.

Baseline laboratory evaluation showed hemoglobin (Hb) 9.8 g/dL, hematocrit (HCT) 32.1%, mean corpuscular volume (MCV) 51.9 fL, mean corpuscular hemoglobin (MCH) 16.0 pg, and red cell distribution width (RDW) 17.4%. Total leukocyte count was 10.7 × 10^9/L, and platelet count was elevated at 487 × 10^9/L indicating reactive thrombocytosis. Iron studies revealed severe deficiency: serum iron 22 µg/dL, total iron-binding capacity (TIBC) 559 µg/dL, transferrin saturation 3.39%, and serum ferritin 3.0 ng/mL. Serum folate was markedly reduced at 0.396 µg/dL, while vitamin B12 was in the low-normal range at 309 pg/mL. HbA_2 was elevated to 5.9%, confirming beta thalassemia

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Article received on:
20/09/2025
Accepted for publication:
28/11/2025

minor. Reticulocyte count was 1.2%, and lactate dehydrogenase (LDH) was also in normal range at 209 U/L. Her peripheral blood smear showed severe hypochromic, microcytic RBCs with marked anisopoikilocytosis and occasional macrocytes and the pictures of peripheral blood smear is shown in Figure-1. The patient was treated with intravenous ferrous sulfate 200 mg once weekly for four weeks, oral ferrous sulfate 14 mg daily and folic acid 5 mg daily for 10 weeks, and intramuscular vitamin B12 500 µg on alternate days for seven doses. Dietary advice for iron- and folate-rich foods was also given. At week 4, Hb increased to 10.2 g/dL, MCV to 55.6 fL, and RDW decreased to 16.6%. By week 10, Hb improved to 10.7 g/dL, MCV to 58.1 fL, RDW normalized to 14.1%, serum ferritin increased to 37 ng/mL, folate normalized to 8.4 µg/dL, and vitamin B12 rose to 423 pg/mL. Platelet count reduced to 349. All laboratory results of our patient at day 1, Week 4 and Week 10 are enlisted in table below.

In beta thalassemia minor, hypochromia and microcytosis is due to reduced beta-globin chain synthesis; however, concurrent nutritional deficiencies can exacerbate anemia and cause more pronounced hematological abnormalities i.e., markedly low MCV and MCH. Our patient's severe iron deficiency was evident from very low iron and ferritin with elevated TIBC, and thrombocytosis while folate deficiency was confirmed by extremely reduced serum folate levels. Elevated RDW at presentation reflected anisocytosis due to mixed deficiency states, which improved as nutritional deficiencies were corrected.

A slight increase in MCV during treatment is expected because the underlying thalassemia minor continues to produce microcytic red cells despite iron and folate repletion. Folate deficiency is common in thalassemia carriers due to chronic hemolysis and increased red cell turnover, and folate supplementation is essential in order to support erythropoiesis and prevent megaloblastic changes.[4] Vitamin B12 supplementation was also given to ensure that borderline levels did not limit hematological recovery and also because starting folic acid therapy alone can cause neural damage.[5]

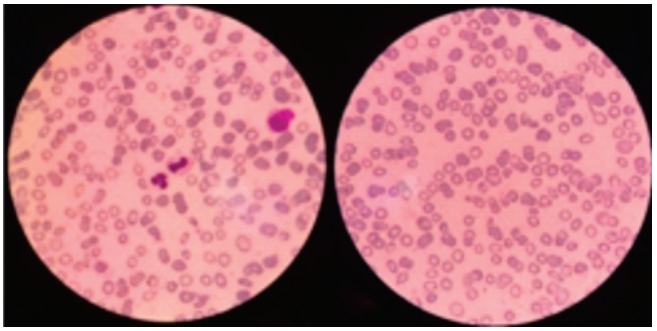
TABLE-I

Various hematological and biochemical parameters of subject at Day1, Week4 and Week10 respectively

