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Editorial

Artificial Intelligence in Medical Education and Clinical Practice: Navigating Innovation Responsibly

Uzma Ahsan

Artificial intelligence (AI) has promptly progressed and incorporated itself from a theoretical framework into a practical and progressively obligatory component of modern healthcare and medical education. Its prospect spans across clinical decision making, documentation, research assistance, and personalized learning owing to the development of machine learning and generative AI systems, particularly large language models.[1] Such speedy amalgamation has already revolutionized the way medicine is taught and practiced, raising significant concerns about its safe, ethical, and effective use.[2]

In medical education, traditional teaching methodologies such as lectures, textbooks, and bedside training are now being gradually supported through AI-based tools. These tools not only generate clinical scenarios, simplify complex concepts, and provide instant feedback, but also assist in more personalized and self-directed learning.[3] For learners in a resource limited country like Pakistan, AI provides an opportunity to partially overcome the gaps in faculty availability and clinical exposure by strengthening accessibility to a structured educational support and virtual clinical involvement.[4]

There is a steadily increasing use of AI in specialties like radiology, dermatology, pathology, and cardiology for image interpretation and evaluation, risk estimation, and diagnostic assistance.[5] This support is further strengthened through generative AI systems by enhancing their competencies in assisting with documentation, summarizing patient records, and synthesizing medical literature, thereby reducing administrative workload and improving efficiency.[6] These tools provide immense support in settings with inadequate healthcare workforce capacity, resulting in upgraded service delivery and improved use of clinicians' time. Use of AI assisted systems may not only help in early detection but can also strengthen accessibility to specialist level input in underserved regions. These benefits still remain dependent on rigorous validation and adaptation to the context.[1,5]

Medical training, however is in principle about developing rational thinking, decision-making, and professionalism, and not simply obtaining information. Excessive dependency and disproportionate reliance on AI tools not only pose a risk of promoting passive learning but also create excessive trust and a selective preference in these automated systems, where learners thoughtlessly trust and accept the outputs without critical evaluation.[5] The use of AI is strictly recommended as a support to teaching, not a substitute for intellectual and critical engagement. A pressing need of the current time is to incorporate AI literacy into medical curricula so that future clinicians appreciate both its utility and its boundaries.[2]

In spite of all the advantages, AI and its consumption in healthcare and medical education must be viewed in the context of its limitations. Generative AI systems from time to time provide information which is either not correct or is fictitious ("hallucinations"), which can be misleading in clinical situations.[5] Additionally, low- and middle-income populations are particularly vulnerable to the detrimental effects of enhanced healthcare inequities arising from algorithmic bias resulting from non-representative training data.[1] In addition, issues pertaining to transparency, understanding, and liability further complicate clinical integration, as the decision-making processes of AI systems are often not fully understandable.[2]

Ethical concerns remain central to the debate. Issues pertaining to patient privacy, data security, informed consent, and accountability in AI assisted decision-making are still progressing.[1] The prime essence of human involvement in medicine must not be dominated by the excessive use and dependency on AI. Empathy, compassion, professional communication, and patient trust continue to be indispensable components of the physician patient connection and cannot be simulated by algorithms.[2]

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Employment of AI in Pakistan offers prospects for better opportunities to support medical education and healthcare services amidst numerous obstacles, such as shortage of qualified workforce, unequal resource distribution, and an accelerating disease load. It is not possible to achieve benefits without improving the resources and framework provided by institutions, and the capacity building of healthcare providers.[7]

Artificial intelligence has one of the most pivotal impacts in medicine's history. However, the major concern is not the smart operation of machines, but how humans will employ them intelligently. The future of healthcare won't be a conflict or competition between doctors and algorithms; instead, it should be a bridge connecting the collaborative working of technological support and human expertise. As medicine advances into an era of intelligence augmentation, maintaining clinical reasoning, ethical responsibility, and compassionate patient care will be as vital as technological progress.[6,8]

The prime objective should not be to produce an artificial intelligence healthcare professional but to train a considerate, thoughtful, and skilled physician empowered by AI. It will certainly redesign healthcare practices, but the outcome and utility will eventually depend on how wisely it is integrated.

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Original Article

Comparative Analysis of Procedural Success of Patients Undergoing Carotid Angioplasty in Tertiary Care Center

Muhammad Faizan Younus, Asim Javed, Asma Shabbir, Zunera Hakim, Mujaddid Mudassir, Adeel ur Rehman

ABSTRACT

Objective: To compare the procedural success between symptomatic and asymptomatic patients who underwent carotid angioplasty in a tertiary care center.

Methodology: This cross-sectional analytical study was conducted at the Rawalpindi Institute of Cardiology, Rawalpindi after taking ethical approval. Data was collected from March 2023 to March 2026. Following written informed consent, 170 patients aged ≥18 years with severe carotid artery stenosis who underwent carotid angioplasty were included using non-probability consecutive sampling. The patients were divided into symptomatic and asymptomatic groups. All cases of carotid angioplasty with stenting were performed electively by the team of interventional cardiologists in the catheterization lab using aseptic protocols. Procedural success was defined as residual stenosis of <30% after stent placement with no major adverse cardiac and cerebrovascular events (MACCEs). Patients were followed up at 30 days and 6 months. Data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 26.

Results: One hundred and forty one (82.9%) patients had a history of stroke, and were symptomatic, whereas, 29(17.1%) patients were asymptomatic, with either no symptom (6%) or planned for coronary artery bypass grafting (16.5%). The technical success was 100%, with <30% residual stenosis. Out of 170 patients, 2(1.2%) patients died, 3(1.8%) patients developed stroke and 1(0.6%) patient had myocardial infarction at 6 months. The overall procedural success was 96.5%. The procedural success was not significantly different between symptomatic and asymptomatic patients (p-value = 1.00).

Conclusion: Carotid angioplasty showed excellent procedural success in symptomatic as well as asymptomatic patients in a tertiary care center.

Keywords: *Carotid stenosis. Stents. Stroke.*

INTRODUCTION

In many developed nations, cerebrovascular accidents (CVAs) are the second or third leading cause of death and the primary cause of disability among adults. Ischemic stroke represents 70-90% of all CVAs. Carotid artery stenosis continues to be a significant factor in ischemic stroke. Atherosclerosis of the internal carotid artery (ICA), causing >50% stenosis, accounts for 9-40% of ischemic strokes.[1,2] First-line treatment for patients with atherosclerosis involves pharmacotherapy. However, literature indicates that pharmacotherapy may not be effective for patients who are at a higher risk of experiencing a CVA.[3] Traditionally, carotid endarterectomy (CEA) has been regarded as the standard treatment. In the last 20 years, carotid artery stenting (CAS) has been introduced as an alternative option, especially for patients at high risk for surgery. Nevertheless, with the increased use of CAS, in-stent restenosis has become a more commonly recognized issue. In-stent thrombosis develops in 20% of patients after undergoing CAS, in contrast to 9% following CEA.[4] With the advancement of endovascular techniques, imaging guidance, embolic protection devices, and procedural success, the complication rates associated with carotid angioplasty have decreased.[2]

The procedural success of carotid artery stenting depends on patient, lesion, and technical factors. Older age, co-morbidities, and complex vascular anatomy can make the procedure more challenging and may increase the risk of complications. Similarly, heavily calcified plaques, long segment disease, and tortuous vessels can lead to technical issues. Outcomes also vary based on the operator's experience, careful selection of stent type and size, and the routine use of embolic protection devices. Adequate antiplatelet therapy and proper intraprocedural management also contribute significantly to procedural safety. [5,6]

Despite widespread adoption, variability exists in reported procedural success rates due to differences in patient selection, operator experience, and procedural techniques. Therefore, evaluating the procedural success of carotid angioplasty in different clinical settings is essential to optimize the outcomes and guide future practice. So, our study was conducted to determine the procedural success of patients who underwent carotid angioplasty in a tertiary care center and compare the outcomes between symptomatic and asymptomatic patients.

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METHODOLOGY

This cross-sectional analytical study was conducted at the Rawalpindi Institute of Cardiology, Rawalpindi, after taking ethical approval (Letter No. RIC/RERC/05A/25, 26-03-2025). Data was collected from March 2023 to March 2026. Data from March 2023 to March 2025 was obtained retrospectively from medical records, while data from March 2025 to March 2026 was collected prospectively. The sample size of 168 (rounded off to 170) was calculated using 87.5% success rate of carotid angioplasty, 5% margin of error, and 95% confidence interval.[7.] After obtaining informed written consent, patients aged ≥18 years with a diagnosis of severe carotid artery stenosis who underwent carotid angioplasty were included using a non-probability consecutive sampling technique. The indications for carotid angioplasty were a history of stroke, planned for coronary artery bypass grafting (CABG) or asymptomatic carotid artery stenosis. The carotid artery stenosis was diagnosed based on duplex ultrasound and computed tomography (CT)/magnetic resonance (MR) angiography. Severe stenosis was defined as greater than 70% stenosis of the internal carotid artery.[8]

Patients who had previous carotid intervention, total carotid occlusion or did not give consent were excluded. All cases of carotid angioplasty with stenting were performed electively by the team of interventional cardiologists in the catheterization lab using aseptic protocols. All patients received a preoperative aspirin and clopidogrel. The procedure was performed through transfemoral access under local anesthesia. The catheter was advanced to common carotid artery. Intravenous heparin was given during the procedure. An embolic protection device was placed distal to the lesion in the internal carotid artery (ICA) to prevent the risk of stroke. A guide wire was passed carefully across the stenosis into distal ICA and stent was positioned across the lesion. The stent length varied from 20 mm to 40 mm and its diameter ranged from 6 mm to 10 mm. The demographic profile of the patients, co-morbidities such as diabetes mellitus (DM), hypertension (HTN), dyslipidemia, & smoking, and lesion characteristics (type & location of lesion) were recorded on a proforma. Patients were divided into two groups: symptomatic and asymptomatic based on their clinical presentation. The patient follow-up was done at 30 days and 6 months.

Technical success was defined as residual stenosis of <30% after stent placement. Patients with technical success and no major adverse cardiac and cerebrovascular events (MACCEs) were labeled as procedural success. The MACCEs included mortality, stroke, and myocardial infarction (MI).[9]

STATISTICAL ANALYSIS

Data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 26. Mean and standard deviation were used for quantitative variables such as age. Frequency and percentage were used for qualitative variables such as gender, co-morbidities, indications for carotid angioplasty, lesion characteristics, stent dimensions, and procedural success. The comparison of variables between symptomatic and asymptomatic patients was done using the Chi-square/Fisher's exact test. The p-value of <0.05 was considered statistically significant.

RESULTS

Patients had a mean age of 64.26±8.76 years, with the minimum and maximum of 40 and 84 years, respectively. There were 136(80%) males and 34(20%) females. One hundred and forty one (82.9%) patients had a history of stroke and were symptomatic. Twenty nine (17.1%) patients were asymptomatic, with either no symptom [1(6%)] or planned for CABG [28(16.5%)]. One hundred and nineteen (70%) patients had hypertension, 74(43.5%) had diabetes mellitus, 60(35.3%) had dyslipidemia, and 42(24.7%) were smokers.

Most of the lesions were non-thrombotic (45.3%). Seventy three lesions were ostial (42.9%), 9(5.3%) were at the bifurcation, and 88(51.8%) were at other sites. The contralateral carotid artery was patent in 93(54.7%) of the patients, subtotally occluded in 54(31.8%), and totally occluded in 23(13.5%) of the patients. There was no significant difference in demographic variables, co-morbidities, and lesion characteristics between two groups (Table 1).

The most commonly used stent lengths were 30 mm (30.6%) and 40 mm (30.6%), followed by 25 mm (26.5%) and 20 mm (11.1%). The stent with a diameter of 8 mm was used in the majority of the patients (50.6%), followed by 7 mm stent (22.9%).

The residual stenosis was <30% in all the patients, showing 100% technical success. Out of 170 patients, 2(1.2%) patients died, 3(1.8%) patients developed stroke and 1(0.6%) patient had MI at 6 months. The overall procedural success was 96.5%. The procedural success was not statistically different between symptomatic and asymptomatic patients (Table 2).

Table 1: Comparison of Demographic Variables, Co-Morbidities, & Lesion Characteristics between Two Groups

Parameters			Symptomatic Patients (n=141)	Asymptomatic Patients (n=29)	Total (n=170)	p-value
Gender		**Male**	114(80.8%)	22(75.8%)	136(80%)	0.54
		Female	27(19.2%)	7(24.2%)	34(20%)	
Co-Morbidities	**Hypertension**	**Yes**	100(71%)	19(65.5%)	119(70%)	0.56
		No	41(29%)	10(34.5%)	51(30%)	
	Diabetes Mellitus	**Yes**	59(41.8%)	15(51.7%)	74(43.5%)	0.32
		No	82(58.2%)	14(48.3%)	96(56.5%)	
	Dyslipidemia	**Yes**	48(34%)	12(41.4%)	60(35.3%)	0.45
		No	93(66%)	17(58.6%)	110(64.7%)	
Smoking		**Yes**	31(22%)	11(37.9%)	42(24.7%)	0.07
		No	110(78%)	18(62.1%)	128(75.3%)	
Lesion Type		**Non-Thrombotic**	67(47.5%)	10(34.5%)	77(45.3%)	0.39
		Thrombotic	35(24.8%)	8(27.5%)	43(25.3%)	
		Calcific	39(27.7%)	11(38%)	50(29.4%)	
Lesion Site		**Ostial**	62(44%)	11(37.9%)	73(42.9%)	0.08
		Bifurcation	5(3.5%)	4(13.8%)	9(5.3%)	
		Others	74(52.5%)	14(48.3%)	88(51.8%)	
Contralateral Carotid Artery		**Patent**	78(55.4%)	15(51.7%)	93(54.7%)	0.33
		Subtotal Occlusion	42(29.8%)	12(41.4%)	54(31.8%)	
		Total Occlusion	21(14.8%)	2(6.9%)	23(13.5%)	

Table 2: Procedural Success in Symptomatic versus Asymptomatic Patients after Carotid Angioplasty

Outcomes		Symptomatic Patients (n=141)	Asymptomatic Patients (n=29)	Total (n=170)	p-value
Technical Success	**Yes**	141(100%)	29(100%)	170(100%)	1.00
	No	0(0%)	0(0%)	0(0%)	
Mortality	**Yes**	2(1.4%)	0(0%)	2(1.2%)	1.00
	No	139(98.6%)	29(100%)	168(98.8%)	
Stroke	**Yes**	3(2.1%)	0(0%)	3(1.8%)	1.00
	No	138(97.9%)	29(100%)	167(98.2%)	
Myocardial Infarction	**Yes**	1(0.7%)	0(0%)	1(0.6%)	1.00
	No	140(99.3%)	29(100%)	169(99.4%)	
Overall Procedural Success	**Yes**	136(96.5%)	28(96.5%)	164(96.5%)	1.00
	No	5(3.5%)	1(3.5%)	6(3.5%)	

DISCUSSION

Carotid angioplasty with stenting has been introduced as a less invasive alternative to surgical endarterectomy. Recent literature has demonstrated that it is a safe and effective alternative to carotid endarterectomy in selected patients. Improvements in techniques and devices, driven by advances in interventional cardiology, have further enhanced the outcomes of carotid angioplasty.[10,11]

The mean age of the patients was 64.26±8.76 years in our study, and 80% were males. Barath et al. revealed that patients had a mean age of 64.8 ± 9.1 years, with 64.1% males.[12] In the current study, 43.5% of patients had diabetes mellitus, 70% were hypertensive, 24.7% were smokers, and 35.3% had dyslipidemia. All patients had DM, HTN, and dyslipidemia in another study.[7] Most of the patients were hypertensive (66.7%), followed by diabetic patients (53.9%) in a study.[12] Ezzeldin et al. observed that 86.08% patients had HTN, and 40.17% had DM, and 26.45% were current smokers.[13]

Our results showed that 82.9% of the patients were symptomatic and 17.1% were asymptomatic. Algahtani et al. and Barath et al. observed that all patients were symptomatic.[7,12] In our study, there was no significant difference in demographic variables, co-morbidities, and lesion characteristics between the two groups. In another study, the two groups only differed in smoking status, with significantly more smokers among symptomatic patients (43% versus 28%).[14]

In our study, the technical success rate was 100%, whereas other studies reported technical success rates of 99.4% and 98.3%.[11,14] Only a few patients (1.8%) in this study developed stroke, and 0.6% experienced myocardial infarction (MI). In a study, stroke occurred in 1.6% of the patients after carotid angioplasty.[14] In another study, 4.15% of the patients developed complications; ischemic stroke in 0.55%, hemorrhagic stroke in 0.28%, and myocardial infarction in 0.07%, and transient ischemic attack in 0.4% of the patients.[13] Another study reported stroke in 2.5%, symptomatic diffusion weighted imaging ischemic lesions (on MRI) in 33%, and repeat stenting in 7.5% of the patients.[15] Malas et al. reported stroke in 2% of the patients after carotid angioplasty.[16] A study conducted in 2025 revealed 2.2% frequency of major adverse events after carotid angioplasty.[17] In contrast, Algahtani et al. reported no episode of MI or stroke in any patient after procedure.[7] Similarly, in another study, none of the patients developed stroke or MI. Other complications were seen in 6.3% of the patients who presented with in-stent thrombosis and symptomatic showering of thrombi.[12] According to our results, the mortality rate was 1.2%. Ezzeldin et al. reported 0.9% mortality.[13] Similar results were reported in another study, where the in-hospital mortality rate was 1.08%, and the 30 day mortality rate was 1.80%[16] In contrast, the mortality rate was higher (7.7% and 18.8%) in other studies.[7,12] The procedural success was achieved in 96.5% of the patients in our study. The success rate was 87.5% and 100% in other studies.[7,12] The procedural success was not different between symptomatic and asymptomatic patients in our study. Similarly, a study conducted in Iraq reported no significant difference in outcomes between the two groups.[14]

Another study reported that carotid angioplasty is linked with a significantly lower risk of mortality or stroke at 30 days as compared to medical therapy or surgical endarterectomy. In patients who underwent angioplasty, these outcomes occurred in 2.8% compared to 6% of the patients on medical treatment and 3.7% in the endarterectomy group.[18] In contrast to our results, a study revealed that surgical endarterectomy was associated with better results than carotid angioplasty. The mortality rate was significantly lower with CEA, with no statistical difference in the rate of postoperative MI and stroke.[19]

CONCLUSION

Carotid angioplasty showed excellent procedural success in symptomatic as well as asymptomatic patients in a tertiary care center. It is a highly effective & minimally invasive technique and should be adopted in tertiary care centers with experienced interventional operators, appropriate patient selection, careful evaluation of lesion characteristics and meticulous endovascular techniques.

LIMITATIONS & RECOMMENDATIONS

This study had a cross-sectional design, was conducted at a single institution, and did not evaluate long term outcomes in patients who underwent carotid angioplasty. Therefore, large multicenter randomized controlled trials with long term follow-up are recommended in the future. Carotid angioplasty with stenting is a recommended catheter based procedure for the treatment of carotid artery stenosis in both symptomatic and asymptomatic patients.

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Authors' Contributions:
M.F.Y: Concept, data collection, analysis, manuscript writing, and final approval.
A.J: Study supervision, methodology, critical review, and final approval.
A.S: Literature review, drafting, and final approval.
Z.H: Data analysis, editing, and final approval.
M.M: Data management, patient follow-up, and final approval.
A.R: Critical revision, supervision, and final approval.

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Original Article

Can Ultrasound Pixel Density Serve as a Non-Invasive Alternative to Thoracentesis in Classifying Pleural Effusions?

Aqsa Javaid, Muhammad Zill-e-Humayun Mirza, Muhammad Khalid Azam Khan, Asif Ullah Khan, Naveed Anjum, Muhammad Hamza

ABSTRACT

Objective: To determine the diagnostic performance of ultrasound pixel density in differentiating exudative from transudative pleural effusions, using Light's criteria as the gold standard.

Methodology: This cross-sectional validation study was conducted at the Pulmonology Department of Pak Emirates Military Hospital, Rawalpindi from January to April 2026, after institutional ethical approval. One hundred and ten patients with pleural effusions confirmed by ultrasound and scheduled for diagnostic thoracentesis were enrolled using a non-probability consecutive sampling technique. Written informed consent was obtained from all patients. A curvilinear ultrasound probe (3-5 MHz) was used with standardized depth (8 cm) and gain (60 dB) settings. Three frozen B-mode images were obtained per patient, and pixel density was quantified within a 1 cm^2 region of interest using ImageJ software. Ultrasonographic pixel density ≥9.5 was classified as exudative. Light's criteria were applied to pleural fluid biochemistry as the gold standard. Data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 27.0.

Results: Among 110 patients (mean age 42.29±9.09 years; 61.8% males), 66(60%) were classified as having exudative and 44(40%) as having transudative pleural effusion according to Light's criteria. At the 9.5 cut-off value, pixel density demonstrated a sensitivity of 25.76%, specificity of 95.45%, positive predictive value (PPV) of 89.47%, negative predictive value (NPV) of 46.15%, and an overall diagnostic accuracy of 53.64%. Receiver operating characteristic (ROC) analysis showed an area under the curve (AUC) of 0.75 (p <0.001). Median pixel density was significantly higher in exudative effusions (3.35) compared with transudative effusions (1.50) (p <0.001).

Conclusion: Pixel density on ultrasound at a cut-off value of 9.5 demonstrated high specificity with low sensitivity for differentiating exudative from transudative pleural effusion. The ROC analysis showed fair diagnostic accuracy of ultrasound pixel density. This technique may serve as a useful adjunct in the evaluation of pleural effusion; however, it cannot be used as the only diagnostic test instead of thoracentesis.

Keywords: *Pleural effusion. Thoracentesis. Sensitivity and specificity.*

INTRODUCTION

Pleural effusion, characterized by excessive fluid in the pleural cavity, is a common clinical condition encountered by pulmonologists, internists, and surgeons alike. It has a wide range of causes, including congestive heart failure, pneumonia, tuberculosis, and cancer.[1] Differentiating between transudative and exudative effusions is the first step in clinical decision-making, which leads to further diagnostic evaluation and specific treatment. The classification is determined through thoracentesis, followed by biochemical analysis using Light's criteria. This is an invasive procedure that can result in complications such as pneumothorax and bleeding, and may be limited by a lack of laboratory support, especially in rural settings.[2]

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Bedside thoracic ultrasound is also frequently used in the detection and evaluation of pleural effusions.[3] Although semi-quantitative sonographic features, such as septations, echogenicity, and pleural thickening, have demonstrated some correlation with exudative effusions, they are subjective and operator-dependent, making them unreliable as independent predictors.[4]

The idea of quantifying pleural fluid echogenicity using pixel density measurements can be more objective and consistent. This quantitative approach minimizes subjective interpretation and reduces inter-observer variability during ultrasound examination.[5] Previous literature revealed that median pixel density was higher in exudative effusions compared to transudative effusions, highlighting the potential of this technique in differentiating pleural fluid types. Therefore, quantitative analysis of pleural fluid echogenicity may serve as a valuable adjunct to conventional thoracic ultrasound and contribute to more accurate clinical decision-making.[6]

The initial studies using ImageJ based platforms for pixel based echogenicity analysis have shown promising results; however, validation across diverse clinical settings remains limited.[5,6] The

rationale of the present study was to address this gap by evaluating the diagnostic utility of ultrasound derived pixel density in a tertiary care hospital in Pakistan, where tuberculosis and infection-related pleural effusions are common. The current study aimed to assess the diagnostic performance of ultrasound-based pixel density in differentiating exudative from transudative pleural effusions, using Light's criteria as the gold standard.

METHODOLOGY

The cross-sectional validation study was carried out from January to April 2026 in the Department of Pulmonology, Pak Emirates Military Hospital, Rawalpindi, following ethical approval from the institutional review committee (Letter No. A/28/ERC/161/25, 30-12-2025). A sample size of 110 was calculated with a 95% confidence level, 10% precision, a prevalence of exudative effusion of 60.2%, and the reported sensitivity and specificity of pixel density (22% and 97%, respectively) using Light's criteria as the gold standard.[6] A non-probability consecutive sampling technique was used to enroll patients after obtaining written informed consent.

Both male and female patients (aged 18 to 60 years) with a pleural effusion of 15 mm or greater on thoracic ultrasound and scheduled for diagnostic thoracentesis as part of their routine care were included. Patients with loculated pleural effusions, history of pleurodesis, hemodynamic instability or respiratory distress, empyema, recent hemothorax or chest trauma, massive pleural effusion requiring urgent drainage, poor ultrasound window (due to subcutaneous emphysema or obesity), and known malignancy with recurrent effusions were excluded.

Chest ultrasound was performed using a curvilinear 3-5 MHz probe with a fixed depth (8 cm) and gain (60 dB). The patient was examined in a seated, or semi-recumbent position, and the probe was positioned longitudinally on the chest wall. The operator captured three frozen ultrasound images in the B (brightness) mode. A 1 cm^2 region of interest within the pleural fluid was used to calculate the pixel density using the image processing software program, ImageJ. Pixel values were initially measured on a scale of 0 to 255 and were then proportionately converted to 0 to 100 for consistency. Any effusion with a mean pixel density of $\geq$9.5 was considered exudative, and <9.5 as transudative. The cut-off value of 9.5 for pixel density was selected based on the findings of Soni et al., who demonstrated that pleural effusions with a pixel density $\geq$9.5 were highly suggestive of exudative effusions.[6] All measurements were made independently by two blinded radiologists (with at least 5 years post-fellowship experience in thoracic imaging) and the average of the two pixel densities was taken.

