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AIMS & SCOPE

HMDJ is the research journal of HITEC Institute of Medical Sciences (HITEC-IMS), Taxila. It is an open access, peer-reviewed, bi-annual journal that aims to keep the medical & dental health professionals updated with the latest information relevant to their fields.

HMDJ welcomes scholarly work from medical, dental and allied subjects (basic & clinical), community health issues and medical education. It publishes original research, review articles, case reports, editorials, letters to editor, short communication, book reviews, recent advances, new techniques, debates, adverse drug reports, current practices, and conference reports. All publications of HMDJ are peer reviewed by subject specialists from Pakistan / abroad.

OBJECTIVES

1. To publish original, peer reviewed clinical and basic sciences research articles.
2. To promote research culture in HITEC-IMS and beyond, by inculcating the habit of medical writing in doctors.
3. To assist physicians to stay informed about the developments in their own & related fields.
4. To support knowledge & experience sharing among the health professionals for the benefit of the patients.
5. To attain ethical medical journalism by delivering credible and reader-friendly publications.

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EDITOR'S CUTTING EDGE

EDITORIAL

BRAIN DRAIN AND DISILLUSIONMENT OF OUR YOUNGER GENERATION WITH MEDICAL PROFESSION; A CHALLENGE TO RECKON

Maj Gen Prof Hafeez Ud Din HI(M) (Retd)[1], Professor Iram Tassaduq[2]
[1]Principal HITEC-IMS, [2] Department of Medical Education, HITEC-IMS

CAPSULE SUMMARY

Medical education in Pakistan is increasingly losing its appeal due to high costs, long training periods, poor working conditions, limited career prospects, and low healthcare investment. These factors are fueling burnout and the migration of young doctors abroad, creating a growing shortage of healthcare professionals and further straining the country's healthcare system.

Medicine is a challenging career that requires a lot of dedication and discipline from students, in order to succeed in it. Various motivational factors incline students to a life of the medical profession[1].

Becoming a doctor is an incredible achievement,but it's not the right path for everyone as it takes almost a decade to reach destination after 12 years of basic education. Embarking on the life of medical practice without the proper enthusiasm is not enough to withstand the immense amount of stress involved. The growing number of vacant seats reflects changing trends, with parents and students increasingly reluctant to opt for medical education. Exorbiant tuition fees, limited career prospects, and difficult working conditions for young doctors are some of the decisive factors in countries like ours.

Pakistan's healthcare system is overburdened where the doctor-to-patient ratio is 1:1300, significantly lower than the World Health Organization's recommended ratio of 1:1000. The challenges faced by Pakistan's healthcare system include insufficient funding, (only 0.9% of its Gross Domestic Product (GDP) on healthcare), inadequate healthcare workforce and infrastructure, less focus on preventive health, inequitable distribution of resources, and brain drain[2]. These factors have led the future generation to reassess whether the long haul of medical education guarantees a stable professional future.

The overwhelming workload of long shifts, night calls, and stressful conditions creates burnout and job dissatisfaction among healthcare professionals, affecting their mental and physical health. Healthcare professionals' reduced productivity and high turnover rates further strain the limited workforce, consequently compromising quality of care[3]. Moreover, due to the current economic crises, qualified healthcare professionals migrate abroad for better pay packages, professional growth opportunities & quality of life.

Due to this, Pakistan now has a critical shortfall of trained medical personnel, leading to overburdened healthcare facilities and diminished quality of care[4].

One in three medical students intends to migrate abroad after graduation due to a lack of resources and mismanagement in Pakistan. This has been adversely affecting Pakistan's healthcare system[5].

One of the major indicators of laying stress on health of the citizens is the ratio of spending on health as a percentage of GDP. The developed nations like Organization for Economic Cooperation and Development (OECD) spend from 8.8 to 12.7% of GDP on healthcare. The highest spending on healthcare is in USA (16.6% of GDP)[6]. In contrast to these the spending on health in Pakistan remains less than 1% of the GDP[7]. This clearly highlights the relative lack of importance placed on the health sector in our resource- constrained country.

With rapidly growing population needs and continuously evolving public health challenges, every healthcare system must remain adaptable, acknowledge its limitations, and strengthen its weaknesses by learning from healthcare models around the world. Although there is an increase in human resources, this growth is not enough to cater for the needs of the population. These challenges need comprehensive policy formulation focused on increase in healthcare funding, good service

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structure and allocation of equity-based resources[8].

Key strategies to reduce the disillusionment of younger generation include improved service structure, appropriate pay packages, better working conditions & support groups for burn out coping strategies

Working on these crucial issues can lessen the impending crises of the shortage of healthcare professionals.

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ORIGINAL ARTICLE

EFFICACY OF VAGINAL MISOPROSTOL IN THE TREATMENT OF MISSED MISCARRIAGE BEFORE 24 WEEKS OF GESTATION

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ABSTRACT

Objective: To determine the efficacy of vaginal misoprostol in the treatment of missed miscarriage in less than 24 weeks of gestation.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Obstetrics & Gynecology, Swat Medical Complex, Swat, 06 months (August 2025 to February 2026).

Methodology: This study was conducted on 194 patients, aged 18 to 40 years, with miscarriage of < 24 weeks of gestation. We determined the efficacy of vaginal misoprostol in the treatment of missed miscarriage. The dosage of vaginal misoprostol was adjusted according to the period of gestation and administered in compliance with the International Federation of Gynecology and Obstetrics (FIGO)-recommended protocol for pregnancy termination.

Results: The mean age of the patients was 29.03±6.66 years. The mean gestational age was 16.89±3.19 weeks. 68% patients had parity 0-3, while 32% patients had parity > 3. The efficacy of misoprostol in our study was 93 (47.9%) with p=value 0.05. A greater proportion of successful outcomes was observed in patients with a gestational age of less than 18 weeks (63.4%) compared with those at 18–24 weeks of gestation (36.6%); however, it did not reach statistical significance (p = 0.38).

Conclusion: Vaginal Misoprostol in the treatment of missed miscarriage in less than 24 weeks of gestation was effective in terms of non-surgical complete evacuation of the conception product.

Key words: *Gestational age, miscarriage, misoprostol, pregnancy, termination of pregnancy.*

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INTRODUCTION

The fetus is deemed viable after the 24th week of pregnancy. The evacuation of the fetus prior to 24th week is termed to as an abortion or miscarriage. The surgical procedure and the medical approach are the two options for ending a pregnancy[1]. Since the 1960s, surgical miscarriage of up to 63 days has been undertaken by vacuum aspiration or dilatation and curettage, which has the merits of preventing extended hospital stays, permitting for a fast return to normal life, and in the majority of cases, achieving process completion. However, it calls for competence and anesthesia, and bears a higher risk of anesthesia-related and surgical consequences. Moreover, it is not a particularly effective way to end a second-trimester pregnancy[2].

Mifepristone with prostaglandins, mifepristone, prostaglandins, methotrexate, and methotrexate with prostaglandins are among the abortifacient treatments[3]. The effectiveness of prostaglandins around the world, including Pakistan, is observed. Misoprostol is an E1 prostaglandin analogue that has been approved in around 85 countries; however, it has only been approved for the treatment of gastrointestinal ulcers[4].

Misoprostol, which was primarily used in obstetrics to induce labor, is now utilized for several of purposes, including cervix ripening and postpartum hemorrhage control. A study found that the use of oral or vaginal misoprostol for therapeutically managing missed miscarriages is both highly successful and well accepted, with a shorter time between induction and miscarriage and greater acceptability [5].

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A higher dose may be required to induce miscarriages. The ideal vaginal misoprostol dose for termination of pregnancy in the second trimester is between 50 - 1200 mg, early during the second trimester, whereas a lesser amount would be appropriate in the latter phases[6]. A study showed the efficacy of misoprostol in 56% of patients who had a complete miscarriage without surgical intervention[7].

CAPSULE SUMMARY

Efficacy of vaginal misoprostol in the treatment of missed miscarriage in less than 24 weeks of gestation was determined. It was found to be effective in terms of non-surgical complete evacuation of the conception product.

Missed miscarriage leaves a psychological impact on a patient's life in the form of depression and anxiety that often lasts for months, resulting in a degradation in quality of life[8]. Surgical interventions and costly treatments are available to effectively terminate the pregnancy with lower drawbacks, but these are expensive, and sometime higher dose is recommended. Consequently, a cheaper and effective alternative agent is needed. The goal of this research was determination of the efficacy of misoprostol in patients with missed miscarriage before 24 weeks of gestation.

METHODOLOGY

A cross-sectional study was conducted in the Obstetrics & Gynecology department, Swat Medical Complex, Swat, from August 2025 to February 2026. The sample size is 194, determined with the help of the WHO sample size formula by taking the efficacy of 56% after using misoprostol in patients who had missed miscarriage, with 95% confidence level, and 7% margin of error [7].

Patients in the age range of 18-40 years, with missed miscarriage < 24 weeks of gestation were included. Patients with incomplete, threatened miscarriages, those with gestational trophoblastic disease, and patients with irregular coagulation profiles were excluded.

The research proceeded after proper permission from the hospital's ethical review board. Subjects that met the inclusion requirements were included in the study. Patients were informed about the goals, risks, and advantages of the study. A signed written informed consent form was obtained from the patients and their demographic data, including age and address were noted in the file. To ensure the inclusion criteria, complete medical history was taken, and thorough physical examinations were performed. Patients who had missed miscarriage of less than 24 weeks of pregnancy were given vaginal misoprostol according to International Federation of Gynecology and Obstetrics (FIGO) recommendations, for gestation less than 13 weeks 800ug and after 13 weeks gestation 400 ug was given respectively every 3 hourly till complete expulsion of the product of conception. The efficacy of the treatment was assessed. The information of the patients was stored on dedicated proforma.

Data was analysed by using SPSS version 23. Mean + Standard Deviation were determined for quantitative variables, like age and gestational age. Frequencies and percentages were determined for categorical variables, like efficacy, complications, parity, and socioeconomic status. The efficacy was stratified by age, gestational age, parity, complications, and socioeconomic status to see the effect-modifiers. Post-stratification chi-square test was performed where a p-value of < 0.05 was considered significant. All results were shown in tables.

RESULTS

The current study was conducted on 194 patients with a mean age 29.03±6.66 years. Mean gestational age was 16.89±3.19 weeks. Regarding the age distribution, there were 113 (58.2%) patients in the age range of 18 to 30 years and 81 (41.8%), in the age group of 31 to 40 years. Regarding parity, there were 132 (68%) patients having parity of 0 to 3, while 62 (32%) patients had parity > 3. In our study, 36 (18.6%) patients had nausea, 64 (33%) had vomiting, and 43 (22.2%) had abdominal pain (Table-2). In terms of the socioeconomic status, 30 (15.5%) patients from a rich background (monthly income > 80000 PKR), 96 (49.5%) patients from a middle-class background (monthly income 50000 to 80000 PKR), and 68 (35.1%) patients from a poor background (monthly income < 50000 PKR). The efficacy of misoprostol in our study was 93 (47.9%) (Table-1).

Table:1-Efficacy of Misoprostol

Efficacy of misoprostol	Frequency (n)	Percent (%)
Yes	93	47.9
No	101	52.1
Total	194	100.0

Table:2-Complications Related to Misoprostol

Complications	Frequency (n)	Percent (%)	p-value
Nausea			
Yes	36	18.6	0.05
No	158	81.4	
Total	194	100.0	
Vomiting			
Yes	64	33.0	0.15
No	130	67.0	
Total	194	100.0	
Abdominal pain			
Yes	43	22.2	0.57
No	151	77.8	
Total	194	100.0	

DISCUSSION

The evacuation of the fetus before the end of the 24th week is referred to as an abortion or miscarriage. Pregnancy failure that is detected before the evacuation of fetal and placental tissues in < 24 weeks of gestation is called a missed miscarriage because the fetus is deemed viable after the 24th week of pregnancy. According to estimates, 25% of women are likely to experience an early pregnancy loss during their reproductive life, and between 10% and 15% of confirmed pregnancies result in miscarriage[1]. About 30 million induced miscarriages occur annually, highlighting the need for a safe and efficient method to make it a worldwide concern for gynecologists and patients. Pregnancy can be ended surgically or medically.

Since the 1960s, surgical miscarriage of up to 63 days, by vacuum aspiration or dilatation and curettage, has been the preferred approach as it avoids a lengthy hospital stay, allows for an instant return to normal life, and guarantees that the treatment is completed in the majority of instances However, it calls for expertise, anesthesia, and a higher risk of surgical and anesthetic complications. Additionally, it is not a very good approach for ending a pregnancy in the second trimester. With the advent of prostaglandins in the early 1970s and antiprogesterones in the 1980s, medical miscarriage emerged as a substitute technique of ending a first-trimester pregnancy. Prostaglandins, mifepristone, methotrexate, mifepristone with prostaglandins, and methotrexate with prostaglandins are the most extensively studied abortifacient medications[9].

Prostaglandins E1 (Cytotec) are studied for efficacy all around the world, including Pakistan. Since its initial commercialization in 1985, misoprostol, an E1 prostaglandin analogue, has been approved in more than 85 countries; nonetheless, it is currently solely authorized for the treatment of stomach ulcers. Since its initial use in obstetrics in 1993 to induce labor, misoprostol (Cytotec) has been utilized for a variety of purposes, including cervix ripening and postpartum hemorrhage control. A study found that using oral or vaginal misoprostol to treat missed miscarriages is both highly effective and acceptable, with a short induction to miscarriage time [10]. A higher dose may be required to induce miscarriages early in the 2nd trimester, whereas a smaller dose may be adequate in the late 2nd trimester. The ideal dosage of vaginal misoprostol for termination in the 2nd trimester is between 50 to 1200 µg. Two tablets (400µg) orally or vaginally, repeated 4 hourly till expulsion, or 4-tablets (800µg) vaginally 24 hourly till expulsion, if a miscarriage occurs between 4 - 12 weeks of gestation. Prostaglandin E2 is expensive and requires a high dosage, yet it is successful in miscarriage and pregnancy termination with fewer side effects[11].

Misoprostol has been safely and efficiently utilized in patients with fetal mortality for labor induction and cervical ripening. Oral misoprostol (400µg, 4 hourly) to induce labor after fetal death was originally documented by Mariani-Neto and colleagues. Twenty individuals with fetal death were the subjects of the authors' report. With an average delivery time of 552 minutes, every patient gave birth successfully. Misoprostol was taken at a mean dose of 1000 µg. Misoprostol's safety and effectiveness in treating fetal death have been evaluated in a few more trials[9].

Current research primarily compares different dosages, intervals between doses, and administration methods in order to optimise misoprostol dosing regimens. Misoprostol was administered at intervals of 3-12 hours, with dosages ranging from 100 to 1200 µg. Misoprostol is more effective when administered at shorter intervals (3 to 4 hours) at a higher dose (400–800 µg). However, because the oral route was more convenient, less painful, and offered greater privacy, women preferred it[12].

In our study, we sought to determine the efficacy of misoprostol in terminating a pregnancy that was unviable at less than 24 weeks of gestation, with respect to its dosage and success rate. Whenever a medication is administered, cost and safety are crucial considerations. Numerous prior research have shown prostaglandin E2 to be safe for pregnancy termination. But it's by no means inexpensive. We found that misoprostol's efficacy was 93 (47.9%), which is comparable to a study that revealed misoprostol's efficacy to be 56%[7].

Misoprostol had a 78.5% success rate, with 58.3% of patients experiencing full evacuation as verified by ultrasonography[13]. Misoprostol has a 46.5% success rate[14]. At the initial follow-up scan (10–14 days), an overall effectiveness rate of 68.8% was obtained[15]. The mean gravidity was higher (3 vs. 2, p = 0.007), and the frequency of vaginal bleeding or abdominal pain at presentation was higher (18.9% vs. 31.6%, p = 0.037) in another successful treatment (84.2%)[16].

When compared to manual vacuum aspiration, misoprostol has a lower full evacuation rate (84% vs. 94%, p=0.1123)[17]. The sublingual group had a considerably greater percentage of complete abortion than the vaginal group (86.1% vs. 77.1%, P=0.048)[18], In our study, however, the vaginal route accounted for 47.9%. Another study in Nowshera, KPK, found that oral misoprostol had a much lower success rate (64.9%) than vaginal misoprostol (87.6%) (p=0.001)[19]. However, in our study, the vaginal route accounted for 47.9%.

Oral misoprostol (75.0%) was not as effective as vaginal misoprostol (93.1%) (p=0.009)[20]. Success rates for manual vacuum aspiration were much greater than those for oral misoprostol (98.8% vs. 82.7%, p<0.001)[21]. According to a study conducted in Karachi on first-trimester miscarriages, the main reasons for medical termination were missed miscarriages, which accounted for 67.5% of cases, and 14.5%of cases among patients in the second trimester. In this case, the effectiveness was 59% for pregnancies under 18 weeks and 34% for those between 28 and 24 weeks[22].

When the two groups' safety rates were compared, group A's was 68.0% and group B's was 91.7%, with a gestational age of 15–20 weeks. With a p-value of 0.25, group A's safety rate for gestational ages under 15 weeks was 78.6%, while group B's was

89.7%[23].

In Islamabad, the rate of success was significantly higher (p-value < 0.05) in the sublingual misoprostol group (76.67%) than in the vaginal misoprostol group (58.33%)[24]. Of the patients treated with misoprostol, 23.3% required additional surgical evacuation, 76.7% were successfully managed by medical treatment, 73.3% reported overall satisfaction, and 76.7% demonstrated treatment acceptance.

The results may not be as applicable to different healthcare settings and demographics because the study was carried out in a single-center hospital. Due to regional and institutional differences in patient characteristics and healthcare practices, the sample population could not accurately reflect the larger community. Misoprostol reaction may have been impacted by differences in patients' gestational age, parity, and prior obstetric history. The study did not compare results with alternative treatment techniques, such as surgical evacuation or expectant management, and instead concentrated solely on medicinal care using misoprostol. The evaluation of long-term problems and patient satisfaction may have been constrained by short-term follow-up.

Treatment results and monitoring may have been impacted by resource constraints and disparities in clinical expertise.

CONCLUSION

In terms of non-surgical full evacuation of the conception product, we conclude that vaginal misoprostol was effective in treating missed miscarriages in less than 24 weeks of gestation.

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ORIGINAL ARTICLE

FROM STRESS TO STRATEGY: A MIXED- METHOD STUDY OF DAILY STRESSORS, COPING STRATEGIES AND WELL-BEING AMONG FIRST-YEAR MEDICAL STUDENTS

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ABSTRACT

Objective: To explore the daily stressors and coping strategies among first-year MBBS students..

Study Design: Mixed- method study.

Place and duration of study: Bahria University Health Sciences Campus, Islamabad, 06 months (November 2025 to April 2026).

Methodology: This mixed- method study assessed stressors and coping strategies in first-year MBBS students at a private medical college using the Perceived Stress Questionnaire (PSQ) and Coping Self Efficacy Scale (CSE). Students also provided a qualitative narrative identifying their daily stressors and created personal stress management plans which included coping strategies after self-reflection. Thematic analysis of narratives using Braun & Clarke method was done.

Results: Eighty-seven valid responses from the students were obtained for PSQ and 58 students responded to Coping Self Efficacy Scale. The overall PSQ indicated moderate perceived stress (mean=0.456, SD=0.131). The highest stressor was associated with having too many things to do. CSE score revealed a moderate to high level of coping self-efficacy (mean= 6.05-7.16), with participants reporting strong confidence in finding solutions to problems.

Conclusion: First- year medical students experienced moderate stress accompanied with moderate to high coping self-efficacy. Self-reflection proved effective in identifying daily stressors and their coping strategies. Targeted interventions, specifically creating personal stress management plans, can help them prevent burnout. Ultimately, institutional support within medical institutions can enhance both academic resilience and the overall student wellbeing.

Key Words: *Coping strategies, Medical education, Mental health, Self-efficacy, Stress management, Undergraduate medical students*

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INTRODUCTION

Medical training is known to be one of the most demanding academic journeys, where students must adapt to the heavy academic workload, fear of failure and social isolation. These challenges have a significant impact on students' mental health and wellbeing[1]. To ensure academic excellence, it is essential for the medical colleges to support students in preventing burnout.

When the daily stressors are unmanaged, they often lead to poor academic outcomes. Globally, studies show that this burnout can lead to low motivation and shift in professional values[2]. Keeping in view, the evolving landscape of medical education and rapid digitalization, students need to adapt quickly to handle the transition effectively[3]. To overcome this, resilience training is one of the proven methods to lower stress levels in medical students worldwide, especially in preclinical years[4].

Stress and the coping behaviors don't remain same throughout the five-year medical training[5]. This makes it vital that the institution understands the specific coping skills that the

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students use to prevent stress[6]. In Pakistan, evidence shows that heavy academic pressure and fear of failure is one of the dominant stressors. Overcoming these stressors can ensure students' psychological wellbeing. Medical students' mental wellbeing is a direct predictor of their academic performance[7]. Thus timely interventions are required to prevent the harmful effect of stress due to medical training.

Variable coping strategies are employed by the students to keep them afloat during these stressful times. These can be adaptive or maladaptive strategies in nature[8]. Improving access to support services within medical colleges should be an institutional priority[9]. Ultimately helping students navigate stress and cope successfully is paramount for achieving excellence within their medical journey[10].

This study explores the quantitative levels of stresses and coping self-efficacy in first-year medical students while exploring their qualitative narrative of daily stressors and personal stress management plans.

CAPSULE SUMMARY

The study assessed stressors and coping strategies in first-year MBBS students at a private medical college using the Perceived Stress Questionnaire (PSQ) and Coping Self Efficacy Scale (CSE). The students were found to experience moderate stress, accompanied with moderate to high coping self-efficacy. Targeted interventions institutional support can help prevent burnout and enhance both academic resilience and the overall wellbeing of the students.

METHODOLOGY

This mixed- method study was conducted in a private medical college Bahria University Health Sciences Campus, located in Islamabad, from November 2025 to April 2026. Ethical Review Board approval was taken. First year medical students were included in the study as they are transitioning to a different academic environment.

A total of 100 first- year medical students were included in the study. The participation in the study was voluntary. Informed consent was taken from the participants before the study. To ensure confidentiality, student identities were not linked to their responses.

Perceived Stress Questionnaire (PSQ)[11] and Coping Self Efficacy Scale (CSE)[12] were used in the study after getting permission from the owners. Eighty-seven students returned valid PSQ responses and 57 completed CSE scales. Students were asked to provide their daily stressors and develop their personalized stress management plans after self-reflection through email, afterwards.

Numerical data of PSQ and CSE scales were analyzed using SPSS version 27. The written narratives and stress management plans were analyzed thematically using Braun & Clarke's method.

RESULTS

Table 1 summarizes the descriptive statistics for the 30 items of the PSQ. The mean scores across individual PSQ items ranged from 2.16 to 2.70, indicating an overall moderate level of perceived stress among first-year medical students (Figure 1). Most items demonstrated a median and mode Table 1 summarizes the descriptive statistics for the 30 items of the PSQ. The mean scores across individual PSQ items ranged from 2.16 to 2.70, indicating an overall moderate level of perceived stress among first-year medical students (Figure 1). Most items demonstrated a median and mode of 2, suggesting consistency in students' responses across stress domains.

Figure 1 – Mean Scores of Perceived Stress Questionnaire Items

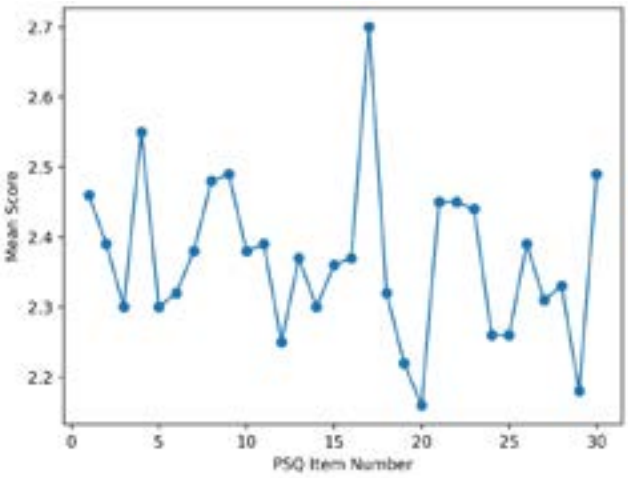


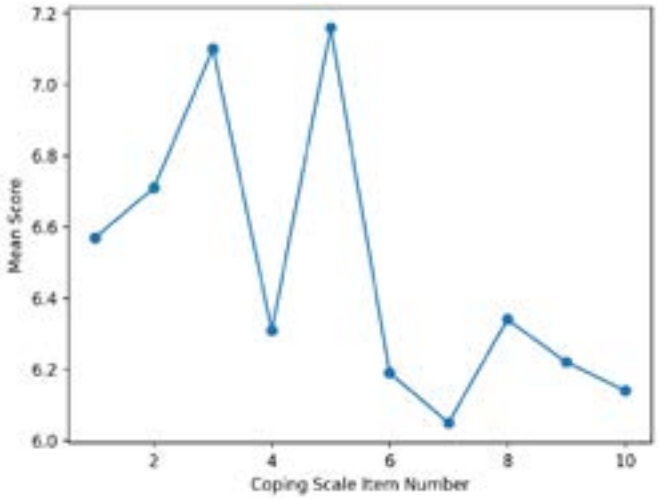
Table 1: Descriptive Statistics of Perceived Stress Questionnaire Responses

	q1	q2	q3	q4	q5	q6	q7	q8	q9	q10	q11	q12	q13	q14	q15	q16	q17	q18	q19	q20	q21	q22	q23	q24	q25	q26	q27	q28	q29	q30
Mean	2.46	2.39	2.30	2.55	2.30	2.32	2.30	2.46	2.39	2.30	2.39	2.25	2.37	2.30	2.16	2.37	2.70	2.32	2.22	2.16	2.45	2.45	2.46	2.26	2.26	2.39	2.51	2.33	2.38	2.49
Median	2.00	2.00	2.00	3.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	3.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
Mode	2	2	2	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
SD	.709	.690	.694	1.110	.670	.650	.905	.900	.951	.790	.894	.790	.670	.809	.915	.794	1.001	.669	.692	.694	.932	.915	.670	.756	1.005	.909	.932	.670	.670	.909
Range	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3

The highest mean score was observed for Question 17 (You feel safe and protected) (Mean = 2.70, SD = 1.001), followed by Question 4 (You have too many things to do) (Mean = 2.55, SD = 1.118) and Question 30 (You feel under pressure from deadlines) (Mean = 2.49, SD = 0.926), reflecting areas where students reported comparatively higher perceived stress. Conversely, the lowest mean score was recorded for Question 20 (You feel discouraged) (Mean = 2.16, SD = 0.834), suggesting relatively lower perceived stress for this domain.

Standard deviations ranged from 0.684 to 1.118, indicating moderate variability in responses, with certain items reflecting greater individual differences in perceived stress levels. All PSQ items demonstrated a uniform range of 3, confirming consistent scale utilization across respondents.

Figure 2 – Mean Scores of Coping Self-Efficacy Scale Items



The overall mean PSQ Index, calculated to reflect cumulative perceived stress, was 0.4563 (SD = 0.1311), with values ranging from 0.14 to 1.00. The median PSQ index was 0.4444, indicating that at least half of the participants experienced stress levels near the overall mean.

The distribution of PSQ index scores suggested that most students fell within the moderate perceived stress range, with a smaller subset experiencing either very low or high stress levels. The observed range (0.86) reflects considerable inter-individual variation in perceived stress among first-year medical students.

The mean item scores ranged from 6.05 to 7.16 for Coping Self-Efficacy Scale, indicating an overall moderate to high level of perceived coping self-efficacy among participants (Figure 2).

The highest mean score was observed for Question 5 (Find solutions to your most difficult problems) (Mean = 7.16, SD = 2.15), followed closely by Question 3 (Sort out what can be changed and what cannot be changed) (Mean = 7.10, SD = 1.91), suggesting stronger confidence in certain coping abilities. The lowest mean score was recorded for Question 7 (Leave options open when things get stressful) (Mean = 6.05, SD = 2.40), reflecting comparatively lower self-efficacy in this coping domain.