Parameters	Day 1	Week 4	Week 10	Reference ranges
TLC	10.7	8.9	10.3	4-11 x10^9/L
RBC	6.18	6.0	5.91	3.8-5.8 x10^{12}/L
Hb	9.8	10.2	10.7	11.5-16.5 g/dL
HCT	32.1	33.4	34.7	36-46 %
MCV	51.9	55.6	58.1	76-96 fL
MCH	16.0	17.1	18.2	26-32 %
RDW	17.4	16.6	14.1	12-16 %
Platelets count	487	421	349	150-400 x10^9/L
Retics Count	1.2			0.5-2.5%
HbA_2	5.9			1.5-3.5%
Total Bilirubin	0.3			Less than 1.2mg/dL
LDH	209			Less than 228U/L
Serum Iron	22			50-170 µg/dL
TIBC	559			240-425 µg/dL
Transferrin saturation	3.39			20-50 %
Serum Ferritin	3.0		37	22-322 ng/mL
Serum Folate	0.396		8.4	3-17 mcg/dL
Serum B12	309		423	200-900pg/mL

FIGURE-1

The peripheral blood smear of the patient showing hypochromia2+, microcytosis 2+, marked anisopoikilocytosis and occasional macrocytes



CONCLUSION

Coexistent iron and folate deficiency in beta thalassemia minor patients can lead to severe anemia and complicate symptoms. This case report marks the need that comprehensive laboratory evaluation, including iron profile, folate, and vitamin B12, should be performed in thalassemia minor patients having moderate to severe anemia to better treat their symptoms. Timely correction with appropriate supplementation can restore hematological parameters and improve patient outcomes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Muhammad Irtza Tanveer:** Conceptualization of study, Data collection.
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https://doi.org/10.29309/TPMJ/2026.33.02.9958 www.theprofesional.com

CASE REPORT

CRS-IV (Chronic Renocardiac syndrome) in a female child. Heart and Kidney Dysfunction intertwined.

Aisha Haleem[1], Amanullah Lail[2], Aamina Shaikh[3], Noor Fatima Suri[4], Laraib Ghangro[5]

ABSTRACT… Renal artery stenosis is the major cause of renovascular hypertension, can be found isolated or have association with syndromes or autoimmune conditions. It can be due to atherosclerotic deposition in vessels, autoimmune etiology or fibromuscular dysplasia, the latter is the commonest cause, however, needs biopsy for diagnosis and exclusion of other possible causes. Patients can have diverse presentation, disease may be discovered as incidental finding, with hypertensive crises, Nephropathy or cardiac manifestations. We report a case of 7 years female patient presented with severe respiratory distress, hypertension, Grade 1 BL pitting edema, hepatomegaly, basal crackles in chest and gallop. He had no history of any diagnosed medical condition prior. However, symptoms were evident for last 2 months with Headache, fatigue, cough, exertional dyspnea, edema and decreased urine output. She had no history of arthralgia, frothy urine, hematuria or any skin rashes. Evaluation for Hypertension revealed small sized right kidney with decreased perfusion in segmental arteries. Echocardiography showed Biventricular dilation, dysfunction with Ejection fraction of 40%. She initially managed with iv labetalol infusion later started enalapril and amlodipine then referred to specialty where percutaneous transangioplasty planned abut deferred by pediatrics nephrology as patient responded with medical management and it is considered for resistant hypertension or persistent high renin and aldosterone. The case concluded with diagnosis of Reno cardiac type-iv syndrome, as manifestations are concordant with chronic kidney disease – right SSK due to hypoperfusion that resulted in renovascular hypertension and Cardiac failure.

Key words: Hypertension, Renal Artery Stenosis, Congestive Cardiac Failure.