The lead researcher and clinical team performed thoracentesis within 30 minutes of the ultrasound examination under aseptic conditions. Collected pleural fluid and paired serum samples were analyzed for total protein and lactate dehydrogenase (LDH) concentrations. Effusions were categorized as exudative or transudative based on Light's criteria, which served as the gold standard throughout. An effusion was considered exudative when $\geq$1 of the following criteria was fulfilled: a pleural fluid protein-to-serum protein ratio exceeding 0.5, a pleural fluid LDH-to-serum LDH ratio exceeding 0.6, or a pleural fluid LDH value greater than two-thirds the upper reference limit for serum LDH.[7]

Patients with exudative pleural effusion according to Light's criteria and ultrasound pixel density ≥9.5 were considered true positives (TP)**.** Patients with transudative pleural effusion according to Light's criteria, but a pixel density ≥9.5 were considered false positives (FP**)**. Patients with exudative pleural effusion according to Light's criteria but a pixel density <9.5, were considered false negatives (FN)**.** Patients with transudative pleural effusion according to Light's criteria and a pixel density <9.5 were considered true negatives (TN).

STATISTICAL ANALYSIS

Data was entered and analyzed using the Statistical Package for the Social Sciences (SPSS) version 27.0. Normality of continuous variables was assessed using the Shapiro-Wilk test before analysis. Categorical variables were presented as frequencies and percentages. Normally distributed continuous variables were expressed as mean±standard deviation, while non-normally distributed continuous variables were presented as median and interquartile range (IQR). The Mann-Whitney U test was used to compare non-normally distributed continuous variables.

The diagnostic utility of pixel density was assessed by calculating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), overall diagnostic accuracy, and ROC curve analysis with estimation of the AUC. An AUC equal to or greater than 0.6 is considered meaningful. Values ≥0.6 and <0.7 indicate poor diagnostic accuracy, ≥0.7 to <0.8 suggest fair accuracy, ≥0.8 to <0.9 reflect good accuracy while values ≥0.9 represent excellent diagnostic accuracy.[8] The

optimal cut-off value was determined using the Youden index. Diagnostic accuracy parameters were reported with 95% confidence intervals (CI). A p-value <0.05 was considered statistically significant.

RESULTS

The Shapiro-Wilk test confirmed normal distribution for all continuous variables (p >0.05) except pixel density (p <0.001). The mean age of patients was 42.29±9.09 years, with 68(61.8%) being males and 42(38.2%) being females. The mean body mass index (BMI) was 23.22±3.05 kg/m². Among BMI categories, 72(65.5%) patients had normal weight, 28(25.5%) were overweight, 8(7.3%) were underweight, and 2(1.8%) were obese. Non-smokers formed the largest group with 58(52.7%) patients followed by smokers 30(27.3%) and ex-smokers 22(20%). The most common co-morbidity was diabetes mellitus [22(20.0%)], hypertension [21(19.1%)], combined hypertension and diabetes [16(14.5%)], and dyslipidemia [13(11.8%)]. The mean duration of symptoms was 3.32±1.53 months.

Based on Light's criteria, 66(60%) patients were classified as having exudative and 44(40%) as having transudative pleural effusions. Using the pixel density cut-off of 9.5, 19(17.3%) patients were classified as having exudative and 91(82.7%) as transudative effusions. The median pixel density was significantly higher in exudative effusions (3.35, IQR:1.45-10.33) compared to transudative effusions (1.50, IQR:0.53-2.41) (p <0.001). The 2x2 contingency table comparing ultrasound pixel density-based classification of pleural effusion with Light's criteria as gold standard is shown in Table 1.

The diagnostic accuracy parameters of ultrasound pixel density at the 9.5 cut-off are presented in Table 2. The ROC curve analysis showed an AUC of 0.75 (p <0.001), indicating fair discriminatory ability (Figure 1). The Youden index suggested an optimal cut-off of 1.65, which offered higher sensitivity (89.4%) but at the cost of reduced specificity (56.8%) and a greater risk of false positives in clinical use.

Stratified analysis demonstrated variation in sensitivity across different subgroups. Sensitivity was higher among females (39.3%) compared to males (15.8%), while specificity remained comparable (92.9% vs 96.7%). In the 46-60 years age group, sensitivity was higher (45%) compared to the 31-45 years group (17.5%). Across BMI categories, normal weight patients showed higher sensitivity (31.8%) than overweight patients (11.8%). By smoking status, specificity remained consistently above 90% across all subgroups. These findings are descriptive and should be interpreted with caution due to variability in subgroup sample sizes (Table 3).

Table 1: 2×2 Contingency Table of Ultrasound Pixel Density-Based Classification of Pleural Effusion versus Light's Criteria (Gold Standard)

Pixel Density-Based Classification of Pleural Effusion	Light's Criteria on Thoracentesis (Gold Standard)		Total
	Exudative	Transudative	
Exudative (≥9.5)	17(89.5%) (TP)	2(10.5%) (FP)	19(100%)
Transudative (<9.5)	49(53.8%) (FN)	42(46.2%) (TN)	91(100%)
Total	66(60%)	44(40%)	110(100%)

Table 2: Diagnostic Performance of Ultrasound Pixel Density for Classification of Pleural Effusion

Parameters	Value	95% Confidence Interval
Sensitivity	25.76%	16.7% - 37.4%
Specificity	95.45%	84.9% - 98.7%
Positive Predictive Value	89.47%	68.6% - 97.1%
Negative Predictive Value	46.15%	36.3% - 56.3%
Diagnostic Accuracy	53.64%	44.4% - 62.7%

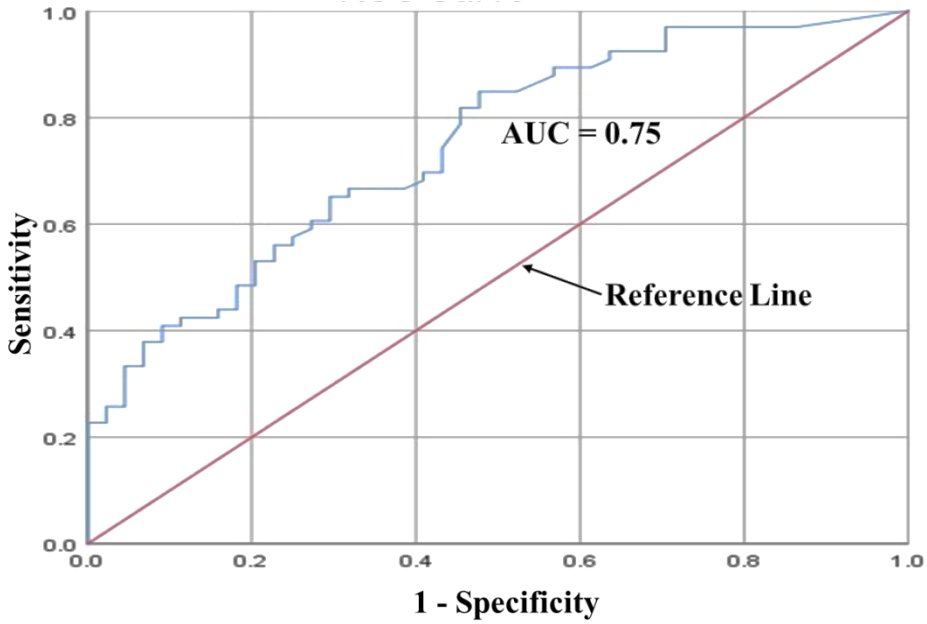

Figure 1: Receiver Operating Characteristic Curve for Ultrasound Pixel Density in Differentiating Exudative and Transudative Pleural Effusion

Table 3: Stratified Diagnostic Performance of Ultrasound Pixel Density by Patient Characteristics

Variables		Total n(%)	Sensitivity	Specificity	Overall Diagnostic Accuracy
Gender	**Male**	68(61.8%)	15.8%	96.7%	51.5%
	Female	42(38.2%)	39.3%	92.9%	57.1%
Age (Years)	**18-30**	9(8.2%)	16.7%	100.0%	44.4%
	31-45	60(54.5%)	17.5%	95.0%	43.3%
	46-60	41(37.3%)	45.0%	95.2%	70.7%
BMI	**Normal BMI**	72(65.5%)	31.8%	92.9%	55.6%
	Overweight	38(34.5%)	11.8%	100.0%	46.4%
Smoking	**Smoker**	30(27.3%)	26.3%	90.9%	50.0%
	Non-smoker	58(52.7%)	25.7%	100.0%	55.2%
	Ex-smoker	22(20.0%)	25.0%	90.0%	54.5%

DISCUSSION

Pleural effusion is a common condition encountered in a variety of benign and malignant diseases. The ability to characterize pleural effusions non-invasively without thoracentesis would be particularly beneficial in low resource settings.[9] This study revealed that, at the 9.5 cut-off value, pixel density yielded a sensitivity of 25.76%, specificity of 95.45%, PPV of 89.47%, NPV of 46.15%, and an overall diagnostic accuracy of 53.64%. Receiver operating characteristic analysis demonstrated an AUC of 0.75, with fair discriminative ability (p <0.001). These findings are comparable to those reported by Soni et al., who observed a specificity of 97% and sensitivity of 22% at the same pixel density cut-off (9.5) in a study of 83 patients.[6] Similarly, El-Dakkak et al. quantified pleural fluid echogenicity using ultrasound derived pixel density in 140 patients and reported an AUC of 0.77 (p <0.001), with specificity of 90.62%, sensitivity of 47.7%, PPV of 70%, and NPV of 79.1% at a cut-off value of ≤0.2363 for transudative effusions.[10] These findings are broadly comparable with the present study, demonstrating high specificity and fair discriminative ability on ROC analysis. The observed variations in sensitivity and specificity between studies may be attributed to differences in cut-off values, patient populations, ultrasound equipment, and imaging techniques. The Youden index in the present study suggested an alternative

threshold of 1.65, which provided higher sensitivity (89.4%) at the expense of lower specificity (56.8%). Although this cut-off would identify a greater proportion of exudative effusions, it would also increase the number of false positive results. The trade-off between sensitivity and specificity across different thresholds supports the conclusion that pixel density alone cannot serve as a definitive binary diagnostic test; however, high pixel density values may help rule in exudative pleural effusions.

Kummerfeldt et al. performed a meta-analysis of 5 studies with 1422 effusions, and reported a pooled specificity of 0.92 (95% CI:0.59 to 0.99) and sensitivity of 0.71 (95% CI:0.57 to 0.82) for echogenic ultrasound patterns in detecting exudates, with an overall AUC of 0.81 indicating good discriminatory ability.[11] Although the magnitude of sensitivity in our study was lower, both findings consistently support that ultrasound based echogenicity or pixel density analysis has better specificity than sensitivity in differentiating exudative from transudative pleural effusion.

Gardiner et al. introduced the score including Diaphragmatic Nodularity, Unilateral Effusion, Echogenicity, Pleural Thickening, and Septations (DUETS). Using a threshold of ≥2, the DUETS score demonstrated a sensitivity of 100%, specificity of 94.6%, PPV of 98.8%, and NPV of 100%. An excellent diagnostic performance was indicated by AUC of 0.999 on ROC curve analysis.[12] This suggests that a combination of ultrasound features may offer superior diagnostic accuracy compared to a single parameter such as pixel density. In contrast, Rampradeep et al. developed the score including Pleural Thickening, Echogenicity, Loculations, and Laterality (TELL) based on multiple ultrasonographic parameters. At a cut-off value of 2, they reported a sensitivity of 98.4% but a lower specificity of 40.0%, with an AUC of 0.79, indicating fair discriminatory ability.[13] Mutlu et al. reported that a sonographic scoring system combining patterns of echogenicity with pleural thickness had a sensitivity of 84.38% and a specificity of 75%, which was better than pixel density alone.[14]

The median pixel density scores were significantly higher in exudative effusions than in transudative effusions (3.35 vs. 1.50; p <0.001) in the present study. A previous study also reported that the median pleural fluid pixel density was significantly higher in exudates compared to transudates (3.53 vs. 2.32; p=0.038).[6] These findings are supported by biological evidence that exudates have higher levels of protein, cell debris, and inflammatory factors, all of which contribute to greater echogenicity of pleural fluid.[15] In a study of 582 patients, Wang et al. reported that complex sonographic appearances of pleural effusion were significantly more frequent in exudative than in transudative effusions: 99.7% of transudative effusions appeared anechoic.[16] Ayoubpour et al. also found pleural thickening, nodules and fluid loculation to be significantly associated with exudative effusions in a study of 72 patients.[17]

Bhutta et al. compared computed tomography (CT) scan with ultrasound in classifying pleural effusions, and found that ultrasound was superior in the detection of loculations.[18] Marchi et al. conducted a narrative review of new imaging techniques and noted that although quantitative pixel density analysis is promising, methodological challenges such as interoperator variability, lack of device standardization, and small sample sizes, continue to limit its use.[19] Another study examined correlations among Light's criteria, pleural fluid procalcitonin levels, and sonographic features in 89 patients. Complex septate patterns and pleural thickening strongly favored exudative effusions, while an anechoic appearance pointed toward transudates.[20] These findings suggest that combining biochemical and ultrasound data may yield better diagnostic results than relying on either approach alone.

Subgroup analysis showed some interesting trends in our study. Sensitivity was higher among females (39.3%) than males (15.8%), and among patients aged 46-60 years (45%) compared with those aged 31-45 years (17.5%). These findings may reflect variations in the inflammatory and proteinaceous composition of pleural effusions across demographic strata. It has been previously reported that ultrasound derived pixel density is significantly higher in exudative pleural effusions, likely related to increased cellular and protein content.[6] However, unlike the present study, they did not evaluate diagnostic performance across age, gender, or BMI subgroups. The consistently high specificity across all strata in our study suggests that elevated pixel density remains a reliable predictor of exudative effusion irrespective of demographic characteristics. Therefore, the present findings also provided additional insight into potential demographic variations in the diagnostic performance of ultrasound derived pixel density.

CONCLUSION

Ultrasound derived pixel density demonstrated fair diagnostic performance in differentiating exudative from transudative pleural effusions, with an AUC of

0.75. At the optimal cut-off value of 9.5, the technique showed high specificity but low sensitivity, indicating a greater ability to identify exudative effusions. Stratified analysis revealed variability in sensitivity across demographic and clinical subgroups, whereas specificity remained consistently high. These findings suggest that pixel density may serve as a useful adjunctive tool in the evaluation of pleural effusions; however, it cannot replace thoracentesis or established diagnostic methods.

LIMITATIONS & RECOMMENDATIONS

The cross-sectional, single-centered design of this study may restrict the generalizability of the findings to other healthcare settings. The relatively small sample size, particularly within subgroup analysis, may limit the precision and robustness of the estimates. The use of consecutive sampling may introduce selection bias. The study also did not assess the etiological spectrum of pleural effusions; therefore, diagnostic performance across specific causes such as tuberculosis, malignancy, and heart failure could not be determined. Further large scale, multi-centered studies with standardized imaging protocols are warranted to validate and extend these findings.

Conflict of interest: None.
Source of funding: None.

Authors' Contributions:
A.J: Conceptualization, data collection, analysis, and manuscript writing.
M.Z.H.M: Study supervision, methodology, and critical review.
M.K.A.K: Data interpretation, statistical analysis, and manuscript review.
A.U.K: Patient recruitment, data collection, and manuscript review.
N.A: Ultrasound assessment, data acquisition, and manuscript editing.
M.H: Literature review, data entry, and manuscript formatting.

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Original Article

Clinical Spectrum, Laboratory Profile, and Antimicrobial Resistance in Pediatric Enteric Fever: A Cross-Sectional Study from Lahore, Pakistan

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ABSTRACT

Objective: To assess the clinical presentation, laboratory abnormalities, and antimicrobial response patterns among children diagnosed with enteric fever.

Methodology: This cross-sectional analytical study was conducted at the Department of Pediatrics, Ittefaq Hospital (Trust), Lahore from January to June 2025. Ethical approval was obtained from the Institutional Review Committee. Informed written consent was sought from parents/guardians of study participants. A sample size of 131 was calculated and children suspected of enteric fever were enrolled using non-probability consecutive sampling technique. Demographic and clinical data was documented. Blood samples were obtained aseptically before antimicrobial therapy and processed for *Salmonella typhi* identification and antimicrobial susceptibility. Data was analyzed using Statistical Package for the Social Sciences (SPSS) version 26.0.

Results: The median age of 131 children was 7.0 years [inter-quartile range (IQR) 3.0-9.0]. Blood culture was positive for *Salmonella typhi* in 75(57.3%) cases including 42(32.1%) multidrug-resistant (MDR) and 33(25.2%) extensively drug-resistant (XDR) strains. Abdominal pain (p=0.004) and constipation (p=0.010) were more frequent in XDR cases. Leukopenia occurred only in XDR cases (p=0.009), and raised C-reactive protein (CRP) was more common in MDR (85.7%) and XDR (90.9%) samples compared to no growth samples (p <0.001).

Conclusion: *Salmonella typhi* was identified in over half of the cases with a high proportion of MDR and XDR strains. Abdominal pain, constipation, and leukopenia were significantly more common among XDR patients compared to MDR patients. C-reactive protein was significantly elevated in both MDR and XDR cases, while erythrocyte sedimentation rate (ESR) showed no association. Multidrug-resistant strains showed sensitivity to ceftriaxone and XDR strains to azithromycin & carbapenems.

Keywords: *Enteric fever. Salmonella typhi. Blood culture. Antimicrobial Resistance.*

INTRODUCTION

Enteric fever is mainly caused by *Salmonella enterica*, *serotypes typhi*, and *paratyphi*, and considered a major public health issue especially among developing countries.[1] Last few decades have seen major improvements in sanitation and overall healthcare access, but still enteric fever causes considerable morbidity and mortality.[2] The Global Burden of Disease study reported 9.3 million cases of enteric fever and approximately 107,000 deaths in 2021, with 40% of fatalities occurring in children under five. The highest burden was observed in endemic regions, particularly South Asia.[3]

The most common symptoms in enteric fever include prolonged fever, abdominal pain, headache, and gastrointestinal disturbances. Atypical presentations like intestinal perforation, hemorrhage, and encephalopathy are somewhat uncommon but can still occur among severe cases. The emergence and spread of multidrug-resistant and extensively drug-resistant *Salmonella typhi* strains have compromised the effectiveness of commonly used antibiotics like chloramphenicol, ampicillin, and trimethoprim sulfamethoxazole.[4]

Recent local data documented a high prevalence of MDR and XDR *Salmonella typhi* in Pakistan, which leaves very few treatment options like azithromycin and carbapenems. The evolving resistance patterns pose significant challenges for treating physicians, increasing the risk of complications, treatment failure, and prolonged disease spans.[5] The local literature exhibits that only one oral antibiotic, azithromycin, is predominantly left as a treatment option in XDR enteric fever.[6]

Enteric fever continues to pose a significant public health burden in children, particularly in resource limited settings where sanitation and access to safe drinking water remain suboptimal. The clinical presentation in children is often diverse and may overlap with other febrile illnesses, while laboratory abnormalities are not always specific, leading to diagnostic uncertainty.[4] Evolving antimicrobial resistance has also reduced the effectiveness of commonly used antibiotics, complicating empirical management. Given these concerns, it is important to generate updated local data on the clinical profile,

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laboratory derangements, and antimicrobial response patterns of pediatric enteric fever to inform evidence based diagnosis and treatment strategies. This study aimed to determine the clinical characteristics, laboratory abnormalities, and antimicrobial responses in children diagnosed with enteric fever.

METHODOLOGY

This cross-sectional analytical study was conducted at the Department of Pediatrics, Ittefaq Hospital (Trust), Lahore from January to June 2025. Ethical approval was obtained from the Institutional Review Committee (Letter No. IHT/Admin/30, 23-12-2023). Informed written consent was sought from parents/guardians of study participants. A sample size of 131 was calculated using a 95% confidence level and a 7% margin of error, based on an anticipated 79% prevalence of XDR *Salmonella typhi* strains.[7] Inclusion criteria were children aged 1 to 14 years, who were suspected to have enteric fever based on criteria of fever for more than 5 days, without any identifiable focus or with gastrointestinal symptoms like vomiting, abdominal pain, or loose stools. Children with a clear alternate diagnosis, ongoing antibiotic therapy before hospital presentation were excluded. Non-probability consecutive sampling technique was adopted.

Upon admission, detailed demographic, and clinical data including gender, age, and associated symptoms were documented on a preformed proforma. Laboratory investigations were conducted as per hospital protocol through the institutional laboratory, and parameters like leukocyte count, ESR, and CRP were evaluated. Blood samples were collected under strict aseptic conditions prior to the initiation of antimicrobial therapy and processed using the BACTEC automated blood culture system. Culture and sensitivity testing were performed to identify the presence of *Salmonella typhi*, and to determine antimicrobial susceptibility patterns. Positive cultures were sub-cultured on blood agar and MacConkey agar. *Salmonella typhi* was identified by colony morphology, gram staining, standard biochemical tests, and confirmed serologically using specific *Salmonella* O and H antisera. Antimicrobial susceptibility testing was performed by the Kirby-Bauer disc diffusion method on Mueller-Hinton agar. Zone diameters were interpreted according to clinical and laboratory standards. The outcomes were categorized as no growth, MDR, and XDR *Salmonella typhi*. Multidrug-resistant *Salmonella typhi* was defined as resistance to first line agents like ampicillin, chloramphenicol, and co-trimoxazole, while XDR *Salmonella typhi* was defined as resistance to first-line agents, fluoroquinolones, and third-generation cephalosporins.[4] Leukocyte count was categorized as normal (4,000-11,000 cells/mm^3), leukocytosis (>11,000 cells/mm^3, and leukopenia (<4,000 cells/mm^3). C-reactive protein was considered normal if ≤6mg/L and raised if >6mg/L.[8] Erythrocyte sedimentation rate was considered normal if ≤10 mm/hr and raised if >10 mm/hr.[9]

STATISTICAL ANALYSIS

The data was entered and analyzed using Statistical Package for Social Sciences (SPSS) version 26.0. Categorical variables were presented as frequencies & percentages, while continuous variables were summarized as median and inter-quartile range (IQR). The comparison of demographic, clinical, and laboratory characteristics was done across outcome categories of blood culture findings (no growth, MDR, and XDR *Salmonella typhi*). The Chi-square test or Fisher's exact test was applied, taking $p < 0.05$ as statistically significant.

RESULTS

Among a total of 131 children, 67(51.1%) were females and 64(48.9%) were males. The median age was 7.00 years (IQR: 3.0-9.0). Vomiting, anorexia, abdominal pain, and loose stools were reported in 63(48.1%), 55(42.0%), 52(39.7%), and 32(24.4%) children, respectively. The median leukocyte count, ESR, and CRP levels were 9.10(6.40-11.81), 28.00(22.00-46.00), and 23.00(9.80-58.00), respectively. Leukocyte count was normal in 92(70.2%) children, while 36(27.5%) had leukocytosis, and 3(2.3%) had leukopenia. Raised ESR was observed in 123(93.9%) children and raised C-reactive protein in 97(74.0%) children.

Blood culture was positive for *Salmonella typhi* in 75(57.3%) cases, of which 42(32.1%) were MDR and 33(25.2%) were XDR strains. No growth was observed in 56(42.7%) cases. There were no significant differences in gender, age groups, or ESR status among the no growth, MDR, and XDR groups ($p > 0.05$). Abdominal pain was significantly more common in XDR cases (63.6%) compared to MDR and no growth cases ($p=0.004$), while constipation was observed only in XDR patients ($p=0.010$). Leukocyte count status showed a significant difference among groups ($p=0.009$), with leukopenia seen only in XDR cases. Raised CRP was significantly more frequent in MDR and XDR cases compared to no growth cases ($p < 0.001$) (Table 1).

When demographic, clinical, and laboratory characteristics were compared between MDR and

XDR groups only, no significant differences in gender, age, leukocyte count, ESR, or CRP levels were recorded (p >0.05). However, abdominal pain (p=0.002) and constipation (p=0.04) were significantly more common in XDR *Salmonella typhi* infections compared to MDR cases. Antimicrobial sensitivity pattern among children with enteric fever is shown in Table 2.