Median scores across most items ranged between 6.0 and 8.0, with modes clustering between 7 and 8, indicating that a substantial proportion of students perceived themselves as reasonably capable of managing stress. Standard deviations ranged from 1.91 to 2.78, suggesting notable variability in coping self-efficacy across individuals. All items demonstrated a wide response range (8–9), highlighting diverse coping perceptions within the cohort.

Based on the narratives shared by the students, following themes for daily stressors and coping strategies were identified:

Themes: Daily Stressors

Five themes were identified in the domain of daily stressors; these are as follows:

1.Academic and Performance Pressure: "Fear of failure" and the "fast-paced medical curriculum" leads to mental fatigue caused by the high-pressure environment. This was one of the most dominant stressors within first- year medical students.

2.Time Management Issues: The students are faced with the stress of "managing schedules and multiple deadlines" leading to "procrastination" and "feeling overwhelmed" due to the volume of academic overload.

3.Parental and Societal Expectations: Multiple students reported that the external "expectations from parents and society" had built high pressure on them which led to "social isolation" and pressure to maintain "professional image."

4.Psychological and Emotional Strain: Students reported of internal struggles in the form of "self-doubt and impostor phenomenon." This has led to overthinking regarding "future career progression" and "professional identity formation."

5.Lifestyle Alteration: Tough medical training routine was taking toll on the students' lifestyle. They experienced "lack of self-care, sleep deprivation and financial stressors". All these had immense impact on the overall wellbeing of the students.

Themes: Coping Strategies

The thematic analysis of the coping strategies revealed seven themes mentioned as follows:

1.Structured Study Time: Many students mentioned practical techniques in their personalized stress management plans including "pomodoro method", "chunking information", "prioritizing tasks" and "following the schedules" to manage time and meet deadlines.

2.Emotional Regulation: To gain emotional stability, students

mentioned "deep breathing", "mindfulness", "practicing yoga" and "guided imagery" techniques. They mentioned that these techniques helped them manage pressure effectively. Similarly, "being self-aware" came out to be one of the coping strategies to emotionally regulate oneself.

3.Social and Professional Support: Students shared that seeking "social support from family members" and "professional support from teachers and mentors" could help them reduce their stress. These interactions could be source of relief and emotional support especially through "high pressure events." Spending times with other hostelites also came out to be part of social support system for students living away from their homes.

4.Spiritual and Religion Connection: One of the most prominent coping strategies was "reconnecting with religion", "reciting Quran "and "offering five times prayers." Students referred to medicine as a source of "giving back to the community" and "living for a bigger purpose of life." By focusing on the spiritual and religious connections, students were able to cope with high- pressure interactions within medical training.

5.Lifestyle Modifications: Personalized stress management plans showed that "leading a healthy lifestyle" could make a huge difference in the wellbeing of the students. By "doing regular exercise", "going for walks" and "engaging in healthy hobbies such as listening to music and reading" while ensuring "adequate 8 hours sleep" had been a few of the interventions that could change the outlook of stressed medical students.

6.Active Self Reflection: Lastly, the most important theme shared by the students was "involving in self-reflection" where they "acknowledge the stressors" and "take actionable steps" to cope with them.

DISCUSSION

Medical training is one of the most challenging academic degrees in the world. For first -year students, transitioning from high school to an academic overloaded medical journey is a test of patience and emotional resilience[13]. Academic overload, fear of failure and unable of manage time are one of the most common challenges faced by all medical students. This aligns very well with both national and international literature[14].

Research within Pakistan has shown that academic pressure with intense examination schedules is one of the major stressors[15]. These take direct toll on the physical health of students who are hostelites with sleep deprivation issues as shared by our students in their narratives[16]. It is very vital that the learning environment is conducive for learning by the students so that good academic outcomes are achieved.

Similarly, research from Ethiopia identifies academic overload and emotional fatigue as prominent stressors, particularly for students transitioning from preclinical to clinical years[17]. Pakistani students show reliance on religious and spiritual practices to cope with the ongoing stress. This practice helps them face the intense medical training. Future career expectations from parents and colleagues also create immense pressure on the learner[18].

The use of self-reflection creates a vital bridge between experiencing stress and developing a coping strategy. By creating personalized stress management plans, students will be able to shift their focus from stressors to coping strategies[19]. At institutional level, there needs to be support systems in place, which go beyond traditional counseling by incorporating wellbeing services within the policies[20].

By identifying the potential stressors, institutions can map out targeted interventions to address their effects within lives of medical students[21]. Moving forward, integrating mental health and wellbeing initiatives within the medical curriculum is essential to promote a culture of empathy and long-term academic excellence among the future healthcare professionals[22].

CONCLUSION

First- year medical students face complex academic and social dilemmas during medical training. Our findings demonstrate that the students possess moderate levels of coping systems. However, targeted institutional support is required to reduce the academic burnout. Identifying students' daily stressors and coping strategies can be helpful in making data- driven decisions, ensuring long- term student well-being and better academic outcomes.

Limitations: This study is limited by single institution data which may restrict the generalizability of the findings. Furthermore, the cross-sectional nature of the study is only a snapshot in time rather than longitudinal data.

Recommendations: Future studies should explore the long-term effect of the coping strategies and the personal stress management plans for preventing academic burnout.

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- ***Nayyab Zehra:*** *Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision*
- ***Anzah Babar:*** *Acquisition of data, Drafting the article, Critical revision*
- ***Ahmed Hassaan Malik:*** *Analysis and interpretation of data, Drafting the article, Critical revision*
- ***Hina Akhtar Khan:*** *Analysis and interpretation of data, Drafting the article, Critical revision*

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ORIGINAL ARTICLE

EVALUATING TREATMENT OUTCOMES OF INTRAVITREAL AFLIBERCEPT IN RETINOPATHY OF PREMATURITY

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ABSTRACT

Objective: To evaluate the anatomical treatment outcomes of intravitreal aflibercept in infants with severe Stage 3 retinopathy of prematurity (ROP).

Study Design: Prospective cohort study.

Place and Duration of Study: LRBT Tertiary Teaching Eye hospital, Karachi, 06 months (August 2025 to January 2026).

Methodology: This prospective cohort study was conducted at a tertiary care eye hospital. Sixteen infants (32 eyes) with gestational age <34 weeks and birth weight <2000 g, who had treatment-requiring Stage 3 ROP received intravitreal aflibercept (0.4 mg/0.01 mL). Outcomes were assessed at 1–2 weeks, 4–6 weeks, and 3 months. Continuous variables were summarized as mean ± SD and categorical variables as frequencies and percentages. Descriptive statistics were used. Because of the small sample size and the low number of unfavorable outcomes, any univariate analyses were considered exploratory.

Results: At 3 months, complete regression was achieved in 26 eyes (81.3%), partial regression in 4 eyes (12.5%), and no change in 2 eyes (6.2%). No eye showed disease progression or recurrence during follow-up. Two eyes (6.2%) belonging to one infant required rescue laser photocoagulation. Mild subconjunctival hemorrhage occurred in 4 eyes (12.5%); no major ocular or systemic adverse events were observed. Exploratory analysis shows that lower gestational age, lower birth weight, Zone I disease, and aggressive ROP were more in infants with unfavorable outcomes.

Conclusion: Intravitreal aflibercept appears to be a safe and effective option for the initial management of severe Stage 3 ROP, with high anatomical regression and few short-term complications. Larger studies with longer follow-up are needed to confirm long-term ocular and systemic safety.

Key words: *Aflibercept; Infant; Intravitreal injections; Retinopathy of prematurity; Treatment outcomes*

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INTRODUCTION

Retinopathy of prematurity (ROP) is a potentially blinding vasoproliferative retinal disorder that affects premature and low-birth-weight infants. Abnormal retinal vascular development after premature birth may lead to ischemia, pathological neovascularization, retinal detachment, and permanent visual impairment [1-3].

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ROP remains an important cause of childhood blindness, particularly in low- and middle-income countries where survival of preterm infants has improved but screening and treatment systems remain inconsistent[3,4]. On average, about 15 million preterm infants are born annually all around the world, and about 20,000 to 30,000 infants are born with severe ROP[5]. ROP differs a great deal regarding the gestational age, birth weight, and quality of the provided neonatal care. The incidence of ROP is increasing in South Asia and developing countries, as extremely premature neonates are surviving. The management of this condition requires early therapeutic interventions that are more effective and safer[6]. In Pakistan, reported rates of ROP among preterm infants vary across centres, reflecting differences in neonatal risk profiles, survival, and screening practices[7].

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The pathogenesis of ROP is often described in two phases. Early exposure to supplemental oxygen suppresses vascular endothelial growth factor (VEGF) and interrupts normal retinal vascularization. Subsequent relative retinal hypoxia increases VEGF expression and drives pathologic neovascularization, so this biological mechanism provides the rationale for anti-VEGF treatment [8].

Laser photocoagulation has historically been the standard treatment for threshold and type 1 ROP, but it is associated with peripheral retinal ablation, visual field loss, high myopia, and the need for technically demanding procedures. Intravitreal anti-VEGF therapy offers a targeted alternative that may preserve more peripheral retina [8-12].

Aflibercept is a recombinant fusion protein that binds VEGF-A, VEGF-B, and placental growth factor. Its high binding affinity and relatively prolonged duration of action make it an attractive candidate for severe ROP [11]. Some clinical trials have documented good results with intravitreal aflibercept, such as regression of neovascularization and low rates of recurrence, though there are still some concerns that need to be addressed about systemic absorption, optimal dosage, long-term ocular development, and neurodevelopmental safety in premature babies[12,13]. However, data from low-resource settings remain limited, and real-world evidence on short-term outcomes is still evolving.

The objective of this study was to evaluate the anatomical treatment outcomes and short-term safety of intravitreal aflibercept in infants with severe Stage 3 ROP.

CAPSULE SUMMARY

Treatment outcomes of intravitreal aflibercept in infants with severe Stage 3 retinopathy of prematurity (ROP) were evaluated. It appeared to be a safe and effective option for initial management, with high anatomical regression and few short-term complications.

METHODOLOGY

This prospective cohort study was conducted at a Tertiary Care Teaching Eye Hospital (LRBT Tertiary Teaching Eye hospital, Karachi) from August 1, 2025, to January 31, 2026, after approval from the Ethical Review Committee. Written informed consent was obtained from parents or guardians of all enrolled infants.

The calculated sample size using OpenEpi version 3 was 45 infants, based on an expected favourable outcome proportion of 97%, a 95% confidence level, and 5% margin of error[14]. However, because treatment-requiring severe ROP was infrequent during the study period, only 16 infants (32 eyes) could be enrolled. Therefore, this study should be interpreted as an exploratory prospective cohort providing preliminary real-world evidence.

Non-probability consecutive sampling was used. Eligible participants were premature infants with gestational age <34 weeks, birth weight <2000 g, and treatment-requiring Stage 3 ROP who received intravitreal aflibercept and whose guardians provided consent. Infants with congenital ocular anomalies, prior laser photocoagulation, previous anti-VEGF therapy, systemic congenital syndromes affecting ocular development, or loss to follow-up were excluded.

Baseline demographic and clinical variables included gestational age, birth weight, sex, mode of delivery, oxygen exposure, neonatal intensive care stay, and systemic comorbidities. Ophthalmic assessment included ROP stage, retinal zone, and disease status using indirect ophthalmoscopy and wide-field retinal imaging when available. A trained pediatric ophthalmologist and a vitreoretinal specialist confirmed the findings.

Intravitreal aflibercept (0.4 mg/0.01 mL) was administered under strict aseptic conditions in the operating room by a trained pediatric ophthalmologist. Topical anaesthesia, povidone-iodine antisepsis, and a sterile eyelid speculum were used. Aflibercept was injected through the pars plicata using a 30-gauge needle at an age-appropriate distance from the limbus. Bilateral treatment was performed on the same day when indicated. Topical antibiotics were prescribed post-procedure, and infants were monitored for immediate ocular and systemic adverse events.

Follow-up examinations were scheduled at 1–2 weeks, 4–6 weeks, and 3 months. Outcomes included regression of neovascularization, resolution of plus disease, disease progression or recurrence, and need for additional treatment. A favourable outcome was defined as complete regression without need for retreatment by 3 months. Unfavourable outcomes were considered as partial regression, no regression, recurrence, and requirement for additional treatment.

Data were analysed using SPSS version 26. Continuous variables were assessed for normality using the Shapiro–Wilk test. Continuous variables were summarized as mean ± standard deviation; categorical variables as frequency and percentage. Primary analysis was conducted at the eye level. An exploratory infant-level univariate analysis was performed to compare the characteristics of infants with favourable vs unfavourable outcomes. Continuous variables were compared using the Mann-Whitney U test. The Fisher's exact test was used to compare categorical variables. Given the small sample size and only three unfavourable outcomes, these univariate analyses were considered exploratory and interpreted cautiously. A p-value ≤0.05 was considered statistically significant.

RESULTS

Sixteen infants (32 eyes) were included. The cohort represented a high-risk neonatal population with low gestational age and low birth weight. Primary outcome analysis was done at eye level. All eyes had Stage 3 ROP. Zone II was the most commonly involved retinal zone, while more than one-third of eyes had

Table 1. Baseline demographic, clinical, and ophthalmic characteristics of infants with ROP [n=16 infants; 32 eyes]

Variable	Value
Male sex ; n(%)	9 (56.3)
Female sex ; n(%)	7 (43.7)
Gestational age (weeks) ; mean±SD	28.4 ± 2.1
Birth weight (g) ; mean±SD	1125 ± 285
ROP stage ; n(%)	Stage 3 in 32 eyes (100)
Zone I disease ; n(%)	12 eyes (37.5)
Zone II disease ; n(%)	18 eyes (56.3)
Zone III disease ; n(%)	2 eyes (6.2)
Plus disease present ; n(%)	20 eyes (62.5)
Aggressive ROP ; n(%)	14 eyes (43.8)

Table 2. Frequency of treatment characteristics of intravitreal aflibercept

Variable	Frequency (%)
Dose administered (0.4 mg/0.01 mL)	32 eyes (100)
Bilateral injections	16 infants (100)
Topical anesthesia used	16 infants (100)
Rescue laser photocoagulation	2 eyes (6.2)

Table 3. Frequency of follow-Up outcomes after intravitreal aflibercept (32 eyes)

Outcome	1–2 weeks Frequency(%)	4–6 weeks Frequency(%)	3 months Frequency(%)
Complete regression	14 (43.8)	22 (68.8)	26 (81.3)
Partial regression	12 (37.5)	8 (25.0)	4 (12.5)
No change	6 (18.7)	2 (6.2)	2 (6.2)
Progression	0 (0)	0 (0)	0 (0)
Additional treatment required	0 (0)	2 (6.2)	2 (6.2)

Zone I disease. Plus disease and aggressive ROP were also common at presentation. (Table 1)

All eyes received intravitreal aflibercept at the standard study dose. Bilateral injections were performed for all infants. Most procedures were completed under topical anaesthesia. Two eyes (6.2%), belonging to one infant, later required rescue laser photocoagulation. (Table 2)

Serial follow-up demonstrated progressive retinal vascularization and regression of neovascularization over 3 months. The proportion of eyes with complete regression increased across follow-up visits, whereas partial regression and no-change categories decreased. No eye showed progression during follow-up. (Table 3)

Table 4. Frequency of final treatment outcomes at 3 months (32 eyes)

Outcome	Frequency (%)
Complete regression of ROP	26 (81.3)
Partial regression	4 (12.5)
No change	2 (6.2)
Recurrence of ROP	0 (0)
Need for repeat aflibercept injection	0 (0)
Need for rescue laser photo-coagulation	2 (6.2)
Overall favorable outcome	26 (81.3)

Table 5. Frequency of ocular and systemic complications

Complication	Frequency (%)
Subconjunctival hemorrhage	4 eyes (12.5)
No ocular complications	28 eyes (87.5)
Systemic complications	0 (0)

By 3 months, 26 eyes (81.3%) had complete regression, 4 eyes (12.5%) had partial regression, and 2 eyes (6.2%) showed no change. No recurrence was documented within the follow-up period, and no repeat aflibercept injection was required. (Table 4)

Treatment was generally well tolerated. Mild subconjunctival haemorrhage occurred in 4 eyes (12.5%) and resolved without intervention. No retinal detachment, endophthalmitis, cataract, vitreous haemorrhage, or systemic adverse events were documented. (Table 5)

Table 6. Exploratory comparison of characteristics of infants with Favourable versus Unfavourable Outcomes

Variable	Favorable outcome (n=13 infants)	Unfavorable outcome (n=3 infants)	p-value
Gestational age (weeks) ; mean±SD	29.1 ± 1.9	26.4 ± 1.6	0.02
Birth weight (g) ; mean±SD	1210 ± 260	890 ± 190	0.03
Zone I disease ;n(%)	4 (30.8)	2 (66.7)	0.04
Plus disease ;n(%)	7 (53.8)	3 (100)	0.08
Aggressive ROP;n(%)	4 (30.8)	2 (66.7)	0.04
Need for laser therapy ;n(%)	0 (0)	1 (33.3)	0.01
Subconjunctival hemorrhage ;n(%)	2 (15.4)	2 (66.7)	0.09

Exploratory risk factor analysis was performed at the infant level. On exploratory analyses, lower gestational age, lower birth weight, Zone I disease, aggressive ROP, and need for rescue laser were more common in infants with unfavourable outcomes. (Table 6)

DISCUSSION

This prospective cohort suggests that intravitreal aflibercept may provide favourable short-term anatomical outcomes in severe Stage 3 ROP. More than four-fifths of treated eyes achieved complete regression by 3 months, and no recurrence was observed during the follow-up period. The low complication rate further supports its short-term tolerability in this cohort.

Our findings are broadly consistent with published studies reporting good anatomical regression after aflibercept in treatment-requiring ROP. The presence of Zone I disease, aggressive posterior features, and greater prematurity in infants with less favourable outcomes also aligns with the established understanding that both systemic immaturity and posterior disease severity influence prognosis [15,16]. The low complication rate further supports its short-term tolerability in this cohort [17].

Only two eyes required rescue laser photocoagulation, suggesting that aflibercept was adequate as primary therapy for most eyes in this series. However, infants with severe posterior disease may still need adjunctive treatment, emphasizing the need for close follow-up after anti-VEGF therapy [18,19,20,21]. The FIREFLEYE next study at longer-term follow-up confirmed that sustained disease control with aflibercept could be maintained to at least two years of age with minimal reactivation and reduced late adverse effects, consistent with the durability of anti-VEGF therapy in the present study's short-term, three-month follow-up[20].

The safety profile in this study was reassuring, with only minor subconjunctival haemorrhage and no observed major ocular or systemic complications. Nevertheless, the follow-up duration was short, and this study was not powered to evaluate uncommon adverse events or long-term visual and neurodevelopmental outcomes.

Limitations: The sample size was smaller than originally calculated, limiting statistical power and generalizability. The single-centre design and 3-month follow-up reduce the ability to assess late recurrence, peripheral vascularization, refractive outcomes, and systemic safety. In addition, because of the low number of unfavourable events, multivariable regression analysis was not performed, and exploratory univariate analysis should be interpreted with caution.

Despite these limitations, this study provides useful preliminary real-world evidence from a resource-constrained setting and supports further larger prospective studies evaluating aflibercept in ROP.

CONCLUSION

Intravitreal aflibercept appears to be a safe and effective short-term treatment option for severe Stage 3 ROP. High complete regression rates and low complication rates were observed. Lower gestational age, lower birth weight, Zone I disease, and aggressive ROP were common in infants with less favourable outcomes. Larger multicentre studies with longer follow-up are needed to establish long-term ocular and systemic safety and to evaluate the long-term efficacy of intravitreal aflibercept in ROP.

ETHICAL APPROVAL: *Approval No: LRBT/TTEH/ERC/4597/39, 30th July 2025.*

CONSENT FOR PUBLICATION: *Written, informed consent was obtained from the study participants.*

AVAILABILITY OF DATA: *Data is available from the corresponding author on a justified request.*

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CONFLICT OF INTEREST: *None*

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AUTHORS' CONTRIBUTION

- ***Muhammad Usama Idrees:*** *Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision*
- ***Saima Amin:*** *Conception and design, Acquisition of data, Critical revision*
- ***Zeeshan Kamil:*** *Acquisition of data, Analysis and interpretation of data, Drafting the article*
- ***Amna Ali:*** *Drafting the article, Critical revision*
- ***Muhammad Tanweer Hassan Khan:*** *Conception and design, Acquisition of data, Analysis and interpretation of data*
- ***Sabrina Mehmood:*** *Analysis and interpretation of data, Critical revision*

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ORIGINAL ARTICLE

THE ROLE OF RADIOLOGICAL IMAGING IN ASSESSING MDR-TB SEVERITY: A STUDY OF CXR FEATURES AND THEIR ASSOCIATION WITH SOCIO-DEMOGRAPHIC AND CLINICAL VARIABLES

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ABSTRACT

Objective: To assess chest X-ray patterns in multidrug-resistant tuberculosis (MDR-TB) patients and determine their association with socio-demographic and clinical characteristics.

Study Design: Cross sectional, analytical study.

Place of Study and Duration: Bacha Khan Medical College (BKMC)/Mardan Medical Complex (MMC) MTI, Mardan, 01year(From January 2025 to December 2025).

Methodology: A total of 147 confirmed MDR-TB patients, aged ≥18 years, were enrolled through consecutive sampling. A structured proforma was used to gather data, related to socio-demographic profile, clinical characteristics, and behavioral factors. Chest X-ray (CXR) patterns were classified as abnormal (cavitation, consolidation, pleural effusion, infiltration) or normal. SPSS version 26 was used to analyze the data. Descriptive statistics were calculated and associations were evaluated by Chi-square test and multivariable logistic regression.

Results: The incidence of abnormal CXR findings was 74.8% of 147 patients. Infiltrations and cavitations were the most prevalent abnormalities, found radiologically. The percentage of abnormal CXR results was higher in the patients with low BMI (47.6%), anemia (51.7%) and comorbidities (19.7%). Significant associations were found between abnormal CXR findings and BMI ($p = 0.046$), comorbidities ($p = 0.001$), daily labor occupation ($p = 0.014$), and HIV status ($p = 0.021$).

Conclusion: The prevalence of abnormal chest X-ray findings among MDR-TB patients is high and related to poor nutritional status, anemia, comorbid conditions and immunosuppression. The chest X-ray is useful and cost effective for use to determine disease severity in a resource-limited community context.

Keywords: *Anemia; Chest X-ray; Comorbidity; Multidrug-resistant tuberculosis*

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INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is tuberculosis (TB) that is resistant to isoniazid and rifampicin, and is one of the greatest public health threats in the world[1]. Although there has been great progress in the development of diagnostic and therapeutic approaches, MDR-TB still remains a major cause of morbidity, mortality and healthcare burden, especially in low- and middle-income countries[2]. The World Health Organization (WHO) Global Tuberculosis Report ,2025, reports that 10.8 million people globally suffered from tuberculosis in 2024, with an estimated 410,000 cases being rifampicin-resistant or multidrug-resistant [3]. Pakistan remains one of the highest burdened countries for TB and MDR-TB, and continues to be the most affected country in South Asia [4]. Low healthcare coverage and limited resources, malnutrition, poverty, overcrowding, and lack of diagnosis are key factors that drive the increasing incidence of drug-resistant TB[5].

Radiological imaging plays a crucial role in the diagnosis,

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evaluation, and monitoring of pulmonary tuberculosis[6]. Chest X-ray (CXR) is one of the most available, affordable and commonly used imaging modalities, particularly in resource-limited areas[7]. Pulmonary tuberculosis is accompanied by various features on radiographs including cavitary lesions, infiltrates, fibrosis, nodules, pleural effusion, consolidation, bronchiectasis, and bilateral lung involvement[8]. These radiological changes are more extensive and severe in patients with MDR-TB, as a result of longer duration of illness, recurrent infections, delayed treatment start and higher bacillary load[9].Several studies have shown that extensive cavitation and bilateral pulmonary involvement are correlated with increased infectivity, delayed sputum conversion, poor treatment outcomes and increased mortality rates[10,11].

CAPSULE SUMMARY

Chest X-ray (CXR)patterns in the patients of multidrug-resistant tuberculosis (MDR-TB) were assessed, and their association with socio-demographic and clinical characteristics was determined. The prevalence of abnormal CXR findings among MDR-TB patients was high and related to poor nutritional status, anemia, comorbid conditions and immunosuppression. The CXR remains a helpful and cost-effective tool for determining illness severity in a resource-limited community context.

Chest radiography is still a significant adjunctive test for TB severity worldwide[12]. Cavitary lesions have been reported in around 40-80% of MDR-TB patients and bilateral lung involvement has been seen in almost 50-70%[13]. The fibrotic changes and large amounts of parenchymal destruction are also more common with drug-resistant TB than with drug-sensitive TB[14].

There is little local information on the association of socio-demographic and clinical features with radiological severity of MDR-TB in Pakistan, where TB is still endemic. However, most information available about these studies is limited to microbiological diagnosis and treatment outcomes and the use of chest radiographic signs as markers of disease severity and predictors of disease burden has not been well studied. Radiological patterns and their link with patients' features could help the clinician to perform early risk stratification, prognosis assessment and designing patient-specific management of MDR-TB.

Chest radiography (CXR) is a widely available, low cost, imaging modality that can offer a lot of information about the extent and severity of pulmonary involvement. There is insufficient local information about the relationship between specific radiological characteristics of MDR-TB and socio-demographic and clinical parameters of patients. These relationships can be clinically useful for identifying those at higher risk of developing a more severe clinical course, for early risk stratification, planning treatment, and allocating resources. The results of this study are likely to be useful for pulmonologists, radiologists, TB control programmes and policymakers for the comprehensive management of MDR-TB. Therefore, this study was designed to evaluate the role of radiological imaging in assessing the severity of multidrug-resistant tuberculosis by analyzing chest X-ray features and determining their association with socio-demographic and clinical variables among MDR-TB patients.

METHODOLOGY

It was a cross-sectional analytical study carried out at the Department of Pulmonology, Bacha Khan Medical College (BKMC)/Mardan Medical Complex (MMC), MTI, Mardan for a period of one year, from 1st January 2025 to 31st December 2025. The study was granted ethical approval by the Association for Community Development (ACD) Ethical Review Committee (ERC) of Khyber Pakhtunkhwa, Pakistan. The sample was calculated using OpenEpi sample size calculator version 3.01 with a prevalence of cavitary lesions on chest x-ray in MDR-TB patients of 43.24%, a 95% confidence interval and an 8% margin of error[15]. The sample size calculated was 147 participants.

The study participants were selected using a non-probability consecutive sampling technique. Patients aged 18 years and above, regardless of gender, who were diagnosed with multidrug-resistant tuberculosis (MDR-TB) using drug susceptibility testing (DST) or GeneXpert MTB/RIF assay and had chest X-ray (CXR) records at the time of their diagnosis were included in the study. Patients with complete clinical, laboratory and radiological data and informed consent were recorded. Patients who had incomplete medical records, poor quality chest radiographs, or had a previous diagnosis of alternative chronic lung disease including malignancy of the lungs, interstitial lung disease other than TB, and severe trauma to the lungs were excluded from the study. Furthermore, the critically ill patients who could not be radiologically assessed at the time of data collection and those who refused to take part were also excluded to ensure reliability and accuracy of the data collected.

The study was conducted at the Programmatic Management of Drug-Resistant TB (PMDT) center at MMC, Mardan, where all eligible patients who attended the PMDT center for diagnosis of multidrug-resistant tuberculosis (MDR-TB) were selected after obtaining approval from the institutional ethical review committee. For uniform data collection, a structured and pre-tested proforma was used. Socio-demographic data such as age, gender, residence and occupation were collected directly from patients and checked with hospital records. Clinical and behavioural information included body mass index (BMI), anemia status, HIV status, co-morbidities and first and second line anti-tuberculosis treatment history in patient's clinical records, laboratory results, and treatment registers.