Article Citation: Haleem A, Lail A, Shaikh A, Suri NF, Ghangro L. CRS-IV (Chronic Renocardiac syndrome) in a female child. Heart and Kidney Dysfunction intertwined. Professional Med J 2026; 33(02):377-380. https://doi.org/10.29309/TPMJ/2026.33.02.9958

INTRODUCTION

Hypertension in children is secondary most commonly linked to renal then endocrine disorders.[1] Renal artery stenosis however rare, can progress to Cardiorenal Syndrome (CRS) causing cardiac distress and has a significant mortality risk. Majority of these lesions are fibromuscular in nature arising from second and third renal artery branches.[1] Other causes of Renal Artery Stenosis reported include Atherosclerosis and Vasculitis.[2] Although, its mostly asymptomatic, the most common manifestation is severe hypertension.[2,3] Cardiorenal syndrome are the co-existence of cardiac and renal pathophysiology and can present with either acute or chronic failure of either cardiac or renal functions.[4] In 2008, five different manifestations of CRS were classified by Acute Disease Quality Initiative (ADQI).[5] Type I and II describes Renal dysfunction originating from cardiac failure, where type I refers to Acute heart failure resulting in Acute Kidney Injury (AKI) while Type II includes chronic heart failure leading to renal failure. Type III, also referred as Acute Reno-Cardiac Syndrome, refers to AKI causing acute heart failure. On the other hand, Type IV is referred as Chronic Reno-Cardiac Syndrome, where a chronic kidney disease results in heart failure. Type V is acute failure of both cardiac and renal functioning secondary to a systemic cause.[4,5] In this study we present a case of CRS Type IV in an 7-year-old female.

CASE PRESENTATION

We report a case of 7 years female patient weighing 16 kg, height of 116 cm at 10th centile presented in emergency with severe respiratory distress getting worsen with lying supine. She was Hypertensive BP 170/110 mm Hg.

Her symptoms became significantly evident for last 2 months with headache that significantly impaired her school learning temporarily relived with

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Article received on:
08/07/2025
Accepted for publication:
12/09/2025

analgesics however she remained fatigue most of time and had persistent dry cough throughout day and night aggravating during sleeping and getting her awake from the sleep as well, she experienced exertional dyspnea and was not able to walk longer, play with kids, developed edema for last 1 month and decreased urine output was noted for last 2 days before presenting in our emergency.

At Presentation she was tachycardiac, tachypneic, severely anemic, with grade 1 pitting edema, hepatomegaly, basal crackles, hyper precordium, displaced apex beat at 6th intercostal space lateral to midclavicular line, there was gallop but no murmur was audible.

She stabilized with keeping her elevated at 45 degrees to decrease cardiac load, IV labetalol infusion started with intermittent Lasix doses (0.5mg/kg/dose x 6 hourly), switched to oral enalapril, amlodipine, Lasix and spironolactone after 36 hours as her condition stabilized and she weaned off from oxygen as well.

It was noted as her blood pressure improved her urine output improved as well.

She was investigated for hypertension, 4 limb BP does not show any change, urine DR did not show any sediments, US KUB with Doppler showed Right small sized kidney with size 3.4 x 4.1 and reduced perfusion in segmental arteries left sided kidney was normal in size with normal Doppler flow.

Her echocardiography done that was suggestive of biventricular dilation, dysfunction with poor contractility and ejection fraction of 40%, no structural deformity noted in valve or cardiac structure.

She had no history of arthralgia, frothy urine, hematuria or any skin rashes and clinically there were no evidence of any xanthomas. Her Baselines, including lipid profile, autoimmune markers were normal except severe anemia that stabilized with PCV transfusion, reports are summarized in Table-I.

Among possible causes of RAS, she was suspected case of fibromuscular dysplasia as autoimmune workup was also negative, but patient need Renal biopsy for the confirmation of diagnosis of FMD, it was not performed as intervention will not change the management, histopathology is done if nephrectomy is done or there is conflict in some mixed disorder.

Patient's CT angiogram findings were consistent with Doppler ultrasonography. Her percutaneous transangioplasty dilation is deferred as Blood pressure normalized with enalapril and amlodipine, renin and aldosterone were also decreased in follow up as mentioned in Table-II.

She is kept in follow up. Her blood pressure is normalized and anti-failure medicines for cardiac care are continued by cardiologist with follow up with echocardiography imaging is advised after 3 months.