DISCUSSION

In this study, the culture positivity rate for *Salmonella typhi* was 57.3%, slightly higher than the 50% reported by Nusrat et al.[10] The high proportions of MDR (32.1%) and XDR (25.2%) *Salmonella typhi* strains observed in the current study are consistent with the alarming rise in resistant typhoid reported by Zakir et al, where majority of culture positive cases were XDR (46.1%) followed by MDR (24.5%) strains.[11]Another study found that 55.2% of isolates were XDR and 34.7% were MDR.[12] A study conducted in Pakistan demonstrated a similar trend, with 50.7% of children with typhoid having MDR, 47% having XDR, and only 2.3% exhibiting non-resistant infection.[13] Another study documented high rates of resistant *Salmonella typhi*, with 50.5% XDR, 46.6% MDR, and only 2.9% drug sensitive strains, and observed a notable shift from MDR to XDR, along with a decline in drug sensitive cases over one year period.[14]

The resistance patterns in our study with MDR strains remaining largely sensitive to ceftriaxone and XDR strains responsive only to azithromycin or meropenem, align with the findings of Herekar et al., who reported the use of cephalosporins for MDR infections and azithromycin or meropenem, alone or in combination, for XDR cases.[14]

Table 1: Comparison of Clinical and Laboratory Characteristics according to Blood Culture Results in Children with Suspected Enteric Fever

Characteristics			Blood Culture Results				p-value
			No Growth (n=56)	MDR *Salmonella typhi* (n=42)	XDR *Salmonella typhi* (n=33)	Total	
			Frequency & Percentage				
Presenting Complaints	Vomiting	Yes	24(42.9%)	18(42.9%)	21(63.6%)	63(48.1%)	0.118
		No	32(57.1%)	24(57.1%)	12(36.4%)	68(51.9%)	
	Anorexia	Yes	22(39.3%)	21(50.0%)	12(36.4%)	55(42.0%)	0.427
		No	34(60.7%)	21(50.0%)	21(63.6%)	76(58.0%)	
	Abdominal Pain	Yes	19(33.9%)	12(28.6%)	21(63.6%)	52(39.7%)	0.003*
		No	37(66.1%)	30(71.4%)	12(36.4%)	79(60.3%)	
	Loose Stools	Yes	17(30.4%)	6(14.3%)	9(27.3%)	32(24.4%)	0.169
		No	39(69.6%)	36(85.7%)	24(72.7%)	99(75.6%)	
	Constipation	Yes	0(0%)	0(0%)	3(9.1%)	3(2.3%)	0.010*
		No	56(100%)	42(100%)	30(90.9%)	128(97.7%)	
Leukocyte Count Status (cells/mm^3)	Normal		35(62.5%)	33(78.6%)	24(72.7%)	92(70.2%)	0.009*
	Leukocytosis		21(37.5%)	9(21.4%)	6(18.2%)	36(27.5%)	
	Leukopenia		0(0%)	0(0%)	3(9.1%)	3(2.3%)	
ESR (mm/hr)	Normal		2(3.6%)	3(7.1%)	3(9.1%)	8(6.1%)	0.544
	Raised		54(96.4%)	39(92.9%)	30(90.9%)	123(93.9%)	
CRP (mg/L)	Normal		25(44.6%)	6(14.3%)	3(9.1%)	34(26.0%)	<0.001*
	Raised		31(55.4%)	36(85.7%)	30(90.9%)	97(74.0%)	

**Significant p-value*

Table 2: Distribution of Antimicrobial Sensitivity Pattern among Children with Enteric Fever

Salmonella Isolates	Antimicrobial Agent	Sensitivity Frequency (Percentage)
MDR *Salmonella typhi* (n=42)	Ciprofloxacin	3(7.1%)
	Ceftriaxone	39(92.9%)
XDR *Salmonella typhi* (n=33)	Azithromycin	33(100%)
	Meropenem	33(100%)
	Ertapenem	33(100%)
	Piperacillin/Tazobactam	28(84.8%)

Both MDR and XDR strains were found to be sensitive to meropenem and azithromycin in another study.[15] Irfan et al. reported that *Salmonella typhi*, including XDR strains, remained fully susceptible to meropenem and azithromycin, while tigecycline and fosfomycin were identified as alternative treatment options.[16] The universal sensitivity of XDR strains to azithromycin and meropenem underscores their role as last resort agents, highlighting the clinical importance of reserving these antibiotics for confirmed resistant infections to prevent further escalation of resistance.[13] Although 84.8% of XDR *Salmonella typhi* isolates in our series were sensitive to piperacillin/tazobactam, this observation should be interpreted cautiously. In vitro activity against XDR *Salmonella typhi* has been described for piperacillin/tazobactam, but clinical experience is limited, and current treatment discussions more consistently support azithromycin and carbapenems as the principal options for XDR typhoid.

Among 131 children of this study, 51.1% were females and 48.9% were males, with a median age of 7.00 years (IQR: 3.0-9.0). No significant differences in age or gender distribution were observed among the no growth, MDR, and XDR groups in our study ($p > 0.05$). The median age of 7 years, and nearly equal gender distribution reflect the typical vulnerability of the pediatric age group to enteric fever, slightly different from observations made by Shahid et al. who documented median age of 5 years (IQR: 2.0-8.0), with 58% males and 43% females.[13] Herekar et al. reported that children aged 5-6 years were most commonly affected by *Salmonella typhi* infection with no significant differences in age or gender distribution between MDR and XDR strains.[14] Similarly, Irfan et al. observed a mean age of 4.2 years among children under 10 with 59.3% males and 40.7% females, and found no significant differences in age ($p=0.566$) or gender ($p=0.103$) distribution between XDR and non-XDR strains.[16] This demographic pattern supports the notion that school age children remain a key target population for preventive interventions, including vaccination and hygiene education.

The predominance of fever as a universal presenting symptom aligned with previous reports, where fever was consistently reported in all culture positive cases followed by vomiting and anorexia.[13] A study highlighted that the majority of XDR patients had prolonged fever (more than 7 days) at the time of presentation as compared to non-XDR patients ($p < 0.01$). Similar to our results, vomiting, anorexia and loose stools showed no significant differences among XDR and non-XDR groups ($p > 0.05$).[7] Clinical symptomatology in our study showed that abdominal pain was significantly more frequent in children with XDR *Salmonella typhi* (63.6%) compared to MDR (28.6%) and culture negative cases ($p=0.004$). This finding is consistent with others who also identified abdominal pain as a common and prominent symptom in enteric fever patients.[17] Rahim et al. suggested that abdominal pain in XDR typhoid may result from ileocolic inflammation, ulceration, or mesenteric lymphadenitis, which typically resolves with appropriate antibiotics. They also noted that severe or atypical gastrointestinal symptoms could indicate resistant infections, highlighting the need for prompt culture and sensitivity testing.[18] These clinical distinctions reinforce the value of symptom based risk stratification in resource limited settings where immediate culture results may not be available.

Leukocyte count patterns in our study revealed that normal counts predominated across all culture samples, but leukocytosis was notably higher in culture negative patients. Leukopenia was observed only in the XDR patients ($p=0.009$). These findings were consistent with findings from Nusrat et al., where normal counts were reported in the majority (74.5%) of enteric fever children. Leukopenia and other haematological abnormalities, such as anaemia and thrombocytopenia were linked to severe or complicated typhoid infections.[10] Another retrospective study reported normal leukocyte count in 70% cases of suspected enteric fever.[8] In this study, raised ESR was observed in over 90% of patients irrespective of culture status ($p=0.544$), while raised CRP was significantly ($p < 0.001$) more frequent in MDR and XDR infections compared to culture negative cases. Ravi Teja et al. also highlighted the potential utility of elevated acute phase reactants in the inflammatory assessment of enteric fever.[19] However, these laboratory parameters alone are insufficient to differentiate MDR from XDR infections, emphasizing the necessity for microbiological confirmation.

CONCLUSION

Blood culture identified *Salmonella typhi* in more than half of the cases, with a substantial proportion demonstrating MDR and XDR patterns. Multidrug-resistant isolates retained high sensitivity to ceftriaxone, whereas XDR isolates remained uniformly sensitive to azithromycin and carbapenems. Abdominal pain, constipation, and leukopenia were significantly more common among XDR patients compared to MDR patients. Raised CRP levels were significantly observed in both

MDR and XDR cases compared to culture negative cases, while ESR levels showed no such association.

LIMITATIONS & RECOMMENDATIONS

The single-centered setting of this study may limit generalizability to other regions with differing epidemiologic profiles. The cross-sectional design precludes assessment of temporal changes or causality between clinical features and resistance patterns. Lack of molecular characterization of resistance genes limits mechanistic insights into antimicrobial resistance. Future studies should consider multicentre designs with longitudinal follow-up to better capture resistance dynamics and clinical outcomes. Incorporation of molecular diagnostics could enhance detection sensitivity and elucidate resistance mechanisms, guiding more precise treatment and containment strategies. The study also did not evaluate vaccination status or detailed socioeconomic factors, which may influence disease susceptibility and clinical course. Future research incorporating these variables could clarify their roles in disease epidemiology and inform public health interventions. Additionally, the absence of standardized severity scoring may have limited the assessment of clinical correlations with resistance.

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Authors' Contributions:
S.H: Conception and design, proofreading, critical revisions, approved for publication.
M.U.R: Data collection, drafting, proofreading, critical revisions, approved for publication.
A.S: Data collection, data analysis, proofreading, critical revisions, approved for publication.
S.Y: Literature review, data collection, proofreading, critical revisions, approved for publication.
R.A.R: Literature review, data collection, proofreading, critical revisions, approved for publication.
A.C: Literature review, data collection, proofreading, critical revisions, approved for publication.

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Original Article

Association between High-Altitude Residence and Risk of Prostate Cancer in Misgar, Gilgit-Baltistan

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ABSTRACT

Objective: To determine the association between high-altitude residence and the risk of prostate cancer based on prostate-specific antigen density (PSAD) among residents of Gilgit-Baltistan.

Methodology: This cross-sectional analytical study was conducted at Misgar, Gilgit Baltistan, by Sharif Institute of Urology & Renal Transplant (SIURT), Sharif Medical City Hospital, Lahore, from July to December 2025, following ethical approval from the institutional review board. After meeting the selection criteria, 96 male residents of high altitude, having age ≥40 years, were enrolled using a non-probability consecutive sampling technique, irrespective of digital rectal examination (DRE) or ultrasound findings. The patients then underwent clinical evaluation, and blood samples were collected to measure their prostate-specific antigen (PSA) levels. Prostate size (ml) was measured using abdomino-pelvic ultrasound by a consultant radiologist in the nearest health facility, and PSAD was calculated. Based on PSA density, patients were categorized as having low, intermediate, and high risk of cancer. Data was analyzed using Statistical Package for the Social Sciences (SPSS) version 26.

Results: The mean age of the patients was 59.38±11.12 years. Among patients residing at high altitude for ≥10 years, a high risk of prostate cancer based on PSA density was observed in 4(4.2%) cases, whereas among those living at high altitude for <10 years, high risk was not found in any of the patients (p <0.001). Most of the smokers, hypertensives, diabetics, and those with positive family history of prostate cancer had intermediate or high risk of prostate cancer (p <0.05). However, alcohol use showed no such association (p-value=0.18).

Conclusion: Residents living at high altitude for more than 10 years had a significantly higher risk of developing prostate cancer compared to those residing at high altitude for less than 10 years.

Keywords: *Prostate Cancer. Prostate-specific antigen. Ultrasonography. Digital rectal examination.*

INTRODUCTION

Prostate cancer is a major malignancy in men and a leading contributor to male mortality worldwide. It may present as either a localized or an advanced stage disease. Prostate cancer is classified as either androgen sensitive or androgen insensitive, reflecting its dependence on testosterone stimulation or guiding potential treatment options.[1] Globally, prostate cancer is the most common cancer among males and the prevalence and mortality increase with increasing age.[2] A high prostate-specific antigen level can be a sign of prostate cancer, but it can also be caused by non-cancerous conditions like benign prostatic hyperplasia, acute or chronic prostatitis and urinary tract infections.[3] Biopsy is the gold standard diagnostic method. Most prostate cancers are fortunately low-grade and not very aggressive.[4]

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Prostate cancer incidence varies globally, with higher rates typically found in Northern America, Australia, and Northern and Western Europe (Norway) compared with lower rates in South-Central and East/Southeast Asian countries (India, China, Thailand).[5] The incidence has been associated with older age, unhealthy diet, lack of physical activity and environmental factors. The patients usually present with lower abdominal pain, difficult micturition, hematuria, and bone pains. Most cases are localized but metastasis to bone and lymph nodes can occur in advanced cases.[6]

High-altitude residence and prostate disease, though distinct, are both linked to hypoxic conditions. To adapt to this oxygen scarcity, the body activates systemic, cellular, and molecular mechanisms. This response impacts the entire body, including the cardiovascular, respiratory, and reproductive systems. Conversely, malignant prostate tissue is associated with oxygen deprivation in the tissue microenvironment, resulting from both limited oxygen availability and elevated consumption caused by rapid cellular proliferation.[7]

Direct evidence linking high altitude to the risk of developing prostate cancer is lacking in our population, despite previous research showing the adverse impact of high altitude on other male

reproductive parameters, such as altered testosterone levels, reduced testicular volume, and decreased sperm concentration and motility.[7] To fill this gap, this study was planned and conducted among residents of a high-altitude area to generate local evidence and to make recommendations regarding screening accordingly.

METHODOLOGY

This cross-sectional analytical study was conducted at Misgar, Gilgit Baltistan, by Sharif Institute of Urology & Renal Transplant (SIURT), Sharif Medical City Hospital, Lahore, from July to December 2025, following ethical approval from the institutional review board (Letter No. SMDC/SMRC/342-24, 26-06-2024). A medical camp was organized in Misgar, Gilgit-Baltistan on 14th and 15th July 2025 for the purpose of data collection. The sample size of 96 was calculated using a 90% confidence level, 8% margin of error and 36.3% proportion of patients at higher risk of prostate cancer with PSA density levels greater than 0.15 ng/ml^2.[8] After obtaining informed written consent, 96 male residents of high altitude, aged ≥40 years, were enrolled using non-probability consecutive sampling, irrespective of digital rectal examination (DRE) or ultrasound findings, to ensure uniform and unbiased assessment of prostate cancer risk. The exclusion criteria included patients having prior diagnosis of prostate cancer, history of transurethral resection of the prostate and/or prostatectomy for cancer, prostatitis, acute urinary retention and intake of drugs increasing PSA levels such as betamethasone and testosterone replacement therapy.

Data regarding the history of co-morbidities & risk factors, DRE, abdomino-pelvic ultrasound and laboratory findings were recorded on a predesigned proforma. Those living at ≥2,500 meters above sea level were labelled as high-altitude residents.[7] The residents living at high altitude were divided into 2 groups (≥10 years and <10 years) on the basis of duration of high-altitude residence. The participants' digital rectal examination was done by residents of urology with minimum of 2 years of experience to assess nodularity. A firm or hard nodule on DRE was considered to be suggestive of prostate cancer.[4] Prostate size (ml) was measured using abdomino-pelvic ultrasound by a consultant radiologist in nearest health facility. A 5 ml venous blood sample was collected and sent to the laboratory for PSA levels estimation. The normal cutoff value for PSA levels is 4.0 ng/ml.[3] After obtaining PSA reports from the laboratory, PSA density (PSAD) (ng/ml^2) was calculated by using the formula as [PSA density=PSA levels (ng/ml)/prostate size (ml)].[3] Participants were classified for prostate cancer risk based on PSA density as follows: low risk for PSAD <0.10 ng/ml², intermediate risk for PSAD ≥0.10 to <0.15 ng/ml², and high risk for PSAD ≥0.15 ng/ml².[9] Those with suggestive findings on DRE and with abnormal PSA density levels were counselled on getting biopsies.

STATISTICAL ANALYSIS

Data was entered and analyzed with Statistical Package for the Social Sciences (SPSS) version 26. Continuous variables like age and PSA metrics were summarized as mean±standard deviation. Categorical variables, such as high-altitude residence status, smoking status, and other comorbidities were reported as frequencies & percentages. The association between high-altitude residence and PSA density level categories, comorbidities and digital rectal examination findings was assessed using the Chi-square and Fisher's exact test with a p-value <0.05 considered statistically significant.

RESULTS

The mean age of the participants was 59.38±11.12 years and the mean duration of residence at high altitude was 23.60±14.24 years. The mean PSA level of the study population was 5.46±3.50 ng/ml. Similarly, the mean value of PSAD of the patients was 0.16±0.07 ng/ml^2. The majority of participants (85.4%) had been living at high altitude for 10 years or more. More than half of the participants were smokers (56.3%), while only a small proportion reported alcohol use (5.2%). The prevalence of diabetes mellitus and hypertension was 9.4% and 20.8%, respectively. Additionally, 8.3% of participants reported a family history of prostate cancer.

The nodularity on digital rectal exam was exhibited by only 5(6.1%) participants of long term high-altitude residence (≥10 years). None of the high-altitude residents of less than 10 years duration had shown any abnormal findings. However, these findings were statistically insignificant (p >0.999).

Based on PSA density, 37(38.5%) out of 96 participants were categorized as having low risk, 55(57.3%) as intermediate risk, and 4(4.2%) as high risk for prostate cancer. Among those residing at high altitude for ≥10 years, the majority (55.2%) had intermediate risk of prostate cancer indicated by PSA density and only 4(4.2%) of participants were at high risk. Among those living at high altitude for <10 years, most (12.5%) had low risk, followed by

only 2 (2.1%) participants with intermediate risk of cancer. None of them had high risk of prostate cancer (p <0.001) (Table 1).

The comparison of comorbidities with categories of prostate cancer risk showed that smoking, hypertension, diabetes mellitus and family history of prostate cancer were significantly associated with prostate cancer risk categories based on PSAD. Most of the smokers, hypertensives, diabetics, and those with positive family history of prostate cancer were at intermediate or high risk of prostate cancer (p <0.05). However, alcohol use showed no such association (p-value=0.18) (Table 2).

DISCUSSION

Prostate cancer represents a major public health concern in Pakistan. Data from the Pakistan National Cancer Registry indicated that it is the second most prevalent cancer among males in the country. However, the prognosis is generally very good. It typically progresses slowly and is often discovered at an early, curable stage, leading to successful outcomes for the majority of patients.[10]

The mean age of our study participants was 59.38±11.12 years. Most of them (85.4%) were residents of high altitude for a duration of ≥10 years. Those residing at high altitude for ≥10 years demonstrated a high risk of prostate cancer based on PSA density in 4(4.2%) cases, while no such cases were observed among patients living at high altitude for <10 years (p <0.001). The mean PSA (5.46±3.50 ng/ml) and PSA density (0.16±0.07 ng/ml²) levels of our study population were above the normal cutoff values. Previous literature has also shown that exposure to high altitude is associated with changes in male reproductive hormones, including altered testosterone levels.[7] Serum testosterone concentrations were found to be higher among high altitude residents as compared to individuals residing at sea level, which influenced metabolic adaptation in individuals not fully acclimatized to high altitudes.[11] However, research showed that the effects of high-altitude exposure on semen quality and reproductive hormones in young men were reversible.[12] In contrast to our results, Alcantara-Zapata et al. documented cases of excessive erythrocytosis (Hb >21 g/dl) in subjects from the three highest cities in their study and levels of PSA did not increase significantly with altitude.[13]

Table 1: Association of PSA Density based Prostate Cancer risk with Duration of High-Altitude Residence

Duration of High-Altitude Residence (Years)	Risk of Cancer (on basis of PSA Density)			Total	p-value
	Low risk	Intermediate risk	High risk		
≥10	25(26%)	53(55.2%)	4(4.2%)	82(85.4%)	<0.001*
<10	12(12.5%)	2(2.1%)	0(0%)	14(14.6%)	
Total	37(38.5%)	55(57.3%)	4(4.2%)	96(100%)	

**Significant p-value*

Table 2: Association of Risk of Prostate Cancer Based on PSA Density with Risk Factors and Co-Morbidities

Risk Factors and Comorbidities		Risk of cancer (on basis of PSA Density)			Total (n=96)	p-value
		Low risk (n=37)	Intermediate risk (n=55)	High risk (n=04)		
Smoking	**Yes**	15(40.5%)	36(65.5%)	3(75%)	54(56.3%)	0.03*
	No	22(59.5%)	19(34.5%)	1(25%)	42(43.7%)	
Diabetes Mellitus	**Yes**	1(2.7%)	6(10.9%)	2(50.0%)	9(9.4%)	0.01*
	No	36(97.3%)	49(89.1%)	2(50.0%)	87(90.6%)	
Hypertension	**Yes**	4(10.8%)	14(25.5%)	2(50.0%)	20(20.8%)	0.04*
	No	33(89.2%)	41(74.5%)	2(50.0%)	76(79.2%)	
Alcohol Use	**Yes**	1(2.7%)	3(5.5%)	1(25.0%)	5(5.2%)	0.18
	No	36(97.3%)	52(94.5%)	3(75.0%)	91(94.8%)	
Family History of Prostate Cancer	**Yes**	1(2.7%)	5(9.1%)	2(50.0%)	8(8.3%)	0.006*
	No	36(97.3%)	50(90.9%)	2(50.0%)	88(91.7%)	

**Significant p-value*

Burtscher et al. also reported that incidence and mortality of cancers among males and females significantly decreased with increasing altitudes. This difference can be attributed to varied environmental and lifestyle factors like physical activity, healthy diet, smoking and use of alcohol.[14]

More than half of our participants were smokers (56.3%) and only 5.2% were alcoholics. Most of the smokers, hypertensives, diabetics and those with positive family history of prostate cancer were at intermediate or high risk of prostate cancer ($p < 0.05$). However, alcohol use showed no such association. Raphael et al. also found no statistically significant relationship between cigarette smoking, alcohol consumption, and the risk of prostate cancer.[15] However, another study found that healthier lifestyles, such as reduced smoking and alcohol consumption, showed an opposite association for prostate cancer, where a higher lifestyle index was linked with a slightly increased risk [hazard ratio (HR) 1.04, 95% confidence interval (CI):1.01-1.08], possibly due to greater screening and detection among individuals with healthier lifestyles.[16] A meta-analysis reported that cardiometabolic diseases like hypertension and diabetes significantly influenced the risk of aggressive prostate cancer.[17] Patients with a family history of prostate cancer also demonstrated a significantly higher risk of developing prostate cancer in a study [Relative Risk (RR)=1.25, 95% CI:1.16-1.35, $p < 0.001$].[18]

In our study, 38.5% males were at low risk as their PSAD levels were below the cut-off value of 0.10 ng/ml^2. Those (57.3%) with PSAD between 0.10 to 0.15 ng/ml^2 were at intermediate risk of prostate cancer. Only 4.2% were at high risk where PSAD was $\geq$0.15 ng/ml^2. Park et al. showed that prostate cancer risk increased among those with high PSAD ($\geq$0.218 ng/ml^2) as compared to those with lower PSAD [odds ratio=3.51; 95% CI:1.306 - 9.415]. The use of PSAD levels to determine risk of prostate cancer had additional benefits of reduction in missed diagnosis and unnecessary biopsies.[19] Nazir et al. also reported that PSA levels were non-specific for prostate cancer. However, PSAD levels were independent predictors of clinically significant prostate cancer and those patients with PSAD below 0.10 ng/ml^2 had a significantly low likelihood of getting clinically significant prostate cancer.[20] Similarly, Girometti et al. revealed that PSAD threshold of 0.10 ng/ml^2 demonstrated greater clinical utility in stratifying prostate cancer risk.[21] Maeda-Minami et al. observed that even PSA levels above a specific high value posed a threat for malignancy and mitigating these PSA levels could prove an effective preventive strategy.[22]

CONCLUSION

Residents living at high altitude for more than 10 years had a significantly higher risk of developing prostate cancer compared to those residing at high altitude for less than 10 years. Therefore, males residing at high altitude for longer durations should undergo periodic screening to facilitate early detection and timely management of prostate cancer.

LIMITATIONS & RECOMMENDATIONS

The cross-sectional design, small sample size, and use of a non-probability sampling technique are key limitations, as they restrict the generalizability of the findings to the broader population. Additionally, risk assessment was based solely on prostate-specific antigen density (PSAD) and was not validated through biopsy. Another limitation is the absence of previously published studies exploring the direct relationship between high-altitude residence and prostate cancer risk using PSAD, which constrained comparison with existing literature. Future studies with longitudinal follow-up, larger sample sizes, and probability-based sampling methods are recommended to validate and strengthen these results.

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Authors' Contributions:
M.R.Z: Conceptualization, Supervision, study design, supervision, final approval of the manuscript
M.H: Data collection, clinical assessment, manuscript drafting.
A.H: Methodology, data interpretation, manuscript editing.
B.S: Statistical analysis, data interpretation.
F.H: Data collection, literature review.
M.H: Data acquisition, patient coordination.
E.H: Data analysis, manuscript proofreading.
A.B: literature review, manuscript review.

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Original Article

Efficacy and Safety of Oral Itraconazole vs Oral Itraconazole Plus Oral Isotretinoin in Treatment of Chronic Recurrent Dermatophytosis

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ABSTRACT

Objective: To compare the efficacy and safety of oral itraconazole alone versus oral itraconazole in combination with oral isotretinoin in the treatment of chronic recurrent dermatophytosis.

Methodology: This quasi-experimental study was conducted in the Department of Dermatology, Services Hospital, Lahore, over a duration of one year from January to December, 2025, after institutional ethical approval. Written informed consent was obtained, and a total of 125 patients with recurrent tinea cruris and/or tinea corporis were enrolled using a non-probability consecutive sampling technique. Patients were allocated into two groups: group A (n=61) received oral itraconazole alone, while group B (n=64) received oral itraconazole in combination with oral isotretinoin for one month. Patients were followed weekly during the treatment period to assess clinical cure and adverse effects. Mycological cure was assessed at the end of one month of treatment, and patients were then followed monthly for three months posttreatment to evaluate relapse. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 26.

Results: The mean age of our study participants was 33.95±7.59 years. This study found no statistically significant difference in clinical and mycological cure at treatment completion between the groups (p=0.06). However, relapse was significantly more frequent in group A (55.7%) compared to the group B (34.4%) (p=0.013). Group B experienced a significantly higher frequency of adverse effects, particularly cheilitis and lip dryness (p <0.001).

Conclusion: There was no significant difference in initial clinical or mycological cure rates between the groups. However, group B receiving combination therapy significantly reduced relapse rates but was associated with a higher frequency of adverse effects in the treatment of chronic recurrent dermatophytosis.