Chest X-ray was retrieved from the radiology department records. All radiographs were assessed by experienced

radiologists and findings were classified as cavitation, pleural effusion, consolidation, infiltration, or normal CXR appearance. Patients who presented with more than one radiologic feature were included in each relevant category to provide full documentation of the pattern of disease severity. Quality control was used during the data collection process to ensure that the data is accurate and complete. The records were inconsistently completed with reference to hospital information systems and ambiguous records were confirmed with reference to attending clinicians.

Drug-resistant tuberculosis (DR-TB) was defined as tuberculosis (TB) caused by Mycobacterium tuberculosis (MTB) that is resistant to at least one first-line or second-line anti-TB drug confirmed by drug susceptibility testing (DST). Multidrug-resistant tuberculosis was specifically defined as tuberculosis that is resistant to at least isoniazid and rifampicin, and may be resistant to other first or second line anti-TB drugs. Hemoglobin less than 12 g/dl was used to define the diagnosis of anemia in females and less than 13 g/dl in males. Chest X-ray abnormalities were classified as either cavitation, consolidation, pleural effusion or infiltration, and a normal CXR was defined as no radiological abnormality that suggested pulmonary disease. Comorbidities were defined as the presence of any other chronic medical condition in the patient, including, but not limited to, diabetes mellitus, hypertension, asthma, cardiovascular disease, or other systemic diseases which may affect the severity of the disease or clinical outcome.

Data collected were entered and analyzed within SPSS version 26.0. All variables were summarized, using descriptive statistics and categorical data were presented in the form of frequencies and percentages. The normality of continuous data was tested with the Shapiro-Wilk test. The Chi-square test was used to test the association of socio-demographic variables with CXR findings. The Fisher exact test was used where any expected cell count was less than 5. Likewise, clinical/behavioral variables were correlated with radiological pattern by means of Chi-square analysis. A binary logistic regression analysis was used to determine independent predictors of abnormal CXR results. The variables that had p-value ≤ 0.25 in univariate analysis were entered into the multivariable regression model. Crude odds ratios (COR) as well as the adjusted odds ratios (AOR) with 95% confidence interval (CI) were determined. A p value of ≤0.05 was deemed statistically significant.

RESULTS

There was a slight preponderance of the female population and majority of the patients were in younger age group of less than 40 years. The majority of patients lived in urban settings and the distribution of employment was found to be skewed with higher proportion of patients doing informal and low income activities. Overall, the demographic profile can be described as a largely young, urbanized, and occupationally diverse population living with MDR-TB, potentially impacting disease transmission and access to care. (Table 1)

The clinical picture revealed that almost half of the patients had low BMI and a considerable number of the patients had anemia, thus a generally poor nutritional and hematological status. Most patients had abnormal CXR imaging and HIV co-infection was uncommon in this group. A large number had a previous history of first line treatment for TB, indicating previous exposure and potential treatment failure as a cause of drug resistance. In a significant sub-population of patients, there were comorbid conditions which added to the clinical complexity. (Table 2)

The radiological assessment of all socio-demographic groups showed that abnormal CXR patterns were more common in all the groups, infiltrative changes being most common in the overall assessment. Cavitary and pleural effusion patterns were relatively more common among the rural people and those with physically demanding jobs, indicating possible links with delayed diagnosis and disease progression. There was greater disease infiltration in younger age groups and relatively higher number of patients with pleural and fibrotic changes, suggesting chronicity and progression of pulmonary disease. (Table 3)

Similarly, clinical and behavioral factors showed that abnormal radiographic findings were consistently observed across all BMI, anemia, and comorbidity categories. More severe radiological abnormalities were noted in underweight patients and patients with comorbid disease, especially cavitation and infiltrative disease. There was more extensive radiological involvement in HIV infected patients, albeit there were fewer of these. Overall, the results indicate that nutritional deficiency, systemic disease

Table 1: Distribution of Socio-Demographic Characteristics among Study Participants (n = 147)

Variable	Category	Frequency	Percentage (%)
Gender	Male	71	48.3
	Female	76	51.7
Age group (years)	18–28	58	39.5
	29–38	43	29.3
	39–48	27	18.4
	≥49	19	12.9
Residence	Urban	102	69.4
	Rural	45	30.6
Employment status	Government employee	13	8.8
	Private sector worker	19	12.9
	Farmer	7	4.8
	Student	12	8.2
	Daily wage laborer	10	6.8
	Homemaker	3	2.0
	Unemployed	18	12.2

Table 2: Clinical and Behavioral Profile of MDR-TB Patients (n = 147)

Variable	Category	Frequency	Percentage (%)
Body Mass Index (BMI)	<18.5 kg/m²	70	47.6
	≥18.5 kg/m²	77	52.4
Anemia status	Present	76	51.7
	Absent	71	48.3
CXR findings	Abnormal	110	74.8
	Normal	37	25.2
HIV status	Positive	2	1.4
	Negative	145	98.6
Presence of comorbidities	Yes	29	19.7
	No	118	80.3
History of first-line anti-TB treatment	Yes	94	64.0
	No	53	36.0
History of second-line anti-TB treatment	Yes	21	14.3
	No	126	85.7

Table 3: Chest X-ray Patterns According to Socio-Demographic Characteristics (n = 147)

Variable	Abnormal Chest X-ray				Normal Chest X-ray
	Cavitation n(%)	Pleural Effusion n(%)	Consolidation n(%)	Infiltration n(%)	n(%)
Sex					
Male	17 (23.9)	12 (16.9)	12 (16.9)	16 (22.5)	14 (19.8)
Female	19 (25.0)	11 (14.5)	13 (17.1)	19 (25.0)	14 (18.4)
Age (years)					
18–28	13 (22.4)	6 (10.3)	9 (15.5)	20 (34.5)	10 (17.3)
29–38	14 (32.6)	7 (16.3)	8 (18.6)	7 (16.3)	7 (16.3)
39–48	7 (25.9)	8 (29.6)	6 (22.2)	3 (11.1)	3 (11.1)
≥49	2 (10.5)	5 (26.3)	4 (21.1)	4 (21.1)	4 (21.1)
Residence					
Urban	20 (19.6)	13 (12.7)	18 (17.6)	36 (35.3)	15 (14.7)
Rural	16 (35.6)	10 (22.2)	7 (15.6)	12 (26.7)	7 (15.6)
Occupational status					
Government employee	4 (30.8)	3 (23.1)	3 (23.1)	3 (23.1)	0 (0.0)
Private job	4 (21.1)	3 (15.8)	4 (21.1)	5 (26.3)	3 (15.8)
Farmer	3 (42.9)	2 (28.6)	1 (14.3)	1 (14.3)	0 (0.0)
Student	3 (25.0)	1 (8.3)	2 (16.7)	4 (33.3)	2 (16.7)
Daily laborer	5 (50.0)	2 (20.0)	2 (20.0)	1 (10.0)	0 (0.0)
Homemaker	1 (33.3)	1 (33.3)	1 (33.3)	0 (0.0)	0 (0.0)
Unemployed	4 (22.2)	4 (22.2)	3 (16.7)	3 (16.7)	4 (22.2)

Table 4: CXR Findings According to Clinical and Behavioral Variables (n = 147)

Variable	Abnormal Chest X-ray				Normal Chest X-ray
	Cavitation n(%)	Pleural Effusion n(%)	Consolidation n(%)	Infiltration n(%)	n(%)
BMI					
<18.5 kg/m²	14 (20.0)	12 (17.1)	13 (18.6)	19 (27.1)	12 (17.1)
≥18.5 kg/m²	22 (28.6)	10 (13.0)	14 (18.2)	19 (24.7)	12 (15.6)
Anemia status					
Yes	18 (23.7)	15 (19.7)	11 (14.5)	19 (25.0)	13 (17.1)
No	18 (25.4)	9 (12.7)	16 (22.5)	19 (26.8)	12 (16.9)
HIV status					
Positive	0 (0.0)	1 (50.0)	0 (0.0)	1 (50.0)	0 (0.0)
Negative	36 (24.8)	23 (15.9)	27 (18.6)	37 (25.5)	22 (15.2)
Comorbidities					
Yes	8 (27.6)	7 (24.1)	6 (20.7)	8 (27.6)	0 (0.0)
No	28 (23.7)	17 (14.4)	21 (17.8)	30 (25.4)	22 (18.6)

Table 5: Multivariable Logistic Regression Analysis of Factors Associated with Abnormal CXR Findings

Variable	Chest X-ray		COR (95% CI)	AOR (95% CI)	P-value
	Abnormal n (%)	Normal n (%)			
Age 18–28	40 (69.0)	18 (31.0)	1.52 (0.68–3.41)	1.10 (0.40–3.02)	0.85
Age 29–38	33 (76.7)	10 (23.3)	1.05 (0.44–2.51)	0.88 (0.30–2.47)	0.81
Age 39–48	21 (77.8)	6 (22.2)	0.96 (0.38–2.47)	1.02 (0.34–3.10)	0.74
Urban residence	76 (74.5)	26 (25.5)	1.38 (0.79–2.42)	1.20 (0.61–2.34)	0.59
Daily laborer	9 (90.0)	1 (10.0)	0.11 (0.01–0.78)	0.12 (0.01–0.60)	0.014
BMI <18.5 kg/m²	51 (72.9)	19 (27.1)	1.18 (0.70–1.95)	1.76 (1.01–3.05)	0.046
HIV positive	1 (50.0)	1 (50.0)	2.10 (1.01–4.25)	0.42 (0.21–0.88)	0.021
Comorbidity present	25 (86.2)	4 (13.8)	0.35 (0.18–0.69)	0.31 (0.14–0.66)	0.001

and immunocompromised conditions may play a role in the more advanced pulmonary radiological features of MDR-TB. (Table 4)

Several factors were important in determining the presence of abnormal CXR findings in a multivariable procedure. Low BMI, HIV positivity, and presence of comorbidities were found to be significant predictor of abnormal CXR pattern, while occupation as a daily labourer was significantly associated with radiological severity. After adjustment, age and place of residence were not statistically significant. These results suggest that clinical and nutritional parameters are more influential than only demographic parameters in the prediction of radiological severity of MDR-TB. (Table 5)

DISCUSSION

The current study aimed to investigate the value of CXR finding in determining the radiological severity of MDR-TB and their correlation with social and demographic and clinical parameters. The results showed that the radiological patterns were abnormal in large proportions, including most cases of cavitation and infiltrative changes, and that there were significant relationships with important clinical and demographic factors. The study revealed that the male gender had a higher proportion of abnormal CXR findings, similar to previous studies showing that males are more likely to be affected by severe pulmonary TB as a result of higher exposure to environmental risk factors and delay in seeking healthcare. Ahmad et al. 2022 reported the same trend in Pakistan where male patients had significantly more cavitary lesions on CXR among MDR-TB patients[16]. Similarly, a large scale screening study by Zaidi et al. in Pakistan also showed that the younger and economically active populations were more likely to be diagnosed with more advanced forms of TBs, in line with the demographic pattern in the present study[17].

In the present study, abnormal chest radiographic findings were significantly higher in underweight individuals (BMI <18.5 kg/m^2). This is in accordance with that of Saqib et al. who found malnutrition to be a strong predictor of atypical and extensive radiological features of TB such as bilateral consolidation and cavitation[18]. Likewise, Khattak et al. noted that poor nutritional status was significantly associated with more bacillary load and greater disease extent in multi-drug resistant TB (MDR-TB) patients[19].

Abnormal CXR pattern was also significantly associated in the current study. This is consistent with other studies showing anemia as a marker of chronic disease burden and immunological suppression in TB patients. In TB patients, Dholakia et al. found that the haematological abnormalities, such as anaemia, were significantly associated with greater pulmonary involvement on X-rays, especially in patients with longer disease duration[20].

In our study, significant comorbidities were diabetes, COPD and cardiovascular disease, all of which showed significant associations with abnormal radiological findings. This was corroborated by previous study by Saqib et al. which reported high risk of development of cavitary lesions and multilobar involvement in TB patients with comorbid conditions[18]. These conditions have been reported to have a negative effect on immune response and are known to exacerbate the effects of disease.

The prevalence of HIV positivity was very low in our study population, but a higher proportion of HIV-positive patients had abnormal CXR findings. The same trend was noted in a study from Pakistan where the presence of HIV was associated with more diffuse and atypical radiological features, with a lack of classic cavitation in MDR-TB patients. However, because of the very few number of HIV positive cases in our study, meaningful statistical inference is limited.

Interestingly, the history of previous first-line and second-line treatment with anti-TB drugs was not strongly associated with the presence of abnormal CXR findings. This result is opposite to Khattak et al. (2022) who found that there was more extensive destruction of the radiograph and that cavitation was more frequent in the treatment failure cases[19.] This difference may be attributed to the variability in treatment adherence and early detection among our study subjects.

Overall, cavitation and infiltration were the predominant radiological characteristics of MDR-TB in this study, consistent with global studies which highlight these as markers of advanced pulmonary destruction. The prevalence of cavitation has also been reported to be widely ranging from 8% to more than 80% in TB patients in general, depending on disease stage and population characteristics[21].

Importantly, contemporary imaging studies have again demonstrated the importance of using CXR as an initial and cost-effective screening test in TB endemic areas, especially for identifying abnormal lung patterns in resource-limited locations[22]. Recently, there have also been advances that make it possible to use radiological pattern recognition as a surrogate marker for disease severity, particularly in areas where advanced imaging such as CT is not readily available.

The study hypothesis was that there is a significant association between socio-demographic and clinical factors and radiological severity of MDR-TB on chest X-ray. This hypothesis is partially supported since the BMI, anemia, sex, age and comorbidities were associated. However, not all clinical variables appeared to have uniform statistical significance, with HIV status and previous history of anti-TB treatment not being significant. The results indicate that nutritional status, systemic comorbidities and demographic factors play a major role in the severity of the disease on chest radiography, which is consistent with the hypothesis that the radiological appearance of the disease is greatly determined by host factors.

Limitations: As a single center cross-sectional study, the relationship between socio-demographic and clinical

parameters and the radiological severity of MDR-TB could not be determined. This may have contributed to the fact that subtle or early changes in the lungs were not detected, which could have been better characterized using advanced imaging techniques like CT scan. Further, the size of the subgroups, especially the HIV-positive group, was relatively small which limited more powerful statistical comparisons. Self-reported clinical and treatment history may also be subject to recall bias, with an attempt to confirm information using medical records.

Recommendations: Future studies to further assess the causal association between risk factors and radiological progression of MDR-TB are suggested, which should be done in a multicenter longitudinal study with more number of participants. Advanced imaging techniques like high-resolution computed tomography could help give a more detailed picture of the severity of the disease and structural lung damage, in addition to chest X-ray. Routine screening of high-risk groups, including those with undernutrition and patients with comorbidities, could help to detect severe radiological patterns earlier. In addition, use of radiologic scoring systems for clinical practice is recommended to enhance the standardization of MDR-TB severity and treatment response. Using validated TB radiology scoring systems like, the Timika score or other standardised TB radiographic severity scores, would further improve objectivity and reproducibility.

CONCLUSION

Abnormal CXR findings are common among MDR-TB patients, and that low BMI, anemia and presence of comorbidities are significantly associated with abnormal CXR findings. Radiological features like cavitation and infiltration are still significant indicators of the severity of the disease. These results validate the utility of CXR as a useful and cost-effective tool for determining the severity of MDR-TB when using it in areas with limited resources and underscore the need to identify high-risk groups early to optimize clinical outcomes.

ETHICAL APPROVAL: *Ref No. 102/ERC/ACD dated 03/01/2022.*

CONSENT FOR PUBLICATION: *Written, informed consent was obtained from the study participants.*

AVAILABILITY OF DATA: *Data is available from the corresponding author on a justified request.*

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AUTHORS' CONTRIBUTION

- ***Sajjad Ali:*** *Conceptualization of study, supervision of research work, and final approval of manuscript.*
- ***Laila Khan:*** *Study design, radiological interpretation, and critical revision of the manuscript.*
- ***Aleina Ali Shah:*** *Data collection, literature review, and manuscript drafting.*
- ***Rumman:*** *Statistical analysis, interpretation of results, and preparation of tables.*
- ***Akmal Naveed:*** *Data acquisition, clinical evaluation of patients, and proofreading of the manuscript.*
- ***Umair Zaman:*** *Manuscript editing, review of references, and coordination of final submission.*

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ORIGINAL ARTICLE

RADIOLOGICAL AND PHARMACOVIGILANCE COMPARISONS BETWEEN DRUG-RESISTANT TUBERCULOSIS AND DRUG SENSITIVE TUBERCULOSIS PATIENTS AT MARDAN MEDICAL COMPLEX

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ABSTRACT

Objective: To compare the radiological features and pharmacovigilance profile between drug-resistant TB (DR-TB) and drug-sensitive TB (DS-TB) patients.

Study Design: Retrospective, comparative cross-sectional study.

Place and duration of Study: Programmatic Management of Drug-Resistant Tuberculosis (PMDT) Center, Mardan Medical College, Mardan , 03 years(February 2022 to February 2025).

Methodology: Medical records of 200 tuberculosis patients (100 DR-TB and 100 DS-TB) were reviewed, using structured a proforma. Collected data consisted of demographic information, radiological features (extent of disease, infiltrates, consolidation, cavitary lesions, bronchiectasis, fibrosis, and non-parenchymal changes), and pharmacovigilance details like type, frequency, severity, causality, and outcomes of the adverse drug reactions (ADR). SPSS version 26 was used for data analysis. Chi-square and Fisher's exact tests were applied to assess significance, keeping a $p \leq 0.05$, significant.

Results: DR-TB patients were found to have a significantly greater extent of pulmonary involvement, more cavitary lesions, consolidation, bronchiectasis, and destructive pulmonary changes than DS-TB patients ($p<0.05$). The proportion of DR-TB patients with ADRs was much higher when compared with DS-TB patients ($p<0.001$).

Conclusions: DR-TB patients have more a severe radiological disease and have a higher burden of adverse drug reactions, when compared to DS-TB patients. It is important that radiology is recognized early and pharmacovigilance is reinforced to achieve better treatment results.

Keywords: *Antitubercular agents; Drug resistance; Tuberculosis; Radiography; Pharmacovigilance*

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INTRODUCTION

One of the most serious infectious illnesses in the world, tuberculosis (TB), is a public health concern, especially in low- and middle-income nations[1]. Mycobacterium tuberculosis is the cause, and although it can happen in extrapulmonary locations, it is typically linked to pulmonary illness [2]. Although the treatment is effective, TB is still a major cause of morbidity and mortality because of late diagnosis, non-adherence to treatment, socioeconomic inequities, and emergence of drug-resistant strains[3]. Year 2023 witnessed approximately 10.8 million individuals contracting TB globally, and around 1.25 million, dying of it. Globally ,TB is among the top 10 causes of death by an infectious disease [4].

Drug-resistant tuberculosis (DR-TB) and an even more problematic form, multidrug-resistant tuberculosis (MDR-TB), are becoming a serious problem for TB control programs worldwide[5]. MDR-TB is a type of tuberculosis that is resistant

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to isoniazid and rifampicin, the two most potent medications used in first-line anti-tuberculous therapy[6]. According to WHO, around 390,000 to 400,000 new cases of multidrug-resistant or rifampicin-resistant TB are reported annually across the globe [7]. Unfortunately, only a small number of these patients are diagnosed and treated on time, leading to continued transmission and sub-optimal treatment outcomes. DR-TB is especially prevalent in South Asian countries. Pakistan is one of the countries with highest TB burden in the world[8]. Drug resistance has become more common and has made disease management more difficult since patients with such resistance must be treated for longer periods with second-line drugs that are frequently accompanied by severe adverse drug reactions, higher healthcare costs, and reduced treatment success rates[9].

CAPSULE SUMMARY

The radiological features and pharmacovigilance profile between drug-resistant TB (DR-TB) and drug-sensitive TB (DS-TB) patients was compared. DR-TB patients had more a severe radiological disease and a higher burden of adverse drug reactions(ADRs).Radiological features should be recognized early, and pharmacovigilance reinforced, to achieve better treatment results.

Radiological imaging is important in the diagnosis, assessment, and monitoring of TB[10]. The chest radiograph and computed tomography (CT) scan are useful in determining the severity and extent of pulmonary disease[11]. Patients with drug-sensitive tuberculosis (DS-TB) are more likely to have infiltrates, cavitary lesions, nodules, fibrosis, and pleural effusions in the upper lobes, whereas patients with DR-TB typically have more extensive lung disease with multiple thick-walled cavities, bronchiectasis, fibrosis, and destructive lung changes[12]. These differences in the radiology may be due to chronicity of the disease, delayed diagnosis, and inadequate response to therapy in resistant cases. A comparative evaluation of the radiological manifestations of DS-TB patients with DR-TB patients, therefore, can help the clinician in early detection of resistance patterns and prompt intervention[13].

Pharmacovigilance has also become an integral part of TB management as well as the radiological assessment[14]. Tuberculous drugs, particularly second-line drugs for DR-TB, have a broad range of adverse drug reactions that may involve hepatotoxicity, nephrotoxicity, ototoxicity, peripheral neuropathy, gastrointestinal disturbances, psychiatric manifestations, and dermatological complications[15]. These adverse events must be monitored, as they have a tremendous impact on adherence, patient quality of life, and therapeutic outcomes. The pharmacovigilance systems are designed to identify, document, and manage TB-related complications, thereby enhancing the safety and effectiveness of TB treatment programs[16]. However, there is limited data on comparing the pharmacovigilance profile of DR-TB patients with that of DS-TB patients in the local Pakistani healthcare facilities.

There is limited local data available, which compares the radiological manifestations and pharmacovigilance profile of DR-TB and DS-TB patients in Pakistan, particularly in Khyber Pakhtunkhwa. The burden of disease, access to health care, treatment adherence, and socioeconomic status may all play large roles in both imaging results and adverse drug reactions(ADRs) to treatment in the local population. Comparative comparison of these parameters may be helpful to recognize resistant cases early, to assess the severity of the disease, and to manage the disease on time, without complications due to the use of drugs. This study will contribute to the understanding of the situation and help clinicians, radiologists, pulmonologists, and public health officials in making better diagnoses, enhancing pharmacovigilance practices, optimizing patient management strategies, and ultimately improving the treatment outcomes of TB patients. The present study aimed to compare the radiological findings and pharmacovigilance profiles between DR-TB and DSTB.

METHODOLOGY

The study was a retrospective comparative cross-sectional study that was done at the Programmatic Management of Drug-Resistant Tuberculosis (PMDT) Center, Mardan Medical College. Medical record of patients who had been treated for TB from 1st February 2022 until 1st February 2025 were reviewed. Ethical approval was obtained from the Association for Community Development, Khyber Pakhtunkhwa.

The sample size was not determined in advance, but for comparative analysis, a total of 200 patients were involved, consisting of 100 DR-TB and 100 DS-TB, selected consecutively. All eligible cases registered and managed at the PMDT Center, Mardan Medical Complex, were reviewed, patients who had complete medical records, and fulfilled the inclusion criteria were included. The final sample size was based on the availability of complete records over the time period of the study.

Patients with pulmonary tuberculosis who attended the PMDT Center, MMC, Mardan, from 1st February 2022 to 1st February 2025 were included, regardless of gender. This included both DR-TB and DS-TB cases, diagnosed using GeneXpert, culture, drug susceptibility testing, and/or medical records with radiological and clinical evaluation. All patients with complete clinical, radiological, and pharmacovigilance data available in their files were included in the final analysis. The cases were retrieved from hospital record archives for all eligible cases. Those who had incomplete or missing medical or ADR recording/reporting were excluded. Patients who were lost to follow-up before the baseline assessment and patients with co-existing major chronic diseases, including advanced malignancy or severe immunosuppressive conditions other than those related to TB, that could affect radiological and pharmacovigilance outcomes were also excluded.

A structured data collection proforma was employed to gather

information, including the demographic variables (like age and gender), radiological data including extent of disease, infiltrates, consolidation, cavitary disease, bronchiectasis, fibrosis, calcification, lymph node involvement, atelectasis, bullae formation, hyper-aeration, and non-parenchymal changes, and pharmacovigilance including type, frequency, severity, causality assessment, preventability, and outcomes of ADRs. Radiological findings were documented in chest X-ray and/or CT scan reports interpreted by radiologists, and adverse drug reactions were detected and classified from patient treatment records and pharmacovigilance reporting forms.

The data were analyzed through the use of the Statistical Package for Social Sciences (SPSS) Version 26. The quantitative variables, like age, were reported in mean ± SD, and the qualitative variables, like gender, radiological findings, and adverse ADRs were reported in frequencies and percentages. Categorical variables were compared between DR-TB and DS-TB groups by either the Chi-square test or the Fisher exact test, and continuous variables were compared by the independent sample t-test. A p-value of ≤0.05 was considered significant.

RESULTS

The demographic characteristics of patients with DR-TB and DS-TB are summarized in Table 1. There were statistically significant differences in gender distribution between the two groups, but not in age distribution. Participants' mean ages were similar across both groups. There were significant differences between the two groups for lesions, infiltrative changes, consolidation, cavitary lesions, bronchiectasis, calcification pattern, selected nodular changes, and non-parenchymal abnormalities. Patients with DR-TB had more extensive pulmonary involvement, and they were more likely than DS-TB patients to have cavitary and destructive lung alterations. However, no significant differences were noted for most cases of ground glass opacity, atelectasis, bullae formation, hyper-aeration, and several nodal characteristics (Table 2).