DISCUSSION

Coexisting cardiac and kidney failure is referred to as cardiorenal syndrome (CRS), which affects up to 50% of persons overall.[6,7] The idea of CRS was developed to span a range of illnesses in which primary acute or chronic malfunction in one organ causes acute or chronic dysfunction in the other, emphasizing "organ crosstalk" and the special interaction between the heart and kidneys. The current conceptual description of CRS was provided by the Acute Disease Quality Initiative (ADQI) in 2008[8,9] and was divided into five subtypes: acute cardiorenal, chronic cardiorenal, acute Reno cardiac, chronic Reno cardiac and secondary to systemic disorders.

According to Pradhan SK et al.'s systemic review, type 4 CRS is the least frequently reported in children, with just 7% of papers describing combined type 4 and 5 CRS. Chronic renal dysfunction is the primary pathophysiology of type 4 CRS (CKD), resulting in ventricular hypertrophy, cardiac dysfunction, and a higher chance of cardiovascular events. The kidneys and the heart interplay are bidirectional; chronic kidney disease (CKD) causes a series of pathological changes that eventually affect cardiac function.[10] Renal artery stenosis (RAS) is a significant contributor to chronic kidney disease (CKD), with various studies highlighting

its prevalence and impact. Research indicates that About 18% of patients with chronic kidney disease (CKD) have RAS, compared to 6% of people without CKD, and 22.9 percent of patients had RAS more than 50%. Although RAS is a known cause of chronic kidney disease (CKD), it is important to remember that other variables, such as diabetes and hypertension, also significantly contribute to the progression of kidney disease.[11-13] Unilateral RAS causes activation of renin-angiotensin-aldosterone system (RAAS), natriuresis from opposite kidney and suppression of its renin secretion. Angiotensin II thus formed, also results in secondary hypertension due to vasoconstriction. Up to 30% reduction in renal blood flow can be adapted by renal cortex and medulla without development of severe hypoxia. 70 to 80% stenosis of vascular lumen causes marked cortical hypoxia leading to activation of inflammatory cascades that eventually lead to chronic ischemic injury and interstitial fibrosis.[2,3]

Doppler ultrasound (US KUB) remains non-invasive and valuable initial modality for detecting RAS, as was utilized in our case.[15] Initial management essentially involves antihypertensives to stabilize blood pressure and reduce cardiovascular complications. PTRA with stenting has been stabilized as an effective therapy in children restoring perfusion and improving hypertension control, in refractory cases.[2]

In our patient renovascular hypertension (RVH) and ischemic nephropathy due to renal artery stenosis, interact intricately leading to Bi-ventricular hypertrophy and a reduced ejection fraction. While RAS is a well-documented cause of secondary hypertension in pediatric population, its presentation with left ventricular hypertrophy, symptomatic heart failure having respiratory distress at such a young age is relatively uncommon. Our case underscores the need for early cardiovascular assessment in hypertensive children to prevent irreversible myocardial damage. Renal artery stenosis should be considered in children with this clinical presentation.

CONCLUSION

CKD has diverse presentation, stage-1 may be diagnosed incidentally with renal structural malformation or SSK or patient may land with stage-5 complications and need urgent dialysis. This patient labelled stage 1 CKD with RSSK, normal RFTs is good prognosis at time of presentation. However RAS presentation with cardiac failure is rare which was due to long standing chronic hypertension. Multimodal management, including medical stabilization and interventional therapy, plays a crucial role in improving prognosis. Regular follow-up is necessary to assess long-term renal and cardiac outcomes and need of surgical intervention.