Keywords: *Dermatophytes. Itraconazole. Drug Resistance. Isotretinoin. Antifungal agents.*

INTRODUCTION

Superficial fungal infections affect approximately 20-25% of the global population.[1] Dermatophytosis accounts for 31.29% of all superficial skin infections in Pakistan.[2] Commonly used antifungal treatments are terbinafine and itraconazole. But literature has shown that the cure rates of these treatments are declining, and there is an increasing incidence of terbinafine and itraconazole resistance. A multicenter study in France observed terbinafine resistance in their patients.[3] The molecular basis for this terbinafine resistance is a mutation of the squalene epoxidase enzyme gene, which is involved in the biosynthesis of ergosterol in the fungal cell membrane. [3] Similarly, a study in India also recorded an increased incidence of tinea corporis & tinea cruris, which are resistant to terbinafine and itraconazole, because of irrational use of over-the-counter corticosteroid and antifungal combinations.[4] Dermatophyte infection rates are increasing worldwide due to a complex interaction of host factors, environmental conditions, fungal characteristics, and antifungal drug use.[5] Contributing factors include hot and humid climates, unsupervised use of corticosteroid containing antifungal creams, self-medication with antibiotics, widespread use of oral antifungal agents, extensive agricultural use of antifungals, and the rising incidence of antifungal resistance.[6] To overcome treatment resistance, dermatologists have increasingly prescribed oral antifungal agents at higher doses or for prolonged durations in an attempt to improve cure rates. Previous studies have reported comparatively better treatment outcomes in recurrent dermatophytosis with the combination of oral antifungal therapy and oral isotretinoin. Retinoids are believed to enhance epidermal desquamation, thereby accelerating the shedding of keratinocytes and removal of fungal spores, which may help reduce the fungal burden.[7]

A study conducted in Pakistan in 2021 concluded that combination therapy with oral itraconazole and isotretinoin is efficient and safe for the treatment of chronic tinea.[8] However, clinical evidence regarding the efficacy and safety of combining itraconazole with isotretinoin remains limited in our local population. This study was designed to evaluate

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whether the addition of oral isotretinoin to itraconazole provides superior clinical outcomes and reduces relapse and adverse effect rates compared with itraconazole alone in patients with chronic recurrent dermatophytosis. The findings are intended to address an existing evidence gap and to contribute to the development or modification of evidence-based local clinical guidelines.

METHODOLOGY

This quasi-experimental study was conducted in the Department of Dermatology, Services Hospital, Lahore, over a period of one year from January to December 2025, after obtaining ethical approval from the Institutional Review Board (Letter No. IRB/2025/1511/SIMS, 15-01-2025). Prior studies have reported cure rates of approximately 50-60% with itraconazole monotherapy and 70-90% with combination or higher dose regimens.[9,10] Assuming a cure rate of 55% in the itraconazole group and 80% in the combination group, with a confidence level of 95% and 80% power, the minimum required sample size was 56 patients per group, which was increased to account for potential dropouts and non-compliance. Therefore, a total of 125 patients were enrolled using non-probability consecutive sampling and allocated into two groups: group A (n=61) receiving oral itraconazole alone and group B (n=64) receiving a combination of oral itraconazole and oral isotretinoin. The allocation to one of the two groups was based on clinical decision and eligibility, which resulted in a minor variation in group sizes. This difference in group size was minimal (<5%) and unlikely to introduce significant bias.

Patients aged 18 to 60 years, of either gender, and having chronic recurrent infection with a history of two or more episodes having more than 5 lesions, in the last 6 months, that clear up with treatment but return shortly within 4 weeks were included. Exclusion criteria encompassed the patients who were pregnant, lactating, immunocompromised, with comorbidities such as diabetes mellitus, depression, dyslipidemia, hepatic, renal, cardiac, or neurological disorders, as well as those hypersensitive to itraconazole or isotretinoin, and patients with a history of photosensitive disorders or drug-induced photosensitivity reactions (e.g., exaggerated sunburn, photodermatitis).

A detailed, informed written consent was obtained from all the patients before enrollment, and clear instructions were provided regarding the use of contraception for married females during the study period, as isotretinoin is a potentially teratogenic drug. Additionally, all females of childbearing age underwent monthly pregnancy testing. Patients fulfilling inclusion criteria underwent baseline investigations, including complete blood count (CBC), liver function tests (LFTs), renal function tests (RFTs), fasting blood sugar, lipid profile, and urine pregnancy test (for women of reproductive age).

Group A received oral itraconazole monotherapy (ICON, Ferozesons Laboratories) at a dose of 100 mg twice daily. Group B received combination therapy consisting of oral itraconazole (ICON, Ferozesons Laboratories) 100 mg twice daily, and oral isotretinoin (Arynoin-Pharma health) 10 mg once daily. Both groups received treatment for a duration of four weeks. Patients were followed weekly during the treatment period to assess clinical cure and adverse effects. Mycological cure was assessed at the end of one month of treatment, and patients were then followed monthly for three months posttreatment to evaluate relapse.

Efficacy was measured by clinical cure, mycological cure, and relapse rate. The safety profile was assessed based on adverse effects. Potassium hydroxide (KOH) examination was performed at baseline to confirm the diagnosis of dermatophytosis and repeated after one month of treatment to assess mycological cure, defined as the absence of fungal elements on KOH microscopy. Clinical cure was considered as >80% resolution of erythematous plaques, while incomplete clinical cure was <80% lesion improvement. Any treatment related side effects like dryness of the eyes and mouth, skin irritation, and redness, reported by the patient or observed during follow-up, were also recorded. Relapse was defined as recurrence of clinical lesions with positive KOH within 12 weeks after completion of therapy.[11]

STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 26. Continuous variables were expressed as mean±standard deviation, while categorical variables were reported as frequencies & percentages. Categorical variables were compared using the Chi-square and Fisher's exact tests, and a p-value <0.05 was considered statistically significant.

RESULTS

The mean age of the 125 patients was 33.95±7.59 years. The majority (57.5%) were females, and nearly half (51%) had <5% body surface area involvement. The disease duration in 44.8% of patients was between six months and one year.

Tinea cruris was the most common presentation (36.8%), followed by tinea corporis with cruris (32.8%) and tinea corporis (30.4%). Family history of dermatophytosis was positive in 84.8% of patients. Both groups had comparable baseline clinical and mycological characteristics, and all patients showed positive KOH findings at baseline. (Table 1). No statistically significant difference was observed between the two groups regarding baseline demographic and clinical characteristics ($p > 0.05$).

By the end of treatment, KOH negativity and clinical cure were achieved in 55.7% of patients in group A and 71.9% in group B. Although a higher proportion of patients in the group B achieved KOH negativity and clinical cure, the difference was not statistically significant (p=0.06). However, a significant difference was observed in relapse rate, with 55.7% in group A compared to 34.4% in group B (p=0.016), suggesting a lower relapse rate with the addition of isotretinoin. Adverse effects such as dryness of eyes and mouth, skin irritation, and erythema were significantly more common in group B (42.2%) than in the itraconazole only group (6.6%) ($p < 0.001$) (Table 2). However, these effects were mild to moderate in severity, managed symptomatically with supportive care (e.g., emollients and lubricating eye drops), and did not require treatment discontinuation.

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants

Variables		Group A Itraconazole Only (n=61)	Group B Itraconazole & Isotretinoin (n=64)	Total (n=125)	p-value
Age (Years)	**Mean±SD**	34.12 ± 7.44	33.79 ± 7.76	---	0.81
Gender	**Male**	25(41.0%)	28(43.8%)	53(42.4%)	0.74
	Female	36(59.0%)	36(56.2%)	72(57.6%)	
Body Surface Area Involvement	**<5%**	30(49.2%)	34(53.1%)	64(51.2%)	0.69
	5–10%	22(36.1%)	21(32.8%)	43(34.4%)	
	>10%	9(14.7%)	9(14.1%)	18(14.4%)	
Duration of Disease	**6 Months - 1 Year**	27(44.3%)	29(45.3%)	56(44.8%)	0.77
	>1 Year	34(55.7%)	35(54.7%)	69(55.2%)	
Clinical Type	**Tinea Cruris**	22(36.1%)	24(37.5%)	46(36.8%)	0.83
	Tinea Corporis with Cruris	21(34.4%)	20(31.3%)	41(32.8%)	
	Tinea Corporis	18(29.5%)	20(31.3%)	38(30.4%)	
Positive Family History of Dermatophytosis		51 (83.6%)	55(85.9%)	106(84.8%)	0.72
KOH Positivity at Baseline		61 (100%)	64(100%)	125(100%)	—

Table 2: Comparison of Mycological Cure, Clinical Cure, Relapse Rate, and Adverse Effects between Treatment Groups

Outcome Variables		Group A (Itraconazole) (n=61)	Group B (Itraconazole & Isotretinoin) (n=64)	p-value
Mycological Cure (KOH at the end of Treatment)	**Positive**	27(44.3%)	18(28.1%)	0.06
	Negative	34(55.7%)	46(71.9%)	
Clinical Cure at the end of Treatment	**Complete**	34(55.7%)	46(71.9%)	0.06
	Incomplete	27(44.3%)	18(28.1%)	
Relapse	**Yes**	34(55.7%)	22(34.4%)	0.016*
	No	27(44.3%)	42(65.6%)	
Adverse Effects	**Observed**	4(6.6%)	27(42.2%)	<0.001*
	Not Observed	57(93.4%)	37(57.8%)	

**Significant p-value*

DISCUSSION

A study from India showed that the cure rates of commonly used antifungal treatments, such as terbinafine and itraconazole are declining due to increased virulence of dermatophytes and development of antifungal resistance in patients. For the same reasons, 17% dermatologists reported adding isotretinoin to their routine antifungal regimen.[12] The mean age of the 125 patients in our study was 33.95±7.59 years, and the disease duration in 44.8% of patients ranged between six months and one year. A study from Pakistan reported a mean age of 36.03±6.11 years and a mean disease duration of 6.83±1.86 months. However, unlike our findings, which demonstrated a female predominance, their study reported a male predominance. Furthermore, only 15% of patients in their study had a family history of dermatophytosis compared to 84.8% in the present study.[13]

Our study evaluated the effect of combining isotretinoin with itraconazole and found no statistically significant difference in clinical and mycological cure rates at the end of treatment between both groups (p=0.06). However, relapse was significantly more frequent in group A (55.7%) compared with group B (34.4%) (p=0.016). In contrast, a study reported that 88.3% of 60 patients treated with a combination of itraconazole and isotretinoin achieved significant clinical improvement, while only 5% experienced relapse. The authors concluded that pulse therapy with itraconazole combined with daily adjunctive isotretinoin is an effective treatment regimen for recurrent and recalcitrant superficial dermatophytosis.[13] Alhamdi et al. evaluated low dose isotretinoin combined with itraconazole and reported significantly higher cure rates (97.5%) and lower relapse rates (12.8%) compared with itraconazole monotherapy (53.7% cure and 68.1% relapse). In contrast to their findings of no significant adverse effects, the present study observed significantly more adverse effects, particularly cheilitis and lip dryness, in the group B receiving combination therapy (p <0.001).[11] The evidence indicates variable effects of isotretinoin-itraconazole combination therapy on efficacy and safety outcomes across different studies. Khattab et al. also reported significantly higher clinical (70%) and mycological (83.3%) cure rates in the isotretinoin/itraconazole combination group compared to the itraconazole monotherapy group. Contrary to our findings, they observed no significant adverse effects in the isotretinoin group. They also reported higher cure rates in the voriconazole group, which were comparable to those achieved with combination therapy, highlighting its potential as an effective antifungal agent with relatively low resistance.[14]

A study from India concluded that oral isotretinoin may serve as an effective adjunct in the management of superficial dermatophytosis by promoting earlier remission and reducing recurrence rates. In that study, an earlier mycological cure was achieved with combination therapy. However, no statistically significant difference was observed in mycological cure rates between the combination therapy group (97.5%) and the itraconazole monotherapy group (89.2%) (p=0.06). A significantly lower recurrence rate was observed in the combination therapy group (p=0.01), consistent with our findings.[15] Verma et al. conducted an open label trial comparing isotretinoin plus terbinafine with terbinafine alone in recurrent dermatophytosis and found no significant difference in cure or relapse rates between the groups. Both groups achieved cure rates of approximately 43% with comparable relapse rates (63-65%), suggesting limited additional benefit of isotretinoin with terbinafine therapy. Consistent with the present study, the isotretinoin group experienced more adverse effects, particularly cheilitis and lip dryness.[16]

Difficult to treat dermatophytosis leaves clinicians with the options of increasing the dose, prolonging the duration of therapy, or using combination treatment. The regimens other than retinoids combined with itraconazole are also being explored. Hassaan et al. evaluated the combination of terbinafine with itraconazole and reported no statistically significant difference in clinical and mycological cure rates compared with monotherapy (p=0.207). Notably, the cure rate in the itraconazole monotherapy group (86.7%) was higher than that observed in the present study (55.7%).[17] Another study reported a lower cure rate in the itraconazole group for recurrent chronic dermatophytosis compared to groups receiving higher (supra-pharmacological) doses of itraconazole or combination therapy.[9]

Khurana et al. conducted a broader narrative review of therapeutic strategies in dermatophytosis and highlighted both the potential benefits and safety concerns of combining isotretinoin with antifungals. The keratolytic and epidermal turnover–promoting effects of isotretinoin may enhance fungal clearance. However, the authors concluded that the available evidence remains insufficient to recommend isotretinoin routinely as an adjuvant therapy because

of unresolved safety concerns.[18] To minimize these concerns, Alhamdi et al. used a shorter (2 month) duration combination regimen with low dose isotretinoin (10 mg on alternate days) and reported no significant adverse effects.[11] In contrast, the present study observed a significantly higher frequency of adverse effects in group B receiving combination therapy at the end of the one month treatment period. These findings suggest that the safety profile of isotretinoin remains a key limiting factor, particularly with shorter yet relatively intensive regimens.

CONCLUSION

The addition of isotretinoin to itraconazole did not result in a significant difference in initial clinical or mycological cure rates between the treatment groups. A significantly higher frequency of adverse events was observed in patients receiving itraconazole & isotretinoin combination therapy. However, the combination of isotretinoin significantly reduced relapse rates in patients with chronic recurrent dermatophytosis.

LIMITATIONS & RECOMMENDATIONS

The non-randomized design may introduce selection bias and limit comparability between groups. The single-centered setting restricts the applicability of the findings. The short follow-up period may not adequately capture long term recurrence and delayed adverse effects. In addition, potential confounders such as treatment adherence and environmental factors were not fully controlled, which may have influenced the outcomes.

Adding retinoids to itraconazole is recommended to prevent relapse in patients with chronic recurrent dermatophytosis not responding to itraconazole or terbinafine monotherapy, but the safety concerns should be carefully considered before recommending routine use. Future studies with longer follow-up periods are recommended to assess the durability of response, recurrence patterns, and late onset adverse effects, thereby providing more robust evidence to guide clinical decision-making.

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Authors' Contributions:
A.A: Conceptualization, study design, data collection, manuscript drafting.
H.T: Data collection, patient follow-up, data analysis.
S.B: Literature review, data interpretation, manuscript writing.
U.A: Methodology, supervision, critical revision of manuscript.
F.A: Statistical analysis, results interpretation, manuscript editing.
J.B.T: Study supervision, final review and approval of manuscript.

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Original Article

Antimicrobial Resistance Pattern of Bacterial Isolates from ICU Patients in a Tertiary Care Hospital

Aqsa Aslam, Sadaf Nasir, Anwar Hussain Abbasi, Uzma Ali, Hina Andaleeb, Naila Rafique

ABSTRACT

Objective: To determine the frequency and antimicrobial resistance (AMR) pattern of bacterial isolates among intensive care unit (ICU) patients in a tertiary care hospital.

Methodology: This cross-sectional descriptive study was carried out in the Microbiology Laboratory of Provincial Headquarter Hospital, Gilgit, from October 2025 to March 2026 after ethical approval. After taking informed consent, 150 culture specimens received from ICU patients were tested by non-probability consecutive sampling. Each specimen was inoculated onto the appropriate culture media, then incubated and carefully identified based on colony morphology, Gram stain, and biochemical tests. The antimicrobial sensitivity testing (AST) was performed by the Kirby-Bauer disc diffusion method. The antibiotic zone diameters were reported following the Clinical and Laboratory Standards Institute (CLSI) guidelines 2025. The statistical analysis was done by the Statistical Package for the Social Sciences (SPSS) version 27.

Results: The most common pathogen isolated was *Staphylococcus* (31.6%), succeeded by *Escherichia coli* (17.3%), *Klebsiella pneumoniae* (15.3%), *Pseudomonas aeruginosa* (13.3%), *Acinetobacter baumannii* (10.2%), *Enterococcus species* (9.2%), and *Proteus* species (3.1%). *Staphylococcus aureus*, Coagulase-negative *Staphylococcus* species (CoNS) and *Enterococcus* species were sensitive to vancomycin and linezolid. *Staphylococcus aureus* and CoNS showed less resistance to gentamicin (35.7% versus 23.5%) and doxycycline (28.6% and 17.6%). Carbapenems showed 100% susceptibility in all Gram-negative isolates. Piperacillin-tazobactam, amikacin and nitrofurantoin showed better sensitivities as compared to other antibiotics. *Escherichia coli, Klebsiella pneumoniae, Proteus* and *Pseudomonas* showed 29.4%, 33.3%, 0% & 38.5% resistance to piperacillin-tazobactam and 17.6%, 20%, 33.3% & 46.1% to amikacin. Resistance to nitrofurantoin was 27.3% for *E. coli*, 0% for *Klebsiella pneumoniae*, and *Proteus* species. *Acinetobacter baumannii* exhibited higher antibiotic resistance.

Conclusion: Gram-negative bacteria constituted 59.2%, whereas Gram-positive bacteria made up 40.8% of the isolates. Around 71.4% isolates of *Staphylococcus aureus* were methicillin-resistant and 70.6% *Escherichia coli* & 73.3% *Klebsiella pneumoniae* were extended-spectrum beta-lactamase (ESBL) producers. A higher antimicrobial resistance was seen in the isolates.

Keywords: *Drug resistance. Bacterial infections. Anti-bacterial agents. Intensive care units.*

INTRODUCTION

Intensive care units (ICUs) have a central role in managing critically ill patients. However, these units also present a major challenge for infection control because patients are often immunocompromised, require prolonged hospital stays and extensive antibiotic therapy.[1,2] Environmental surfaces and fomites in ICUs can act as important reservoirs for infectious microorganisms. These fomites include medical equipment, bed rails, doorknobs, countertops, ventilators, catheters, and other frequently touched surfaces.[3] Patients in ICU often require invasive devices which makes them more vulnerable to infections. In addition, multidrug-resistant (MDR) organisms may arise and spread as a result of regular usage of antibiotics in these patients.[1] Healthcare-associated infections (HAIs) remain a significant public health issue in ICUs across the world. These infections not only increase morbidity and mortality but also prolong hospital stays and add substantial financial burden to health care systems.[3] The World Health Organization estimates 42.7 million cases of HAIs each year, emphasizing the significant global impact of these infections. In the United States, the estimated annual cost associated with HAIs ranges from $96 to $147 billion, whereas in Africa, the annual economic burden is estimated at nearly $13 billion. Studies have consistently shown that patients admitted to ICUs are at a much higher risk of developing HAIs compared with patients in general hospital wards.[4] Patients admitted to ICUs are particularly vulnerable to infections caused by *Staphylococcus aureus*, *Enterococcus* species, *Escherichia coli (E. coli)*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*. These organisms are a growing concern worldwide due to their resistance to multiple antibiotics and their association with high morbidity and mortality rates.[5] Detecting infections early in ICU patients can be difficult because common clinical signs such as fever and tachycardia are often nonspecific in critically ill

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individuals. For this reason, laboratory tests such as complete blood count (CBC), C-reactive protein (CRP), and microbiological cultures are essential for accurate diagnosis, appropriate antimicrobial therapy, and infection prevention measures.[6] Effective cleaning, disinfection, and adherence to infection control guidelines are therefore essential to reduce contamination and prevent healthcare-associated infections.[7] The purpose of this study was to ascertain the frequency and AMR pattern of bacterial isolates among ICU patients in a tertiary care facility. Such efforts can help lower the burden of HAIs, decrease the emergence of MDR organisms, and improve prognosis in ICU patients.

METHODOLOGY

This cross-sectional descriptive study was carried out in the Microbiology Laboratory of Provincial Headquarter Hospital, Gilgit, from October 2025 to March 2026 after ethical approval (Letter No. 1103/PHQ/2025, 03-10-2025). The sample size of 143 (rounded off to 150) was calculated by using 95% confidence interval, 6% margin of error, and 84% assumed prevalence of multidrug-resistant pathogens from the ICU.[8]

After taking written informed consent from patients or their attendants, 150 culture specimens received from ICU patients, irrespective of age or gender, were tested using a non-probability consecutive sampling. The clinical samples received included blood, urine, sputum, pus, and catheter tips. Samples with improper labeling, or evidence of contamination or repeat samples from the same patient were excluded. Each specimen was inoculated onto the appropriate culture media under aseptic conditions, then incubated and carefully identified by an experienced microbiologist based on colony morphology, Gram stain, and biochemical tests. Among biochemical tests, catalase, coagulase and bile esculin hydrolysis tests were done for Gram-positive cocci. For Gram-negative bacteria, citrate utilization, triple sugar iron (TSI), urease, motility, indole, and oxidase tests were used. The antimicrobial sensitivity testing (AST) was performed by the Kirby-Bauer disc diffusion method. The antibiotic zone diameters were reported as sensitive, intermediate, and resistant following the Clinical and Laboratory Standards Institute (CLSI) guidelines 2025.[9] All the required information was recorded on a predesigned proforma.

The classes of antibiotics that were applied for Gram-positive bacteria were penicillin (P), ampicillin (AMP), cefoxitin (FOX), ciprofloxacin (CIP), levofloxacin (LEV), gentamicin (CN), trimethoprim-sulfamethoxazole (SXT), erythromycin (E), clindamycin (DA), doxycycline (DOX), vancomycin (VA), and linezolid (LZD). Cefoxitin was used to report methicillin sensitivity in *Staphylococcus*.[9]

The antibiotic panel used for Gram-negative bacteria included amoxicillin-clavulanic acid (AMC), cefotaxime (CTX), ceftazidime (CAZ), ceftriaxone (CRO), gentamicin (CN), amikacin (AK), ciprofloxacin (CIP), trimethoprim-sulfamethoxazole (SXT), imipenem (IPM), meropenem (MEM) and piperacillin-tazobactam (TZP). Only urinary isolates were subjected to nitrofurantoin susceptibility testing, in line with CLSI recommendations. The double-disc synergy test (DDST) was used to identify extended-spectrum beta-lactamase (ESBL). Amoxicillin-clavulanic acid was placed in the center with cefotaxime and ceftazidime discs placed 20 mm (center-to-center) from AMC. Increased zone diameters of CTX and CAZ caused by synergy of AMC disc was considered as ESBL production. Antibiotics not recommended for a particular organism according to the CLSI guidelines were excluded from that organism's testing panel.[9]

STATISTICAL ANALYSIS

The statistical analysis was done by the Statistical Package for the Social Sciences (SPSS) version 27. Categorical variables such as the most common isolates, types of specimens, predominant bacteria isolated from various specimens, and their antibiotic resistance pattern were presented as frequency and percentage. The Chi-square test was done to evaluate the relation between specimen type and organisms isolated, with a p-value <0.05 showing statistical significance.

RESULTS

Out of 150 clinical specimens, 98(65.3%) showed bacterial growth. Gram-negative bacteria constituted 58(59.2%) isolates, whereas Gram-positive bacteria accounted for 40(40.8%) isolates. The most common pathogen isolated was *Staphylococcus* species (31.6%), succeeded by *Escherichia coli* (17.3%), *Klebsiella pneumoniae* (15.3%), *Pseudomonas aeruginosa* (13.3%), *Acinetobacter baumannii* (10.2%), *Enterococcus* species (9.2%), and *Proteus* species (3.1%) (Table 1).

The majority of the clinical specimens were blood samples (35.7%), followed by sputum (28.6%), urine (24.5%), pus (6.1%), and catheter tips (5.1%). A significant relation existed between clinical

specimens and isolated organisms (p <0.0001), indicating that the distribution of bacterial isolates differed significantly across various specimens. The distribution of bacterial isolates according to specimen type is shown in Figure 1.

Among 14(14.3%) isolates of *Staphylococcus aureus*, 10(71.4%) were methicillin-resistant *Staphylococcus aureus* (MRSA), while 4(28.6%) were methicillin-sensitive (MSSA). Among 17(17.3%) CoNS, 6(35.3%) were methicillin-resistant, and 11(64.7%) were methicillin-sensitive. Eight (88.9%) isolates of *Enterococcus* species were resistant to penicillin and ampicillin. All isolates of *Staphylococcus aureus*, CoNS, and *Enterococcus* species were sensitive to vancomycin and linezolid. High resistance rates to other antibiotics were observed among Gram-positive bacteria (Table 2).

Among Gram-negative bacteria, 12(70.6%) isolates of *E. coli* and 11(73.3%) isolates of *Klebsiella pneumoniae* were ESBL producers, whereas none of the *Proteus* species produced ESBL. Carbapenems demonstrated 100% susceptibility against all Gram-negative isolates. Piperacillin-tazobactam, amikacin, and nitrofurantoin exhibited comparatively better antimicrobial activity than other antibiotics tested. Among Gram-negative bacteria, *Acinetobacter baumannii* demonstrated the highest level of antimicrobial resistance (Table 3).