Table 1. Demographic Characteristics of DR-TB and DS-TB Patients (n =200)

Characteristic	DR-TB (n=100)	DS-TB (n=100)	p-value
Gender			0.014
Male	52 (52.0)	69 (69.0)	
Female	48 (48.0)	31 (31.0)	
Age Group (Years)			0.063
<30	19 (19.0)	27 (27.0)	
30–39	30 (30.0)	21 (21.0)	
40–49	31 (31.0)	23 (23.0)	
50–59	16 (16.0)	16 (16.0)	
>59	4 (4.0)	13 (13.0)	
Mean Age ± SD	39.87 ± 11.59	41.03 ± 12.82	—

Table 2. Comparison of Radiological Findings between DR-TB and DS-TB Patients (n=200)

Variable	DR-TB (n=100)	DS-TB (n=100)	p-value
Area of Lesion			<0.001
Small	0 (0.0)	30 (30.0)	
Medium	3 (3.0)	43 (43.0)	
Large	97 (97.0)	27 (27.0)	
Infiltrates			
Lung Region			
Upper right lung	37 (37.0)	67 (67.0)	<0.001
Upper left lung	23 (23.0)	55 (55.0)	<0.001
Middle right lung	27 (27.0)	42 (42.0)	0.026
Middle left lung	25 (25.0)	38 (38.0)	0.048
Lower right lung	12 (12.0)	27 (27.0)	0.007
Lower left lung	9 (9.0)	28 (28.0)	<0.001
Consolidation			
Lung Region			
Upper right lung	57 (57.0)	21 (21.0)	<0.001
Upper left lung	53 (53.0)	17 (17.0)	<0.001
Middle right lung	48 (48.0)	15 (15.0)	<0.001
Middle left lung	56 (56.0)	15 (15.0)	<0.001
Lower right lung	21 (21.0)	10 (10.0)	0.032
Lower left lung	25 (25.0)	7 (7.0)	<0.001
Cavitary Lesions			
Location of Cavities			
Upper right lung	58 (58.0)	6 (6.0)	<0.001
Upper left lung	49 (49.0)	7 (7.0)	<0.001
Middle right lung	39 (39.0)	7 (7.0)	<0.001
Middle left lung	52 (52.0)	5 (5.0)	<0.001
Lower right lung	7 (7.0)	3 (3.0)	0.194
Lower left lung	9 (9.0)	3 (3.0)	0.074
Cavity Characteristics			
Cavity less than or equal to 4 cm	66 (66.0)	14 (14.0)	<0.001
Cavity more than 4 cm	14 (14.0)	2 (2.0)	0.002
Solitary cavity	5 (5.0)	2 (2.0)	0.248
Multiple cavities	68 (68.0)	14 (14.0)	<0.001
Ground Glass Opacity			
Lung Region			
‘Upper right lung	1 (1.0)	3 (3.0)	0.312
‘Upper left lung’	1 (1.0)	1 (1.0)	1.000

'Middle right lung'	1 (1.0)	2 (2.0)	0.561
'Middle left lung'	1 (1.0)	1 (1.0)	1.000
'Lower right lung'	1 (1.0)	1 (1.0)	1.000
'Lower left lung'	0 (0.0)	1 (1.0)	0.316
Fibrosis			
Lung Region			
Upper right lung	23 (23.0)	15 (15.0)	0.149
Upper left lung	11 (11.0)	13 (13.0)	0.663
Middle right lung	8 (8.0)	7 (7.0)	0.788
'Middle left lung'	7 (7.0)	8 (8.0)	0.788
'Lower right lung'	0 (0.0)	4 (4.0)	0.043
Lower left lung	1 (1.0)	7 (7.0)	0.030
Bronchiectasis			
Lung Region			
Upper right lung	4 (4.0)	5 (5.0)	0.733
'Upper left lung'	3 (3.0)	2 (2.0)	0.651
'Middle right lung'	14 (14.0)	3 (3.0)	0.005
'Middle left lung'	9 (9.0)	4 (4.0)	0.152
'Lower right lung'	9 (9.0)	5 (5.0)	0.268
Lower left lung	5 (5.0)	2 (2.0)	0.248
Calcification			
Lung Region			
Upper right lung	6 (6.0)	3 (3.0)	0.306
'Upper left lung'	8 (8.0)	0 (0.0)	0.004
'Middle right lung'	4 (4.0)	1 (1.0)	0.174
'Middle left lung'	6 (6.0)	0 (0.0)	0.013
'Lower right lung'	2 (2.0)	0 (0.0)	0.155
'Lower left lung'	2 (2.0)	0 (0.0)	0.155
Location of Nodes			
'Upper right lung'	5 (5.0)	6 (6.0)	0.756
'Upper left lung'	4 (4.0)	2 (2.0)	0.407
'Middle right lung'	5 (5.0)	2 (2.0)	0.248
'Middle left lung'	6 (6.0)	2 (2.0)	0.149
'Lower right lung'	2 (2.0)	1 (1.0)	0.561
'Lower left lung'	4 (4.0)	0 (0.0)	0.043
Lymph Nodes			
Node Characteristics			
'1–2 cm nodes'	10 (10.0)	7 (7.0)	0.447
'2–3 cm nodes'	0 (0.0)	0 (0.0)	—
'Solitary node'	5 (5.0)	2 (2.0)	0.248
Multiple nodes	5 (5.0)	5 (5.0)	1.000
Atelectasis			
Lung Region			
Upper right lung	2 (2.0)	4 (4.0)	0.407
Upper left lung	2 (2.0)	0 (0.0)	0.155
'Middle right lung'	1 (1.0)	1 (1.0)	1.000
'Middle left lung'	1 (1.0)	3 (3.0)	0.312
'Lower right lung'	1 (1.0)	0 (0.0)	0.316
'Lower left lung'	1 (1.0)	0 (0.0)	0.316
Bullae and Hyper-aeration			
Bullae			
'Upper right lung'	2 (2.0)	1 (1.0)	0.561
'Upper left lung'	3 (3.0)	0 (0.0)	0.081
'Middle right lung'	2 (2.0)	1 (1.0)	0.561
'Middle left lung'	1 (1.0)	0 (0.0)	0.316
'Lower right lung'	1 (1.0)	1 (1.0)	1.000
'Lower left lung'	1 (1.0)	0 (0.0)	0.316
Hyper-aeration			
'Upper right lung'	0 (0.0)	0 (0.0)	—
'Upper left lung'	1 (1.0)	0 (0.0)	0.316
'Middle right lung'	0 (0.0)	0 (0.0)	—
'Middle left lung'	1 (1.0)	0 (0.0)	0.316
'Lower right lung'	1 (1.0)	0 (0.0)	0.316
'Lower left lung'	1 (1.0)	0 (0.0)	0.316
Non-Parenchymal Findings			
Right tracheal deviation	13 (13.0)	3 (3.0)	0.009
Left tracheal deviation	17 (17.0)	3 (3.0)	<0.001
'Right hilar elevation'	19 (19.0)	2 (2.0)	<0.001
'Left hilar elevation'	16 (16.0)	2 (2.0)	<0.001

A higher proportion of ADRs was seen in DR-TB than DS-TB patients. There were considerable variations in causality assessment, severity of ADRs, treatment interruption because of ADRs, preventable ADRs, and formal pharmacovigilance reporting. Gastrointestinal, hepatological, neurological, psychiatric, musculoskeletal, haematological, cardiac, auditory, skin-related, and/or general systemic adverse drug reactions were reported more frequently among DR-TB patients. Some adverse reactions, such as hyperuricaemia, hypothyroidism, myalgia, thrombocytopenia, renal impairment, skin hyperpigmentation, hair-related complaints, and drug fever, however, did not show statistically significant differences between the two groups (Table 3).

ADR reporting, causality assessment, severity of reaction, and pharmacovigilance-related outcomes were more prominent among DR-TB patients. The DR-TB group experienced greater gastrointestinal, hepatic, neurological, psychological, musculoskeletal, haematological, cardiac, renal, auditory, cutaneous, and general systemic adverse medication responses than the DS-TB group. Additionally, the picture shows that several ADR-related factors differed statistically substantially between the two groups, indicating that DR-TB patients

Table 3. Comparison of Pharmacovigilance Profile and Reported ADRs Between DR-TB and DS-TB Patients (n=200)

Variable	DR-TB (n=100)	DS-TB (n=100)	p-value
Overall ADR Reporting			
At least one ADR reported	52 (52.0)	10 (10.0)	<0.001
No ADR reported	48 (48.0)	90 (90.0)	<0.001
Causality Assessment			
Possible ADR	10 (10.0)	2 (2.0)	0.040
Probable ADR	30 (30.0)	7 (7.0)	<0.001
Definite ADR	5 (5.0)	1 (1.0)	0.165
Severity of ADRs			
Mild ADR	25 (25.0)	5 (5.0)	0.003
Moderate ADR	15 (15.0)	3 (3.0)	0.004
Severe ADR	10 (10.0)	1 (1.0)	0.005
Serious ADR	7 (7.0)	1 (1.0)	0.015
Pharmacovigilance Outcomes			
ADR requiring treatment interruption	12 (12.0)	1 (1.0)	0.013
ADR requiring hospitalization	5 (5.0)	1 (1.0)	0.067
Suspected drug withdrawn/changed	3 (3.0)	1 (1.0)	0.315
Preventable ADR	20 (20.0)	3 (3.0)	<0.001
ADR was formally reported to the pharmacovigilance center	50 (50.0)	1 (1.0)	<0.001
Gastrointestinal ADRs			
Gastrointestinal disturbance	25 (25.0)	7 (7.0)	<0.001
Nausea and vomiting	20 (20.0)	5 (5.0)	<0.001
Abdominal pain and anorexia	14 (14.0)	4 (4.0)	0.014
Diarrhea	8 (8.0)	2 (2.0)	0.052
Hepatic and Metabolic ADRs			
Hepatotoxicity / raised liver enzymes/jaundice	10 (10.0)	2 (2.0)	0.022
Hyperuricaemia	5 (5.0)	1 (1.0)	0.089
Hypothyroidism	2 (2.0)	0 (0.0)	0.176
Neurological and Psychiatric ADRs			
Peripheral neuropathy	10 (10.0)	1 (1.0)	0.027
Dizziness/vertigo	5 (5.0)	1 (1.0)	0.058
Psychiatric issues	9 (9.0)	0 (0.0)	0.001
Visual disturbance / optic neuritis	4 (4.0)	0 (0.0)	0.059
Musculoskeletal ADRs			
Arthralgia	9 (9.0)	1 (1.0)	0.004
Myalgia	3 (3.0)	1 (1.0)	0.244
Haematological ADRs			
Anemia/ myelosuppression	8 (8.0)	0 (0.0)	0.003
Thrombocytopenia/ leukopenia	2 (2.0)	0 (0.0)	0.157
Cardiac ADRs			
QT interval prolongation	8 (8.0)	0 (0.0)	0.019
Palpitation / ECG abnormality other than QT prolongation	2 (2.0)	0 (0.0)	0.314
Renal and Auditory ADRs			
Renal impairment	3 (3.0)	0 (0.0)	0.085
Ototoxicity	4 (4.0)	0 (0.0)	0.028
Skin ADRs			
Rash/itching/ hypersensitivity	11 (11.0)	4 (4.0)	0.035
Skin hyperpigmentation	3 (3.0)	0 (0.0)	0.058
Hair fall / hair-related complaints	2 (2.0)	1 (1.0)	0.476
General Symptoms			
Fatigue/weakness	15 (15.0)	6 (6.0)	0.018
Drug fever	3 (3.0)	0 (0.0)	0.071

were more likely to experience treatment-related side effects (Figure 1).

DISCUSSION

In terms of radiological severity and pharmacovigilance profile, the current investigation demonstrated clinically significant differences between DR-TB and DS-TB patients. Patients with DR-TB were more likely than DS-TB cases to have pulmonary involvement, cavitary lesions, bronchiectasis, consolidation, and destructive lung alterations. They also experienced more ADRs.

The majority of the DR-TB patients in our study had large areas of lung involvement and multiple cavitary lesions, especially in the upper lung zones. This is in line with the findings of Cheng

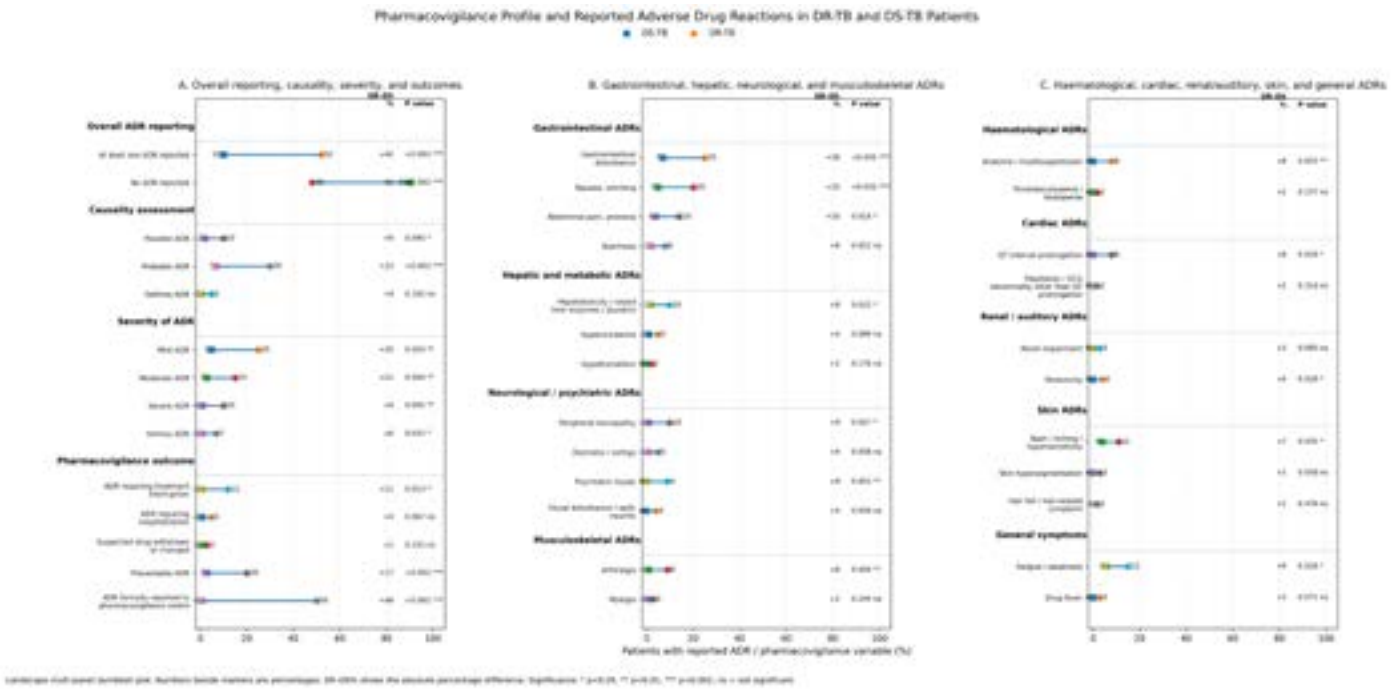

Figure 1. Comparison of ADRs between DR-TB and DS-TB patients.

et al. (2021) where DR-TB cases showed more bilateral, more extensive, and more cavitary disease patterns in their computed tomography (CT) scans, which may be attributed to delayed diagnosis and long disease course of DR-TB[17]. Similarly, comparative radiological studies from China and other high-burden countries have revealed that cavitary disease and upper lobe destruction occur much more frequently in DR-TB, as a result of higher bacillary load and treatment resistance[18].

Increased prevalence of bronchiectasis and fibrosis in DR-TB patients in our study is similar to the findings of imaging-based studies that consistently showed that drug resistance is linked with chronic structural lung damage and post-infective sequelae. The findings indicate that DR-TB is a more advanced and progressive form of pulmonary destruction than DS-TB.

Our results also showed significantly higher consolidation and infiltrative changes in DR-TB patients. The same was observed in the retrospective study in Pakistan by Atif et al. 2022, where radiological severity scores were found to be significantly higher in MDR-TB patients than in DS- TB patients, suggesting more aggressive disease behavior in the resistant strains[19]. The differences in these radiological parameters may be due to delayed diagnosis, inadequate initial treatment, and continued bacterial multiplication in the DR-TB patients.

Pharmacovigilance findings of our study showed that the burden of ADRs in DR-TB was much higher than in DS-TB, with 52% and 10% of the patients, respectively, having at least one ADR, respectively. This finding is robustly supported by Massud et al. (2022), who noted that a large proportion (over 50%) of DR-TB patients experienced multiple ADRs while receiving second-line treatment, including gastrointestinal and neurological ADRs[20]. Likewise, Khan et al. (2022) from Pakistan found that there was a strong association between second-line anti-TB drugs and frequency of adverse events necessitating clinical intervention[21].

Gastrointestinal, hepatic, neurological, psychiatric, and musculoskeletal ADRs were significantly more prevalent among DR-TB patients in our study. These results corroborate worldwide pharmacovigilance data, which have shown that linezolid, fluoroquinolones, and aminoglycosides can be associated with a broad range of toxicities, such as neuropathy, QT prolongation, and ototoxicity. A study from India, in 2024, also identified gastrointestinal and neurologic side effects as the commonest side effects among DR-TB patients, especially among those receiving the longer oral treatment regimens[22].

Moreover, treatment disruptions, preventable ADRs, and formal pharmacovigilance reporting were significantly higher in DR-TB patients. This is an indication of the complexity of DR-TB management and the need for better monitoring systems. Similar observations have been made in international pharmacovigilance databases, which show that DR-TB treatment is linked with increased treatment discontinuation and the need for well-designed supervision systems to enhance treatment adherence and safety[23]. In our study, the difference in causality and severity of DR-TB and DS-TB further corroborates the findings of earlier studies that second-line anti-TB drugs are more toxic and need to be adjusted on an individual basis and monitored closely.

Overall, the results of the present study are aligned with the

global and regional literature and confirm that DR-TB is accompanied by a significantly increased burden of radiological disease and a greater burden of complications related to pharmacovigilance as part of TB management programs.

Limitations: A retrospective study relying on medical records may not be accurate or complete, including reports on ADRs and radiologic interpretations. Second, the study was carried out in a single tertiary care PMDT centre, making it difficult to extrapolate the results to other areas or healthcare environments. Thirdly, radiological findings were not reassessed independently, which could have led to inter-observer variation in findings. Further, the study did not measure the long-term outcome of treatment, like cure rate, relapse, or mortality, which might have strengthened the clinical implications of differences between DR-TB and DS-TB patients in both radiological and pharmacovigilance parameters.

Recommendations: Routine radiological evaluation of all suspect cases of tuberculosis is suggested to facilitate early detection of drug-resistant tuberculosis, especially in cases with extensive and/or cavitary lungs. Enhancing pharmacovigilance systems, with active monitoring of ADRs in particular, for DR-TB patients on second-line anti-TB treatment is needed. Health care workers need to be trained regularly in recognizing, documenting, and reporting ADRs to enhance patient safety and adherence to treatment. Larger, multicenter prospective trials are also advised to confirm these outcomes and investigate the long-term effects of TB treatment based on the radiological severity and burden of adverse drug reactions.

CONCLUSION

Drug resistant tuberculosis that is resistant to any drug has a significantly more extensive and destructive radiological involvement of the lung tissue when compared with drug-sensitive TB. Furthermore, ADR frequency, severity, and complexity are significantly higher in DR-TB patients, leading to an increased pharmacovigilance burden in this population. DR-TB is not just a microbiological problem but a more aggressive clinical form of TB and one with increased toxicity of the treatment. To achieve the best patient care, minimize complications, and maximize therapeutic success in TB treatment, it is critical to identify resistant patterns early in the course of disease and to have strong pharmacovigilance monitoring.

ETHICAL APPROVAL: *Ref No. 103/ERC/ACD; Dated 19-01-2022.*

CONSENT FOR PUBLICATION: *Written, informed consent was obtained from the study participants.*

AVAILABILITY OF DATA: *Data is available from the corresponding author on a justified request.*

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AUTHORS' CONTRIBUTION

- ***Laila khan:*** *Conceptualization of study, supervision of research work, and final approval of manuscript.*
- ***Sajjad Ali:*** *Study design, radiological interpretation, and critical revision of the manuscript.*
- ***Rumman:*** *Data collection, literature review, and manuscript drafting.*
- ***Aleina Ali Shah:*** *Statistical analysis, interpretation of results, and preparation of tables.*
- ***Akmal Naveed:*** *Data acquisition, clinical evaluation of patients, and proofreading of the manuscript.*
- ***Nazar ul Islam:*** *Manuscript editing, review of references, and coordination of final submission.*

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ORIGINAL ARTICLE

MICROBIOLOGICAL SPECTRUM, ANTIBIOTIC RESISTANCE AND CLINICAL OUTCOMES OF PROSTHETIC JOINT INFECTIONS

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ABSTRACT

Objective: To determine the frequency of prosthetic joint infections (PJIs), causative organisms, their antimicrobial susceptibility profile, and clinical outcomes in patients who underwent joint replacement.

Study Design: Descriptive, cross-sectional study.

Place and duration of study: Sharif Medical City Hospital and Alrazi Healthcare Hospital, Lahore, 04 years (January 2021 to December 2025).

Methodology: The study was done after obtaining the ethical approval. A total of 843 patients with severe joint disease, who met the eligibility criteria for joint replacement surgery, were enrolled written, informed using a nonprobability convenience sampling technique. A written, informed consent was obtained from the participants. Patients received a single preoperative dose of second-generation cephalosporin and a post-operative broad-spectrum oral antibiotic for 1 week. Patients were followed up at 2 weeks, 6 weeks, and 3 months. For patients with PJIs, the causative organisms were isolated on culture, and their antimicrobial susceptibility was tested. Patients were treated either by using debridement, antibiotics and implant retention (DAIR) or two-staged revision. The Statistical Package for the Social Sciences version 27 was used for statistical analysis.

Results: Fifteen (1.8%) patients developed PJIs. Out of 15 infected cases, 7(46.7%) were Staphylococcus aureus, 4(26.6%) were Coagulase-negative Staphylococci(CoNS), 2(13.3%) were Streptococcus species, 1(6.7%) was Pseudomonas aeruginosa, and 1(6.7%) was E. coli. Three (42.9%) isolates of Staphylococcus aureus were methicillin-resistant Staphylococcus aureus (MRSA), while 4(57.1%) were methicillin-sensitive(MSSA). E. coli and Pseudomonas showed no resistance to imipenem, meropenem, and tazocin. Sixty and forty percent of the patients underwent DAIR and two-staged revision, respectively, and recovered completely. The incidence of PJIs was associated with advanced age and diabetes mellitus (p-value = 0.01).

Conclusion: Prosthetic joint infection occurred in 1.8% of joint replacement cases, with gram-positive cocci being the predominant pathogens. Vancomycin, linezolid, tigecycline, carbapenems, and piperacillin-tazobactam showed excellent antimicrobial efficacy. Both DAIR and two-stage revision were effective treatment strategies. Advanced age and diabetes mellitus were important risk factors for PJI.

Keywords: *Joint Prosthesis; Microbial Drug Resistance; Staphylococcus aureus.*

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INTRODUCTION

Prosthetic joint replacement is an extremely effective treatment for end-stage arthritis. It reduces pain significantly and improves functional outcomes of the joint. It is now becoming a popular regime for arthritis in low- to middle-income countries. Complications associated with arthroplasty are prosthetic joint infections (PJI), deep venous thrombosis, pulmonary embolism, prolonged hospitalization, increased healthcare costs, repeated surgical interventions, and substantial patient morbidity[1].

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The global incidence of PJI was reported to be approximately 1–2% following primary joint replacement procedures. This rate may vary depending on patient characteristics, healthcare infrastructure, and surgical practices[2]. In low & middle-income countries, including Pakistan, the increasing number of joint replacement surgeries poses additional challenges due to evolving antimicrobial resistance patterns and limited infection control resources[3]. Factors such as old age, obesity, and diabetes mellitus predispose to PJIs[2].

CAPSULE SUMMARY

The frequency of prosthetic joint infections (PJIs), causative organisms, their antimicrobial susceptibility profile, and clinical outcomes was determined in patients after joint replacement. Prosthetic joint infection(PJI) occurred in 1.8% of joint replacement cases, gram-positive cocci were the predominant pathogens. Vancomycin, linezolid, tigecycline, carbapenems, and piperacillin-tazobactam revealed excellent antimicrobial efficacy. Both DAIR and two-stage revision were effective treatment strategies. Advanced age and diabetes mellitus were important risk factors for PJI.

Prosthetic joint infection is predominantly caused by gram-positive organisms, particularly Staphylococcus aureus and coagulase-negative staphylococci (CoNS). These organisms have the ability to adhere to prosthetic surfaces and form biofilms[3]. This not only protects them from host immune responses but also reduces the efficacy of antimicrobials. Methicillin-resistant Staphylococcus aureus (MRSA) is linked to worse clinical outcomes and their treatment more difficult[4]. Recent literature highlighted that in PJIs, the involvement of gram-negative bacteria like, Escherichia coli and Pseudomonas aeruginosa, is increasing. These organisms are often associated with multidrug resistance, which makes their management more complicated[5]. As antimicrobial resistance patterns vary across different areas, local epidemiological data is essential for empirical antibiotic therapy and better treatment[6]. Inappropriate and excessive use of antibiotics, further increases the global burden of antimicrobial resistance[7]. The management of PJI requires early diagnosis, targeted antimicrobial therapy and appropriate surgical intervention. Treatment strategies such as debridement, antibiotics, and implant retention (DAIR), as well as revision surgeries depend on severity and chronicity of infection[8].

The data on PJIs, their causative organisms, and clinical outcomes is limited in Pakistan. This study was designed to determine the frequency of PJIs, causative organisms, their antimicrobial susceptibility profile, and clinical outcomes in patients who underwent joint replacement. This will help us in selecting appropriate empirical antibiotic therapy, developing local antimicrobial stewardship strategies, improving infection prevention protocols, enhancing patient outcomes, and reducing morbidity and healthcare costs associated with PJIs.

METHODOLOGY

This descriptive cross-sectional study was done at Sharif Medical City Hospital and Alrazi Healthcare Hospital, Lahore from January 2021 to December 2025, after ethical approval. The sample size of 753 was calculated, using 2% prevalence of PJIs, 1% margin of error and 95% confidence interval[9]. After obtaining informed, written consent, 843 patients who underwent knee and hip joint replacements were included using a nonprobability convenience sampling. All the patients who presented in the outpatient department (OPD) with severe joint disease, and fulfilled the criteria for joint replacement, according to clinical and radiological findings, were enrolled. The demographic profile and comorbidities of the patients were noted on a proforma. The exclusion criteria were patients who did not give consent, had evidence of acute infection or were unfit for anesthesia.

All surgeries were performed by the same Orthopedic surgeon with expertise in joint replacement in the modular operation theater, with laminar air flow and high-efficiency particulate filters. All the patients received a prophylactic single intravenous (IV) dose of 1.5g of Zinacef (Cefuroxime; second-generation cephalosporin) preoperatively, 30 minutes before the incision. To reduce the possibility of infection, stringent measures were implemented. Wound closure in all the patients was performed using a stapling device. Zinacef (Cefuroxime) was given in all the patients post-operatively. Initially 1.5g intravenous stat dose was given, followed by 750mg IV BD for 2 days. After discharge, 250mg was given per oral BD for 5 days to 1 week. The post-operative dressings were changed only if wet or soaked. Staple pins were removed after 2 weeks in the hospital setup. Follow-up of the patients was done at 2 weeks, 6 weeks, and 3 months. Prosthetic joint infection was diagnosed by suggestive clinical manifestations, X-rays and synovial fluid analysis & culture. The synovial fluid was sent to the laboratory for analysis and culture. The fluid was inoculated on blood, chocolate and macConkey agar, and incubated at 35-37°C for 24-48 hours. For positive cultures, antibiotic sensitivity testing was done, by the Kirby-Bauer method, using the recommended antibiotics, and was interpreted according to the Clinical and Laboratory Standards Institute (CLSI) guidelines 2026[10]. Prosthetic joint infection was diagnosed based on the Musculoskeletal Infection Society (MSIS) criteria. The patients were diagnosed as having PJI if 1 major criterion is positive or the score of minor criteria is ≥ 6. The score of 2-5 shows possible infection, for which intraoperative criteria could be evaluated[11] (Table 1).

Patients with PJIs were treated either by using DAIR or two-staged revision. In DAIR, patients underwent debridement along with antibiotic therapy and implant retention. In two-staged revision, the infected implant was removed, antibiotics were administered, using an antibiotic spacer, and a new prosthetic joint was implanted.