Legends

FIGURE-1

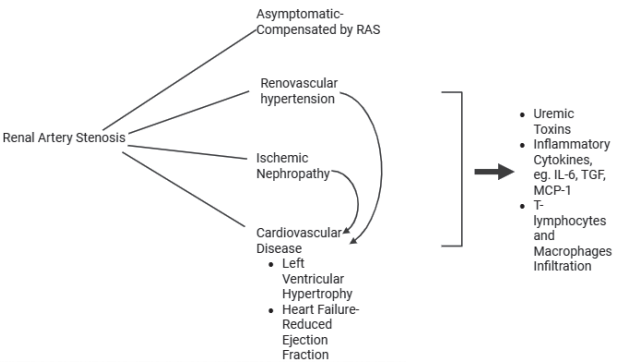

TABLE-I

Hemoglobin (g/dL)	6	9	BUN (mg/dL)	12	Total (mg/dL)	125
Mean Corpuscular Volume (fL)	69	72	Cr (mg/dL)	0.2	Triglyceride (mg/dL)	135
Total Leukocyte Count (L)	4.9 x 10^{-6}	5.2 x 10^{-6}	Na (mEq/L)	136	Serum HDL	50 mg/dl
Neutrophils (%)	56	50	K (mEq/L)	3.4	Serum LDL	110 mg/dl
Lymphocytes (%)	36	40	Cl (mEq/L)	102	triglyceride	135 mg/dl
Platelets (x 10^9)	162	182	HCO_3 (mEq/L)	22		

MONTHLY

IMAGE

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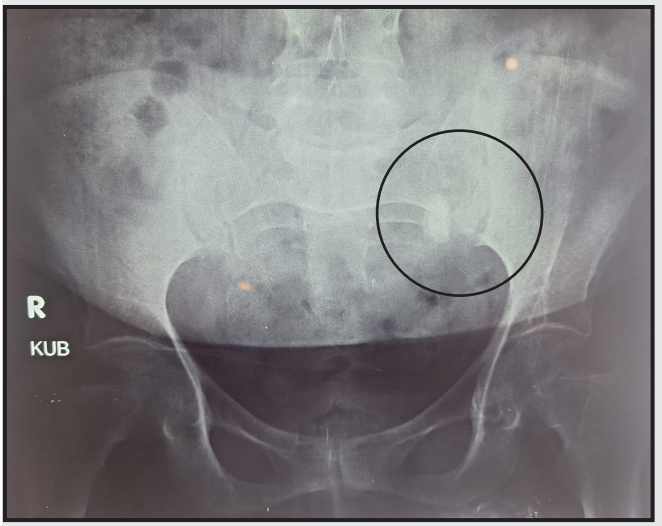
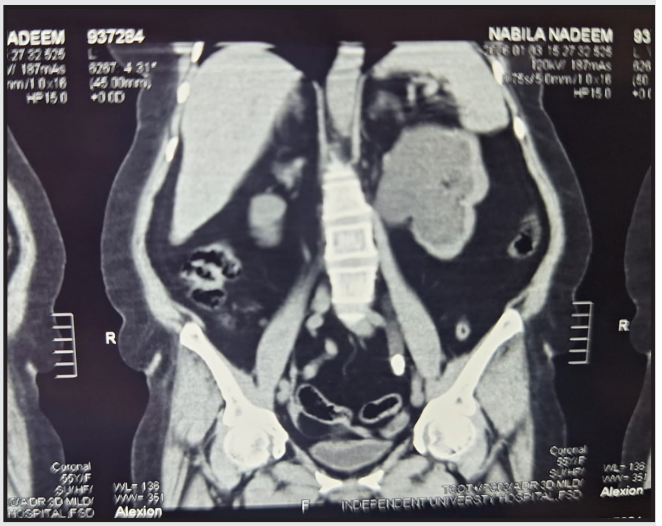
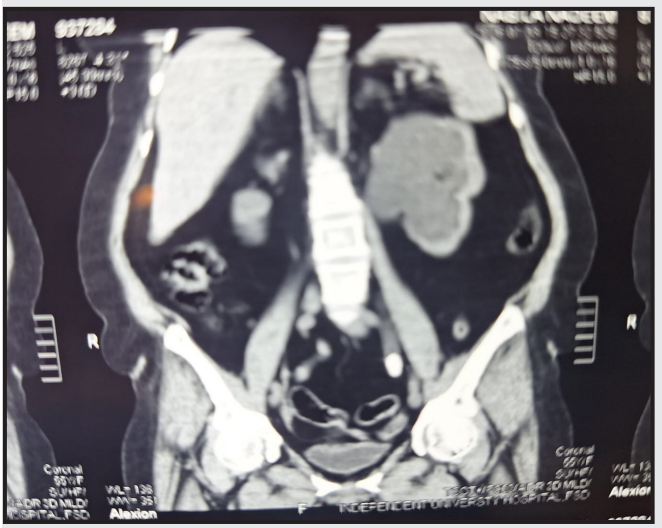
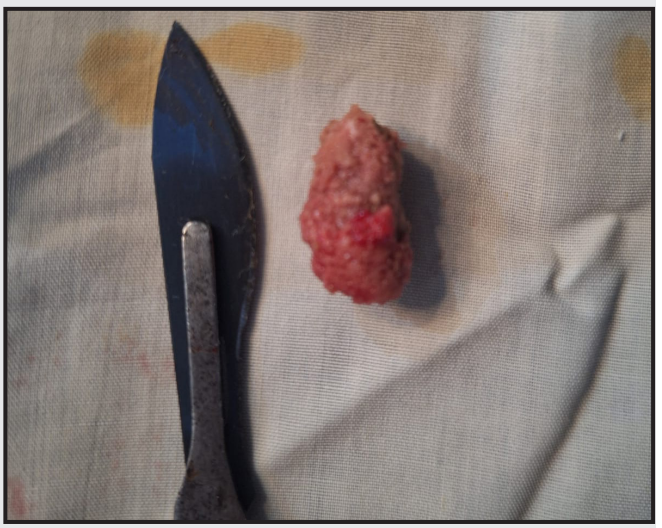
LEFT URETERIC CALCULUS