Table 1: Distribution of Gram-Positive and Gram-Negative Bacterial Isolates among ICU Patients

Gram Stain Classification	Bacterial Isolates	Frequency (Percentage)
Gram-Positive Bacteria	**CoNS**	17(17.3%)
	Staphylococcus aureus	14(14.3%)
	***Enterococcus* species**	9(9.2%)
	Total	40(40.8%)
Gram-Negative Bacteria	***E. coli***	17(17.3%)
	Klebsiella pneumoniae	15(15.3%)
	Pseudomonas aeruginosa	13(13.3%)
	Acinetobacter baumannii	10(10.2%)
	***Proteus* species**	3(3.1%)
	Total	58(59.2%)

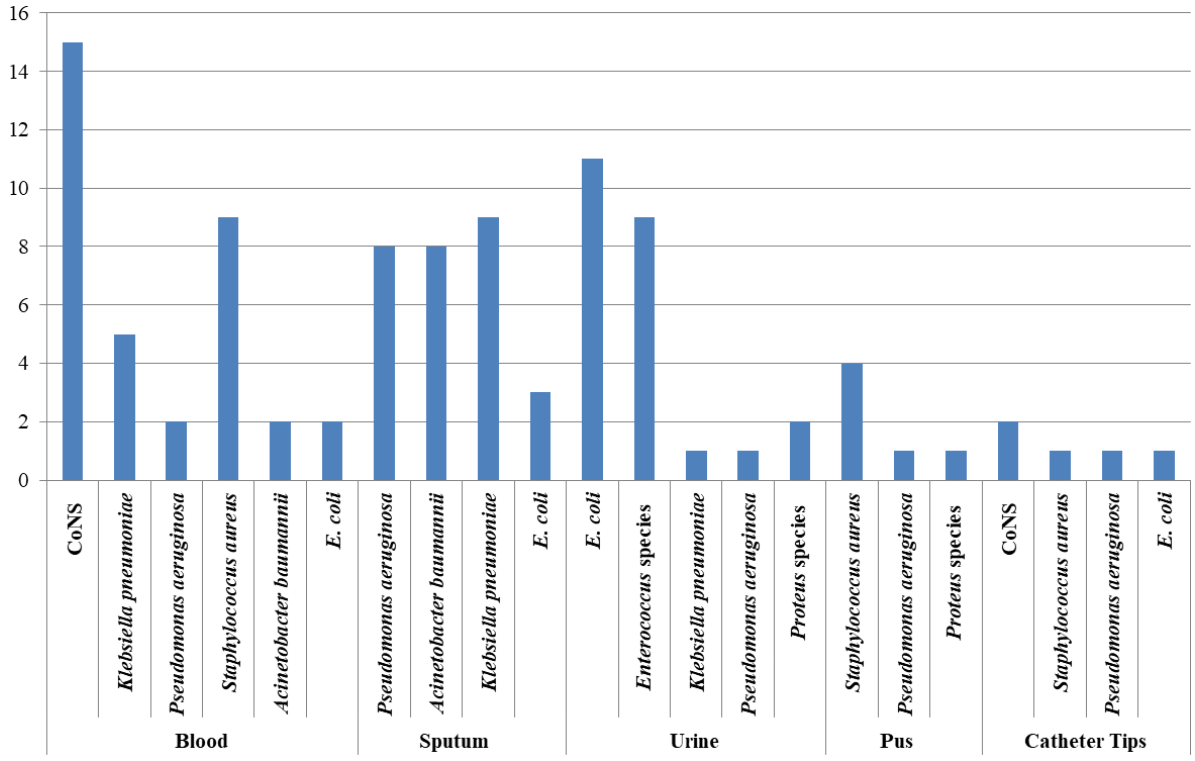

Figure 1: Bar Chart showing the Distribution of Bacterial Isolates from Different Clinical Specimens

Table 2: Antimicrobial Resistance Pattern in Gram-Positive Bacteria

Gram-Positive Bacteria	VA	LZD	CIP	LEV	CN	DOX	SXT	E	DA	F**
Staphylococcus aureus **(n=14)**	0(0%)	0(0%)	10(71.4%)	8(57.1%)	5(35.7%)	4(28.6%)	8(57.1%)	13(92.9%)	10(71.4%)	---
CoNS (n=17)	0(0%)	0(0%)	10(58.8%)	9(52.9%)	4(23.5%)	3(17.6%)	8(47.1%)	14(82.3%)	7(41.2%)	---
Enterococcus **species (n=9)**	0(0%)	0(0%)	6(66.7%)	6(66.7%)	NA*	NA*	NA*	NA*	NA*	2/9(22.2%)

**NA means Antibiotics not recommended for those organisms*
***Only for urinary isolates*

Table 3: Antimicrobial Resistance Pattern in Gram-Negative Bacteria

Gram-Negative Bacteria	AMC	CAZ	CTX	CRO	SXT	CIP	CN	AK	IPM	MEM	TZP	F**
E. coli **(n=17)**	12(70.6%)	12(70.6%)	12(70.6%)	12(70.6%)	14(82.4%)	11(64.7%)	5(29.4%)	3(17.6%)	0(0%)	0(0%)	5(29.4%)	3/11(27.3%)
Klebsiella pneumoniae **(n=15)**	11(73.3%)	11(73.3%)	11(73.3%)	11(73.3%)	13(86.7%)	10(66.7%)	4(26.7%)	3(20%)	0(0%)	0(0%)	5(33.3%)	0/1(0%)
Proteus species **(n=3)**	2(66.7%)	1(33.3%)	1(33.3%)	1(33.3%)	1(33.3%)	2(66.7%)	1(33.3%)	1(33.3%)	0(0%)	0(0%)	0(0%)	0/2(0%)
Pseudomonas aeruginosa **(n=13)**	NA*	5(38.5%)	NA*	NA*	NA*	11(84.6%)	8(61.5%)	6(46.1%)	0(0%)	0(0%)	5(38.5%)	NA*
Acinetobacter baumannii **(n=10)**	NA*	8(80%)	NA*	NA*	NA*	10(100%)	8(80%)	7(70%)	0(0%)	0(0%)	6(60%)	NA*

**NA means Antibiotics not recommended for those organisms*
***Only for urinary isolates*

DISCUSSION

The spread of multidrug resistant pathogens in an ICU setting is a serious concern for all tertiary care hospitals globally.[10] Continuous ICU surveillance is essential for monitoring healthcare-associated infections and antimicrobial resistance patterns, thereby supporting infection prevention and antimicrobial stewardship strategies.[11] In our study, the majority of the clinical specimens were blood (35.7%) followed by sputum (28.6%), urine (24.5%), pus (6.1%) and catheter tips (5.1%). Similarly, in another study, most of the positive cultures were from blood (56%), 27% from respiratory samples and 17% from urine.[12] Altaf et al. from Karachi reported positive cultures from blood (30%), urine (26%), respiratory samples (34%), pus, catheter tips and body fluids (10%).[13] In contrast, the most common specimen was urine (48.7%) followed by sputum (19.7%), blood (17.1%), catheters (9.1%) and endotracheal tube (5.3) in a study conducted in 2025.[14] Kumar et al. revealed that cultures were positive in 65.4% of the respiratory samples, 22.2% of the blood, and 12.35% of the urine samples.[15] Saleem et al. reported that the frequency of respiratory samples was highest (43%) followed by urine (24%), blood (15%), and pus (8.6%) among positive ICU samples.[16]

Our results showed that Gram-negative bacteria constituted 59.2%, whereas Gram-positive bacteria made up 40.8% of the isolates. The most common pathogens isolated were *Staphylococcus* (31.6%), *E. coli* (17.3%), *Klebsiella pneumoniae* (15.3%), *Pseudomonas aeruginosa* (13.3%), *Acinetobacter baumannii* (10.2%), *Enterococcus* species (9.2%), and *Proteus* species (3.1%). Chakraborty et al. also reported a predominance of Gram-negative bacteria (66%) as compared to Gram-positive bacteria (28%).[12] Another study revealed the highest prevalence of *E. coli* (39.5%), followed by *Klebsiella pneumoniae* (30.3%), *Enterococcus faecalis* (6.6%), *Acinetobacter baumannii* (6.6%), *Pseudomonas aeruginosa* (3.9%), MSSA (3.9%), *Proteus* (2.6%), and *Enterobacter* (1.3%).[14] A study reported *Acinetobacter baumannii* as the most prevalent pathogen from ICUs (36.6%). The other pathogens were *Klebsiella pneumoniae* (15.5%), *Pseudomonas aeruginosa* (11.5%), and *E. coli* (11.8%).[17] In another study, *Acinetobacter* spp. (22%) was most prevalent, followed by isolation of *E. coli* (14%), *P. aeruginosa* (10%), *S. aureus* (10%), and *Enterococcus spp.* (8%).[13] *Klebsiella* (32.69%) was most common in a study conducted in Kurnool, India, followed by *Acinetobacter* (26.4%), *Pseudomonas aeruginosa* (19.2%), *E. coli* (9.13%), *Staphylococcus aureus* (6.73%), *Enterobacter* species (3.84%), and *Citrobacter* species (1.92%).[18] According to our study, CoNS (42.9%) and *Staphylococcus* (25.7%) were the most common pathogens from blood culture, *Klebsiella*

pneumoniae (32.1%), *Pseudomonas aeruginosa* (28.6%) and *Acinetobacter baumannii* (28.6%) from sputum, *E. coli* (45.8%) and *Enterococcus* (37.5%) from urine, *Staphylococcus aureus* (66.6%) from pus, and CoNS (40%) from catheter tips. Just like our study, CoNS was most frequent in blood samples. The organisms isolated from respiratory samples were *Pseudomonas*, *Klebsiella, E. coli*, *Acinetobacter*, and CoNS. Pus samples grew *Staphylococcus aureus*, *Pseudomonas*, *Klebsiella and E. coli.*[19] In another study, the most common pathogens from respiratory specimens were *Pseudomonas aeruginosa* (27%) and *Acinetobacter baumannii* (22%). *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* (22% each) were frequent in blood, and *Enterococcus* was most common in urine specimens. [15] In our study, 71.4% isolates of *Staphylococcus aureus* were MRSA. Another study revealed that 57.1% of ICU pathogens were MRSA isolates.[18] All strains of *Staphylococcus aureus* were MRSA according to Chakraborty et al.[12] *Staphylococcus aureus* showed 57.1% resistance to trimethoprim-sulfamethoxazole, 35.7% aminoglycoside resistance, and 71.4% ciprofloxacin resistance in our study. None of them were resistant to vancomycin and linezolid. Another study revealed 55% resistance to co-trimoxazole, 30% to aminoglycosides, and 65% to fluoroquinolones. All of them were sensitive to vancomycin and linezolid. In our study, *Enterococcus* showed 88.8% ampicillin resistance and 66.7% ciprofloxacin resistance. All the strains were sensitive to vancomycin and linezolid. Around 96% of the *Enterococcus* species were ampicillin-resistant, 98% were resistant to fluoroquinolones and 33% to vancomycin in another study.[12] Around 70.6% of *E. coli* and 73.3% of *Klebsiella pneumoniae* were ESBL producers in our study. Similarly, 72.4% of *E. coli* and *Klebsiella pneumoniae* were ESBL producers in a study.[20] In another study, 56% of the *Klebsiella pneumoniae* were ESBL producing.[16] In our study, 70.6% of *E. coli* and 73.3% of *Klebsiella pneumoniae* were resistant to beta-lactams and third-generation cephalosporins, 82.4% and 86.7% to trimethoprim-sulfamethoxazole, 64.7% and 66.7% to ciprofloxacin and 17.6% & 20% to amikacin, respectively. *Proteus* showed 66.7% resistance to beta-lactams & ciprofloxacin and 33.3% to third-generation cephalosporins, amikacin & trimethoprim-sulfamethoxazole. Around 38.5% of *Pseudomonas* were resistant to ceftazidime, 84.6% to ciprofloxacin, and 46.1% to amikacin. All isolates of *Acinetobacter baumannii* were resistant to ciprofloxacin, 80% to ceftazidime, and 70% to amikacin. A much higher antibiotic resistance was seen in other studies. Another alarming concern in these studies was carbapenem resistance in all the isolates, whereas in our study, carbapenem resistance was not seen. According to Chakraborty et al, *Escherichia coli* showed 95% resistance to cephalosporins, beta-lactams & fluoroquinolones, 85% to co-trimoxazole, and 75% to carbapenems & aminoglycosides. Ninety four percent of *Klebsiella pneumoniae* were resistant to beta-lactams, 96% to third-generation cephalosporins, 92% to fluoroquinolones (92%), 88% to carbapenems, 83% to co-trimoxazole, and 36% to aminoglycosides. *Acinetobacter* was 100% resistant to second-generation cephalosporins, 97% to third-generation cephalosporins, 91% to beta-lactams, 97% to fluoroquinolones, 89% to carbapenems, and 66% to aminoglycosides. *Pseudomonas* spp. was 100% resistant to third-generation cephalosporins. 89% to carbapenems, 74% to beta-lactams & fluoroquinolones (74%), and 63% to aminoglycosides. *Proteus* species showed only cephalosporin resistance (100%).[12] In another study, 90% of *Klebsiella pneumoniae* were resistant to beta-lactams, 70-80% to third-generation cephalosporins, 89.7% to ciprofloxacin, and 85.7% to amikacin and 56.7% to imipenem. Sixty percent of *E. coli* were resistant to beta-lactams & cephalosporins, 90% to ciprofloxacin, 10% to amikacin, and 20% to imipenem. *Acinetobacter* showed 100% resistance to ciprofloxacin, 97% resistance to ceftazidime, 85.7% to amikacin, and 88.6% to imipenem. *Pseudomonas* was 80% resistant to ceftazidime, 64% to ciprofloxacin, 28% to amikacin, and 44% to imipenem.[16] In our study, carbapenem resistance was not detected in any Gram-negative bacteria. In contrast, studies have reported 15% and 38% carbapenem resistance from Karachi, Pakistan.[21,22]

CONCLUSION

Gram-negative bacteria constituted 59.2%, whereas Gram-positive bacteria made up 40.8% of the isolates. Around 71.4% isolates of *Staphylococcus aureus* were methicillin-resistant and 70.6% *E. coli* & 73.3% *Klebsiella pneumoniae* were ESBL producers. A higher antimicrobial resistance was seen in the isolates. These findings are a serious concern in clinical practice because they limit the options available for effective treatment and can lead to treatment failure and longer hospital stays.

LIMITATIONS & RECOMMENDATIONS

The single-centered study and limited sample size may affect the generalizability of the results. Multicenter studies with a larger sample size should be conducted for broader and more representative results. Only bacterial pathogens were included, while fungal pathogens were not studied.

Higher AMR among bacterial isolates highlights the importance of regular microbiological surveillance, and adherence to infection prevention practices in intensive care settings. It also underscores the necessity for comprehensive antimicrobial stewardship initiatives to ensure judicious use of antimicrobials, help prevent the spread of resistant bacteria, and improve outcomes for critically ill patients.

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Authors' Contributions:
A.A: Conceptualization, data collection, manuscript drafting.
S.N: Laboratory work, data interpretation, manuscript writing.
A.H.A: Statistical analysis, critical revision.
U.A: Literature review, data management.
H.A: Quality control, data acquisition.
N.R: Supervision, manuscript review and final approval.

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Original Article

Serum Copper, Zinc, Iron, and Superoxide Dismutase Levels as Biomarkers in Depression

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ABSTRACT

Objective: To assess levels of hemoglobin, serum copper (Cu), zinc (Zn), iron (Fe), and superoxide dismutase (SOD) levels in individuals with depressive disorder and to evaluate their diagnostic utility as biomarkers using receiver operating characteristic (ROC) curve analysis.

Methodology: This cross-sectional comparative study was conducted at the University of Health Sciences, Lahore from September 2025 to March 2026 and serum samples were collected from Combined Military Hospital, Muzaffarabad. After obtaining institutional ethical approval, 30 healthy controls and 60 patients with depressive disorder diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria were included. Study participants were recruited using non-probability consecutive sampling technique. After obtaining informed written consent, blood samples were analyzed for hemoglobin, copper, zinc, iron, and SOD levels using standard laboratory methods. Statistical Package for the Social Sciences (SPSS) version 25.0 was used for data analysis and a p-value <0.05 was considered statistically significant.

Results: Patients with depression had significantly higher serum copper levels (129.31±45.81 vs. 101.32±14.14 µg/dL, p=0.001) and Cu/Zn ratio (1.71±1.05 vs. 1.15±0.44, p=0.001), but lower hemoglobin levels (10.89±0.92 vs. 11.35±1.01 g/dL, p=0.040) and SOD activity (54.14±44.66 vs. 84.02±28.72 U/mL, p=0.001) compared to healthy controls. In the depression group, serum copper showed significant inverse correlations with zinc (r=-0.38, p=0.004) and SOD activity (r=-0.41, p=0.002). Regarding diagnostic performance, serum copper demonstrated fair discriminatory ability [area under the curve (AUC)=0.70, 95% confidence interval (CI):0.58-0.82], while a combined model of serum copper and Cu/Zn ratio showed improved performance (AUC=0.82, 95% CI:0.71-0.90), indicating good discriminatory ability.

Conclusion: The depression group showed significantly elevated serum copper, increased Cu/Zn ratio, reduced SOD activity, and lower hemoglobin levels as compared to healthy controls. Serum copper was inversely correlated with zinc and SOD in the depression group. Serum copper and the Cu/Zn ratio combined showed good diagnostic performance on ROC analysis. Serum zinc and iron levels were not significantly different between groups.

Keywords: *Depressive disorder. Copper. Zinc. Superoxide dismutase. Oxidative stress.*

INTRODUCTION

Depression is a complex and multifactorial psychiatric disorder influenced by the interaction of genetic, environmental, and biochemical factors. In recent years, increasing attention has been paid to the role of oxidative stress and trace element imbalances in its pathophysiology.[1] Trace elements, particularly Cu, Zn, and Fe, play essential roles in normal brain function; however, their imbalance may contribute to disease processes. Copper functions as an important enzymatic cofactor but may act as a pro-oxidant in excess, promoting the generation of reactive oxygen species and neuronal damage.[2] In contrast, zinc is critical for synaptic plasticity, neurogenesis, and regulation of glutamatergic neurotransmission, and its deficiency has been associated with depressive symptoms.[3] The copper-to-zinc (Cu/Zn) ratio is considered a useful indicator of oxidative stress and trace element imbalance. An elevated Cu/Zn ratio has been associated with mood disorders and may better reflect the biological changes underlying depression than individual copper or zinc levels alone.[4] Hemoglobin reflects oxygen carrying capacity and overall iron status. Reduced hemoglobin levels may impair cerebral oxygen delivery and neurotransmitter metabolism, contributing to depressive symptoms and cognitive dysfunction. Previous evidence has shown that iron deficiency and related hematological abnormalities are associated with a higher burden of depressive and internalizing symptoms.[5] Iron is essential for monoamine neurotransmitter synthesis and cellular energy metabolism, and its dysregulation has been linked to mood disturbances and cognitive dysfunction.[5,6]

The antioxidant defense system also plays a vital role in maintaining neuronal integrity.[7] Emerging evidence suggests that disruption of redox homeostasis contributes to neuronal dysfunction through mechanisms including neuroinflammation, mitochondrial impairment, and altered neurotransmission.[1] Superoxide dismutase (SOD), a key antioxidant enzyme, neutralizes reactive oxygen species and helps preserve cellular redox balance. Reduced SOD activity has been reported in

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depressive disorders, suggesting impaired antioxidant defense and increased oxidative stress.[7]

Although previous studies have explored the association of trace elements and oxidative stress with depression, the findings remain inconsistent across different populations, with some studies reporting significant alterations in serum copper, zinc, iron, and antioxidant enzyme levels, while others have found non-significant associations. Moreover, limited data are available regarding the simultaneous assessment of these biomarkers within the same clinical setting. Considering the opposing biological effects of copper and zinc, the copper-to-zinc ratio may provide a more reliable indicator of redox imbalance than individual measurements alone. Therefore, the present study aimed to evaluate hemoglobin, serum copper, zinc, iron, and SOD levels in patients with depressive disorder and healthy controls, and to determine their individual and combined diagnostic potential.

METHODOLOGY

This cross-sectional comparative study was conducted at the University of Health Sciences, Lahore from September 2025 to March 2026. Serum samples were collected from Combined Military Hospital, Muzaffarabad. Ethical approval was obtained from the Institutional Review Board (Letter No. UHS/DPS-25/1198, 12-08-2025), and written informed consent was obtained from all participants. The sample size was calculated using OpenEpi software as 53 cases and 27 controls (total n=80), based on a 95% confidence level, 80% power, and mean serum copper levels of 0.88±0.13 mg/L in depressed patients and 1.02±0.24 mg/L in healthy controls, with a control-to-case ratio of 0.5.[4] The sample size was increased to 90 participants (60 cases and 30 controls) to enhance statistical power and account for missing data. Participants were recruited using non-probability consecutive sampling technique.

The study included adult participants aged ≥18 years. Cases were diagnosed with depressive disorder by a consultant psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).[8] Depression severity was assessed using the Beck Depression Inventory-II (BDI-II) and categorized as minimal, mild, moderate, and severe according to standard scoring criteria.[9] Healthy hospital controls were age & gender-matched individuals with no history of psychiatric illness, confirmed through psychiatric evaluation. Participants in both groups were excluded if they had pregnancy or lactation, acute or chronic inflammatory conditions, hepatic, renal, or endocrine disorders, malignancy, recent surgery or blood transfusion, alcohol or substance dependence, or were currently using mineral supplements, antioxidant therapy, or immunomodulatory drugs.

Sociodemographic data were recorded on a preformed proforma. A total of 10 ml of venous blood was collected aseptically from each participant. Blood samples were distributed into ethylenediaminetetraacetic acid (EDTA) tubes for hemoglobin estimation and serum separator tubes for detection of trace elements (copper, zinc, and iron) and SOD. Serum was separated by centrifugation at 3000 rpm for 10 minutes, aliquoted, and stored according to assay requirements.

Hemoglobin was measured using an automated hematology analyzer (Sysmex XT-1000i, Sysmex Corporation, Kobe, Japan). Serum trace elements (copper, zinc, and iron) were analyzed using atomic absorption spectrophotometry (Hitachi U-2800/2900, Hitachi High-Technologies, Tokyo, Japan) at wavelengths of 324 nm (Cu), 214 nm (Zn), and 248 nm (Fe), following standard procedures. Superoxide dismutase activity was measured using a commercially available enzyme-linked immunosorbent assay (ELISA) based 96-well assay kit (SOD Kit, Catalog No. EIASODC, Glory Scientific, China). The assay was performed according to the manufacturer's protocol (Pub. No. MAN0019052, Rev. A.0). Absorbance was measured at 405 nm using a Bio-Rad ELISA microplate reader.

For laboratory interpretation, the reference serum concentrations in adults are approximately as follows: hemoglobin 12-16 g/dL (females) and 14-18 g/dL (males); copper 100-200 µg/dL; zinc 75-140 µg/dL; and iron 50-150 µg/dL.[10] The reference range for serum SOD is approximately 80-120 U/mL (according to kit literature), and it may vary depending on assay methodology and manufacturer specifications.

STATISTICAL ANALYSIS

Statistical Package for the Social Sciences (SPSS) version 25.0 was used for data analysis. Mean±standard deviation was calculated for continuous variables, while categorical variables were presented as frequencies & percentages. Chi-square test was used to compare categorical variables. Independent t-test and one-way analysis of variance (ANOVA) were applied for comparison of means between two groups and more than two groups, respectively.

Correlation analysis of biochemical parameters within groups was performed using Pearson's correlation coefficients. Diagnostic performance was evaluated using ROC curve analysis, and AUC was calculated with 95% CI. An AUC equal to or greater than 0.6 is considered meaningful. Values between ≥0.6 and <0.7 indicate poor diagnostic accuracy, ≥0.7 to <0.8 suggest fair accuracy, ≥0.8 to <0.9 reflect good accuracy while values ≥0.9 represent excellent diagnostic accuracy.[11] A p-value of <0.05 was considered statistically significant.

RESULTS

The proportion of females was slightly higher in both groups (63.33% in depression vs. 76.67% in controls). Participants in both groups had statistically similar distribution in terms of age, gender, educational level, and occupational status (p >0.05).

Patients with depression exhibited significantly elevated serum copper levels of 129.31±45.81 µg/dL compared to 101.32±14.14 µg/dL in healthy controls, along with a higher Cu/Zn ratio of 1.71±1.05 versus 1.15±0.44 (p=0.001). Furthermore, the depression group showed lower hemoglobin levels of 10.89±0.92 g/dL compared to 11.35±1.01 g/dL (p=0.040), along with markedly decreased SOD activity of 54.14±44.66 U/mL versus 84.02±28.72 U/mL (p=0.001). Serum zinc and iron levels were not significantly different between the groups (Table 1).

Among the 60 cases, 26(43.3%) had mild depression, 22(36.7%) had moderate depression, and 12(20.0%) had severe depression, while none of the participants had minimal depression. Serum copper levels increased significantly (p=0.001) with increasing severity of depression, while zinc levels showed a significant decline (p=0.005). In addition, the Cu/Zn ratio exhibited a highly significant rise (p=0.001), indicating a marked disturbance in trace element balance with disease severity. In contrast, hemoglobin, serum iron, and SOD levels did not show statistically significant differences across categories of depression severity (p >0.05) (Table 2).

Correlation analysis revealed significant inverse relationships between serum copper and zinc (r=-0.38, p=0.004) and between copper and SOD activity (r=-0.41, p=0.002) in the depression group. These findings indicate that higher copper levels were associated with lower zinc concentrations and reduced antioxidant activity. In the control group, no significant correlations were found (Figure 1).