The Statistical Package for the Social Sciences version 27 was used for statistical analysis. Qualitative variables such as gender,

Table 1: The Musculoskeletal Infection Society (MSIS) Criteria for Prosthetic Joint Infections[11]

	Score	Decision
Major criteria (at least one of the following)		
Two positive cultures of the same organism		
Sinus tract with evidence of communication to the joint or visualization of the prosthesis		Infected
Minor criteria (preoperative)		
Elevated CRP or D-dimer (serum)	2	≥6: Infected
Elevated ESR (serum)	1	
Elevated synovial WBC count or LE (synovial)	3	2–5: Possibly infected
Positive alpha-defensin (synovial)	3	
Elevated synovial PMN (%) (synovial)	2	0–1: Not infected
Elevated synovial CRP (synovial)	1	
Intraoperative diagnosis		
Preoperative score	–	≥6: Infected
Positive histology	3	
Positive purulence	3	4–5: Inconclusive
Single positive culture	2	≤3: Not infected

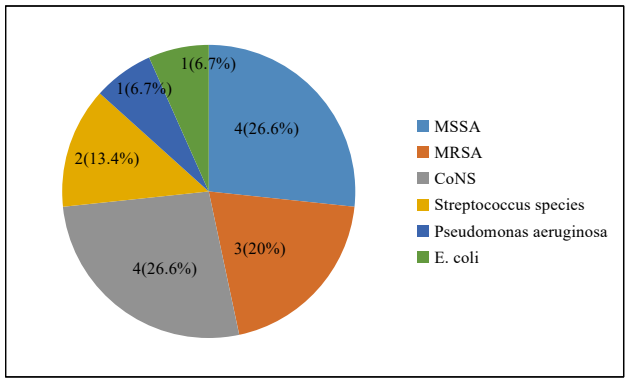

Figure 1: Organisms Isolated from Patients with PJIs

(MSSA: Methicillin-sensitive Staphylococcus aureus, MRSA: Methicillin-resistant Staphylococcus aureus, CoNS: Coagulase-negative Staphylococcus species)

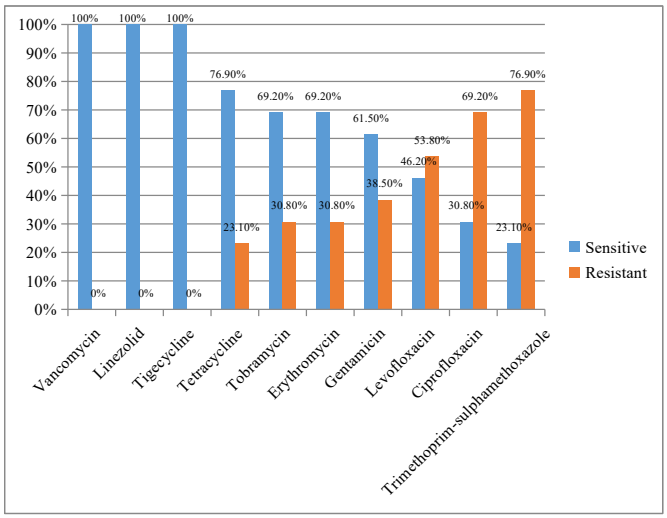

Figure 2: Antibiotic Sensitivity Pattern of Gram Positive Cocci

incidence of prosthetic joint infections, causative organisms, antibiotic sensitivity, and clinical outcomes were presented as frequencies and percentages, whereas quantitative variables such as age and body mass index (BMI) were reported as mean/standard deviation. The association of demographic variables and comorbidities with PJIs was evaluated by the Pearson Chi-square test, considering p-value <0.05 as significant.

RESULTS

The mean age of the patients was 65.3±5.73 years. Out of total 843 patients 72.4% were females, and 27.6% were males. Mean BMI of the patients was 33.9±4.25 kg/m2. Most of the patients were obese (65%), followed by overweight (24.9%) and normal weight (10.1%). Around 356(42.2%) of the patients were diabetic, 200(23.7%) were hypertensive and 90(10.7%) were smokers.

The 843 joint replacements consisted of 387(45.9%) knee and 456(54.1%) hip replacements. Out of these, 15(1.8%) of the patients developed PJIs. Eight (2.1%) of the infections developed in knee replacement patients and 7(1.5%) in hip replacement patients. Out of 15 infected cases, 7(46.7%) were Staphylococcus aureus, 4(26.6%) were CoNS, 2(13.4%) were Streptococcus species, 1(6.7%) was Pseudomonas aeruginosa and 1(6.7%) was E. coli (Figure 1).

The antibiotic sensitivity pattern of Staphylococcus aureus showed that 3(42.9%) isolates of Staphylococcus aureus were MRSA and 4(57.1%) were MSSA. The Streptococcus species

Table 2: Association of Prosthetic Joint Infections with Risk Factors

Risk Factors		Prosthetic Joint Infections		Total	Chi-Square Statistic	p-value
Yes		No		n(%)		
Age (Years)	51-60	1	84	85(10.1)	8.512	0.01*
	61-70	5	526	531(63)		
	71-80	9	218	227(26.9)		
	Total n(%)	15(1.8)	828(98.2)	843(100)		
BMI (kg/m^2)	18.5-24.9 (Normal)	3	82	85(10.1)	4.354	0.11
	25-29.9 (Overweight)	6	204	210(24.9)		
	>30 (Obese)	6	542	548(65)		
	Total n(%)	15(1.8)	828(98.2)	843(100)		
Diabetes mellitus	Diabetic	11	345	356(42.2)	6.048	0.01*
	Nondiabetic	4	483	487(57.8)		
	Total n(%)	15(1.8)	828(98.2)	843(100)		
Hypertension	Hypertensive	3	197	200(23.7)	0.116	0.73
	Nonhypertensive	12	631	643(76.3)		
	Total n(%)	15(1.8)	828(98.2)	843(100)		
Smoking	Smoker	1	89	90(10.7)	0.257	0.61
	Nonsmoker	14	739	753(89.3)		
	Total n(%)	15(1.8)	828(98.2)	843(100)		

Significant p-value

were sensitive to penicillin, ampicillin, amoxicillin and tazocin. The sensitivity pattern of gram-positive cocci to other antibiotics is shown in Figure 2.

E. coli was sensitive to ciprofloxacin, levofloxacin, gentamicin, tobramycin, amikacin, tazacin, imipenem, and meropenem but resistant to amoxicillin-clavulanate, cefotaxime, ceftazidime, ceftriaxone, and trimethoprim-sulphamethoxazole. Pseudomonas aeruginosa had sensitivity to imipenem, meropenem, tazocin, and resistance to ciprofloxacin, levofloxacin, amikacin, tobramycin, gentamicin, and ceftazidime.

Nine (60%) patients with PJIs underwent DAIR, and in 6(40%) patients, a two-staged revision was done. All the patients recovered completely. The incidence of PJIs was associated with advanced age and diabetes mellitus. The association of prosthetic joint infections with the risk factors is shown in Table 2.

DISCUSSION

Prosthetic joint infection is a serious complication that occurs after joint replacement surgery (like hip or knee replacement). It involves infection of the implanted prosthesis and surrounding tissues. The present study reported 1.8% frequency of prosthetic joint infections. Similar rates of PJIs, ranging between 0.5–2% for primary joint replacement procedures, were reported globally[12]. Three studies showed 0.5%, 2.18% and 2.6% prevalence of PJIs[13-15]. Another study revealed 4.03% frequency of PJI after total hip replacement and 2.94% after total knee replacement[16]. The frequency of PJIs was 1.08% according to a study, but the frequency differs in various geographical regions[2].

Our results revealed the mean age of the patients to be 65.3±5.73 years. Similarly, the average age was 67±13.2 years in another study[17]. In our study, 72.4% of the patients were females, and the mean BMI of the patients was 33.9±4.25 kg/m2. In another study, males constituted 51.96% of the study population, and the mean BMI was 30.59 kg/m2[18]. There were 58.2% female patients in a study by da Salva et al[17]. Females constituted 85.2% of the patients, and the average age was 69.2 years[13]. In contrast, in a study, the majority of the patients were males (94.8%). The mean BMI was greater than 30 kg/m2 in most of the cases[19].

Our results showed that 46.7% of the isolated organisms were Staphylococcus aureus, followed by CoNS species (26.6%). Gram-negative rods constituted 13.4% of the organisms. This is in strong agreement with other studies. Staphylococcus was the most common organism in PJIs[16]. In another study, 73.4% of the PJIs were caused by gram-positive cocci, with CoNS being the most predominant. Around 12.8% of the infections were caused by gram-negative rods[18]. da Silva et al. revealed that Acinetobacter was the most common causative organism, followed by Staphylococcus aureus (20.2%). Other organisms were Enterobacter (13.3%), Klebsiella (10%), E. coli (8.3%), Proteus (6.7%), and Pseudomonas (5%)[17]. In another study, CoNS was the most common organism (30%), followed by Staphylococcus aureus (26%)[20]. Staphylococcus aureus was responsible for 42.1% of the cases of PJIs, Streptococcus

species for 36.8%, CoNS for 10.5%, and gram-negative rods for 5.2% of the patients in a study[13]. In our study, 57.1% of the Staphylococcus aureus were MSSA and 42.9% were MRSA. Another study showed 76.2% MSSA and 23.8% MRSA in PJIs[17]. Yoon et al. revealed that out of Staphylococcus species, 75% were MSSA and 25% were MRSA[13]. According to a study, Staphylococcus aureus and CoNS were responsible for causing 50-60% cases of PJIs. Streptococcus and gram-negative rods also caused PJIs, but they were less frequent than Staphylococcus[14]. In another study, gram-positive organisms caused 48.2% and gram-negative rods caused 11.1% of the infections[19]. Tekin-Tas et al. reported MSSA as the most frequent pathogen (35.2%), followed by Klebsiella (23.5%) and Pseudomonas (11.7%) in PJIs[21]. According to a study by Chang et al., Staphylococcus accounted for 58.91% of the cases of PJIs and gram-negative rods were responsible for 14.36% of the cases. Similar to our study, Chang et al. reported that all the gram-positive cocci were sensitive to vancomycin, linezolid, and tigecycline[22]. In our study, E. coli was sensitive, but Pseudomonas was resistant to ciprofloxacin, gentamicin, tobramycin, and amikacin. Both strains were resistant to cephalosporins but sensitive to imipenem and meropenem. In another study, greater than 50% of the gram-negative rods were resistant to cephalosporins, gentamicin, ciprofloxacin and tobramycin[22].

In our study, DAIR was done in 60% and two-staged revision in 40% of the patients with PJIs. These findings are in line with current literature suggesting that DAIR is effective in PJIs[23]. In another study, DAIR was done in 50% of the patients, while 20% of the patients underwent two-staged revision surgery[20]. The frequency of prosthetic joint infections was associated with advanced age and diabetes mellitus in our study. This is consistent with a previous study showing delayed wound healing and impaired immune response in advanced age and diabetic patients[24]. In contrast, diabetes mellitus and obesity were not linked to PJIs according to another study[15]. In our study, high BMI did not show a statistically significant association with PJI. On the contrary, another study found obesity to be an independent risk factor associated with PJI[25]. According to our results, hypertension and smoking were not significantly associated with PJI. Similar results were also reported in another study[9]. The risk factors associated with PJIs in a study were hypertension, smoking, increased BMI, anemia, and heart failure[19].

CONCLUSION

Our study showed 1.8% frequency of prosthetic joint infections after joint replacement. Gram-positive cocci, including Staphylococcus aureus and Coagulase-negative Staphylococcus species, account for the majority of the cases of PJIs followed by gram-negative rods. The antimicrobials of choice for gram-positive cocci are vancomycin, linezolid, and tigecycline. For gram-negative rods, carbapenems and tazocin showed no resistance.. Advanced age and diabetes mellitus are linked to a higher incidence of PJIs.

Recommendations: The findings of this study reinforce the predominance of gram-positive organisms in PJIs, highlight the growing challenge of antimicrobial resistance, and emphasize the importance of infection control practices and evidence-based management strategies.

ETHICAL APPROVAL: *SMDC/SMRC/384A-25/2025.*
CONSENT FOR PUBLICATION: *Written, informed consent was obtained from the study participants.*
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CONFLICT OF INTEREST: *None*
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AUTHORS' CONTRIBUTION

- ***Aqsa Aslam:*** *Drafting the article.*
- ***Farooq Azam Khan:*** *Conception and design, Acquisition of data.*
- ***Muhammad Kashif Jamal:*** *Acquisition of data.*
- ***Bilal Ahmad Abbas:*** *Acquisition of data.*
- ***Sadaf Nasir:*** *Critical revision.*
- ***Maria Aslam:*** *Analysis and interpretation of data.*

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ORIGINAL ARTICLE

COMPARISON OF SERUM URIC ACID LEVELS WITH OUTCOMES IN PATIENTS WITH ACUTE ISCHEMIC STROKE

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ABSTRACT

Objective: To determine the link between uric acid levels and outcome in acute ischemic stroke (infarct).

Study Design: Cross-sectional, observational study.

Place and duration of study: Department of Medicine, Pakistan Ordnance Factories (POF) Hospital, Wah Cantt , 06 months (August 2023 to January 2024).

Methodology: We included 100 patients in our study. All patients underwent serum uric acid level during their admission. After 72 hours, following their admission their Modified Rankin score was calculated and recorded.

Results: The analysis reveals a strong positive correlation between uric acid levels and the Modified Rankin Score (mRS) in acute stroke(infarction). The Pearson correlation coefficient is 0.920, indicating a very high degree of association with p <0.001.

Conclusion: Serum uric acid levels are significantly linked with the Modified Rankin Score while considering the disease outcome in acute cerebral infarction.

Keywords: *Acute Ischemic stroke, Prognosis, Uric acid*

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INTRODUCTION

Stroke, also called Cerebrovascular accident or Acute brain attack is a condition caused by either disruption in the blood flow to the brain or because of rupture of blood vessels leading to a spectrum of various clinical manifestations due to impairment in brain function[1]. Ischemic stroke occurs when the blood supply to the brain is impaired due to the occlusion of the blood vessel supplying that part. The Global burden of disease data revealed very high disease prevalence of stroke and is the second highest cause of mortality worldwide among all the non-communicable disorders with approximately more than 7 million deaths annually[2]. The prognosis of acute stroke is poor with high mortality rates particularly for those requiring intensive care management. Various factors affect the outcomes and the survival rates are poor in those with increase age group and those with severe impairment in their conscious level during the time of admission to the intensive care[3]. Some of the advanced management interventions like re-perfusion therapy and decompressive craniectomy have been found to improve the survival rates in stroke patients. The in-hospital mortality of stroke patients is dependent on many factors like age, complications, severity on admission and resource limitation while deciding appropriate therapy[4]. Delirium has also been found to negatively affect the stroke outcomes with increased risk of complications and higher mortality[5]. Similarly, those non-diabetic patients with stroke who developed hyperglycemia during admission had a bad prognosis compared with those with normal sugars[6].

Hyperuricemia has been found to be an important parameter that is linked with the prognosis and survival in stroke patients. Patients with elevated serum acid are at more risk of developing

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acute stroke with increased mortality rates mediated by the inflammatory mechanisms[7]. Elevated uric levels or Hyperuricemia is an independent risk factor linked with disease severity and progression in cerebral small vessel disease[8]. Therefore, serum uric acid levels, although a simple investigation can be a useful marker in assessment of the disease severity and overall prognosis in patients with acute stroke. The major objective of our study was to determine the association between serum uric acid and stroke outcome in our patient population, with the aim of informing and optimizing future management and preventive strategies.

CAPSULE SUMMARY

A link between uric acid levels and outcome in acute ischemic stroke (infarct) was determined. Serum uric acid levels were significantly linked with the Modified Rankin Score. Serum uric acid levels may prove as a useful biomarker for predicting the severity of disability following a stroke.

METHODOLOGY

We conducted this cross-sectional study in the Department of Medicine, POF Hospital, Wah Cantt, from 10-07-2023 to 09-01-2024 after taking the ethical approval from the hospital ethical review board . A total of 100 patients, between age 18 to 80 years, of both genders who suffered from an acute ischemic stroke presenting with 48 hours of onset of symptoms were included. The diagnosis of stroke was confirmed based on clinical evaluation and CT findings in patients with persistent neurological deficit after 24 hours. Sample size was calculated, using parameters of uric acid in predicting the presence of adverse outcomes in patients with acute ischemic stroke as described by Perveen et al using correlation of coefficient calculated as follows: Level significance: 5%, Power of test: 90%, Correlation of coefficient: r 0.511, Expected sample size: n 100[9]. Consecutive non-probability sampling was utilized. Those with a previous history of CVA, gout, taking urate lowering therapy, alcohol consumers, history of malignancy or taking drugs affecting uric acid levels like Aspirin and diuretics were excluded from the study. Informed consent was obtained from the patients or from their attendants. Serum uric acid levels were checked on admission by taking the blood samples and values expressed in mg/dl. and modified Rankin score was measured after 72 hours of admission. All the data was collected on the proforma and saved.

SPSS v 26 was used for the data analysis. Descriptive statistics was calculated for all variables. Quantitative variables particularly age, height, weight, BMI, serum uric acid level at admission was measured by mean and standard deviation. The modified Rankin score calculated at 72 hours was calculated as mean and standard deviation. A p-value of ≤0.05 was taken as significant. Stratification was also done on the basis of age, gender and BMI, post stratification correlation coefficient was checked.

RESULTS

The mean age of the patients was 57.97±11.66 years (Table-1). Out of 100 patients, 66 (66.0%) were male, while 34 (34.0%) were female (Table-1). The distribution of patients by BMI shows that a majority of the study population, 61.0% had BMI of ≥30 kg/m². The analysis reveals a strong positive correlation between uric acid levels and the Modified Rankin Score (mRS) in people with acute infarct. The Pearson correlation coefficient is 0.920, indicating a very high degree of association, and the p <0.001. The values of uric acid more than 8 mg/dl generally correlate with mRS scores of 4 or higher, indicating a stronger association with more severe disability.

In the younger age group (≤50 years), the Pearson correlation coefficient was 0.954 (p = 0.000), suggestive of positive correlation (Table 5). The stratification by gender revealed significant positive correlations between levels of uric acid and the Modified Rankin Score (mRS) in both males and females which revealed that elevated uric acid is linked with increased disability across genders. In males, the Pearson correlation coefficient was 0.914 (p = 0.000), showing a very strong positive correlation between serum uric acid levels and mRS scores. In females, the correlation was even stronger, with a Pearson

Table 1: Age and Gender distribution

AGE (Years)	Number	Percentage(%)
50	27	27
51-80	73	73
	100	100
GENDER		
Male	66	66
Female	34	34
	100	100

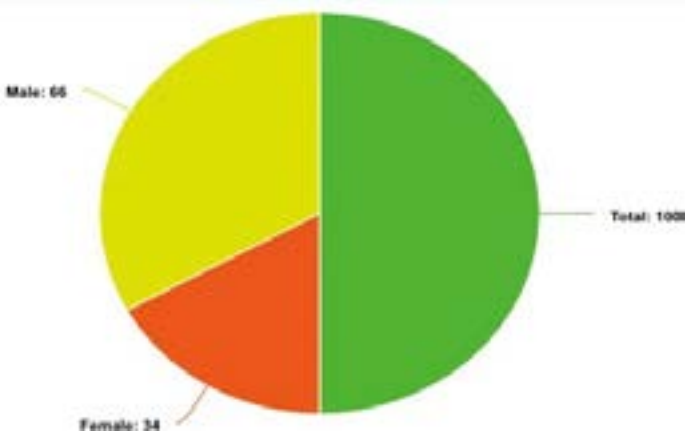

Figure 1: Gender distribution

Table 2: Mean and Standard Deviations of different variables

Variables	Mean	SD
Age (Years)	57.96	11.66
Weight (Kg)	70.2	9.17
Height (cm)	165	7.0
BMI (kg/m2)	36.68	4.92
Uric acid mg/dl	7.71	2.35
mRS	3.48	1.64

Table 3: Stratification for BMI

		BMI < 30 (kg/m2) Uric acid (mg/dl)	Modified Rankin Score (mRS)	BMI ≥30 (kg/m2) Uric acid (mg/dl)	Modified Rankin Score (mRS)
Uric acid	Pearson Correlation	1	0.943	1	0.905
	Sig. (2-tailed)	0.000	0.000		0.000
	N		39	61	61
mRS	Pearson Correlation	0.943	1	0.905	1
	Sig. (2-tailed)	0.000		0.000	
	N	39	39	61	61

Table 4: Stratification for Gender

		Male Uric acid (mg/dl)	Modified Rankin Score (mRS)	Female Uric acid (mg/dl)	Modified Rankin Score (mRS)
Uric acid	Pearson Correlation	1	0.914	1	0.943
	Sig.(2-tailed)	66	0.000		0.000
	N		66	34	34
mRS	Pearson Correlation	0.914	1	0.943	1
	Sig.(2-tailed)	0.000		0.000	
	N	66	66	34	34

Table 5: Stratification for Age

		Age ≤50 (Years) Uric acid (mg/dl)	Modified Rankin Score (mRS)	(Age51-80) (Years) Uric acid (mg/dl)	Modified Rankin Score (mRS)
Uric acid	Pearson Correlation	1	0.954	1	0.893
	Sig. (2-tailed)		0.000		0.000
	N	27	27	73	73
mRS	Pearson Correlation	0.954	1	0.893	1
	Sig. (2-tailed)	0.000		0.000	
	N	27	27	73	73

correlation coefficient of 0.943 (p = 0.000) as highlighted in the Table 4. The average weight of the patients was 70.20 kg, with a standard deviation of 9.17 kg, indicating moderate variability in body weight. The mean BMI was calculated to be 36.68 kg/m², with a standard deviation of 4.92, 62 indicating that the majority of the population was in the obese category. At admission, the mean serum uric acid level was 7.71 mg/dl with a SD of 2.35 mg/dl suggesting notable variability in uric acid levels among patients. The mean Modified Rankin Score (mRS) was 3.48, with a S.D of 1.64, reflecting a moderate degree of functional impairment in the study population.

DISCUSSION

Our study results revealed a significant link between the high uric acid levels and the stroke outcomes using modified Rankin scale (mRS). We observed that those patients who had high uric acid levels on admission had poor outcomes compared with those having normal levels. A recent study conducted in India also showed that high uric acid levels are linked to more disability risk in acute stroke patients[10] similar to our observations. Hyperuricemia is well recognized entity in chronic inflammatory conditions including the Metabolic syndrome. S Khanna et al reported that the critically ill patients admitted with acute stroke who had high uric acid levels had a high mortality rate with a bad prognosis, both in males and females[11]. These observations were quite similar to our study findings and we found a significant association of hyperuricemia with poor outcome in stroke, both in males as well as female patients. Interestingly, a study that was done to find out the link of stroke severity using NIHSS scale with common biomarkers found no significant link between hyperuricemia and stroke severity[12]. The link of elevated uric acid with stroke prognosis has been remained controversial however majority of the studies showed its detrimental effects on cerebral blood flow via pro-inflammatory mechanisms and some data showing its potential good effects as well[13]. Majority of the patients in our study were obese and hyperuricemia was more frequent in those people, which also suggests hyperuricemia, obesity and bad prognosis of acute ischemic stroke triggered by the inflammation.

Hyperuricemia has been shown to cause various pro inflammatory effects like impairment in endothelial function and insulin resistance[14]. These effects caused by high uric acid leads to increased cell apoptosis and oxidative stress. This in turn causes increased propensity towards development of atherosclerosis. The association of hyperuricemia with stroke prognosis is more in ischemic stroke while most of the studies have shown that the risk of hemorrhagic stroke is not significant[15]. The risk of stroke with hyperuricemia was more in females in one study, however we didn't find any gender related differences in our study[15]. The clinical evidence suggests that urate lowering therapy has a potential role in reducing the cardiovascular risk including stroke and ischemic heart disease[16]. It has also been found that elevated NLR i.e Neutrophil to Lymphocyte ratio in stroke patients has additive effects on uric acid-stroke prognosis association[17]. The risk of cognitive impairment is also high in those patients with acute stroke who have elevated uric acid levels[17]. Recently some studies have also shown the prognostic association of raised serum uric acid in patients with hemorrhagic stroke[18]. A study conducted in Peshawar Pakistan found that elevated serum uric acid levels can be used as predictor of stroke risk highlighting the importance of this useful laboratory test[19]. A longitudinal descriptive study from Bangladesh also revealed uric acid levels as a simple, cheap and convenient method to determine the prognosis in acute stroke patients[20].

Stroke is among the important causes of mortality and affects quality of life both nationally and worldwide therefore our study highlighted the use of an important and simple biomarker, uric acid therefore showing its good potential in improving the prognosis in these patients by timely diagnosis and management of hyperuricemia prior to the development of complications. Serum uric acid is a cost effective and widely available investigation that should be done in patients with

acute cerebral infarct to assess the overall prognosis. The role of elevated uric acid levels has always remained a controversial issue with some studies showing its neuroprotective benefits while majority showing its deleterious effects, that's why we conducted this study to see the effects particularly in our population.

Our study had a few limitations as well. First of all, it was a single centered study with a relatively smaller sample size so results could not be generalized. There may be some confounding effects of obesity as well as majority of our patients were obese. Lack of a control group also makes the validity of results not very high.

CONCLUSION

Elevated uric acid levels are strongly linked to greater disability at 72 hours post admission in patients with stroke. These findings suggest that serum uric acid levels may prove as a useful biomarker for predicting the severity of disability following a stroke. We recommend further larger prospective studies to further strengthen our findings.

ETHICAL APPROVAL: *IRB/POFH/022023/MED/12.*
CONSENT FOR PUBLICATION: *Written, informed consent was obtained from the study participants.*
AVAILABILITY OF DATA: *Data is available from the corresponding author on a justified request.*
FINANCIAL DISCLOSURE/ FUNDING: *None*
ARTIFICIAL INTELLIGENCE TOOLS DISCLOSURE: *None*
CONFLICT OF INTEREST: *None*
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AUTHORS' CONTRIBUTION

- ***Danial Mateen:*** *Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article.*
- ***Muzamil Jamil:*** *Conception and design, Analysis and interpretation of data, Drafting the article, Critical revision.*
- ***Syed Asim Ali Shah:*** *Conception and design, Analysis and interpretation of data, Drafting the article, Critical revision.*
- ***Wajahat Sultan Baig:*** *Conception and design, Drafting the article, Critical revision.*
- ***Izza Sohail:*** *Acquisition of data.*
- ***Junaid ur Rehman:*** *Acquisition of data, Analysis and interpretation of data.*

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ORIGINAL ARTICLE

INCIDENCE OF RECURRENCE OF LUMBAR DISC HERNIATION FOLLOWING ENDOSCOPIC DISCECTOMY

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ABSTRACT

Objectives: To determine the six-month incidence of symptomatic recurrent lumbar disc herniation following endoscopic discectomy and to evaluate associated pain and functional outcomes.

Study Design: Prospective Cohort Study.

Place and Duration of Study: Khairpur Medical College Hospital (KMCH), Sindh, Pakistan. 01 year (January 2024 to December 2025).

Methodology: This study enrolled 180 patients, aged 18–60 years, undergoing percutaneous endoscopic lumbar discectomy and percutaneous endoscopic transforaminal discectomy for single-level lumbar disc herniation (LDH). Follow-up was conducted for 6 weeks, 3 months, and 6 months. The primary outcome was MRI-confirmed symptomatic recurrence; secondary outcomes were Visual Analogue Scale(VAS) for leg pain and Oswestry Disability Index (ODI).

Results: Symptomatic recurrence occurred in 11 of 180 patients (6.1%; 95% CI: 3.1–10.7%). Mean time to recurrence was 3.2 months. VAS improved from 7.8 ± 1.1 to 2.1 ± 0.9, and ODI from 62.4% to 18.3% at six months (both $p < 0.001$). The overall complication rate was 3.9%. No difference in recurrence found between techniques ($p = 0.612$).

Conclusion: Endoscopic discectomy yields a low 6-month recurrence rate, with clinically significant pain and functional improvement in a Pakistani provincial setting, supporting its adoption in resource-appropriate tertiary care centres.

Key words: *Lumbar disc herniation; endoscopic discectomy; recurrent disc herniation; Oswestry Disability Index; Visual Analogue Scale*

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INTRODUCTION

Lumbar disc herniation (LDH) continues to be one of the most common and disabling musculoskeletal and neurological disorders, worldwide. The disorder occurs when the nucleus pulposus (hydrated proteoglycan-rich portion of the intervertebral disc) herniates through a defect in the annulus fibrosus, and mechanically or chemically compresses or irritates adjacent spinal nerve roots [1,2]. This clinical syndrome, lumbar pain with unilateral or bilateral radiation into the lower extremity, sensory disturbance, and in severe cases motor deficit , is called sciatica, and has a lifetime prevalence in the general population to be between 10 and 40% [3]. Low back pain, of which disc herniation is a major aetiology, is the leading cause of disability adjusted life years (DALYs), at 64.9 million per year across 204 countries [4,5].

Lumbar disc disease in Pakistan, with a population of over 230 million people, has a significant epidemiological profile, but this remains poorly defined. Sindh province, with about 47 million people, ranges from the highly technologically advanced city of Karachi to the rural farming areas like Khairpur, where the working-age population is subjected to heavy labour, prolonged stooped posture, and manual labour, all risk factors for accelerated disc degeneration and herniation [6-8].