A 59 year female presented with left lumbar fulness and pain. On investigation she had impacted left lower ureteric calculus. She underwent ureterolithotomy.

Post-operative recovery was uneventful.

Courtesy:
Prof. Awais Shuja FRCS, FCPS, MCPS-HPE
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HISTOLOGY

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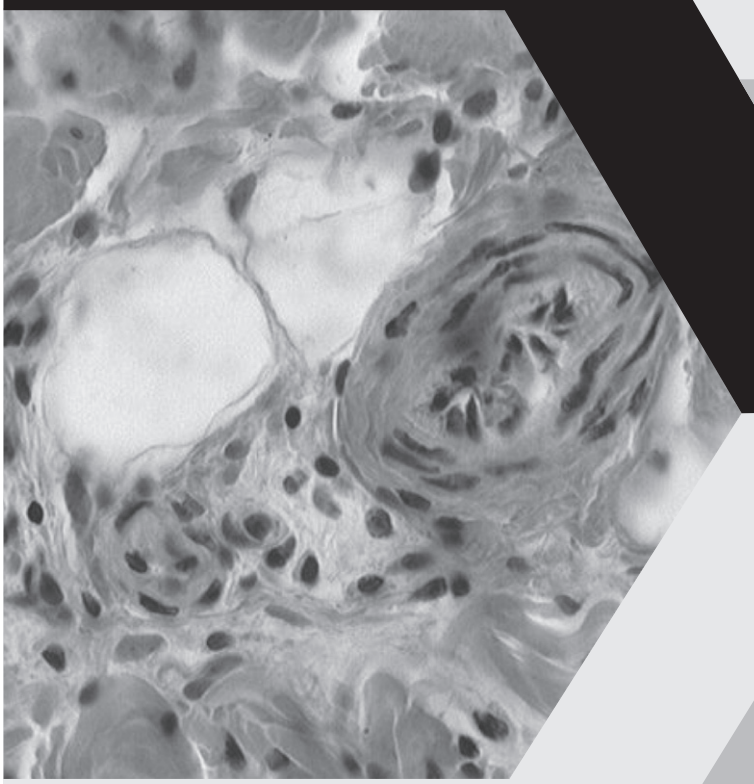
Prof. Dr. Irfan Ahmed Mughal



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Emphasize the new and important aspects of the study and the conclusions that follow from them in the context of the totality of the best available evidence. Do not repeat the data detail given in other parts of the manuscript. This section should include author's comment on the result supported references. Link conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data.

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