Assessment of diagnostic performance showed that serum copper demonstrated fair discriminatory ability (AUC=0.70, 95% CI:0.58-0.82). In contrast, zinc, Cu/Zn ratio, iron, and SOD exhibited poor diagnostic performance (Figure 2). A combined model incorporating serum copper and the Cu/Zn ratio demonstrated improved diagnostic performance, with an AUC of 0.82 (95% CI:0.71-0.90), indicating good discriminatory ability (Figure 3).

DISCUSSION

Alterations in essential micronutrients and disruption of redox homeostasis have been implicated in the processes leading to depression. Serum copper levels were significantly higher in patients with depression in the present study (129.31±45.81 µg/dL) compared with controls (101.32±14.14 µg/dL). Similarly, Huang et al. reported significantly higher serum copper concentrations (123.88±26.05 µg/dL) in adults with depressive symptoms as compared to healthy controls (116.99±29.00 µg/dL) (p <0.001).[12] It was reported in a meta-analysis that patients with depression exhibit significantly elevated serum copper levels [standardized mean difference (SMD)=+0.42; 95% CI:+0.18 to +0.66] compared with healthy individuals.[13] Another meta-analysis included 24 studies and identified significantly higher serum copper levels in patients suffering from major depressive disorder as compared to controls (p=0.001).[14] A systematic review was conducted on Wilson's disease, where copper hemostasis becomes disturbed, and free copper accumulates in various organs, including the brain. Patients with this disease demonstrated a high prevalence (up to 47%) of depression.[15]

Although serum zinc levels were lower in the depression group (86.11±24.60 µg/dL) compared with controls (95.05±23.05 µg/dL), the difference did not reach statistical significance (p=0.095). In contrast, a meta-analysis reported significantly lower serum zinc levels (SMD=-0.62; 95 % CI:-0.78 to -0.46) in patients suffering from major depressive disorder when compared to controls.[13] Yosaee et al. also reported in their meta-analysis that individuals with the highest zinc intake had a 28% lower risk of depression compared to those with lower intake [Relative Risk (RR):0.66; 95% CI: 0.50-0.82]. Furthermore, their analysis of randomized controlled trials demonstrated that zinc supplementation significantly improved depressive symptoms in patients with depression (p <0.01).[16] The lack of statistical significance in our study may reflect sample size limitations, dietary variability, and the multifactorial nature of depression.

Table 1: Comparison of Biochemical Markers between Patients with Depression and Healthy Controls

Biochemical Markers	Depression Group (Mean±SD)	Control Group (Mean±SD)	p-value
Hemoglobin (g/dL)	10.89±0.92	11.35±1.01	0.040*
Copper (µg/dL)	129.31±45.81	101.32±14.14	0.001*
Zinc (µg/dL)	86.11±24.60	95.05±23.05	0.095
Iron (µg/dL)	122.72±62.73	138.91±62.43	0.252
SOD (U/mL)	54.14±44.66	84.02±28.72	0.001*
Cu/Zn ratio	1.71±1.05	1.15±0.44	0.001*

**Significant p-value*

Table 2: Association of Biochemical Markers with the Severity of Disease

Biochemical Markers	Depression Severity (Mean±SD)			p-value
	Mild Depression	Moderate Depression	Severe Depression	
Hemoglobin (g/dL)	11.0±0.7	10.8±1.0	10.7±0.8	0.652
Copper (µg/dL)	104.8±25.1	132.3±43.4	176.7±48.2	0.001*
Zinc (µg/dL)	95.6±21.8	84.1±25.1	69.0±20.2	0.005*
Iron (µg/dL)	117.7±61.8	140.0±65.7	101.8±54.9	0.208
SOD (U/mL)	68.5±53.4	48.4±37.4	33.3±22.1	0.056
Cu/Zn ratio	1.18±0.4	1.70±0.7	2.80±1.4	0.001*

**Significant p-value*

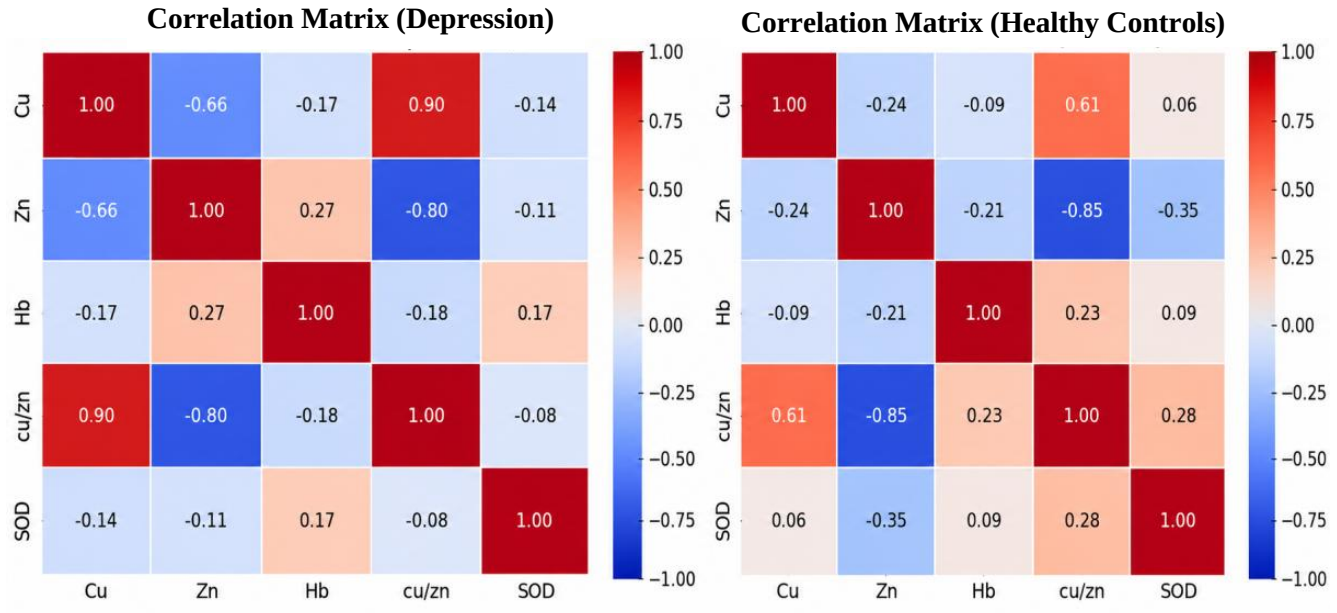

Figure 1: Correlation Matrices showing Relationships among Serum Copper, Zinc, Hemoglobin, Cu/Zn ratio, and SOD Levels in Patients with Depression and Healthy Controls

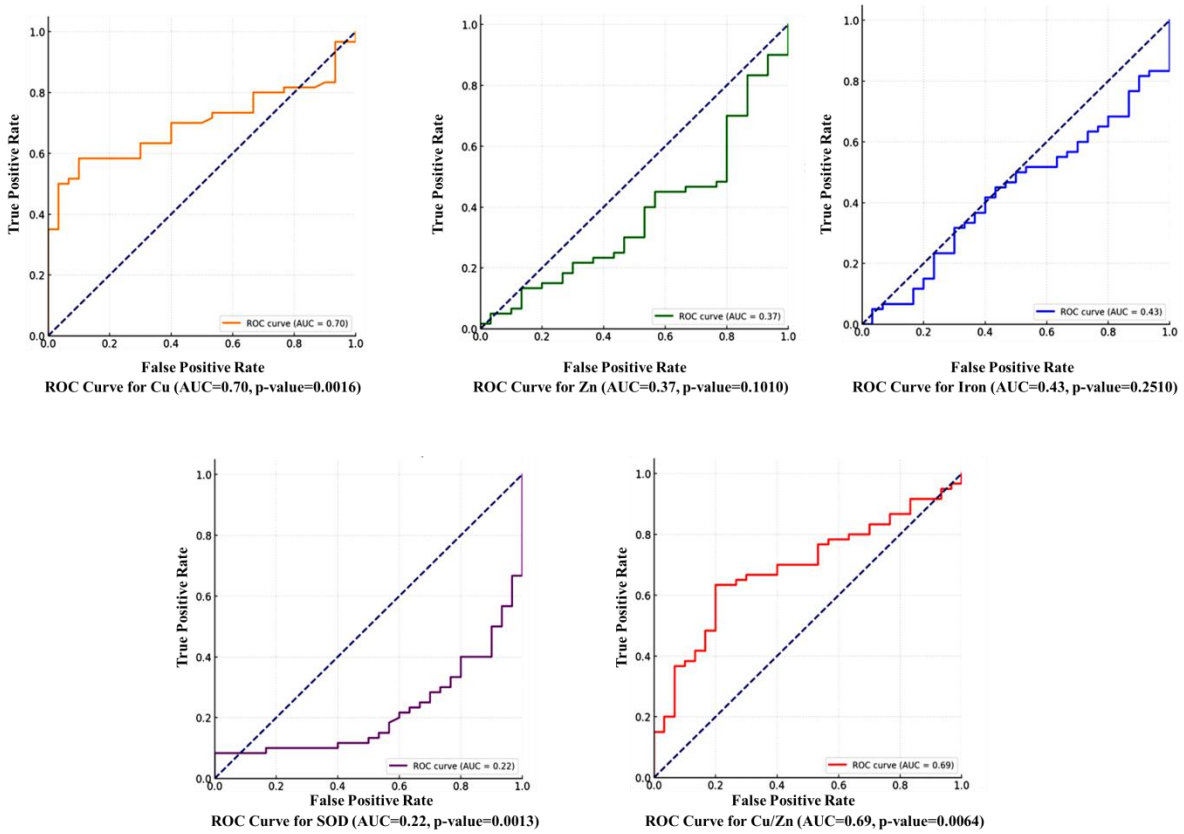

Figure 2: ROC Curves of Individual Biochemical Markers for Distinguishing Patients with Depression from Healthy Controls

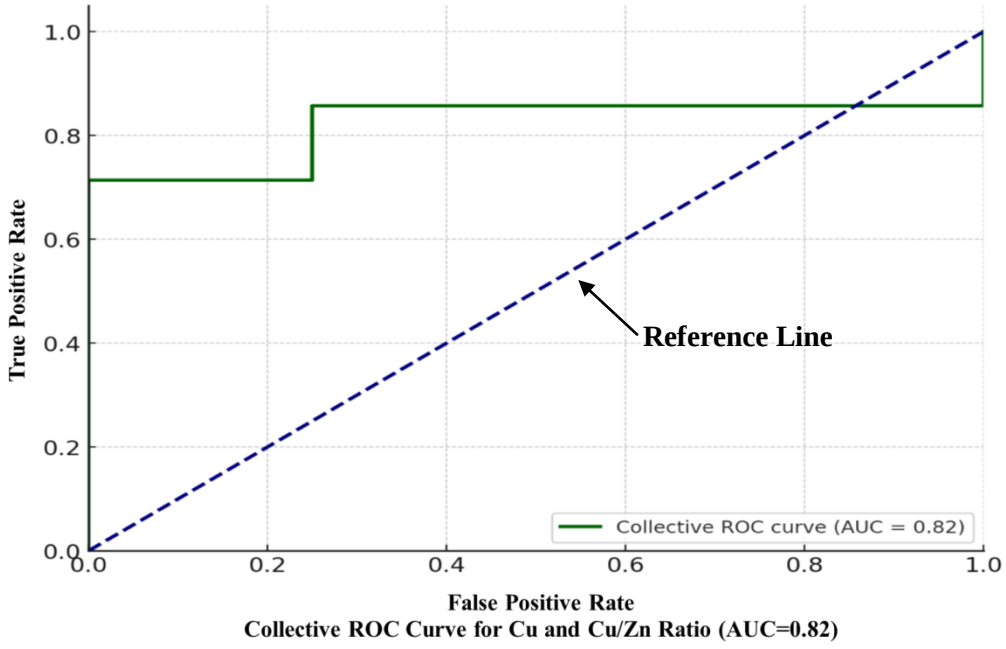

Figure 3: ROC Analysis of the Combined Model using Serum Copper and Cu/Zn ratio for Distinguishing Patients with Depression from Healthy Controls

A notable finding of the present study was the significantly elevated Cu/Zn ratio in patients with depression compared to controls (1.71±1.05 vs. 1.15±0.44). Correlation analysis further demonstrated a significant inverse relationship between serum copper and zinc levels (r=-0.38, p=0.004). Another study highlighted that patients with depressive disorders exhibited an increased Cu/Zn ratio, indicating a possible association between trace element imbalance and mood disorders.[4] Lopez-Alonso et al. found that increased Cu/Zn ratio reflects oxidative imbalance that contributes substantially to depressive pathology.[17] In contrast, another study conducted in 2020 reported that the Cu/Zn ratio did not differ significantly between patients with depression and healthy controls (2.24±2.09 vs. 1.77±1.32, p ≥0.05). They also observed positive correlations of both serum copper levels and the Cu/Zn ratio with interleukin-6 in depressive patients.[18] These findings suggest that disturbances in copper-zinc homeostasis may be linked to inflammatory pathways in depression.

In the present study, patients with depression had significantly lower hemoglobin levels than healthy controls (10.89±0.92 vs. 11.35±1.01 g/dL, p=0.040). Similar observations have been reported in the literature, where iron deficiency and associated hematological disturbances were linked with depressive symptoms and impaired emotional well-being.[5,6] These findings suggest that reduced hemoglobin levels may contribute to the biological mechanisms underlying depressive disorder.

Iron levels were lower in patients with depression in this study; however, the difference was not statistically significant (p=0.208). Leung et al also revealed that more (25.7%) depressed patients had serum iron deficiency as compared to controls (20%), but the results were not significant (p=0.774).[19] Contrary to our findings, a meta-analysis revealed that cases of major depressive disorder had significantly lower serum iron levels (SMD=-0.36; 95% CI: -0.52 to -0.20).[13] This pattern indicates that iron may not follow a uniform trend across all depressive populations, limiting its reliability as an independent marker in cross-sectional assessments.[5]

The present study also demonstrated significantly reduced SOD activity in patients with depression (54.14±44.66 U/mL) compared with healthy controls (84.02±28.72 U/mL). Similar reductions in antioxidant enzyme activity have been consistently reported in depressive disorders. It was reported in a study that Chinese patients with depression exhibited increased oxidative stress, evidenced by significantly altered oxidative stress markers, including reduced catalase activity compared with healthy controls.[20] Abd Elmoneim et al. also found significantly lower SOD levels in depressive patients (5.8±2.4) as compared to healthy controls (19.4±10.5) (p<0.001).[21] Correlation analysis revealed significant inverse relationships between copper and SOD activity (r=-0.41, p=0.002) in the depression group in our study. These findings suggest that elevated copper levels may contribute to oxidative stress through depletion of antioxidant defenses and disruption of trace element balance.[22]

From a diagnostic perspective, the present study demonstrated that serum copper (AUC=0.70, 95% CI: 0.58-0.82) showed fair discriminatory ability. The combined model incorporating serum copper and the Cu/Zn ratio showed improved performance (AUC=0.82, 95% CI: 0.71-0.90), indicating good discrimination between patients and controls. Swiadro et al. highlighted the diagnostic relevance of copper and zinc imbalance in mood disorders, supporting the potential utility of the Cu/Zn ratio as a biomarker.[4] Zinc, iron, and SOD demonstrated poor individual diagnostic performance (AUC <0.50) in this study, suggesting limited value as standalone markers. Another study highlighted the notorious heterogeneity and inconsistency of peripheral oxidative stress biomarkers in depressive disorders. This may be explained by their susceptibility to multiple external and physiological influences, resulting in overlap between patient and control groups.[23]

CONCLUSION

Oxidative stress and trace element imbalance appear to contribute to depressive disorder, as evidenced by significantly elevated serum copper levels, an increased Cu/Zn ratio, reduced SOD activity, and lower hemoglobin levels in patients with depression. No significant differences were observed in serum zinc or iron levels between cases and controls. Serum copper showed significant inverse correlations with both zinc and SOD in the depression group. Moreover, serum copper and the Cu/Zn ratio combined demonstrated good diagnostic performance on ROC curve analysis.

LIMITATIONS & RECOMMENDATIONS

The study is limited by its single-centered, cross-sectional design, which restricts generalizability and causal inference. Potential confounders, including diet, socioeconomic status, inflammation, and medication history, were not fully assessed.

Although serum copper showed fair diagnostic performance, larger multicenter longitudinal studies are needed to confirm its clinical utility in depression.

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Authors' Contributions:
A.T: Conceptualization, data collection, laboratory analysis, statistical analysis, manuscript writing.
U.A: Study design, data interpretation, manuscript revision.
A.S: Data collection, literature review, manuscript drafting.
Y.L: Data collection, data entry, manuscript drafting.
U.S: Statistical analysis, data interpretation, manuscript revision.
S.H: Supervision, conceptual guidance, critical review of the manuscript.

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Original Article

Association between Perception Constructs and Attitude towards Adoption of Artificial Intelligence as a Teaching Tool among Medical Students

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ABSTRACT

Objective: To determine the association between key perception constructs measured using the technology acceptance model (TAM) questionnaire and attitude towards adoption of artificial intelligence (AI) as a teaching tool among medical students in Pakistan.

Methodology: This cross-sectional analytical study was conducted at Allama Iqbal Medical College, Lahore, from September 2025 to February 2026 after ethical approval. Two hundred and eighty five MBBS students aged ≥18 years of any gender were included using a non-probability convenience sampling technique after obtaining informed written consent. Students with prior AI experience or enrollment in AI programs were excluded. A predesigned TAM questionnaire was used to collect data. The data was entered and analyzed using Statistical Package for the Social Sciences (SPSS) version 21. The key perception constructs, perceived usefulness (PU) and perceived ease of use (PEU), were compared with the main dependent outcome, i.e., attitude towards AI use.

Results: The mean age of the participants was 21.5±1.5 years. Most students were females [156(54.7%)] and majority of the students belong to 4th year MBBS [105(36.8%)]. Multivariable regression showed that perceived usefulness had a significantly positive association with attitude towards AI adoption (p-value=0.001) whereas perceived ease of use demonstrated a weak but significant negative association with attitude (p=0.005).

Conclusion: Perceived usefulness is found to be a primary driver of AI adoption among medical students. However, perceived ease of use demonstrated a small but significant negative association with attitude, suggesting that its role may be secondary when usefulness is accounted for in the model.

Keywords: *Artificial intelligence. Machine learning. Adoption. Chatbots. ChatGPT.*

INTRODUCTION

The advent of emerging technologies has significantly rephrased educational paradigms across the globe. In the digital world, students' expectations for learning tools are evolving, and today's era demands the development of personalized, systematic, and innovative tools. However, over the past two decades, the incorporation of artificial intelligence (AI) into medical education has remained limited. This limited use highlights the need to reevaluate teaching methodologies and consider emerging approaches.[1] Artificial intelligence refers to systems and processes that can adapt to the latest information, support decision making, and solve problems.[2] In medical education, AI guides to improve future healthcare professionals' training, enabling them to utilize flexible teaching methods and innovative learning practices.[3]

A study conducted in Kuwait reported on the awareness of AI principles and familiarity with basic terms used in AI among 352 university students. The findings showed moderate awareness (50%) of basic principles, and 60% of respondents had a good understanding of AI concepts. A large majority (93.4%) were comfortable with AI vocabulary. Most students (83.5%) believed that using AI would enhance their efficiency and productivity, but many also reported a need for training on the appropriate use of AI.[4]

To address the challenges of AI adoption in medical education, the widely used technology acceptance model (TAM) offers a theoretical framework for understanding how students accept and use AI tools. This model is based on the theory of reasoned action and emphasizes key cognitive constructs such as perceived usefulness (PU) and perceived ease of use (PEU) in determining students' attitudes toward adopting technology.[5]

As healthcare undergoes rapid digital transformation and AI is becoming increasingly integrated into daily life and clinical practice, the willingness of future physicians to adopt these technologies is a key determinant of their successful implementation. However, evidence regarding medical students' perceptions and acceptance of AI remains limited in Pakistan. Evaluating these perceptions can help shape resource allocation, curricular planning, and capacity building initiatives within medical education. Such evidence can also serve as a needs assessment for the integration of AI into medical

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curricula. Therefore, this study was designed to assess medical students' attitudes towards AI adoption and determine their association with the key TAM constructs, perceived usefulness and perceived ease of use.

METHODOLOGY

This cross-sectional analytical study was conducted at Allama Iqbal Medical College, Lahore, from September 2025 to February 2026 after ethical approval from the institutional review board (Letter No. ERB/192/5/07-08-2025/AIMC/JHL, 07-08-2025). A sample size of 212 was calculated at a 95% confidence level, 5% margin of error, and an anticipated prevalence of perceived usefulness at 83.5% among students.[4] However, 285 MBBS students were enrolled using a non-probability convenience sampling technique from a total population of 1,750 medical students. Participants aged ≥18 years of either gender who provided informed written consent were included, while those with prior formal training in artificial intelligence were excluded. Data was collected through Google Forms using a predesigned TAM questionnaire comprising five domains: perceived usefulness, perceived ease of use, attitude towards use, behavioral intention, and actual usage.[5] Responses were measured on a five point Likert scale comprising strongly agree, agree, neutral, disagree, and strongly disagree. Exploratory factor analysis (EFA) was performed to determine the underlying factor structure of the perception items. Sampling adequacy and factorability were confirmed using the Kaiser-Meyer-Olkin (KMO) measure and Bartlett's test of sphericity. Principal component analysis with Varimax rotation was applied, and factors were retained based on Eigenvalues >1, scree plot analysis, and factor loadings ≥0.40. Internal consistency of the identified constructs was assessed using Cronbach's alpha, which demonstrated good reliability for perceived usefulness (α=0.864) and perceived ease of use (α=0.815).

STATISTICAL ANALYSIS

The data was entered and analyzed using Statistical Package for the Social Sciences (SPSS) version 21. Quantitative variables were presented as mean±standard deviation (SD), while qualitative variables were presented as frequencies & percentages. Multivariable linear regression analysis was performed to determine the association of TAM constructs (perceived usefulness and perceived ease of use) with attitude toward AI use. Both unstandardized coefficients (B), representing absolute effect size, and standardized coefficients (β), allowing comparison of relative predictor strength, were reported along with p-values and confidence intervals. Model fit was assessed using the coefficient of determination (R^2) and overall model significance. A p-value <0.05 was considered statistically significant.

RESULTS

This study of 285 medical students reveals a slight female majority (54.7%) and a high proportion of hostel residents (65.6%). The mean age of the participants was 21.5±1.5 years. Participants were enrolled across all years of the MBBS program, with 4th year students constituting the largest cohort (36.8%). Table 1 presents the detailed descriptive analysis of the participants and their responses to the TAM questionnaire.

The mean score of attitudes toward AI adoption was 4.00±0.719. The mean scores for the two key TAM perception constructs, perceived usefulness and perceived ease of use, were 3.96 ± 0.658 and 3.95 ± 0.618, respectively.

Multiple linear regression analysis showed that perceived usefulness and perceived ease of use were significant predictors of attitude toward AI adoption among medical students. The regression model was statistically significant ($p < 0.001$) and explained 78.6% of the variance in attitude toward AI adoption, as accounted for by PU and PEU ($R^2 = 0.786$). Perceived usefulness was a strong positive predictor of attitude toward AI adoption ($B = 1.021$, $\beta = 0.934$, $p = 0.001$), indicating that higher perceived usefulness was associated with a more favorable attitude. Perceived ease of use was a small but statistically significant negative predictor ($B = -0.108$, $\beta = -0.093$, $p = 0.005$). Overall, perceived usefulness emerged as the dominant determinant of attitude toward AI adoption in the model (Table 2).