The surgical management of LDH has evolved over a period of 90 years. In the late 1970s, Caspar (1977) and Williams (1978) independently brought about the refinement of open

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laminectomy, which was first described by Mixter and Barr (1934), into microsurgical discectomy, where a much smaller surgical corridor is used to perform disc removal [9,10,1]. Since then, microdiscectomy has become the "standard" against which all further innovations are judged [11,12]. In the past 20 years, the percutaneous endoscopic spine surgery, especially PELD/TELD and PETD, has developed rapidly with comparable clinical results to microdiscectomy, but with significantly less trauma to the paraspinal muscles, shorter hospital stay, lower blood loss, and early return to activity [13,14]. The endoscopic discectomy provides several advantages over conventional microdiscectomy, including reduced tissue trauma, shorter hospital stays, and quicker postoperative recovery with comparable clinical outcomes. Symptomatic recurrent LDH is a significant postoperative complication, with international studies reporting recurrence rates of between 2% and 8% [13,15].

CAPSULE SUMMARY

The six-month incidence of symptomatic recurrent lumbar disc herniation following endoscopic discectomy was determined. Endoscopic discectomy yielded a low 6-month recurrence rate, with clinically significant pain and functional improvement, supporting its adoption in resource-appropriate tertiary care centres.

Several studies have shown good pain and functional results after endoscopic lumbar discectomy [16-18]. Recurrence after surgery remain a major concern as it may lead to persistent pain, re-operation, and additional healthcare burden [19,20]. Various factors, like, smoking, annular defect, and disc degeneration have also been reported as risk factors for recurrence [21,22].

The most clinically relevant complication after surgery is the symptomatic recurrent disc herniation (reHD), which is defined as reherniation at the same level and side after documented postoperative recovery, which in many cases requires further investigation, long-term disability, and revision surgery. The recurrence rates vary from 2.0% to 8.7 % internationally after endoscopic discectomy [2]. No prospective study has quantified this result in Pakistan. This gap means that locally informed pre-operative counselling and evidence-based planning of surgical follow-up are not possible. Despite the rising use of endoscopic spine surgery in Pakistan, there is still a limitation of prospective data on recurrence and surgical outcomes, especially for those undergoing surgery in tertiary care centres in the province of Sindh.

The present prospective cohort study aimed to find the incidence of symptomatic recurrent lumbar disc herniation after 6 months of endoscopic discectomy performed at Khairpur Medical College Hospital (KMCH), and to assess the pain and functional outcomes using Visual Analogue Scale (VAS) and Oswestry Disability Index (ODI) scores.

METHODOLOGY

This was a prospective cohort study, conducted in the Department of Neurosurgery and Orthopaedic Surgery at KMCH in Khairpur, Sindh, Pakistan, from January 2024 to December 2025. The study protocol was approved by the Institutional Review Board (IRB) of Khairpur Medical College. All procedures followed the guidelines of the Declaration of Helsinki (2013 revision). Each participant provided written, informed, and voluntary consent before enrolment, and the freedom to terminate at any time without repercussion of care.

A sample size of 174 participants was required, based on a published recurrence rate of 5.0% from previous endoscopic discectomy studies, a 95% confidence level, and a 3.2% margin of error using OpenEpi computer software (v3.01)[23]. To anticipate attrition and to solidify the precision of 95% confidence interval around the primary outcome estimate, a final sample of 180 patients was enrolled by consecutive non-probability (convenience) sampling. Only patients between 18 and 60 years old with MRI confirmed single level LDH (Pfirrmann 3–4) with persistent ipsilateral radicular leg pain for ≥ 6 weeks. Despite adequate conservative care (analgesia, physiotherapy, and/or epidural steroid injection), and willing and able to participate in structured follow-up visits were included. Exclusion criteria included, multilevel disc disease, previous lumbar surgery at the index level, significant spondylolisthesis (Meyerding grade ≥ II), lumbar spinal stenosis with need for decompression or fusion, active systemic infection or malignancy and pregnancy.

The choice of surgical approach was made according to the MRI scan results before surgery and surgeon assessment. PELD/TELD was chosen for contained disc herniations, paracentral disc herniations and foraminal disc herniations that were suitable for transforaminal approach; PETD was selected for high migrations disc herniations, extruded disc herniations and anatomically difficult lesions, where direct access to the herniated fragment via the epidural space was felt to be more appropriate[18]. All procedures were performed by surgeons experienced in more than 60 prior endoscopic discectomies [24]. Local anaesthetic and intravenous sedation were used unless patient or anaesthetic factors dictated general anaesthetic. Annular shrinkage and haemostasis were done throughout using radiofrequency bipolar haemostasis.

Symptomatic recurrent lumbar disc herniation was the primary outcome, operationally defined as: (i) ipsilateral radicular pain and/or new neurological deficit ≥ 4 weeks after the index procedure, and (ii) MRI confirmation of reherniation at the same level and side as the index procedure. Secondary outcomes included VAS leg pain score (0–10 numerical scale), ODI (as a percentage of maximum disability) , and incidence of intraoperative and post-operative complications [25]. Assessment was done at baseline, 6 weeks, 3 months, and 6 months for all patients. On clinical indication, symptom-triggered MRI was obtained, and all patients with recurrent radiculopathy had an MRI, regardless of timing.

IBM SPSS Statistics, Version 26.0, was used for data entry and analyses. Categorical variables are presented as frequency and percentage, and continuous variables as mean ± standard deviation (SD). Normality of continuous variables was assessed using the Shapiro–Wilk test. Paired-samples t- test and Wilcoxon signed rank test were used to determine pre- to post-operative change in VAS and ODI (as appropriate). Recurrence rates were compared between PELD/TELD and PETD groups by using the chi-square (χ^2) test. All analyses were performed using a 2-tailed p-value < 0.05 as statistically significant.

Table 1: Baseline Demographic, Clinical, and Surgical Characteristics

Characteristic	Category / Statistic	n (%) or mean ± SD
Demographic Variables		
Age	Years	38.5 ± 11.2
Sex	Male	108 (60.0)
	Female	72 (40.0)
Body mass index	kg/m²	26.4 ± 3.8
Clinical Variables		
Symptom duration	≥ 12 weeks	112 (62.2)
	< 12 weeks	68 (37.8)
Active smoking	Yes	48 (26.7)
Diabetes mellitus	Yes	21 (11.7)
Pre-operative VAS (leg pain, 0–10)	Mean ± SD	7.8 ± 1.1
Pre-operative ODI (%)	Mean ± SD	62.4 ± 9.8
Operative Variables		
Technique	PELD/TELD	95 (52.8)
	PETD	85 (47.2)
Level Distribution		
Disc level	L3–L4	18 (10.0)
	L4–L5	83 (46.1)
	L5–S1	63 (35.0)
	Two adjacent (single dominant)	16 (8.9)

PELD = percutaneous endoscopic lumbar discectomy; TELD = transforaminal endoscopic lumbar discectomy; PETD = percutaneous endoscopic transforaminal discectomy; VAS = Visual Analogue Scale; ODI = Oswestry Disability Index. Percentages may not sum to 100 due to rounding.

RESULTS

There was no patient attrition during 6-month follow-up. The average age of the subjects was 38.5 ± 11.2 years, with the majority being male. The most affected disc level was L4–L5 followed by L5–S1. The number of PELD/TELD and the number of PETD techniques were similar. Detailed baseline demographic, clinical and operative characteristics are shown in Table 1.

Table 2: Primary Outcome: Six-Month Incidence of Symptomatic Recurrent Lumbar Disc Herniation

Parameter	Result
Total participants	180
Confirmed recurrences, n (%)	11 (6.1)
95% Confidence interval	3.1% – 10.7%
Mean time to recurrence, months (range)	3.2 (1.5 – 6.0)
Recurrences within first 4 months, n (%)	8 (72.7)
Managed conservatively, n (%)	3 (27.3)
Requiring revision endoscopic surgery, n (%)	8 (72.7)
Recurrence - PELD/TELD group (n = 95)	5 (5.3%)
Recurrence - PETD group (n = 85)	6 (7.1%)
Chi-square statistic (χ^2)	0.26
p-value (PELD/TELD vs. PETD)	0.612 (not significant)

Among 180 patients 11 (6.1%) (95% CI: 3.1–10.7%) had symptomatic recurrent lumbar disc herniation at 6 months. The average time until recurrence was 3.2 months. No statistically significant differences in recurrence were seen between the PELD/TELD group and the PETD group (p = 0.612). Primary outcome findings are reported in detail in Table 2.

Recurrence definition: ipsilateral radicular symptoms at the index level after ≥ 4 weeks of documented symptom-free interval, confirmed by MRI reherniation at the same level.

All postoperative follow-ups, there was considerable improvement in VAS leg pain and ODI scores when compared to baseline levels (p < 0.001). The most significant improvement was seen in the first 6 weeks after surgery and further improvement was seen at 3 and 6 months. Pain and functional outcomes were clinically improved at 6 months. Trends in outcomes are detailed in Table 3.

The complication rate overall was 3.9%. The complications recorded were dural tearing, transient neurological deficit, surgical site infection (superficial), and a single conversion to open discectomy. No permanent neurological deficits or deaths occurred during follow up. Complication data is summarized in detail in Table 4.

DISCUSSION

This prospective cohort study of 180 patients is the first structured outcome data of endoscopic discectomy in a provincial teaching hospital in Sindh, Pakistan. The main result is a clinically important reduction in leg pain (VAS

Table 3: VAS Leg Pain and ODI Score Trajectories at Follow-up Time Points

Outcome Measure	Pre-operative	6 Weeks	3 Months	6 Months	p-value*
VAS leg pain (0–10), mean ± SD	7.8 ± 1.1	4.2 ± 1.3	3.0 ± 1.0	2.1 ± 0.9	< 0.001
Change from baseline (VAS)	—	−3.6	−4.8	−5.7	—
ODI (%), mean ± SD	62.4 ± 9.8	38.1 ± 8.4	26.5 ± 7.1	18.3 ± 6.2	< 0.001
Change from baseline (ODI, %)	—	−24.3	−35.9	−44.1	—
MCID achieved (VAS ≥ 2.0 pts)	—	Yes	Yes	Yes	—
MCID achieved (ODI ≥ 10 pts)	—	Yes	Yes	Yes	—

**Paired-samples t-test, each post-operative time point versus pre-operative baseline. VAS = Visual Analogue Scale; ODI = Oswestry Disability Index; MCID = minimum clinically significant difference. MCID thresholds: VAS ≥ 2.0 points 15 ODI ≥ 10 percentage points 25.*

Table 4: Intraoperative and Post-operative Complications

Complication	n	%	Management and Outcome
Dural tear	2	1.1	Primary repair; bed rest × 5 days; no sequelae
Transient neurological deficit (L5 paraesthesia)	3	1.7	Conservative; complete resolution by 6 weeks
Superficial surgical site infection	1	0.6	Oral antibiotics; resolved without deep extension
Conversion to open discectomy	1	0.6	Instrument failure; open procedure completed successfully
Permanent neurological deficit	0	0.0	—
Mortality	0	0.0	—
Total complications	7	3.9	

Complication rate calculated per patient; one patient experienced more than one complication. No cauda equina syndrome or post-operative haematoma requiring intervention was recorded.

reduction 5.7 points) and functional disability (ODI reduction 44.1 percentage points) at 6 months, with a complication rate of 3.9% and no permanent neurological morbidity. All these outcomes collectively highlight the safety and efficacy of endoscopic discectomy in the Khairpur, Sindh population as a surgical option for single-level LDH.

The recurrence rate in the present cohort of 6.1% is like the best international evidence available. The most widely cited benchmark for endoscopic disc removal is the YESS series with 307 patients, who reported a recurrence rate of 4.9% at a mean follow-up of 11.5 months[20], which is slightly lower than in the present study and is plausibly explained by the fact that their centre performs a high volume of operations, the longer period of maturity of their programme, and perhaps because their observation period was longer, capturing more late recurrences than our study period of six months. A recurrence rate of 7.2% with a longer follow-up of 16 months, which may be due to the longer follow-up period rather than a less effective technique, as there is known to be a bimodal distribution of recurrences over time [12,26].

The most directly comparable is the systematic review calculated a weighted mean recurrence rate of 5.8% (95% CI: 4.1–7.5%) from 14 prospective endoscopic discectomy studies, which is within the range of the present study's result [15,19]. The pain and functional scores gained are also consistent with published benchmarks; the VAS improvement of 5.7 points and ODI decrease of 44.1 percentage points for this cohort is greater than that observed in the pivotal RCT [13]. The complication rate of 3.9% is in line with the published range of 2.0-6.0% for endoscopic discectomy within the lower limit of the 4.0-10.0% complication rate reported for conventional open discectomy in systematic reviews [11,14,27]. Two dural tears (1.1%) and three transient neurological deficits (1.7%) were recognised endoscopic complications and were within expected incidence and did not result in permanent sequelae.

These results have several clinical implications. First, there was a high proportion of patients (62.2%) who had a duration of symptoms of more than 12 weeks before undergoing surgery, which is most likely due to a lack of timely specialist referral and diagnostic MRI in the upper part of Sindh, which might result in increased annular degeneration and may increase recurrence rates at the time of surgery. Earlier surgical intervention in appropriately selected patients would be expected to occur in rural Sindh with the addressing of referral pathways and MRI access, which could lead to a decrease in the incidence of recurrence. Secondly, 26.7% of this cohort were smokers, and there is a known association between smoking,

disc degeneration, and annular weakening and these patients should be offered structured preoperative smoking cessation counselling[7,28]. Third, the presence of diabetes mellitus (DM) in 11.7% of patients is a condition that causes impaired disc matrix healing and may predispose to higher recurrence rates; therefore, optimal glycaemic control is important prior to surgery [14].

Moreover, the recurrence rate was low, complications were acceptable and functional improvement was significant in the current study. However, the feasibility of adding endoscopic discectomy to the routine neurosurgical practice in the provincial tertiary centres is supported. The minimally invasive nature of the procedure may allow for shorter hospital stays, quicker mobility and better use of surgical beds and health care resources in resource-limited settings. These results offer local evidence which can be supportive for the establishment of endoscopic spine surgeries at similar regional hospitals in Pakistan on a larger scale.

CONCLUSION

The rate of 6-month symptomatic recurrence after endoscopic discectomy (both PELD/TELD and PETD approaches) was low, and patients showed clinically and statistically significant results for leg pain and functional disability. Endoscopic discectomy technique is safe and effective in this context and suggest that it can continue to be used and quality assured at provincial tertiary care centres throughout Pakistan.

Limitations and Future Directions: Although the six-month follow-up period is in line with many published endoscopic discectomy trials, it's likely to be an underestimate of the actual cumulative recurrence rate, based on international data, herniations may recur up to 40% after six months or more [2,20]. A longer follow-up period could show a higher cumulative recurrence.

The single-centre nature of the study restricts the generalisability of results to other health care settings in Pakistan. An accurate systemic measurement of the size of the defect in the annulus was not undertaken, which precludes risk-stratified analysis according to this important predictor[21]. No within-cohort comparison of techniques was possible since there was no concurrent microdiscectomy control group.

Future studies should aim to overcome these limitations with a multicentre, prospective, randomised study design with at least two years of follow-up, systematic documentation of defects, a comparator arm of microdiscectomy, and incorporate patient-reported experience measures (PREMs) along with validated PROMs.

ETHICAL APPROVAL: *KMC-IRB-2024, Dated: 11.05.2026*
CONSENT FOR PUBLICATION: *Written, informed consent was obtained from the study participants.*
AVAILABILITY OF DATA: *Data is available from the corresponding author on a justified request.*
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AUTHORS' CONTRIBUTION

- ***Mukhtiar Ahmed Lakho:*** *Conception and design, Acquisition of data, Drafting the article.*
- ***Hamid Akbar Shaikh:*** *Analysis and interpretation of data, Critical revision.*
- ***Talha Abbas:*** *Drafting the article.*
- ***M Ajmal Khan Ayaz:*** *Conception and design, Analysis and interpretation of data.*
- ***Sundus Ali:*** *Critical revision.*

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ORIGINAL ARTICLE

HIGH-INTENSITY INTERVAL TRAINING VS. MODERATE-INTENSITY INTERVAL TRAINING AND EFFECTS ON STRESS MARKERS

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ABSTRACT

Objective: To find out the acute impact of High-Intensity Interval Training (HIIT) versus Moderate-Intensity Interval Training (MIIT) on salivary cortisol, heart rate variability (HRV), and state anxiety in young, healthy adults.

Study Design: Single-visit, open-label, randomized controlled trial.

Place and Duration of study: Khyber Medical University, Peshawar, Pakistan, 06 months (July to December 2025).

Methodology: Fifty physically active participants (18–30 years of age) were randomly distributed into two groups of 25 participants each, HIIT and MIIT group. Pre- and post-exercise assessments compreised salivary cortisol, heart rate variability(HRV) parameters including Root Mean Square of Successive Differences (RMSSD), Standard Deviation of NN Intervals (SDNN) & low-frequency to high-frequency (LF/HF) ratio, as well as the State-Trait Anxiety Inventory (STAI)-State Anxiety scale. HIIT comprised 10 sets of 1-minute cycling at 85–95% with active recovery. MIIT comprised 10 sets of 1-minute cycling at 55–65% with passive recovery.

Results: HIIT significantly increased salivary cortisol from 0.27± 0.07 to 0.36± 0.08 µg/dL (+32.8%, $p < 0.001$), whereas MIIT induced a decrease from 0.26 ± 0.08 to 0.24 ±0.07µg/dL (-9.3%, $p = 0.041$). The group-by-time interaction for cortisol was significant ($p < 0.001$, $\eta 2p=0.38$, large effect). HIIT decreased RMSSD and SDNN while increasing the LF/HF ratio ($p < 0.001$), indicating sympathetic dominance. Conversely, MIIT increased RMSSD (+18.2%, $p = 0.004$), indicating parasympathetic activation. Both modalities reduced state anxiety, but MIIT demonstrated a significantly greater reduction than HIIT (–20.9% vs. –12.2%, $p = 0.012$).

Conclusion: HIIT elicits a strong acute physiological stress reaction marked by HPA-axis and sympathetic dominance, whereas MIIT promotes parasympathetic reactivation and superior short-term anxiolytic effects. Exercise prescriptions should align with individual stress profiles.

Keywords: *Anxiety; Autonomic nervous system; Exercise therapy; Heart rate variability; High-Intensity interval training; Hydrocortisone; Stress, Physiological*

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INTRODUCTION

Stress is recognized as a major factor in adverse health outcomes, and it is more commonly associated with young adults and university students, who are exposed to academic, social, and environmental stressors. Chronic stress has been shown to be linked to alterations in autonomic nervous system function, dysregulation of hypothalamic-pituitary-adrenal (HPA) axis, and a higher risk of anxiety & mood disorders [1]. It is important to establish lifestyle interventions that can modulate stress biomarkers. Structured interval training, a form of physical activity, has been recognized as an effective strategy in modulating physiological and psychological markers of stress [2].

High-Intensity Interval Training (HIIT) and Moderate-Intensity Interval Training (MIIT) are two popular modalities of exercise. These modalities differ in training intensity and production of physiological stress. HIIT activates the sympathetic nervous system (SNS), which leads to the release of cortisol via the HPA axis, by inducing a rapid increase in catecholamines, heart rate, and metabolic rate [3,4]. Although the acute stress response is beneficial for improving resilience and metabolic fitness, it also

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temporarily increases physiological stress, as indicated by the increase in salivary cortisol[5]. Conversely, MIIT induces a mild autonomic response, resulting in increased parasympathetic activity and psychological relaxation, thereby reducing the release of cortisol and the feeling of stress [6, 7].

Salivary cortisol is a commonly used non-invasive marker for HPA axis activity, particularly for acute responses to exercise-induced stress [8]. An increase in the level of exercise intensity leads to increased cortisol levels, whereas moderate exercise can cause a drop or maintain the level of cortisol, depending on the duration of training and fitness level of the participants[9]. Heart rate variability (HRV) is another potent marker for the autonomic nervous system (ANS) balance. HIIT has been reported to cause a drop in HRV due to increased sympathetic activity, whereas MIIT leads to increased HRV due to increased parasympathetic activity [10, 11].

Aside from physiological biomarkers, the use of the State-Trait Anxiety Inventory (STAI) also helps to evaluate the mental state of an individual. Exercise has been proven to reduce state anxiety, regardless of the exercise intensity[12]. However, emerging data suggest moderate exercise intensity is more beneficial for anxiety relief, whereas high exercise intensity increases anxiety before exerting its benefits [13, 14].

Despite considerable scientific literature on the effects of exercise on stress physiology, direct comparisons of the effects of HIIT versus MIIT on physiological (cortisol, HRV) and psychological (anxiety) stress markers are still limited, particularly in young adults. Additionally, the majority of the literature has concentrated upon the chronic effects of exercise, whereas the effects of single exercise-session are of considerable interest for its prescriptions and stress management in daily life [15, 16].

Understanding the stress response to HIIT versus MIIT is of particular interest for the design of exercise programs for university students, who have different levels of fitness and may have different responses to exercise intensity. The effects of a single bout -exercise may give immediate insights into which type of exercise modality is the best for stress management.

This study examined the acute effects of a single bout of HIIT versus MIIT on salivary cortisol, HRV parameters, and state anxiety in healthy university students. This study offers a comprehensive assessment of exercise-induced stress responses by examining both physiological and psychological markers of stress. This will help in developing recommendations for reduction of stress by employing exercise interventions of optimal intensity.

CAPSULE SUMMARY

The acute impact of High-Intensity Interval Training (HIIT) versus Moderate-Intensity Interval Training (MIIT) on salivary cortisol, heart rate variability (HRV), and state anxiety was determined in young, healthy adults. HIIT elicited a strong acute physiological stress reaction, whereas MIIT promotes parasympathetic reactivation and superior short-term anxiolytic effects. Exercise prescriptions should be align with individual stress profiles.

METHODOLOGY

This parallel group experimental study was conducted as a single-visit open-label randomized controlled trial at the Exercise Physiology Laboratory, Department of Physiology, Khyber Medical University (KMU), Peshawar, from July to December 2025. The study had the approval from the Institutional Review Board (IRB), Ref No: KMU/IBMS/2025/205. Participation was entirely voluntary, and the confidentiality of the participants was maintained throughout. From the participants, informed consent was taken. Participants had the freedom to leave the study any time.

The acute effects of HIIT and MIIT on physiological and psychological stress markers were compared. Using computer-generated randomisation sequences, participants were assigned at random to one of the two intervention groups and were assigned to a single bout of exercise, either HIIT or MIIT. Opaque sealed envelopes were used to ensure allocation concealment. Because of the nature of the exercise interventions, it was not possible to blind participants and investigators. Pre- and post-intervention salivary cortisol, HRV, and anxiety levels were measured. This study was carried out under controlled conditions and lighting to minimize stress induced by external factors. The test was conducted between 8:00 am and 12:00 pm to account for the diurnal variation of cortisol levels and HRV.

Study participants were recruited from the constituent colleges of KMU through classroom announcements, electronic messages, and social media. The study setting was equipped with standard exercise machines, HRV recording devices, and salivary sample collection facilities. One orientation session was conducted before data collection to familiarize the study participants with the exercise machines.

Eligible participants included full-time university students, between 18 and 30 years of age, who were physically active, with at least two exercise sessions per week for a minimum of 30 minutes per session, and without any medical contraindications to high-intensity exercise, as well as without any acute illness, infection, or injury during the study period.

Exclusion criteria included individuals with chronic conditions such as cardiovascular, respiratory, and endocrine disorders, as well as those who were using medication that could affect cortisol, autonomic, and anxiety responses, smokers, and individuals who consumed caffeine within 12 hours of testing, irregular sleep patterns with less than 5 hours of sleep before testing, and those females who were menstruating at the time of cortisol sampling.

The sample size was determined using G*Power software

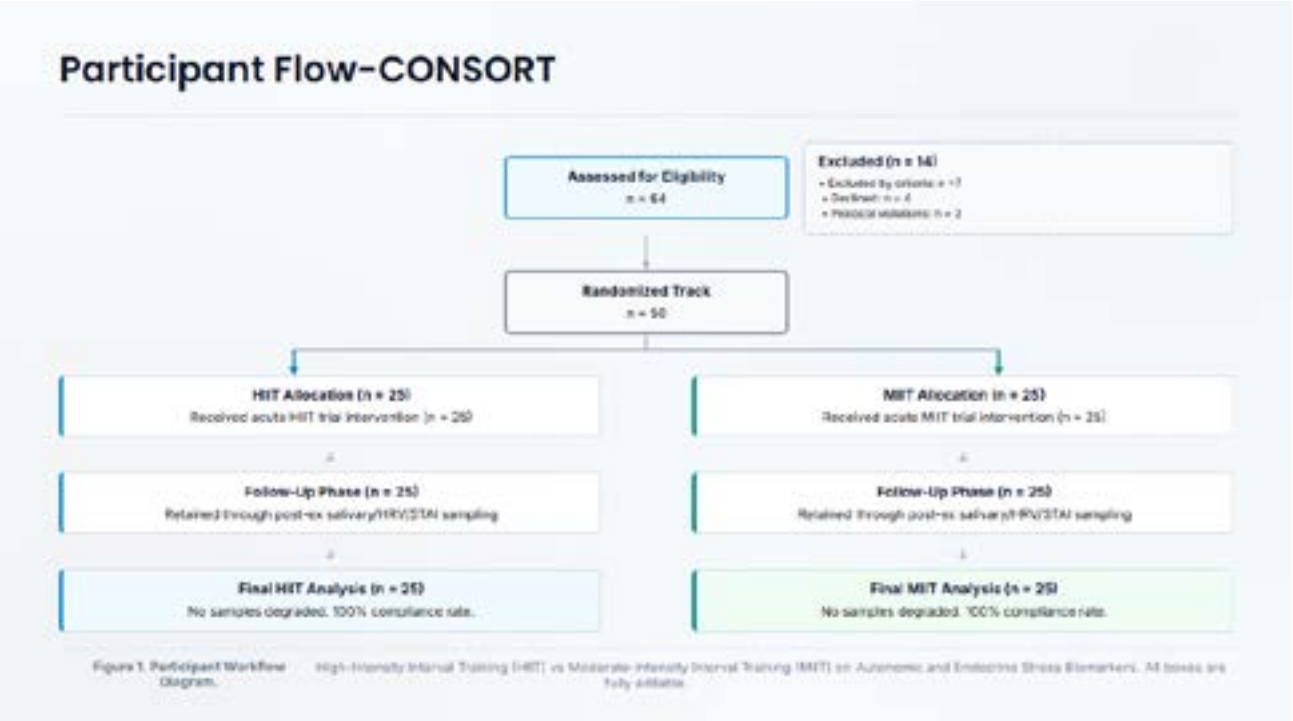

Figure 1. CONSORT Participant Flow Diagram.

(version 3.1), for a repeated measures mixed ANOVA (interaction within x between). The calculation involved two groups (HIIT and MIIT), two measurements (pre- and post-exercise), the level of significance (α) at 0.05, the statistical power (1 − β) at 0.80, correlation among repeated measures at 0.50, and the non-sphericity correction (ε) at 1.0. The effect size (Cohen's f = 0.25) was estimated assuming a medium effect size as recommended by Cohen when similar interaction effect sizes in the literature cannot be used [17]. Even though there are no studies that report the effect size of a similar interaction (effects of HIIT versus MIIT on salivary cortisol, HRV, and anxiety), exercise interventions have shown moderate to large group-by-time interaction effects in autonomic variables. For instance, Ketelhut et al found significant interaction effects on HRV parameters after HIIT interventions corresponding to effect sizes larger than the conventional medium[18]. Thus, a medium effect size (f = 0.25) was chosen a priori. With such assumptions, the required sample size comes out to be 40. Keeping in mind the possibility of attrition and sample loss, the sample size target was increased by 20%, resulting in a final target of 50 participants.

Figure 1 shows the flow of participants from the stages of screening, recruitment, random assignment into either the HIIT group (n=25) or MIIT group (n=25), to the different follow-up periods, and finally to the analysis stage. In HIIT, subjects were subjected to 5 minutes of warm-up, with a light cycle workout at 30-40% of HRmax.