DISCUSSION

The present study demonstrates a high level of adoption of AI tools among medical students, with frequent usage and predominantly positive attitudes. Our participants had a mean age of 21.5±1.5 years with slight female predominance (54.7%). About 67% of participants had been using AI tools for medical studies daily. The mean scores for the key TAM constructs, perceived usefulness and perceived ease of use, were 3.96±0.658 and 3.95±0.618, respectively. The regression model yielded an R^2 value of 0.786, indicating that both factors explained 78.6% of the variance in students' attitudes toward AI adoption. A study conducted in India predicted

the adoption of artificial intelligence in higher education. They reported that most participants were male (54.1%) and aged between 21 and 23 years. A total of 176(43.9%) participants reported using AI in their daily routine. The mean PU and PEU scores were 3.68±0.76 and 3.30±0.87, respectively, and were significantly associated with AI adoption (p <0.01). Further analysis showed that PU and PEU explained 55.8% of the variance in AI adoption among students.[6]

Multivariable linear regression in this study showed that perceived usefulness had a significantly positive association with attitudes toward AI adoption (p=0.001), whereas perceived ease of use demonstrated a small but statistically significant negative association with attitudes (p=0.005). Another study reported the influence of PU and PEU on users' attitudes toward AI chatbot usage. Consistent with our findings, perceived usefulness had a significant positive effect on attitudes (β=0.63, p <0.01). However, in contrast to our results, that study reported a weak but positive and significant association between perceived ease of use and attitudes (β=0.29, p <0.01).[7] Alyoussef et al. examined the factors influencing AI adoption in higher education and reported that a majority of participants were aged between 23 and 26 years, with a slight female predominance (54%). Perceived usefulness (β=0.51, p <0.001) and PEU (β=0.43, p <0.001) were significant predictors of AI adoption, indicating that both utility and usability play important roles in shaping users' attitudes and behavioral intentions toward AI based tools.[8]

Table 1: Distribution of Responses to the TAM Questionnaire among Medical Students

Question	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
Using AI chatbots would improve my performance in studies	78(27.4%)	157(55.1%)	32(11.2%)	9(3.2%)	9(3.2%)
Using AI chatbots during work would improve my productivity	95(33.3%)	126(44.2%)	32(11.2%)	25(8.7%)	7(2.4%)
Using AI chatbots would enhance my effectiveness in studies	71(25%)	171(60%)	22(7.7%)	12(4.2%)	9(3.15%)
Learning to operate the AI chatbots would be easy for me	75(26.3%)	160(56.1%)	37(13%)	8(2.8%)	3(1%)
I would find it easy to get AI chatbots to do what I want them to do	70(24.5%)	153(53.7%)	48(16.8%)	9(3.15%)	5(1.7%)
I would find the AI easy to use	74(26%)	162(56.8%)	37(13%)	8(2.8%)	4(1.4%)
I am confident in using AI within my learning process.	72(25.2%)	133(53.6%)	49(17.2%)	10(3.5%)	1(0.3%)
I have the knowledge and expertise to use AI chatbots for my learning.	48(16.8%)	132(46.3%)	78(27.3%)	26(9.1%)	1(0.3%)
I intend to use AI chatbots for medical education to enhance my learning outcome	74(26%)	151(53%)	45(15.8%)	10(3.5%)	5(1.7%)
I utilize AI within my medical studies daily	62(21.7%)	129(45.2%)	52(18.2%)	26(9.1%)	16(5.6%)
I utilize AI within my medical studies every week	75(26.3%)	162(56.8%)	27(9.4%)	13(4.5%)	8(2.8%)
Using AI for learning processes is a wise idea	74(26%)	155(54.3%)	43(15.1%)	4(1.4%)	9(3.15%)
AI chatbots are a positive tool for learning processes in medical education	75(26.3%)	163(57.2%)	39(13.6%)	6(2.1%)	3(1%)
I plan on using AI for learning purposes regularly in the future.	81(28.4%)	139(48.8%)	43(15.1%)	17(6%)	5(1.7%)

Table 2: Multivariable Linear Regression Analysis showing the Association of Perceived Usefulness and Perceived Ease of Use with Attitude towards AI Adoption

Perception Constructs	Unstandardized coefficient (B)	Standard error	Standardized coefficient (β)	p-value	95% Confidence Interval	
					Lower limit	Upper limit
Perceived Usefulness (PU)	1.021	0.036	0.934	0.001	0.951	1.092
Perceived Ease of Use (PEU)	-0.108	0.038	-0.093	0.005	-0.183	-0.033

A study among business students reported that 16% of participants used AI tools daily, indicating comparatively lower frequency of use than that observed in the present study. The mean PU (4.03±0.72) and PEU (4.04±0.74) scores were slightly higher than those reported in the present study. Perceived usefulness was found to be significantly associated with intention to use AI (β=0.567; p-value=0.000). However, contrary to our results, PEU was not found to be associated with intention to use.[9] Sallam et al. conducted a validation study on medical students, where a TAM based framework was specifically used for one AI chatbot, ChatGPT. They reported high mean scores for PU and PEU, which significantly determine users' attitude towards AI adoption and usage.[10] Similar findings are also reported by a multinational study where ChatGPT usage was found to be directly associated with higher GPA scores.[11] Students who perceived AI as beneficial for improving academic performance showed higher adoption and positive attitudes, reinforcing that perceived usefulness is the primary driver of adoption.[12]

In the present study, most participants demonstrated a positive intention toward adopting AI in medical education. Nearly four fifths of the respondents (78.9%) agreed that they intended to use AI chatbots to enhance their learning outcomes, while 77.2% reported plans to use AI regularly in the future. Furthermore, 80.3% considered the use of AI in learning to be a wise idea, and 83.5% viewed AI chatbots as a positive tool for medical education. These findings are consistent with those of Ibrahim et al., who reported that more than 90% of participants intended to use chatbots in the near future.[13] A study conducted in Abbottabad, Pakistan, among medical and dental students reported the use of various AI tools in academic activities. The most frequently used AI tool among students was ChatGPT, particularly for advanced medical studies and research purposes.[14] Another study was conducted in Pakistan at Jinnah Medical College, Peshawar, and showed that 71% of medical students perceived AI as a potential tool for both undergraduate and postgraduate medical education.[15] The favorable perception of AI observed in our study is further supported by qualitative evidence showing that ChatGPT provides immediate responses to students' queries, timely feedback, and continuous learning support outside the classroom.[16] The proactive behavior of medical students as well as physicians, the perceived usefulness of AI tools, and rapidly evolving medical education demand the adoption of advanced digital technologies to prepare and fully equip our future generation.[17]

CONCLUSION

Medical students perceive artificial intelligence as highly useful, resulting in a positive attitude toward the adoption of AI in their education. Perceived usefulness emerged as the primary driver of AI adoption among medical students. Perceived ease of use demonstrated a small but statistically significant negative association with attitude, suggesting that its role may be secondary when usefulness is accounted for in the model. A majority of respondents reported integrating AI tools into their daily or weekly academic routines, reflecting strong acceptance and perceived enhancement of academic performance. Overall, the findings suggest that AI chatbots are becoming an important component of medical education and are likely to remain integrated into students' future academic practice.

LIMITATIONS & RECOMMENDATIONS

The cross-sectional study design and convenience sampling technique are among the few limitations in this study. Since the study was conducted at a single center with a relatively small sample size, the findings may not be representative of all medical students. Multi-centered study designs with large sample sizes from both public and private medical colleges are recommended. Additionally, the students should be sensitized and trained in AI during medical undergraduate programs to foster a holistic learning environment and develop clinical skills, making a difference in patients' lives.

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Authors' Contributions:
A.A: Conceived and designed the study, interpreted data, and critically revised the manuscript.
S.S: Analyzed data, interpreted results, and drafted the manuscript.
A.R: Conducted literature review, assisted in data collection, and reviewed the manuscript.

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Original Article

Comparison of Efficacy and Safety between CAPOX and FOLFOX6 in Metastatic Colorectal Carcinoma

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ABSTRACT

Objective: To compare the efficacy and safety of CAPOX versus FOLFOX6 in patients with metastatic colorectal carcinoma in terms of disease progression, mortality, and treatment-related toxicities.

Methodology: This randomized controlled trial was conducted at the Department of Oncology, Jinnah Hospital, Lahore, from September 2025 to February 2026, following ethical approval from the institutional review board. Patients aged 20 to 80 years with metastatic colorectal carcinoma planned for postoperative chemotherapy were recruited using a non-probability consecutive sampling technique after obtaining informed written consent. A total of 248 patients were screened, of whom 216 eligible patients were randomized to either CAPOX or FOLFOX6 treatment groups. During follow-up, 15 patients in the CAPOX group and 22 patients in the FOLFOX6 group were lost to follow-up; therefore, the final analysis was performed on 179 patients, including 93 in the CAPOX group and 86 in the FOLFOX6 group. Outcomes included disease progression, dose reduction, hepatotoxicity, diarrhea, neuropathy, treatment discontinuation, and mortality. Data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 26.

Results: Baseline demographic and clinical characteristics were comparable between the two groups ($p > 0.05$). Disease progression occurred in 25(26.9%) patients in the CAPOX group and 32(37.2%) patients in the FOLFOX6 group [odd ratio (OR) 0.62, 95% confidence interval (CI):0.33-1.17; $p=0.138$]. Neuropathy was significantly less frequent in the CAPOX group compared with the FOLFOX6 group (24.7% vs. 47.7%; $p=0.001$). Hepatotoxicity was less frequent in the CAPOX group than in the FOLFOX6 group (5.4% vs. 14.0%); however, this difference did not reach statistical significance ($p=0.051$). Mortality, dose reduction, treatment discontinuation, and diarrhea did not differ significantly between the groups ($p > 0.05$).

Conclusion: In patients with metastatic colorectal carcinoma, CAPOX was associated with a significantly lower frequency of neuropathy compared with FOLFOX6. CAPOX and FOLFOX6 treatment groups showed no statistically significant difference in disease progression, mortality, dose reduction, hepatotoxicity, diarrhea, and treatment discontinuation.

Keywords: *Colorectal Neoplasms. Neoplasm metastasis. Capecitabine. Oxaliplatin.*

INTRODUCTION

Colorectal cancer remains a major contributor to the global cancer burden, with substantial mortality despite advances in prevention, early detection, and systemic therapy. In 2022, an estimated 1,926,425 new colorectal cancer cases and 904,019 deaths were documented worldwide.[1] Regional differences in incidence and outcomes persist, reflecting differences in risk factor profiles, screening uptake, stage at presentation, and access to hospital care.[2] Metastatic colorectal cancer is associated with a markedly poorer prognosis than localized disease. Approximately one fifth of patients present with metastatic disease at initial diagnosis, and a further one fourth develop distant spread after treatment of earlier stage disease.[3] Current population level data show low long term survival in distant stage disease. An effective treatment regimen is needed that patients can easily tolerate and continue for the full course.[4]

Systemic therapy remains the cornerstone of treatment for patients with metastatic colorectal cancer, with regimen selection guided by performance status, tumor biology, prior treatment exposure, and primary tumor location.[5] The commonly used chemotherapeutic regimes are 5-fluorouracil with leucovorin & oxaliplatin (FOLFOX6) and capecitabine with oxaliplatin (CAPOX). The CAPOX regimen offers oral fluoropyrimidine and avoids continuous 5-fluorouracil infusion, but FOLFOX6 needs central venous access for prolonged infusion with implications for catheter related complications and service delivery constraints.[6] Comparative evidence has demonstrated distinct toxicity profiles between CAPOX and FOLFOX6 regimens, with variations in the incidence of neutropenia, diarrhea, and peripheral neuropathy. These differences directly influence dose intensity, treatment modifications, and discontinuation rates, ultimately impacting overall treatment outcomes.[5] A study conducted at a cancer center in Pakistan reported that CAPOX based therapy was generally well tolerated, with diarrhea and peripheral neuropathy being the most frequently observed toxicities.[6]

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In resource limited settings, differences in oncology infrastructure, supportive care, and toxicity monitoring may further influence treatment selection and outcomes. A study from Pakistan reported real world chemotherapy utilization patterns in metastatic colorectal cancer, with FOLFOX being the most commonly used regimen (38.3%), followed by CAPOX (19.9%); and the patients who did not receive chemotherapy had significantly lower survival, emphasizing the vital role of systemic therapy.[7] However, direct comparative evidence between CAPOX and FOLFOX6 in the local setting remains limited. Therefore, this study was conducted to compare disease progression and treatment related toxicities between CAPOX and FOLFOX6 in patients with metastatic colorectal carcinoma, aiming to identify the regimen that offers an optimal balance between efficacy and tolerability in routine clinical practice.

METHODOLOGY

This randomized controlled trial registered at ClinicalTrials.gov (NCT07334587, 31-12-2025) was conducted at the Department of Oncology, Jinnah Hospital, Lahore, from September 2025 to February 2026 after taking ethical approval from the institutional review board (Letter No. ERB193/2/29-08-2025/AIMC/JHL, 29-08-2025). A sample size of 216 patients (108 per group) was calculated using OpenEpi software, based on a 95% confidence level, 80% power, and assumed peripheral neuropathy rates of 31.3% in the FOLFOX4 group and 14.3% in the CAPOX group.[8,9] A total of 248 patients were screened, of whom 216 eligible patients were randomized. During follow-up, 15 patients in the CAPOX group and 22 patients in the FOLFOX6 group were lost to follow-up; therefore, the final analysis was performed on 179 patients, including 93 in the CAPOX group and 86 in the FOLFOX6 group. Participant flow was reported according to Consolidated Standards of Reporting Trials (CONSORT) guidelines (Figure 1).

Adult patients with metastatic colorectal carcinoma presenting to the outpatient oncology department for postoperative systemic chemotherapy were screened and enrolled using a non-probability consecutive sampling technique after obtaining written informed consent. Patients aged 20 to 80 years of either sex were eligible if they had histologically confirmed stage IV metastatic colorectal carcinoma and were planned to receive postoperative chemotherapy. Exclusion criteria included non-metastatic disease at diagnosis, the presence of another active malignancy, prior adjuvant chemotherapy received at another center, documented preexisting neurological disorders, and participation in another interventional trial.

Eligible patients were randomized in a 1:1 ratio to either the CAPOX or FOLFOX6 group using a computer generated random number sequence. Allocation concealment was ensured through sequentially numbered, opaque, sealed envelopes, which were opened only after patient enrolment. Blinding of patients and treating physicians was not feasible due to differences in drug administration route, dosing schedule, and infusion duration between the two regimens.

Baseline data was recorded on a standardized proforma before allocation, including age, gender, body mass index (BMI), duration of disease, primary tumor site, stage, Eastern Cooperative Oncology Group (ECOG) performance status, smoking status, diabetes mellitus, hypertension, anemia, family history of cancer, interval between surgery and chemotherapy, and total number of involved lymph nodes. Prechemotherapy clinical assessment and routine laboratory investigations were performed according to departmental protocol to document baseline hematologic and hepatic status and to confirm fitness for systemic therapy. In the CAPOX group, oxaliplatin 130 mg/m² was administered intravenously on day 1 with oral capecitabine 1000 mg/m² every 12 hours on days 1 to 14, repeated every 3 weeks for 6-8 cycles. In the FOLFOX6 group, oxaliplatin 85 mg/m² and leucovorin 400 mg/m² were administered intravenously on day 1, followed by bolus 5-fluorouracil and 46 hour continuous infusion 5-fluorouracil 2400 mg/m², repeated every 2 weeks for 12 cycles. All injectable chemotherapy drugs were prescribed by the consultant medical oncologist and administered in the oncology daycare chemotherapy unit by trained oncology nursing staff experienced in cytotoxic drug administration, under the supervision of the oncology registrar and consultant medical oncologist. Standard supportive care was provided, and before each cycle, patients underwent clinical assessment and laboratory monitoring to evaluate treatment tolerance. Dose reductions, treatment delays or discontinuation were implemented when clinically indicated based on toxicity, and outcomes were recorded at the end of treatment.

The study follow-up duration was 6 months for all patients. During this period, patients were followed at regular intervals corresponding to each chemotherapy cycle, i.e., every 3 weeks in the CAPOX group and every 2 weeks in the FOLFOX6 group, from treatment initiation until completion of

therapy or disease progression, whichever occurred earlier. Additional unscheduled visits were arranged as needed for toxicity assessment or clinical deterioration.

The primary outcome variable was disease progression during the treatment and follow-up period. Disease progression was assessed according to Response Evaluation Criteria in Solid Tumors RECIST) version 1.1.[10] Progressive disease was defined as at least a 20% increase in the sum of diameters of target lesions compared with the smallest sum recorded during the study, with an absolute increase of at least 5 mm, or the appearance of one or more new lesions. The secondary outcome variables were treatment related toxicities, including dose reduction, hepatotoxicity, diarrhea, peripheral neuropathy, treatment discontinuation, and mortality and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.[11] All outcomes were recorded in a predesigned data collection proforma as binary variables (yes or no).

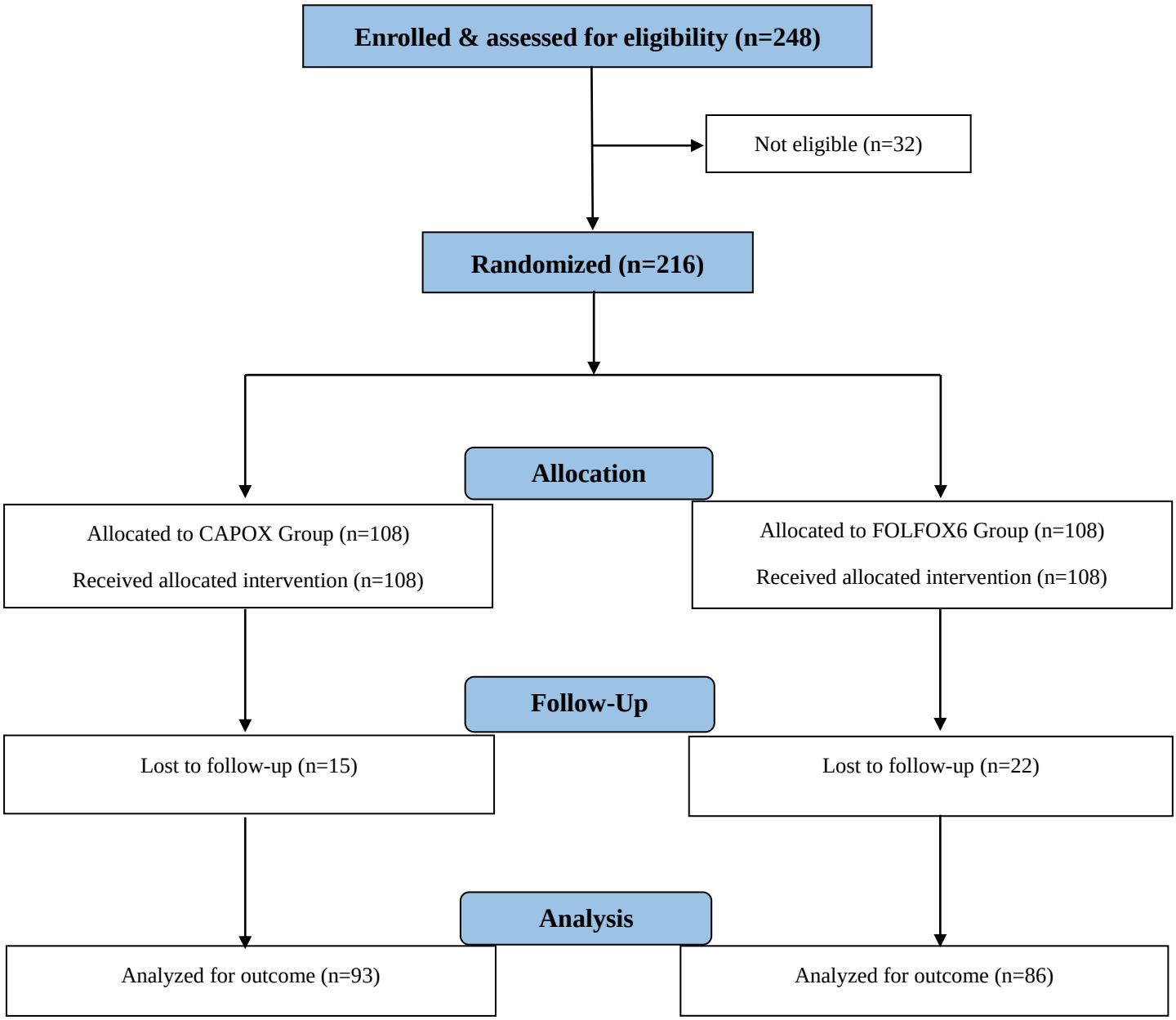

Figure 1: Flow Chart according to CONSORT Guidelines

STATISTICAL ANALYSIS

Data was analyzed using Statistical Package for the Social Sciences (SPSS) version 26. Continuous variables were summarized as mean & standard deviation, while categorical variables were presented as frequency and percentage. Between groups comparisons for continuous variables were performed using the independent samples t-test. Categorical variables were compared using the Chi-square test. For each binary outcome, odds ratios (OR) with 95% confidence intervals (CI) were reported. A p-value less than 0.05 was considered statistically significant.

RESULTS

The mean age was 59.64±7.40 years in the CAPOX group versus 58.59±7.42 years in the FOLFOX6 group (p=0.346). Mean duration of cancer was 7.85±4.17 months versus 8.46±4.48 months (p=0.351). Similarly, BMI was comparable between CAPOX and FOLFOX6 groups (24.70±3.01 kg/m² versus 25.19±3.61 kg/m², p=0.316). The interval from surgery to chemotherapy was also comparable between groups (34.19±14.33 days versus 32.65±13.03 days, p=0.453). Mean number of involved lymph nodes was 4.19±1.83 in the CAPOX group and 4.37±1.86 in the FOLFOX6 group (p=0.518). Other baseline demographic and clinical characteristics of both groups were also not statistically different (Table 1).

Disease progression was observed in 25(26.9%) patients in the CAPOX group and 32(37.2%) patients in the FOLFOX6 group. Although progression was numerically lower in the CAPOX group, the difference was not statistically significant (p=0.138). Hepatotoxicity was less frequent in the CAPOX group than in the FOLFOX6 group (5.4% vs. 14.0%); however, this difference did not reach statistical significance (p=0.051). Neuropathy was significantly less frequent in the CAPOX group compared with the FOLFOX6 group (24.7% vs. 47.7%) (p=0.001). Mortality, dose reduction, treatment discontinuation, and diarrhea did not differ significantly between the groups (p >0.05) (Table 2).

Table 1: Comparison of Baseline Characteristics of Patients in the CAPOX and FOLFOX6 Treatment Groups (n=179)

Baseline Characteristics of Patients		CAPOX Group (n=93)	FOLFOX6 Group (n=86)	p-value
		Frequency & Percentage		
Gender	**Male**	55(59.1%)	51(59.3%)	0.982
	Female	38(40.9%)	35(40.7%)	
Primary Tumor Location	**Right Colon**	36(38.7%)	37(43.0%)	0.557
	Left Colon	57(61.3%)	49(57.0%)	
Stage	**IVA**	36(38.7%)	35(40.7%)	0.815
	IVB	42(45.2%)	35(40.7%)	
	IVC	15(16.1%)	16(18.6%)	
ECOG Performance Status	**0**	58(62.4%)	53(61.6%)	0.961
	1	30(32.3%)	29(33.7%)	
	≥2	5(5.3%)	4(4.7%)	
Smoking	**Yes**	29(31.2%)	26(30.2%)	0.890
	No	64(68.8%)	60(69.8%)	
Diabetes Mellitus	**Yes**	23(24.7%)	26(30.2%)	0.410
	No	70(75.3%)	60(69.8%)	
Hypertension	**Yes**	35(37.6%)	33(38.4%)	0.919
	No	58(62.4%)	53(61.6%)	
Anemia	**Yes**	23(24.7%)	24(27.9%)	0.630
	No	70(75.3%)	62(72.1%)	
Family History of Colorectal Cancer	**Yes**	12(12.9%)	12(14.0%)	0.837
	No	81(87.1%)	74(86.0%)	

Table 2: Comparison of Outcomes between CAPOX and FOLFOX6 Treatment Groups

Outcomes		CAPOX Group (n=93)	FOLFOX6 Group (n=86)	Odds Ratio (95% CI)	p value
		Frequency & Percentage			
Disease Progression	**Yes**	25(26.9%)	32(37.2%)	0.62(0.33 to 1.17)	0.138
	No	68(73.1%)	54(62.8%)		
Dose Reduction	**Yes**	22(23.7%)	27(31.4%)	0.68(0.35 to 1.31)	0.246
	No	71(76.3%)	59(68.6%)		
Hepatotoxicity	**Yes**	5(5.4%)	12(14.0%)	0.35(0.12 to 1.04)	0.051
	No	88(94.6%)	74(86.0%)		
Diarrhea	**Yes**	27(29.0%)	18(20.9%)	1.55(0.78 to 3.07)	0.212
	No	66(71.0%)	68(79.1%)		
Neuropathy	**Yes**	23(24.7%)	41(47.7%)	0.36(0.19 to 0.68)	0.001*
	No	70(75.3%)	45(52.3%)		
Treatment Discontinuation	**Yes**	15(16.1%)	21(24.4%)	0.60(0.28 to 1.25)	0.167
	No	78(83.9%)	65(75.6%)		
Mortality	**Yes**	9(9.7%)	14(16.3%)	0.55(0.23 to 1.35)	0.187
	No	84(90.3%)	72(83.7%)		

***Significant p-value*

DISCUSSION

The present study compared the efficacy and safety of CAPOX and FOLFOX6 in 179 patients with metastatic colorectal carcinoma. Disease progression occurred in 26.9% of the CAPOX group compared with 37.2% in the FOLFOX6 group (p=0.138; OR 0.62, 95% CI 0.33-1.17). Mortality rate was also not significantly different between the two groups. In contrast to our findings, Degirmencioglu et al. demonstrated significantly lower progression (27.36% vs. 42.34%; p=0.016) and mortality (16.04% vs. 35.77%; p=0.001) rates in the CAPOX group.[12] A retrospective study involving patients with metastatic colorectal carcinoma reported a disease progression rate of 30.4% (95% CI: 0.19-0.44) with CAPOX treatment, which was identified as the main reason for chemotherapy discontinuation.[9] Rashid et al. showed the progression rate of 23.8% with the CAPOX treatment regimen in patients with metastatic colorectal carcinoma.[13] Another study found no significant difference between CAPEOX and FOLFOX in progression free survival (p=0.23).[14] The variation across studies may reflect differences in disease stage, molecular profiles, and the use of adjuvant versus palliative treatment settings.

In this study, neuropathy was significantly less frequent in the CAPOX group compared with the FOLFOX6 group (24.7% vs. 47.7%) (p=0.001). In contrast, Degirmencioglu et al. observed no significant difference in the occurrence of neuropathy between the two treatment groups (p=0.21).[12] A study observed significantly lower neuropathy rates in patients receiving CAPOX (30%) compared with FOLFOX6 (56%).[15] Kibudde et al. reported peripheral neuropathy in 14.3% of patients treated with oxaliplatin based regimens.[9] In Pakistan, a study reported a high incidence of neuropathy (81.9%) among patients receiving neoadjuvant CAPOX therapy.[6] Kalkan et al. noted significantly lower neuropathy in patients treated with CAPOX for three months (30%) compared with those receiving CAPOX or FOLFOX for six months (54.5%).[16] A study conducted in 2026 pooled data from six trials, also confirmed reduced neuropathy with a three month duration of oxaliplatin based treatment compared with six months (4.2% vs. 13.6%, p <0.001).[17] Yoshino et al. also reported lower rates of peripheral sensory neuropathy in patients receiving shorter duration CAPOX treatment compared with FOLFOX6.[18]

The current study observed no significant difference (p=0.051) in hepatotoxicity rates between CAPOX (5.4%) and FOLFOX6 (14.0%) treatment groups. Another study noted low hepatotoxicity rates in both groups (2.83% versus 5.11%; p=0.52).[12] The near significant finding in the current analysis, together with results from other studies, suggests that CAPOX may carry a lower hepatotoxic burden.