The main HIIT routine entailed 10 cycles of 1-minute cycling at 85-95% of Hrmax, followed by 1 minute of recovery at 40-50% HRmax (for a total of 20 minutes). After this, there was a 5-minute cool -down period with light cycle exercises. The total time duration for the intervention process was exactly 30 minutes.

Regarding MIIT, participants completed a 5-minute warm-up of light cycling at 30–40%HRmax. The MIIT protocol consisted of 10 intervals of 1-minute cycling at 55–65%HRmax, interspersed with 1-minute passive recovery intervals (totalling 20 minutes). The session concluded with a 5-minute cool-down phase of light cycling, resulting in an identical total intervention duration of 30 minutes. Active recovery was incorporated into the HIIT protocol to maintain the prescribed high exercise intensity across successive intervals and to align with established HIIT programming recommendations. In contrast, passive recovery was employed during MIIT because the exercise intensity remained within the moderate range, and additional activity during recovery could have increased the overall exercise workload beyond the intended moderate-intensity stimulus. The recovery modalities were therefore selected to preserve the distinct physiological characteristics of each training protocol.

Saliva samples were collected using sterile saliva tubes. The samples were collected at pre-exercise (10 minutes seated rest). The second sample was collected at post-exercise (20 minutes after the end of the exercise, which is the time at which the cortisol levels peak)[19]. Before the experiment, participants were prohibited from eating, drinking, or brushing their teeth for an hour.

Salivary cortisol concentrations were determined by using a human cortisol enzyme-linked immunosorbent assay

(ELISA) kit, Calbiotech (Catalog No. CO368S; 96-test format, 12 × 8 breakable strip wells) according to the instructions of the manufacturer. The assay had a standard range of 20–400 ng/mL, an analytical sensitivity of 20 ng/mL, and required a sample volume of 25 µL per well. Cortisol concentrations were calculated from the standard curve generated for each assay and expressed as µg/dL. The ELISA kits were stored at 2–8°C until use.

Continuous electrocardiographic R-R intervals were recorded using a validated chest strap heart rate monitor, linked to the COSMED system. Short-term 5-minute stationary recordings were captured at pre-exercise (following a 10-minute seated stabilization period) and post-exercise (at a designated 5-minute quiet resting window). Time-domain metrics extracted included the Root Mean Square of Successive Differences (RMSSD) and the Standard Deviation of NN Intervals (SDNN), while frequency-domain analysis calculated the low-frequency to high-frequency (LF/HF) ratio.

Acute psychological state anxiety was evaluated using the State subscale of STAI, developed by Spielberger[20]. A validated regional translation of the 20-item scale was utilized, where elevated values correlate directly with higher perceived state anxiety. In this study population, the instrument demonstrated high internal consistency and reliability, achieving a baseline Cronbach's alpha (α) of 0.94.

The participants reported to the lab following a 12-hour abstinence from caffeine, stress, and strenuous exercise. After a 10-minute rest, baseline saliva cortisol, HRV, and STAI-state measures were recorded. The participants then performed the exercise task for which they were randomly assigned. The saliva samples and HRV recordings were collected, following the standardized time intervals post-exercise. The procedures were performed by trained lab staff who were unaware of the hypothesis.

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed using the Shapiro–Wilk test and visual inspection of Q–Q plots. Independent-samples t-test for continuous variables and Chi-square tests for categorical variables were utilised to compare the baseline physiological and demographic characteristics between groups.

Within-group pre-to-post changes in physiological and psychological outcomes were assessed using paired-samples t-tests. The primary study outcomes were analyzed using a 2 × 2 repeated-measures mixed-design ANOVA, with Group (HIIT vs. MIIT) as the between-subject factor and Time (Pre vs. Post) as the within-subject factor. The Group × Time interaction term was considered the primary effect of interest, indicating whether changes over time differed between the intervention groups. Effect sizes were reported as partial eta-squared (η^2p), with values of 0.01, 0.06, and 0.14 representing small, medium, and large effects, respectively. Statistical significance was set at $p < 0.05$.

Table 1. Baseline Characteristics of Participants (n=50)

Variables	HIIT (n = 25) n(%)	MIIT (n = 25) n(%)	t / χ2 value	p-value
Gender Male Female	 13(52) 12(48)	 12(48) 13(52)	0.080	0.79
Variables	HIIT (n = 25) mean±SD	MIIT (n = 25) mean±SD	t / χ2 value	p-value
Age (years)	22.8 ± 2.1	23.1 ± 2.3	-0.485	0.56
BMI (kg/m²)	23.7 ± 2.6	23.4 ± 2.9	0.385	0.68
Resting HR (bpm)	75.6 ± 6.8	76.4 ± 6.5	-0.425	0.62
Salivary Cortisol (µg/dL)	0.265 ± 0.07	0.258 ± 0.08	0.330	0.72
RMSSD (ms)	34.8 ± 10.9	35.2 ± 11.3	-0.127	0.88
SDNN (ms)	48.1 ± 12.4	49.3 ± 13.1	-0.333	0.81
LF/HF ratio	2.41 ± 0.8	2.38 ± 0.7	0.141	0.87
STAI-State	42.6 ± 7.2	43.1 ± 6.9	-0.251	0.78

BMI, Body Mass Index; HR, Heart Rate; STAI, State–Trait Anxiety Inventory; RMSSD, Root Mean Square of Successive Differences; SDNN, Standard Deviation of NN Intervals; HRV, Heart Rate Variability; ms, milliseconds.

Table 2. Pre- and Post-Exercise Salivary Cortisol Levels (n=50)

Group	Pre-exercise (µg/dL) mean±SD	Post-exercise (µg/dL) mean±SD	% Change	Within p-value	Interaction p-value (Time X Group)	Effect size (η^2_p)
HIIT	0.27 ± 0.07	0.36 ± 0.08	32.80	<0.001	<0.001	0.38 Large
MIIT	0.26 ± 0.08	0.24 ± 0.07	−9.3	0.041		

HIIT, High-Intensity Interval Training; MIIT, Moderate-Intensity Interval Training; µg/dL, micrograms per decilitre.

Table 3. Pre and Post Exercise HRV parameters (n=50)

Variable	Group	Pre-exercise mean±SD	Post-exercise mean±SD	% Change	p-value (within group)	Interaction p-value (Time X Group)	Effect size (η^2_p)
RMSSD (ms)	HIIT	34.8 ± 10.9	24.3 ± 8.7	−30.2	<0.001	<0.001	0.44 Large
	MIIT	35.2 ± 11.3	41.6 ± 12.1	18.20	0.004		
SDNN (ms)	HIIT	48.1 ± 12.4	39.7 ± 11.6	−17.5	0.01	<0.001	0.26 Large
	MIIT	49.3 ± 13.1	53.9 ± 14.0	9.40	0.03		
LF/HF ratio	HIIT	2.41 ± 0.8	3.12 ± 1.0	+29.5	<0.001	<0.001	0.32 Large
	MIIT	2.38 ± 0.7	1.92 ± 0.6	−19.3	0.002		

RMSSD, Root Mean Square of Successive Differences; SDNN, Standard Deviation of NN Intervals; LF/HF ratio, low-frequency to high-frequency HRV ratio; HIIT, High-Intensity Interval Training; MIIT, Moderate-Intensity Interval Training; ms, milliseconds.

Group	Pre-exercise mean±SD	Post-exercise mean±SD	Mean Change	% Change	Within p-value	Interaction p-value	Interaction Effect Size (η^2_p)
HIIT	42.6 ± 7.2	37.4 ± 6.8	−5.2	−12.2	<0.001	0.024	0.10 (Medium)
MIIT	43.1 ± 6.9	34.1 ± 6.5	−9.0	−20.9	<0.001		

STAI-State, State Anxiety subscale of the State–Trait Anxiety Inventory; HIIT, High-Intensity Interval Training; MIIT, Moderate-Intensity Interval Training.

Table 4. Pre and Post Exercise State Anxiety levels (n=50)

RESULTS

All 50 participants completed the study without any adverse effects. The compliance rate for the exercise protocol was 100%. The results also showed that the participants in the HIIT and MIIT study groups were similar in terms of demographic and physiological factors such as age, gender, BMI, heart rate, salivary cortisol level, RMSSD, and anxiety level. No significant difference was found in the baseline characteristics of study participants ($p > 0.05$) (Table 1).

There was a marked divergence in the endocrine stress reaction between the two groups following the intervention. The HIIT group showed a marked increase in salivary cortisol levels after the exercise, representing a 32.8% increase. Conversely, the MIIT group showed a mild decline in salivary cortisol levels after the exercise, representing a 9.3% decline. This indicates that high-intensity intervals triggered a marked endocrine stress reaction, whereas moderate-intensity intervals triggered a mild endocrine calming effect (Table 2).

Significant changes in autonomic responses were noted between the two groups. The HIIT group showed a reduction in HRV indices, where the values of RMSSD decreased by 30.2%, SDNN decreased by 17.5%, and the LF/HF ratio increased. This shows an increased level of sympathetic activity. The MIIT protocol resulted in increased parasympathetic activity, where the values of RMSSD increased by 18.2%, while the values of SDNN increased by 9.4%, along with a decreased LF/HF ratio. This shows that MIIT may help in the recovery of the ANS, leading to a relaxed state (Table 3).

Both modes of exercise led to a reduction in psychological stress as measured by the STAI-State scale; however, the degree of change was significantly different. The HIIT group had a reduced STAI-State score reflecting a 12.2% reduction in anxiety. The MIIT group had a more significant change, with the reduced STAI-State score reflecting a 20.9% reduction in state anxiety. These data suggest that, although both modes of exercise have a positive effect on the enhancement of the mood state, the effect of MIIT is more significant (Table 4).

DISCUSSION

This study investigated the acute effects of both HIIT and MIIT on physiological and psychological markers of stress in healthy young adults. The results indicated that clear distinctions exist between both modes of exercise. HIIT was associated with increased salivary cortisol and decreased HRV, whereas MIIT was associated with decreased cortisol, increased HRV, and greater anxiety-reduction responses. These results support the notion that exercise intensity plays an important role in acute stress responses.

The marked rise in cortisol seen in the HIIT group is consistent with previously established evidence showing that high-intensity exercise is a strong activator of the HPA axis, resulting in cortisol secretion in response to increased metabolic demands[21,22]. Although the rise in cortisol in high-intensity exercise is physiological and adaptive, in terms of survival responses, it also represents an increased endocrine stress response[23]. In contrast, the reduction in cortisol, seen in the MIIT group, is consistent with evidence showing that moderate-intensity exercise is associated with homeostasis, decreased endocrine stress, and improved psychological recovery.The results obtained from the HRV analysis again emphasize the different responses of the ANS to the intensity of exercise. The decrease in RMSSD and SDNN, along with an increase in LF/HF, in the HIIT group suggests a sympathetic dominance along with vagal withdrawal, which is a characteristic response of the autonomic ANS to acute physiological stress[24-26].

These changes in the ANS have been found in both trained and untrained subjects who have been subjected to high-intensity exercise[27]. The increase in RMSSD and SDNN, along with a decrease in LF/HF, in the MIIT group suggests a parasympathetic dominance, which has been found in previous studies where the parasympathetic nervous system shows an enhanced response to moderate-intensity exercise[28]. This enhanced parasympathetic response might be the reason for the enhanced anxiolytic response found in the MIIT group.

From a psychological perspective, both modes of exercise resulted in lower state anxiety levels, with MIIT showing almost double the percentage of reduction compared to HIIT.

Existing literature indicates that moderate-intensity exercises elicit optimal levels of arousal and improve affective responses without any discomfort, dyspnea, or fatigue, as observed with high-intensity exercises[29,30]. Although HIIT has been linked to long-term psychological benefits, existing literature indicates that the post-exercise period may lead to increased levels of distress or cognitive load, especially in individuals who are new to HIIT[31].

While these acute findings offer pivotal baseline evidence on single-bout responses, the long-term biological consequences remain a vital avenue for research. Future longitudinal interventional trials spanning 8 to 12 weeks are strongly recommended to evaluate whether chronic adaptations to HIIT modulate or attenuate this initial acute hyper-cortisolemic response through systemic habituation, or if sustained sympathetic stress creates an allostatic load risk in vulnerable student dynamics.

Additionally, it is also necessary to consider these biomarker changes in the regional context. The students studying in developing South Asian countries, particularly in public medical universities of Pakistan, will be facing their own set of baseline stress levels due to high competition and limited resources in the institutions. The regional environment of such stress management studies highlights that any lifestyle change must match the baseline stress of the individual to not exacerbate the already affected neuroendocrine system[31,32].

Overall, it can be concluded that there lies a conceptual

distinction between HIIT as a physiological stressor and MIIT as a modulatory stimulus. There are practical implications that result from the study. People who want to feel a strong stimulus to improve their metabolism or performance may find HIIT satisfactory. However, for people who want to alleviate stress, regulate emotions, or relieve anxiety, MIIT can be a better choice.

This study has several strengths. The randomization of the study design minimizes allocation bias. The measurement of salivary cortisol levels and HRV is a reliable method of assessing physiological responses. The measurement of the STAI-State scale allowed for a psychological measurement to be taken in addition to the biological measures.

Limitations: The study only examined the acute effects of a single session of exercise, and the chronic effects could differ significantly. Secondly, certain factors, such as the lack of blinding, level of fitness, and sleeping status, could have an impact on the levels of stress biomarkers, despite the standardized conditions. Thirdly, the study only examined young healthy adults, and the results cannot be generalized to the elderly and those with certain pathological conditions.

A potential limitation of the study is the use of different recovery modalities between the HIIT and MIIT protocols. Both active recovery for HIIT and passive recovery for MIIT may independently affect the studied parameters. While both recovery types were selected according to common exercise programs and in accordance with the planned exercise intensity range, their impacts may be difficult to separate from those of exercise intensity itself.

No clinical trial registration number is available for the current study. This may limit the transparency and reproducibility of the study.

CONCLUSION

This research highlights the significance of exercise intensity in the development of physiological and psychological stress responses in healthy adults. HIIT increases salivary cortisol levels and reduces HRV, suggesting higher levels of sympathetic and HPA activity. On the other hand, MIIT leads to lower cortisol levels, higher parasympathetic activity, and more change in state anxiety. These results indicate the importance of HIIT as a physiological stress reaction, while MIIT seems to have a more calming effect on physiological stress reactions.

Practical implications of the study show that MIIT is more appropriate for stress reduction or mood stabilization, while HIIT is more appropriate for those who want to improve metabolic responses despite a transient increase in physiological stress reactions.

ETHICAL APPROVAL: KMU/IBMS/2025/205.
CONSENT FOR PUBLICATION: *Written, informed consent was obtained from the study participants.*
AVAILABILITY OF DATA: *Data is available from the corresponding author on a justified request.*
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AUTHORS' CONTRIBUTION

- ***Saman Tauqir:*** *Conception and design, Analysis and interpretation of data.*
- ***Shazia Shakoor:*** *Analysis and interpretation of data.*
- ***Fazeelat Hajra Kareem:*** *Acquisition of data.*
- ***Hira Faisal:*** *Drafting the article.*
- ***Miraj Ahmad Khan:*** *Critical revision.*

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ORIGINAL ARTICLE

DEVELOPMENT OF A PIMS SPECIFIC DENGUE HEPATITIS SEVERITY SCORE: A RETROSPECTIVE CROSS SECTIONAL STUDY OF EMR DATA

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ABSTRACT

Objective: To develop and evaluate a simple PIMS-specific Dengue Hepatitis Severity Score using routinely available clinical variables.

Study design: Retrospective cross-sectional study.

Place and duration of study: Pakistan Institute of Medical Sciences (PIMS), Islamabad, 06 months (June to November 2025).

Methodology: This study was conducted using electronic medical records(EMR) of patients of ≥13 years of age, with lab-confirmed dengue infection and hepatic involvement. The patients were categorized into severe and non-severe dengue hepatitis groups. Independent predictors were identified using multivariate logistic regression, and a clinical severity score was developed. Receiver operating characteristic (ROC) curve analysis was used to evaluate diagnostic performance.

Results: Total patients in this study were 97. Bleeding (OR = 11.24), hypotension (OR = 6.99), and hepatomegaly (OR = 5.95) were independent predictors of severe dengue hepatitis ($p < 0.05$). A three-point severity score was constructed (0–3). The score demonstrated good discrimination with an AUC of 0.761 (95% CI: 0.659–0.863). A cut-off ≥1 showed sensitivity of 77.1% and specificity of 71.0%.

Conclusion: The PIMS Dengue Hepatitis Severity Score is a simple, bedside tool that effectively identifies patients at risk of severe disease. It can be helpful for early triage and clinical decision-making, although external validation is required before general use.

Key words: *Dengue, Hepatitis, Risk Assessment, Severity of Illness Index.*

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INTRODUCTION

Dengue fever is among the most significant mosquito-borne viral infections on the planet, the geographical distribution of which is rapidly expanding and the disease burden is growing exponentially in tropical and subtropical areas. According the World Health Organization(WHO), hundreds of millions of dengue cases are reported every year, and a significant part of these develop into serious disease that needs hospital admission and intensive care [1,2]. In South Asia, including Pakistan, dengue outbreak is still a significant burden of on the healthcare systems [3].

The hepatic involvement is a frequent and clinically relevant symptom of dengue infection. There is a tendency of mild to moderate rise in transaminases. Some patients develop dengue hepatitis, with significant increase of enzymes, hepatomegaly, jaundice, coagulopathy. In rare cases, acute liver failure occurs [4,5]. Dengue liver injury pathogenesis is multifactorial, comprising the direct viral cytopathic effects, immune-mediated hepatocellular injury, hypoxic injury because of shock, and the systemic inflammatory responses [6].

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A number of studies have revealed that dengue patients with hepatic dysfunction are at high risk of bleeding, shock, long hospital stay, and death[7,8]. High Aspartate aminotransferase (AST) levels, hepatomegaly, and clinical instability have been continuously linked to adverse outcomes[9]. Nevertheless, the increasing awareness of dengue hepatitis as a significant complication has not been accompanied by a simple clinical scoring system, one that is widely accepted and solely targeted to predict severe dengue hepatitis based on the use of bedside variables.

CAPSULE SUMMARY

A simple PIMS-specific Dengue Hepatitis Severity Score was developed and evaluated, using routinely the available clinical variables. It effectively identified patients at risk of severe disease, which can helpful for early triage and clinical decision-making, although external validation is required before general use.

Early detection of patients who are at risk of worsening is essential to optimize monitoring intensity, resource allocation, and avoid negative outcomes, especially in resource-constrained environments. The majority of the current dengue severity models use complicated laboratory parameters or imaging results that might not be easily accessible in practice [5].

In this context, no simple dengue hepatitis–specific bedside scoring system currently exists to predict severe hepatic involvement using routinely available clinical variables, particularly in resource-limited settings like South Asian populations. The present study aimed to develop and evaluate a Pakistan Institute of Medical Sciences (PIMS)-specific Dengue Hepatitis Severity Score using routinely available clinical features in adolescents and adults with dengue-associated hepatic involvement. This study aims to enhance early risk assessment and facilitate prompt clinical decision-making in hospitalised dengue patients by developing a simple, practical bedside tool.

METHODOLOGY

This was a retrospective, cross-sectional study, done at the Department of General Medicine, PIMS, Islamabad, from June 2025 to November 2025. After obtaining institutional ethical approval, electronic medical records (EMR) were reviewed for the purpose of developing and validating a dengue hepatitis severity scoring system. The study included patients aged ≥13 years who were diagnosed with lab-confirmed dengue infection; non-structural protein 1 (NS1) antigen and/or dengue antibody (IgM); and hepatic involvement, characterized by high AST or alanine aminotransferase (ALT) levels ≥100U/L. Pregnant patients, patients having pre-existing chronic liver disease, viral hepatitis, concomitant viral infections, taking hepatotoxic drugs, or incomplete EMR were excluded. A consecutive sampling method was used.

The sample size of 96 was calculated with the WHO calculator by keeping the confidence interval of 95%, anticipated prevalence of dengue-associated liver involvement 48%, and absolute precision of 10%[10]. A total of 97 eligible patients fulfilling the inclusion criteria were included in the final analysis, which met and slightly exceeded the calculated sample size.

Taking into account the study objectives and relevant literature, a structured proforma was designed for data collection retrospectively from the EMR system of the PIMS. It included demographic characteristics, clinical presentation, laboratory findings, and outcome variables. To ensure data quality, all extracted records were reviewed for completeness and consistency. Patients with missing clinical / laboratory information were excluded. Data were entered into a password-protected database. To minimize transcription errors before statistical analysis the data were cross-checked by a second investigator.

The main outcome variable was severe dengue hepatitis, defined as "dengue-associated hepatic involvement (ALT/AST ≥100U/L) accompanied by one or more indicators of severe clinical deterioration during hospitalization, which are admission to a high-dependency or intensive care unit, development of hepatic failure, or in-hospital mortality". Patients not meeting the above-mentioned criteria were placed in the category of having non-severe dengue hepatitis. Independent variables were demographic profile (age and sex), clinical features on admission (bleeding manifestations, hypotension and hepatomegaly), and laboratory parameters (platelet count, serum albumin, AST, ALT, serum bilirubin). Bleeding manifestations were recorded as the presence of clinically documented mucosal, gastrointestinal, or other hemorrhagic events. Hypotension was defined as systolic blood pressure <90 mmHg or documentation of hemodynamic instability in the medical record. Hepatomegaly was determined based on the finding of clinical examination documented by the treating physician where the liver edge is palpable >2 cm below the right costal margin during deep inspiration, or when the total liver span exceeds 12 to 15 cm upon percussion in the midclavicular line. These variables were extracted from EMR and evaluated as potential predictors of severe dengue hepatitis.

Variables demonstrating clinical relevance and statistical significance were entered into the multivariable logistic regression model for development of the Dengue Hepatitis Severity Score. The severity of dengue hepatitis was determined, using the severity of dengue hepatitis recorded during the course of hospitalization. Patients with a severe outcome were identified as those who experienced significant clinical deterioration that necessitated advanced care, whereas those who did not were considered non-severe.

IBM SPSS Statistics version 23 was used to analyze data. Continuous variables were checked in terms of normality and presented in the form of mean ± standard deviation or median

with interquartile range (IQR), respectively. Frequencies and percentages were used to depict categorical variables. The Mann-Whitney U test (for continuous variables) and the Chi-square test of association (for categorical variables like bleeding, hypotension, hepatomegaly), were applied to make comparisons between severe and non-severe groups. A multivariate binary logistic regression model was used to enter variables of clinical relevance and get the results as odds ratios (ORs) with 95 percent confidence interval (CI). A Dengue Hepatitis Severity Score was constructed based on the key predictors found in multivariate analysis; 1 point each for bleeding, hypotension, and hepatomegaly was assigned in order to facilitate clinical applicability and ease of bedside use. The overall score was between 0 and 3. The analysis performed was a receiver operating characteristic curve (ROC) analysis to evaluate the discriminative ability of the severity score and to determine the optimum cut-off value. Diagnostic performance was determined using sensitivity, specificity, and area under the curve (AUC). A p-value of less than 0.05 was regarded as being statistically significant.

RESULTS

The sample size was 97 patients. The participants had a mean age of 49.19 ±19.10 years, and their ages ranged between 13 and 80 years. The study population was females, comprised of slightly majority (51.5%), and males, 48.5% (Table 1).

Serum bilirubin and liver enzymes were high and were highly suggestive of hepatic involvement. Thrombocytopenia was prevalent. Serum albumin was within normal range. Results of lab tests indicate the presence of significant hepatic dysfunction in the subjects of the study (Table 1).

The platelet counts were found to be lower in the patients with severe dengue hepatitis than in the non-severe group, but this was not statistically significant. On the contrary, bleeding symptoms were statistically predominant in severe cases.

Table 1. Baseline Characteristics of the Study Population (n = 97)

Variable	Value
Age (years), mean ± SD	49.19 ± 19.10
Male, n (%)	47 (48.5)
Female, n (%)	50 (51.5)
Laboratory parameter	Median (IQR)
ALT (U/L)	193.0 (211.5)
AST (U/L)	344.0 (280.5)
Platelet count ($\times 10^9$/L)	107.0 (82.5)
Serum bilirubin (mg/dL)	2.09 (1.68)
Serum albumin (g/dL)	3.81 (0.72)

Likewise, hypotension and hepatomegaly were statistically more prevalent in the severe group than in non-severe patients. Table 2

Table 2. Comparison between Severe and Non-Severe Dengue Hepatitis (n = 97)

Variable	Non-severe (n = 62)	Severe (n = 35)	p-value
Platelet count, median (IQR)	109 (90.5)	96 (80.0)	0.583†
Bleeding, n (%)	6 (9.7)	18 (51.4)	<0.001‡
Hypotension, n (%)	6 (9.7)	12 (34.3)	0.003‡
Hepatomegaly, n (%)	6 (9.7)	12 (34.3)	0.003‡
ALT (U/L), median (IQR)	196.0 (208.3)	178.0 (201.0)	0.526†
AST (U/L), median (IQR)	344.0 (263.3)	344.0 (275.0)	0.555†
Serum bilirubin (mg/dL), median (IQR)	1.98 (1.65)	2.22 (1.60)	0.406†
Serum albumin (g/dL), median (IQR)	3.81 (0.73)	3.84 (0.73)	0.608†

† Mann–Whitney U test used for continuous variables, ‡ Chi-square test used for categorical variables. A p-value < 0.05 was statistically significant.

The multivariate logistic regression analysis was conducted to detect the independent predictors of severe dengue hepatitis. The complete model was statistically significant (Omnibus $\chi^2 = 39.30$, $p < 0.001$) and had good explanatory power with the Nagelkerke R2 being 0.457, showing that the included variables accounted for about 46% of the variation in the severity of the disease. The model calibration was good based on an insignificant Hosmer-Lemeshow test ($p = 0.550$), which implied that it was in agreement with the observed and the predicted results (Table 3).

ROC curve analysis was conducted in order to find out the discriminative capacity of the individual clinical predictors in relation to severe dengue hepatitis. Bleeding had the greatest diagnostic accuracy with a good discriminatory performance. Hypotension and hepatomegaly were found to have a fair predictive value. These results substantiate the fact that these variables should be added to the dengue hepatitis severity scoring system (Table 4).

The dengue hepatitis severity score had a good discriminating power. An optimal balance between sensitivity and specificity of predicting severe dengue hepatitis was given by a cut-off value of ≥1 (Table 5).

Table 3. Multivariate Logistic Regression Analysis for Severe Dengue Hepatitis (n = 97)

Variable	β coefficient	Adjusted Odds Ratio (AOR)	95% CI	p-value
Platelet count	−0.003	0.997	0.986–1.008	0.624
ALT	0.003	1.003	0.998–1.008	0.178
AST	−0.002	0.998	0.994–1.001	0.235
Bleeding	2.420	11.24	3.28–38.51	<0.001
Hypotension	1.945	6.99	1.73–28.25	0.006
Hepatomegaly	1.783	5.95	1.54–22.94	0.010

Table 4. ROC Analysis of Clinical Predictors for Severe Dengue Hepatitis (n = 97)

Variable	AUC (95% CI)	p-value	Interpretation
Bleeding	0.709 (0.594–0.824)	0.001	Good discrimination
Hypotension	0.623 (0.502–0.744)	0.045	Fair discrimination
Hepatomegaly	0.623 (0.502–0.744)	0.045	Fair discrimination

Table 5. Diagnostic Performance of the Dengue Hepatitis Severity Score (n = 97)

Cut-off value	Sensitivity (%)	Specificity (%)	AUC (95% CI)	p-value
≥ 1	77.1	71.0	0.761 (0.659–0.863)	<0.001

DISCUSSION

The present study developed and evaluated a novel PIMS-specific Dengue Hepatitis Severity Score using routinely available bedside clinical variables among hospitalized patients with dengue-associated hepatic involvement. This study identified bleeding manifestations, hypotension, and hepatomegaly as independent predictors of severe dengue hepatitis. The commonly measured laboratory parameters, including platelet count, AST, and ALT levels, were not independently associated with severe disease after multivariable adjustment in this study. A three-point severity score derived from these predictors demonstrated good discriminatory performance, with an AUC of 0.761, and a good sensitivity and specificity at a cutoff value of ≥1. Collectively, these findings suggest that readily identifiable clinical features may provide an effective and pragmatic approach for early risk stratification of dengue patients with hepatic involvement, particularly in resource-constrained healthcare settings. Recent research has revealed that complications of dengue and increased bleeding and shock to be linked with abnormal liver functioning tests and hepatomegaly [11,12].

The mean age of around 49 years suggests that dengue-associated hepatic complications are not only seen in younger populations but are increasingly affecting the middle-aged and older adults. This is in line with recent regional studies, showing a shift toward greater disease burden among older individuals, who often have a higher risk of organ involvement and severe clinical outcomes [13,14]. The close gender distribution observed of our study indicates severe hepatic involvement occurring across both sexes almost equally. Liver involvement has increasingly been identified as a determinant of dengue infection severity. The median AST and ALT values observed in our cohort reveal significant hepatic injury, with higher AST levels than ALT levels, a finding frequently described in dengue hepatitis. Earlier studies have also reported that AST predominance shows hepatocellular damage as well as injury to skeletal and cardiac muscle tissues as a result of systemic inflammation and viral infection. Studies conducted in Pakistan, Columbia, Nepal, and other dengue-endemic countries have reported similar observations where higher AST levels were associated with more severe clinical picture and longer hospitalization. The current findings therefore reinforce the existing evidence that liver involvement represents a clinically relevant component of dengue pathophysiology [15-17].

Platelet count was not significantly associated with severe dengue hepatitis even after multivariate adjustment although thrombocytopenia remained prevalent in our patients. Recent studies have also made similar observations and propose that platelet count is not a reliable discriminator of severity and must be combined with clinical features [18,19]. Conversely, bleeding manifestations were found as the most robust independent predictor of severe disease in our model [20]. This observation concurs with the current evidence showing that the manifestation of overt bleeding is a sign of progressive capillary leakage, coagulopathy, and approaching clinical worsening [21].

Another predictor of severe dengue hepatitis in our cohort

was hypotension. Hypotension is a manifestation of depletion of intravascular volume and progressive shock, the main mechanisms in severe dengue. Previous study has attested to the fact that an early hypotension closely correlates with intensive care hospitalization and poor outcomes[22]. Hepatomegaly was also predictive of severity by itself, which confirms prior studies that liver enlargement is an indication of hepatic inflammation, congestion, and early dysfunction in relation to complicated disease [14,16].

The Dengue Hepatitis Severity Score had good discriminatory ability, with AUC = 0.761. A cut-off of ≥1 had balanced sensitivity and specificity, and it suggests that even a single high-risk feature can be followed a bit more closely. Our score has a performance that is similar to new-proposed models of dengue severity, most of which incorporate organ involvement and clinical instability to enhance pre-emptive reports [17,18]. The major strengths of this study are that it uses real-world EMR data, a standardized definition of hepatic involvement, and internal validity with a strong statistical tool.

Notably, this score is based on bedside clinical variables, which is particularly appropriate where advanced biomarkers or imaging may not be easily accessible.

Limitation: The limitation of the current study is its retrospective, single-center study design, which may have compromised the generalizability of results. Multicenter prospective studies in different populations should be done in future to validate this score, along with assessment of its effects on clinical decisions and patient outcomes.

CONCLUSION

This study successfully developed and evaluated a simple, three-point PIMS-specific Dengue Hepatitis Severity Score based on bleeding, hypotension, and hepatomegaly. The score had good discriminatory ability for predicting severe dengue hepatitis. With its reliance on easily available bedside clinical parameters, this score is practical and applicable in resource-limited settings. Early use of this scoring system can facilitate timely risk stratification, improve monitoring strategies, and support early clinical decision-making in dengue-associated hepatic involvement. However, external validation in larger, multicenter prospective cohorts is required prior to its routine implementation.

ETHICAL APPROVAL: *Ref No: F-5-2/2024(ERRC)/PIMS*
CONSENT FOR PUBLICATION: *Written, informed consent was obtained from the study participants.*
AVAILABILITY OF DATA: *Data is available from the corresponding author on a justified request.*
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CONFLICT OF INTEREST: *None*
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AUTHORS' CONTRIBUTION

- ***Shaista Faheem:*** *Conception and design, Drafting the article, Critical revision.*
- ***Sana Waqar:*** *Conception and design, Acquisition of data, Aanalysis and interpretation of data, Drafting the article, Critical revision.*
- ***Fareha Rasheed:*** *Conception and design, Acquisition of data, Aanalysis and interpretation of data, Drafting the article.*
- ***Maria Zafar:*** *Acquisition of data, Aanalysis and interpretation of data, Drafting the article, Critical revision.*
- ***Samina Rashid: A****analysis and interpretation of data, Drafting the article.*
- ***Aashar Khalid:*** *Conception and design, Acquisition of data, Drafting the article.*

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CASE REPORT

SECONDARY VESICAL CALCULUS FORMATION DUE TO INTRAVESICAL MIGRATION OF A COPPER-T INTRAUTERINE CONTRACEPTIVE DEVICE; A CASE REPORT

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ABSTRACT

Intrauterine contraceptive devices (IUCDs) are the most effective and long term, reversible, contraceptive method, used worldwide. Uterine perforation resulting in migration of IUCD into adjacent organs is an uncommon but potentially serious complication. Intravesical migration may lead to lower urinary tract symptoms, recurrent urinary tract infections, and bladder stone formation. A 50-year-old multiparous woman presented with intermittent burning micturition for one month. An ultrasound examination performed for evaluation of chronic abdominal pain incidentally revealed a large vesical calculus. Subsequent non-contrast computed tomography (CT) of the abdomen and pelvis demonstrated a 4.8 × 1.4 cm bladder stone surrounding a T-shaped foreign body consistent with a migrated Copper-T IUCD. Further history revealed probable IUCD insertion about 17 years earlier. The patient underwent cystoscopy and endoscopic litholapaxy with successful fragmentation and removal of the vesical calculus and embedded IUCD fragments.The postoperative course was uneventful. The patient experienced complete resolution of urinary symptoms and remained asymptomatic at follow-up. Although rare, intravesical migration of an IUCD should be considered in women presenting with persistent lower urinary tract symptoms or vesical calculi, particularly when there is a history of IUCD insertion. Early diagnosis and timely intervention can prevent long-term complications.

Keywords: *Bladder stone, Copper-T, Cystoscopy, Intravesical migration, IUCD, Vesical calculus.*

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INTRODUCTION

Intrauterine contraceptive devices (IUCDs) are widely used, worldwide, because of their effectiveness, reversibility, safety profile, and affordability. Complications may occur, including expulsion, infection, uterine perforation, and migration into adjacent pelvic or abdominal organs. Uterine perforation is uncommon, with an estimated incidence ranging from 1 to 3 per 1,000 insertions[1].

Migration of an IUCD into the urinary bladder is a rare complication that may remain asymptomatic for years before clinical presentation[2]. Once inside the bladder, the device acts as a nidus for stone formation and can present with symptoms of recurrent urinary tract infections, hematuria, dysuria, or bladder calculi[3]. Because delayed diagnosis can lead to significant morbidity, awareness of this complication is essential.

We report a case of secondary vesical calculus formation around a migrated Copper-T IUCD, diagnosed approximately 17 years after insertion and successfully managed by endoscopic removal.

Case Presentation: A 50-year-old multiparous woman was referred to the Department of Urology at HITEC Institute of Medical Sciences, Taxila, after an abdominal ultrasound revealed a large vesical calculus.

The patient complained of intermittent burning micturition for one month. She denied gross hematuria, urinary retention, urinary incontinence, fever, flank pain, or recurrent urinary tract infections. Her medical history was significant for chronic epigastric pain for approximately three years, for which she had

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been receiving treatment with proton pump inhibitors and antacids.

As part of the evaluation of worsening abdominal pain, a plain x-ray KUB was carried out, demonstrating a large bladder stone (Figure 1). Ultrasound of the abdomen and pelvis confirmed the diagnosis of bladder stone. The patient was subsequently referred for urological assessment.

Further evaluation with a non-contrast CT scan of the abdomen and pelvis revealed a 4.8 × 1.4 cm irregular hyperdense vesical calculus, surrounding a T-shaped foreign body consistent with a Copper-T IUCD (Figure 2). The stone appeared rough and irregular in morphology.

On detailed questioning, the patient recalled being taken to a local birth attendant shortly after the birth of her youngest child, approximately 17 years earlier. Although she had not been informed regarding IUCD insertion or follow-up requirements, this history strongly suggested the placement of a Copper-T IUCD during the postpartum period.

CAPSULE SUMMARY

A case of a woman with intermittent burning micturition is presented who was found to have a large vesical calculus formed around a migrated Copper-T IUCD, 17 years after insertion, which was successfully removed by endoscopic litholapaxy.

Diagnostic Assessment: Based on clinical history and radiological findings, a diagnosis of secondary vesical calculus formed around a migrated intravesical Copper-T IUCD was established.

Management: The patient was admitted for endoscopic management. Diagnostic cystoscopy demonstrated a large irregular vesical calculus, occupying the bladder lumen. The stone was found to be formed around an embedded foreign body, consistent with a migrated IUCD(Figure 3a&b).

Endoscopic litholapaxy was performed. Owing to the large size and hardness of the stone, fragmentation was achieved using a stone punch. During the procedure, the embedded IUCD was also fragmented and removed along with the stone fragments. Complete clearance of visible stone and foreign-body material was achieved (Figure 4).

A two-way Foley catheter was inserted postoperatively and was maintained for three days. The patient received analgesics and prophylactic antibiotics. Following catheter removal, she

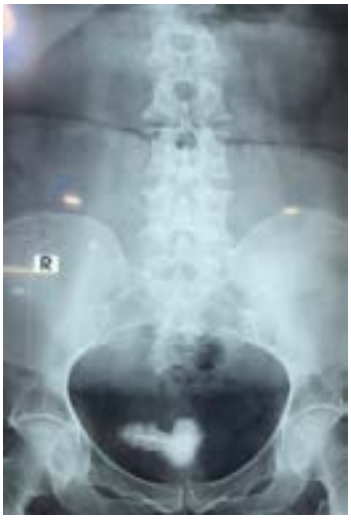

Figure 1:

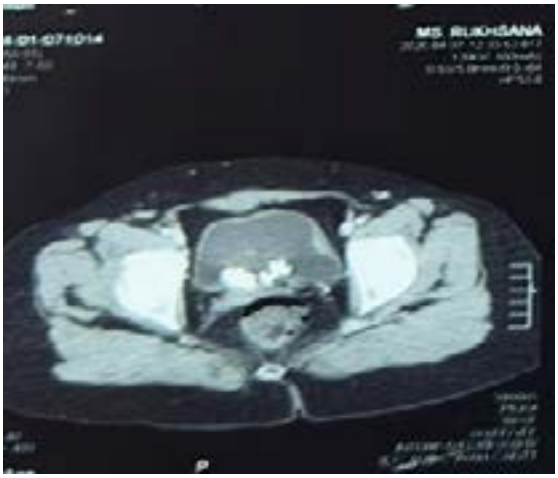

Figure 2:

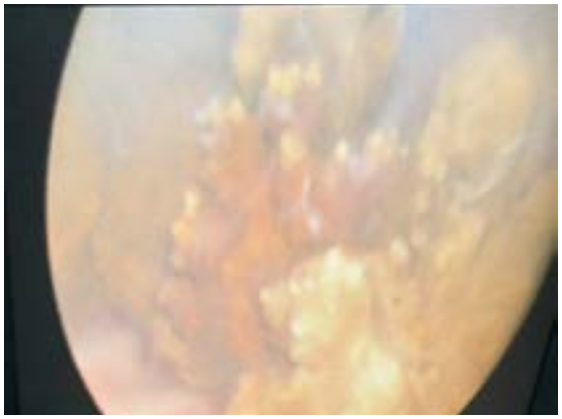

Figure 3a:

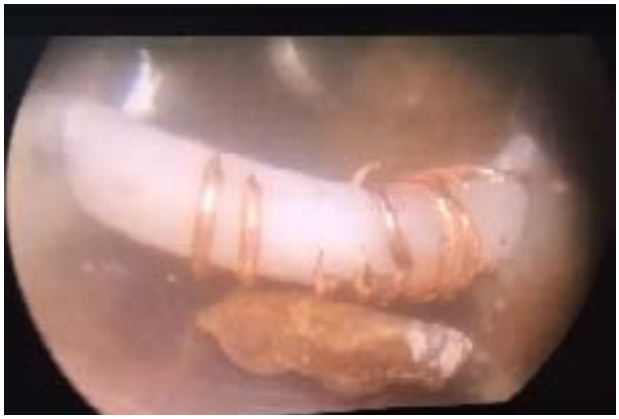

Figure 3b:

Figure 4:

voided satisfactorily and was discharged on oral antibiotics and analgesics for one week.

Outcome and Follow-Up: The postoperative recovery was uneventful. At one-week follow-up, the patient reported complete resolution of burning micturition and had no urinary complaints. She remained clinically stable with satisfactory urinary function.

DISCUSSION

Uterine perforation with intravesical migration of intrauterine device is a very rare complication, with a reported incidence of only 0.04% to 2.8 %[1]. Uterine perforation by IUD is often asymptomatic and most of the authors do not describe any major symptom during the perforation[2]. The bladder migration of IUCD may be responsible for burning micturition and dysuria (as in our case) or even terminal hematuria[3]. The diagnosis is often confirmed on plain X-ray KUB, which shows the IUCD, with its metallic stone, encompassed in an opacity of calcium stone, as the stones are often radiopaque[4]. Abdominal ultrasound confirms the bladder migration of IUCD with or without stone formation. Non-contrast CT scan is the modalitiy of choice, which often demonstrates a hyperdense T-shaped structure within the bladder often encased by a calculus[5]. The IUCD perforation of the uterine wall as well as its migration can sometimes (in 0.1–0.9% of cases) lead to serious complications, like pelvic abscess, intestinal perforation and vesicoureteral fistula[6,7]. In case of vesicouterine fistula, laproscopic repair is the modality of choice for IUCD/Stone removal and fistula repair in the same setting[8–12]. The trans uterine migration of IUCD can go anywhere in the abdomen. A recent review illustrates that the bowel is the most affected organ in case of perforated and migrated IUCD (Intestine 32%, appendix 1%, ileum 5%, colon 4%, rectum 12% and sigmoid 9%). The urinary bladder is the 2nd most common organ where IUCD can migrate which is often associated with stone formation and lower urinary tract symptoms[4]. The recurrent UTI's and chronic inflammation often lead to calculus formation, over the migrated IUCD[2,5]. The stone along with the IUCD, can be removed either endoscopically, as we did in our case or via laparotomy and vesicolithotomy[6]. In case of partial perforation of the bladder wall, laproscopic extraction maybe needed[7]. Vesical calculus secondary to migrated copper IUCD, though rare, should be considered in women with history of IUCD insertion, presenting with refractory lower urinary tract symptoms (LUTS) or recurrent UTI. CT and cystoscopy are the diagnostic mainstays. Management ranges from minimally invasive endoscopic extraction to Vesicolithotomy , which is often reserved for giant calculi. Early recognition and patient education are key to preventing morbidity.

CONSENT FOR PUBLICATION: *Written, informed consent was obtained for publication of this case report and accompanying clinical information.*

AVAILABILITY OF DATA: *Data is available from the corresponding author on a justified request.*

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CONFLICT OF INTEREST: *None*

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AUTHORS' CONTRIBUTION

- ***Ahmad Sajjad:*** *Conception and design, Critical revision.*
- ***Riaz Anwar Bashir:*** *Conception and design, Critical revision.*
- ***Hasnain Ahmad:*** *Drafting the article*
- ***Muhammad Tabish:*** *Drafting the article.*
- ***Nouman Ahmad:*** *Drafting the article.*

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DIAGNOSTIC CHALLENGE

Check the correct answer on page 78

Case 1

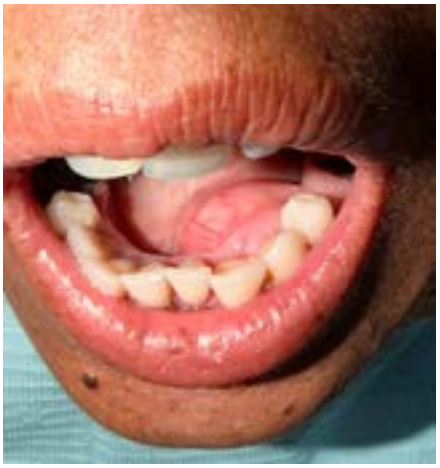

Figure 1a

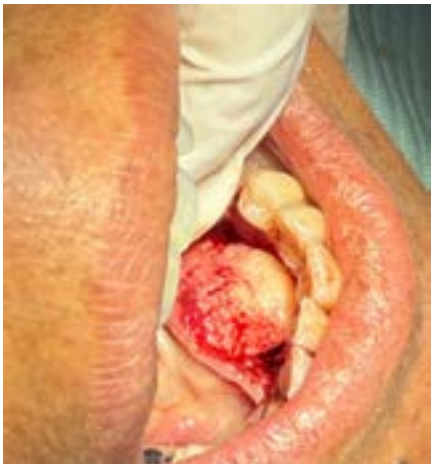

Figure 1b

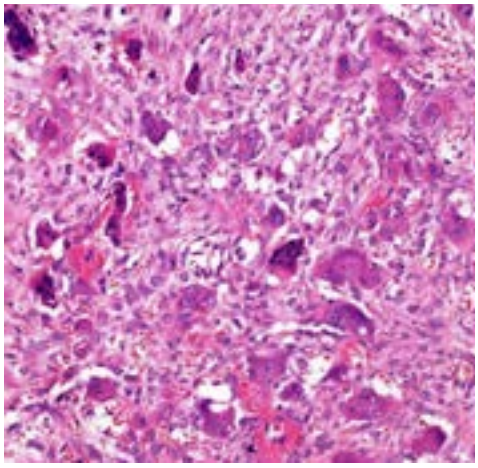

Figure 2

A 35-year-old female presented to the dental outpatient department with a swelling on the lingual aspect of the mandibular anterior gingiva. The lesion was first noticed about 4 months ago as a small gingival nodule and had gradually increased in size. The patient reported occasional bleeding while brushing but denied any pain or paresthesia.

Clinical examination revealed a sessile, pinkish-red nodular mass extending from the mandibular left lateral incisor to the canine region. The lesion appeared to arise from the interdental papilla, extending onto the adjacent lingual gingiva. It had a smooth surface, soft-to-firm consistency, and bled slightly on probing (Figure 1a & b). Local plaque and calculus deposits were present on adjacent teeth. No cervical lymphadenopathy was detected. Histopathology of a biopsy specimen is shown in Figure 2.

Q1. What is the most likely diagnosis based on the clinical and histopathological findings?
Q2. What is the definitive management and key step to prevent recurrence of this lesion?

DIAGNOSTIC CHALLENGE

Check the correct answer on page 79

Case 2

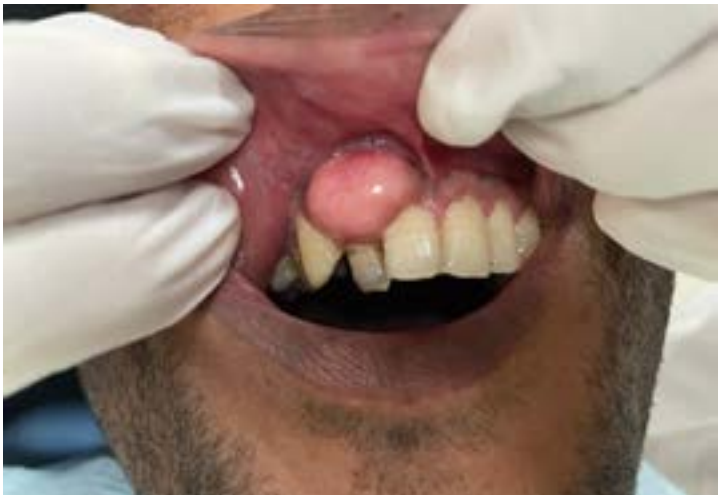

Figure 1

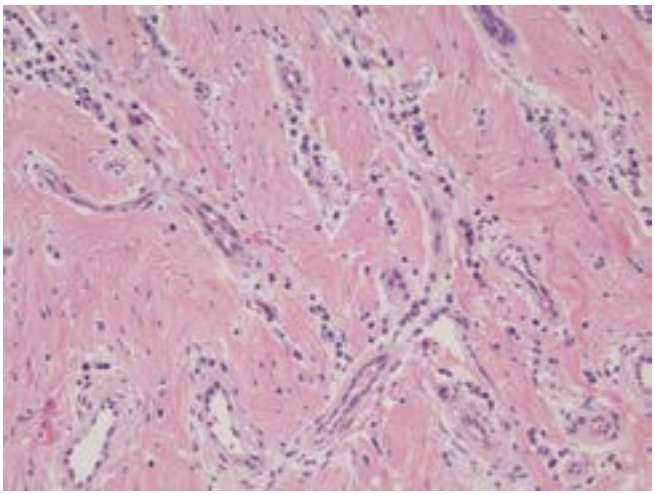

Figure 2

A 42-year-old male presented with a complaint of a swelling in the upper left anterior region of the gingiva that had been present for approximately one year. The lesion initially appeared as a small gingival nodule and gradually increased in size. The patient reported intermittent bleeding during tooth brushing and mastication, but no significant pain.

On clinical examination, a well-defined, sessile, exophytic gingival mass was observed arising from the interdental gingiva in the maxillary left canine-lateral incisor region. The lesion was pink in color with focal erythematous areas, had a smooth surface, and appeared dome-shaped. On palpation, it was hard in consistency, non-tender, and immobile, being firmly attached to the underlying gingival tissues(Figure1). Mild bleeding was elicited on probing. Plaque and calculus deposits were present on the adjacent teeth.

Radiographic examination showed no significant bony involvement or root resorption. The adjacent teeth were vital and exhibited no mobility.

The lesion was excised . Histopathology is shown in Figure 2.

Q1. What is your diagnosis?

Q2. What are the three most important Clinical differential diagnoses for this lesion, and how can they be distinguished ?

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x. Radio broadcast

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2. *Example:* Desert island discs, Lily Allen. BBC Radio 4. 29 June 2014, 11:15.

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DIAGNOSTIC CHALLENGE Answers

Case 1

Diagnosis

1.Peripheral Giant Cell Granuloma

Management

2.Complete surgical excision (excision biopsy) along with curettage of underlying periosteum/periodontal ligament and removal of local irritants (plaque, calculus, and any traumatic factors)

Discussion

Peripheral Giant Cell Granuloma (PGCG) is a reactive, non-neoplastic, hyperplastic lesion that occurs exclusively on the gingiva or alveolar mucosa. It is characterized histologically by the presence of numerous multinucleated giant cells within a vascular fibrocellular stroma. The lesion is considered a localized response to chronic irritation rather than a true neoplasm.

PGCG most commonly arises from the periodontal ligament or periosteum. It is usually triggered by local irritants such as dental plaque, calculus, chronic trauma from mastication, faulty restorations, or food impaction. These irritants induce a reactive proliferation of connective tissue, leading to the formation of the lesion.

Clinically, PGCG is more frequently seen in adults, with a slight female predilection, and is commonly located in the mandibular anterior region. It typically presents as a localized gingival growth that may be sessile or occasionally pedunculated. The lesion appears as a reddish-blue to purple nodular mass that gradually increases in size. It is usually soft to firm in consistency and bleeds easily on probing or minor trauma. In some cases, superficial ulceration may also be present. Larger lesions may cause displacement of teeth or mild discomfort, although pain is generally absent.

Radiographically, early lesions may show no changes; however, in long-standing cases, superficial "cupping" resorption of the underlying alveolar bone may be observed. Occasionally, widening of the periodontal ligament space of adjacent teeth may also be seen.

Histopathologically, PGCG is characterized by the presence of numerous multinucleated giant cells dispersed within a highly cellular fibrovascular stroma. The connective tissue background often shows abundant blood vessels, extravasated red blood cells, and areas of hemosiderin deposition, along with varying degrees of chronic inflammatory infiltrate.

The differential diagnosis includes pyogenic granuloma, peripheral ossifying fibroma, and fibrous epulis, as these lesions may present with similar clinical appearances in the gingiva. Definitive diagnosis relies on histopathological examination.

The treatment of PGCG involves complete surgical excision of the lesion, including thorough curettage of the underlying periosteum or periodontal ligament. It is also essential to eliminate local irritants such as plaque, calculus, and any contributory traumatic factors to minimize recurrence. The prognosis is generally good, although recurrence may occur if excision is incomplete or irritants persist.

Our Patient

An excisional biopsy was performed under local anesthesia. The lesion was completely excised down to the base, and the specimen was submitted for histopathological examination. Oral prophylaxis was carried out, and local irritants were removed. The patient was advised periodic follow-up to monitor for recurrence.

Answers

Case 2

Diagnosis:
Fibrous Epulis

Differential Diagnosis:

Differential Diagnosis	Distinguishing Clinical Features
Peripheral Ossifying Fibroma (POF)	Firm gingival mass arising from interdental papilla; may show calcifications radiographically. Histopathology shows calcification and ossification
Peripheral Giant Cell Granuloma (PGCG)	Usually reddish-purple, bleeds easily, may produce superficial "cupping" resorption of underlying bone. Histopathology shows multiple giant cells
Pyogenic Granuloma (PG)	Soft, highly vascular, bright red lesion with marked tendency to bleed on minor trauma. Histopathology shows marked proliferation blood vessels

Discussion
Fibrous epulis is a common benign reactive lesion of the gingiva that develops in response to chronic local irritation rather than representing a true neoplasm. The term epulis refers to any localized gingival enlargement, while fibrous epulis specifically denotes a fibrous hyperplastic growth arising from the gingival connective tissue. Common etiological factors include plaque accumulation, calculus deposits, food impaction, defective restorations, ill-fitting prostheses, and chronic trauma. The lesion typically presents as a slow-growing, painless, sessile or pedunculated gingival mass that is pink in color and similar in appearance to the surrounding mucosa. It is usually firm to hard in consistency due to the abundance of collagenized fibrous tissue and is often immobile because of its attachment to the underlying gingiva. Although fibrous epulis is generally asymptomatic, larger lesions may interfere with mastication, oral hygiene practices, and esthetics. In some cases, surface ulceration caused by repeated trauma during chewing or tooth brushing may result in intermittent bleeding.
Clinically, fibrous epulis most commonly occurs on the interdental papilla and may be difficult to distinguish from other localized reactive gingival lesions such as pyogenic granuloma, peripheral giant cell granuloma, and peripheral ossifying fibroma. Therefore, clinical examination alone is insufficient for establishing a definitive diagnosis. Radiographic examination is usually performed to assess any underlying bone involvement and to exclude other pathologies, although significant radiographic changes are uncommon. Histopathological examination remains the gold standard for diagnosis and typically reveals dense collagenized fibrous connective tissue containing numerous fibroblasts, varying degrees of chronic inflammatory cell infiltration, and an overlying stratified squamous epithelium that may be hyperplastic or ulcerated. Unlike peripheral giant cell granuloma, multinucleated giant cells are absent, and unlike peripheral ossifying fibroma, there is no evidence of calcified material or bone formation.
The treatment of choice for fibrous epulis is complete surgical excision of the lesion along with elimination of all local irritational factors. Thorough scaling and root planing should be performed, and any contributing factors such as defective restorations or traumatic occlusal forces should be addressed. The prognosis is excellent, with recurrence being uncommon when the lesion is completely removed and local irritants are eliminated.

Our Patient
The lesion was surgically excised under local anesthesia, and the specimen was submitted for histopathological examination. Scaling and root planing were performed to eliminate local irritants. The patient was instructed regarding his oral hygiene and follow-up visits.

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