No significant difference in diarrhea rates between CAPOX and FOLFOX6 groups (29.0% vs. 20.9%; p=0.212) was found in this study. McShane and Armstrong reported substantially higher diarrhea with CAPOX (26.9%) as compared to the FOLFOX regimen (2.99%) (p=0.002).[19] A study from Pakistan reported that diarrhea was the most frequently observed toxicity among patients receiving neoadjuvant CAPOX therapy.[6] A meta-analysis by

Zhan et al. revealed that the rate of diarrhea was higher with FOLFOX compared to CAPOX regimens. Although the CAPOX regimen ranked first in terms of safety profile among 29 different regimens, diarrhea was still reported in a study.[20] Mortality was not significantly (p=0.187) different between the two treatment groups (9.7% vs 16.3%) in our study. Chowdhury et al. reported inferior survival with CAPOX (p <0.001); however, substantial confounding by indication was acknowledged, as patients receiving CAPOX were older and had a higher proportion of stage IV disease.[21] In another study, no significant survival differences were found between regimens.[22] The treatment discontinuation rates in the present study (16.1% versus 24.4%; p=0.167) contrast with McShane and Armstrong, who observed significantly higher discontinuation rates with CAPOX (46.2% vs 10.5%; p <0.001).[19] This inconsistency may reflect differences in patient selection, dose modification, and institutional practices.

CONCLUSION

In patients with metastatic colorectal carcinoma, CAPOX was associated with a significantly lower frequency of neuropathy compared with FOLFOX6. CAPOX and FOLFOX6 treatment groups showed no statistically significant difference in disease progression, mortality, dose reduction, hepatotoxicity, diarrhea, and treatment discontinuation. These findings suggest that both regimens remain clinically usable options, with CAPOX offering a lower neuropathy burden in this study. Regimen selection should be individualized according to toxicity profile, patient preference, treatment adherence, comorbidities, and institutional chemotherapy delivery resources.

LIMITATIONS & RECOMMENDATIONS

This study had several limitations. Firstly, the final analysis included only patients who completed outcome assessment, and those lost to follow-up were excluded; therefore, attrition bias cannot be ruled out. Second, molecular profiling data were unavailable, limiting subgroup analysis. Third, the follow-up duration was relatively short, preventing mature progression free survival and overall survival analyses. Fourth, adverse effects were recorded during routine clinical care, and patient reported symptom burden may not have been fully captured using formal quality of life instruments. Further multicenter randomized trials with larger sample sizes, intention-to-treat analysis, longer follow-up, standardized radiological response assessment, molecular subgroup stratification, and formal quality of life evaluation are recommended.

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Authors' Contributions:
P.A: Conceived and designed the study, interpreted data, critically revised the manuscript, and approved the final version.
K.B: Contributed to study design, data interpretation, manuscript revision, and approved the final version.
R.N: Conducted literature review, interpreted findings, drafted and revised the manuscript, and approved the final version.
H.A: Contributed to clinical data analysis, manuscript revision, and approved the final version.
H.R: Participated in data collection, data organization, manuscript preparation, and approved the final version.
Z.M: Contributed to clinical data acquisition, clinical discussion refinement, and approved the final version.

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Original Article

Outcomes of Donors in Living Donor Liver Transplantation: Effect of Strict Donor Selection Criteria

Muhammad Haroon, Muhammad Imran Khan, Raja Saddam Dildar, Muhammad Ijaz Ashraf, Faisal Hanif

ABSTRACT

Objective: To evaluate the effect of strict institutional donor selection criteria on short term safety outcomes among living liver donors undergoing hepatectomy.

Methodology: This retrospective cross-sectional study on 140 living liver donor records was conducted in the Department of Hepatopancreatobiliary (HPB) and Liver Transplant Surgery at Bahria International Hospital, Orchard, Lahore. The study was carried out from January to March 2026 after obtaining institutional ethical approval. Donors were evaluated by a multidisciplinary team and selected through a structured protocol that included clinical, biochemical, radiological, and psychosocial evaluations. Acceptable graft parameters included graft-to-recipient weight ratio (GRWR) ≥0.8 and future liver remnant (FLR) ≥30%. Those with significant comorbidities, fatty liver, abnormal liver function tests, and fibrosis were not selected for donation. Data was analyzed using Statistical Package for the Social Sciences (SPSS) version 29.

Results: The mean age of donors was 27.0±4.7 years with a mean body mass index (BMI) of 24.0±2.4 kg/m². The mean length of hospital stay was 5.0±0.7 days. Overall, early postoperative complications occurred in 3(2.1%) donors, including bile leak in 2(1.4%) cases and wound infection in 1(0.7%) case. No donor mortality was observed. Donors who developed early complications had a significantly longer hospital stay compared with those without complications (6.67±0.58 days vs 4.98±0.62 days, p <0.001).

Conclusion: The use of a meticulous donor selection protocol, combined with a multidisciplinary assessment, was associated with low complication rates, shorter hospital stays, and no donor mortality.

Keywords: *Living donors. Hepatectomy. Postoperative complications. Patient selection. Length of stay.*

INTRODUCTION

Living donor liver transplantation (LDLT) has become an important strategy for the treatment of end-stage liver disease, particularly in regions where deceased donor transplantation remains limited. In Pakistan and other low- and middle-income areas, LDLT continues to be the principal transplant pathway because of organ scarcity, delayed access to deceased donor transplantation, and a persistent burden of advanced chronic liver disease.[1] Contemporary reviews also show that LDLT offers major recipient advantages, including shorter wait times and timely access to transplantation, but these benefits are acceptable only when donor risk is minimized through rigorous evaluation and careful operative planning.[2] Unlike recipients, living donors are healthy individuals who derive no direct medical benefit from surgery. For this reason, donor safety remains the central principle of every LDLT program. Recent evidence indicates that although donor mortality is rare, donor morbidity remains clinically relevant and requires continuous attention. A recent meta-analysis confirmed that adverse donor outcomes are uncommon overall but still meaningful, underscoring the need for structured donor assessment and perioperative safeguards.[3] In addition, long term follow-up have highlighted that donor outcomes should not be judged solely by early postoperative events, but also by longer term physical and psychological wellbeing after donation.[4]

Current literature emphasizes a comprehensive multidisciplinary evaluation of potential living liver donors, including detailed history taking, laboratory testing, cardiopulmonary assessment, psychosocial evaluation, high resolution cross-sectional imaging, and precise vascular and biliary mapping with volumetric analysis prior to donor acceptance.[4] Parameters such as graft-to-recipient weight ratio (GRWR) and future liver remnant (FLR) remain central to decision-making, as they ensure adequate graft function in the recipient while maintaining donor safety. Anatomical variations of the hepatic vasculature and biliary tree are also critically assessed, as they may increase operative complexity and influence perioperative donor and recipient outcomes.[5]

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Although these core principles are widely applied across transplant centres, variations exist in the strictness of donor selection thresholds, the extent of multidisciplinary consensus, and imaging protocols used for final donor approval. Consequently, differences in institutional selection criteria may contribute to variability in reported donor outcomes across studies.[3] In countries such as Pakistan, where living donation remains the dominant transplant model, locally relevant evidence is needed to determine whether strict institutional screening protocols are associated with safe donor outcomes. The present study was therefore undertaken to evaluate short term outcomes of living liver donors selected through a structured institutional pathway and to assess whether meticulous donor selection and multidisciplinary evaluation were associated with favorable donor safety outcomes in our setting.

METHODOLOGY

This retrospective cross-sectional study was conducted from January to March 2026 at the Department of Hepatopancreatobiliary (HPB) and Liver Transplant Surgery, Bahria International Hospital, Orchard, Lahore, Pakistan. Ethical approval was obtained from the institutional review board (Letter No. IRB/BIHO/2025/09-OR, 22-12-2025). The records of all 140 eligible donors who met the institutional selection criteria and underwent hepatectomy between July 2019 and December 2025 were included.

Donors were admitted for surgery after informed written consent and completion of all required investigations & workup according to predefined, structured selection criteria (Table 1). The donor selection process was performed in a stepwise manner to ensure cost-effectiveness (Figure 1). Donor evaluation included detailed clinical assessment comprising medical and surgical history, physical examination, BMI calculation, Echocardiography (ECG), and overall fitness assessment. Baseline laboratory investigations included complete blood count (CBC), liver function tests (LFTs), renal function tests (RFTs), blood grouping & cross-matching, Hemoglobin A1c (HbA1c), coagulation profile, and viral serology for hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), hepatitis E virus (HEV), and human immunodeficiency virus (HIV). Baseline radiological investigations included Chest X-ray (CXR), ultrasound, and Doppler scan of liver.

Radiological assessment was performed to evaluate liver anatomy and volumetry. Triphasic computed tomography (CT) enabled vascular mapping and volumetric analysis, including calculation of the GRWR and assessment of the FLR. Magnetic resonance cholangiopancreatography (MRCP) was performed to assess biliary anatomy. Transient elastography (Fibro Scan) was used to evaluate hepatic steatosis and fibrosis. Liver biopsy was performed in selected cases where steatosis or fibrosis was suspected.

Key selection criteria included age between 18 and 40 years, normal liver function tests (LFT), absence of hepatic steatosis and fibrosis, negative hepatitis and HIV serology, GRWR $\geq$0.8, and FLR $\geq$30%. Donors with up to two hepatic arteries, two portal veins, and two bile ducts were considered eligible for inclusion. Individuals with significant comorbid conditions (e.g., diabetes mellitus, cardiovascular disease), fatty liver disease, and hepatic fibrosis were excluded during donor selection.

Following completion of clinical, biochemical, and radiological evaluation, donors were assessed by a multidisciplinary team comprising transplant surgeons, hepatologists, anaesthesiologists, psychiatrists, cardiologists, and pulmonologists. Special investigations included metabolic profiling (thyroid and lipid profiles) and autoimmune screening [lupus anticoagulant and antinuclear antibodies (ANA)]. Protein C, Protein S, antithrombin III, D-dimer, and Factor V Leiden levels were performed for thrombophilia screening. Psychological evaluation ensured voluntary consent and excluded coercion. All donor hepatectomy procedures were performed by experienced transplant surgeons using standard surgical techniques. Postoperative care included intensive monitoring, early mobilization, and serial biochemical assessment.

The outcomes were assessed during a 30 day postoperative follow-up period. The primary outcomes were donor mortality and postoperative complications graded using the Clavien-Dindo system, where Grade I indicates minor deviation without treatment, Grade II requires pharmacological or blood transfusion support, Grade III requires surgical/endoscopic/radiological intervention (Grade IIIa: intervention without general anaesthesia; Grade IIIb: intervention under general anaesthesia), Grade IV represents life threatening complications requiring ICU care, and Grade V indicates death.[6] The secondary outcome was length of hospital stay.

Table 1: Institutional Donor Selection Criteria for Living Liver Donors

Parameters	Acceptable	Not Acceptable
Comorbidities	None	Hypertension, Ischemic Heart Disease, and Diabetes Mellitus
LFTs	Normal	Abnormal
Ultrasound Liver	Normal Liver	Fibrosis Fatty Liver
Liver Attenuation Index (LAI) on CT-scan	Greater than +5	<0
Liver Biopsy [for LAI (0 to +4)]	No Fibrosis Steatosis <10%	Fibrosis Steatosis >10%
GRWR	≥0.8	<0.8
FLR	≥30 %	<30%
Arterial Anatomy	Graft with one or up to two Hepatic Arteries	Graft with more than two Hepatic Arteries
Portal Vein Anatomy	Graft with one or up to two Portal Veins	Graft with more than two Portal Veins
Bile Duct Anatomy	Graft with one or up to two Bile Ducts	Graft with more than two Bile Ducts/Complex Biliary Anatomy Unsuitable for Reconstruction

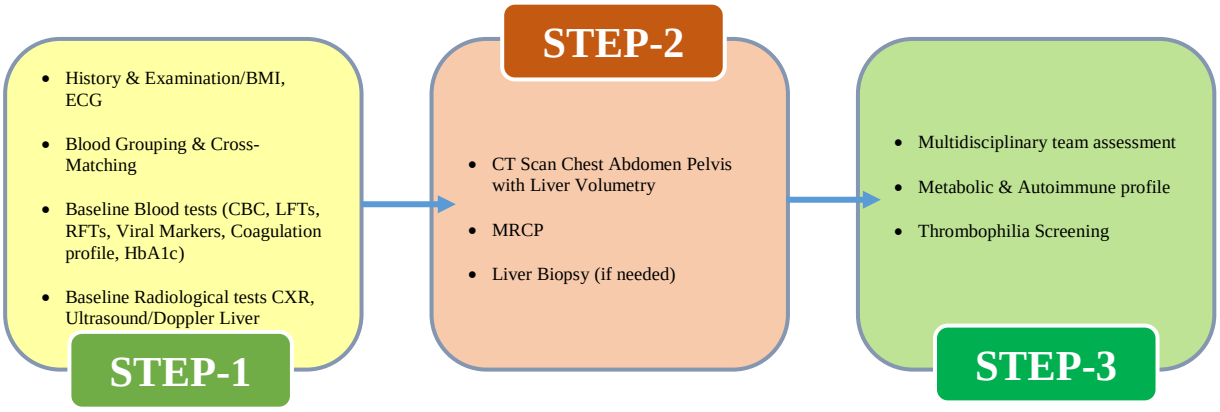

Figure 1: Stepwise Donor Evaluation Protocol for Living Donor Liver Transplantation

STATISTICAL ANALYSIS

Statistical Package for the Social Sciences (SPSS) version 29 was used to analyze the data. Continuous variables were expressed as mean±standard deviation, while categorical variables were presented as frequencies and percentages. Subgroup analysis was performed to compare donors with and without postoperative complications across variables including age, gender, BMI, FLR, GRWR, anatomical variations, and length of hospital stay. The independent t-test was used to compare continuous variables. Fisher's exact test was applied for categorical variables due to small expected cell counts. A p-value of <0.05 was considered statistically significant.

RESULTS

The mean age of the donors was 27.0±4.7 years with a mean BMI of 24.0±2.4 kg/m², mean FLR of 37.1±3.6%, and mean GRWR of 1.02±0.12. The cohort comprised 80(57.1%) males and 60(42.9%) females. Most donors had conventional vascular and biliary anatomy, including a single hepatic artery in 137(97.9%), a single portal vein in 134(95.7%), and a single bile duct in 101(72.1%) donors.

Overall, 137(97.9%) donors had no early postoperative complications. The mean hospital stay was 5.0±0.7 days, and no (0%) donor mortality was observed. Among donors who developed early postoperative complications, bile leak occurred in 2(1.4%) and wound infection in 1(0.7%). According to the Clavien-Dindo classification, both cases of

bile leak were Grade I. The wound infection was classified as Grade IIIa.

Early postoperative complications were not significantly associated with age, gender, BMI, and anatomical variation (p >0.05). Donors without complications had a mean hospital stay of 4.98±0.62 days, whereas those with complications had a significantly longer stay (6.67±0.58 days, p <0.001). Both groups showed no significant difference in mean FLR and mean GRWR. These findings indicate that although early complications were infrequent, they were associated with a clinically meaningful prolongation of hospital stay (Table 2).

DISCUSSION

Current donor safety literature continues to place donor protection at the center of LDLT practice.[7] In our study, early postoperative complications occurred in only 3(2.1%) donors, including bile leak in 2(1.4%) cases and wound infection in 1(0.7%) case. No donor mortality was observed. Xiao et al. included outcomes from 60,829 living liver donors in their meta-analysis and reported a pooled overall donor complication rate of 24.7% [95% confidence interval (CI): 21.6-28.1%]. They also reported a substantially lower mortality (0.06%) and wound related complications (0.7%) in their large cohort. These findings confirm that while adverse events in LDLT remain uncommon, they are not negligible.[3] Tuncer et al. also reported a higher overall complication rate of 11.6% (95% CI: 9.0-14.6%) with no mortality among 502 living liver donors.[6]

The present study also demonstrated that donors who developed early complications had a significantly longer hospital stay compared with those without complications (6.67±0.58 days vs 4.98±0.62 days, p <0.001). Early postoperative complications were not significantly associated with age, gender, BMI, or anatomical variation (p >0.05). Both cases of bile leak were classified as Grade I, while only one wound infection was classified as Grade IIIa, compared with 17 major complications (≥Grade IIIa) reported by Tuncer et al. Most of the complications reported in their study were wound infections, followed by bile leakage. Similar to our results, complications were associated with a significantly longer hospital stay, and no significant independent associations were reported between postoperative complication risk and graft type, remnant liver ratio, graft volume, or BMI.[6] Another review reported an overall mortality of 0 to 0.7%, overall complication rate of 7.8-71.2%, while the average length of hospital stay was from 3.9 to 14.5 days among donors.[8]

Rhu et al. reported that the 30 day complication rate of 636 donors undergoing laparoscopic living donor hepatectomy was 16.8%, with Grade IIIa and IIIb complications occurring in 4.4% and 1.9% of cases, respectively. The most frequent complication was bleeding (6.0%), while bile leakage was observed in 3.3% of cases.[9] In another review, 28 studies were compiled, and the rate of major complications (≥Grade IIIa) was 2.1% to 28%. Only one study reported that complications were associated with a significantly increased length of hospital stay, with an incidence rate ratio of 1.36 (95% CI: 1.16-1.58; p <0.001), indicating that even infrequent adverse events can affect recovery and resource use.[10]

Table 2: Comparison of Donor Characteristics between Patients with and without Early Postoperative Complications

Donor Characteristics		Donors with Complications (n=03)	Donors without Complications (n=137)	p-value
Age (Years)	**(mean±SD)**	28.67±2.89	26.96±4.75	0.538
Gender (Frequency & Percentage)	**Female**	2(66.7)	58(42.3)	0.576
	Male	1(33.3)	79(57.7)	
BMI (kg/m^2)	**(mean±SD)**	22.47±4.27	24.03±2.35	0.264
Anatomical Variation (Frequency & Percentage)	**Present**	2(66.7)	45(32.8)	0.261
	Absent	1(33.3)	92(67.2)	
Future Liver Remnant (%)	**(mean±SD)**	33.63±3.11	37.20±3.56	0.087
Graft-to-Recipient Weight Ratio		1.07±0.21	1.02±0.12	0.488
Hospital Stay (Days)		6.67±0.58	4.98±0.62	<0.001*

**Significant p-value*

In the International LDLT Registry analysis, short term donor complication rates differed substantially ($p < 0.001$) by human development index (HDI), with rates of 9.8% in very high HDI regions versus 21.9% in lower HDI regions, highlighting the sensitivity of outcomes to system level variation in practice and resources.[11] However, the early complication rate of 2.1% in our study appears favorable, likely reflecting conservative donor acceptance and careful perioperative management. Donors in this series were young and had a favorable BMI profile, and our protocol excluded significant comorbidities. This approach was consistent with current donor selection guidance, which emphasizes low risk physiology and adequate hepatic reserve.[5,12] Although broader donor criteria like inclusion of older adults are increasingly discussed, expansion should be approached cautiously. A recent systematic review and meta-analysis found no significant difference in complications and mortality between young and older donors.[13] This finding highlighted that carefully selected older living liver donors may enlarge the donor pool, but such practice still requires careful risk stratification and experienced centers.

Volumetric criteria represented a key strength of the donor selection strategy. All donors met the GRWR ≥0.8 and FLR ≥30%, with a mean GRWR of 1.02±0.12 and a mean FLR of 37.1±3.6%. Kim et al. reported that overall [Odd's ratio (OR) = 1.82; 95% CI: 1.24-2.67; p = 0.002] and minor (OR=1.88; 95% CI: 1.23-2.88; p=0.004) morbidities were significantly lower in donors with a residual liver volume ≥30% compared with those with <30%.[14] Likewise, recipient focused multicenter work has shown that lower GRWR grafts may be feasible in selected circumstances, but that does not eliminate the need for conservative donor protection in routine practice.[8]

Anatomical complexity directly affects surgical planning and reconstruction. Most donors had conventional vascular and biliary anatomy, including a single hepatic artery in 137(97.9%), a single portal vein in 134(95.7%), and a single bile duct in 101(72.1%) donors. Donors with up to two hepatic arteries, bile ducts, and portal vein variations were accepted in this study. The presence of anatomical variations was not significantly associated with postoperative complications. In contrast, Pakistani data from 400 living liver donors reported that vascular and biliary variations were common (34.2%) and therefore must be defined carefully during donor workup.[15] Broader contemporary imaging and donor evaluation reviews also emphasize that anatomical variants are frequent in otherwise healthy donors and that preoperative mapping is indispensable for safe graft procurement.[5,12] Our results suggested that selected minor anatomical variations can be managed safely when operative expertise and preoperative planning are strong.

The long term donor literature showed that donor outcomes should be evaluated not only in terms of mortality, but also through broader measures such as recovery burden, quality of life, psychosocial health, and durable symptoms after donation.[16,17] In the review by Thuluvath et al., 9.1% of donors in studies did not return to baseline physical quality of life scores for at least two years after donation.[16] The absence of donor mortality in our series should be interpreted carefully and should not be presented as evidence that donor risk is absent. A North American data spanning more than three decades and more than 11,000 living donor hepatectomies reinforce that donor death is rare, but not impossible, and that transparent reporting remains essential.[8]

CONCLUSION

A strict donor selection process combined with multidisciplinary evaluation was associated with low complication rates, shorter hospital stays, and no donor deaths in this cohort. Donors with complications had a significantly longer mean hospital stay compared to those without complications. These findings reinforce the importance of careful donor selection as a central factor in ensuring donor safety in LDLT.

LIMITATIONS & RECOMMENDATIONS

This was a retrospective, single-centered study with a relatively small number of complication events, which may limit the generalizability of the findings and restrict detailed risk factor analysis. In addition, long term donor outcomes were not assessed. Future research, particularly larger multi-centered prospective studies with extended follow-up, is recommended to confirm these results and help improve donor selection criteria.

Conflict of interest: None.

Source of funding: None.

Authors' Contributions:

M.H: Conceptualization, study design, supervision, manuscript review and final approval.

M.I.K: Data collection, donor evaluation, interpretation of results and manuscript drafting.

R.S.D: Literature review, statistical analysis and data interpretation.

M.I.A: Radiological assessment coordination, data acquisition and critical revision of manuscript.

F.H: Surgical supervision, final manuscript editing and overall coordination of the study.

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Case Report

Co-Occurrence of Synovial Chondromatosis and Distal Humeral Osteochondroma of the Elbow in a Young Athlete: A Case Report

Farooq Azam Khan

ABSTRACT

Synovial chondromatosis and osteochondroma rarely present concurrently in the elbow. We report a 19-year-old male football goalkeeper with an 8 month history of progressive right elbow pain and restricted range of motion (flexion 90°, extension 30°) likely related to repetitive microtrauma. Imaging revealed multiple intraarticular small, loose bodies; known as rice bodies consistent with synovial chondromatosis and a distal humeral osteochondroma measuring >2.5 cm. In the first stage, arthroscopic synovectomy with excision of rice bodies was performed, while the osteochondroma was left for a planned second stage open resection. This case highlights the importance of staged surgical management and rehabilitation in restoring function in a young patient with concurrent benign elbow pathologies.

Keywords: *Synovial chondromatosis. Osteochondroma. Arthroscopy. Synovectomy.*

INTRODUCTION

Primary synovial chondromatosis is a rare metaplastic disorder with an estimated incidence of approximately 1 per 100,000 individuals, and the elbow is an uncommon site of involvement.[1] Osteochondroma is the most common benign bone tumor, representing approximately 30% of all benign bone tumors; however, its occurrence in an intraarticular location of the distal humerus is exceedingly rare.[2] The simultaneous occurrence of these two distinct entities is exceptionally uncommon, with only a few isolated cases reported in the literature.[3] Repetitive microtrauma has been proposed as a contributing factor in the development of secondary synovial chondromatosis.[4] This case report describes the diagnostic workup, staged surgical management, and early rehabilitation of a goalkeeper affected by both pathologies.

CASE REPORT

A 19-year-old male football goalkeeper presented with an 8 month history of progressive pain and restricted movement of his dominant right elbow, with an insidious onset. He attributed his symptoms to repetitive goalkeeping training, and no significant comorbidities were identified. Physical examination revealed a painful arc of motion with a mechanical block to elbow movement, limited flexion to 90°, and a 30° extension deficit. Routine laboratory investigations were within normal limits. Plain radiographs (Figure 1), magnetic resonance imaging (MRI) (Figure 2a), and computed tomography (CT) (Figures 2b and 2c) demonstrated an osteochondroma measuring >2.5 cm involving the anterior and distal aspects of the humerus, along with numerous intraarticular loose (rice) bodies, confirming the coexistence of synovial chondromatosis.[5]

The treatment plan consisted of staged management, including initial arthroscopic synovectomy and rice body removal followed by planned open osteochondroma excision, with the goals of relieving pain, restoring elbow range of motion, and facilitating a return to sporting activities.

Under general anesthesia, the patient was placed in the lateral decubitus position. Standard anteromedial, anterolateral, and posterior arthroscopic portals were established. Diagnostic arthroscopy (Figure 3a) revealed multiple cartilaginous rice bodies, and extensive synovectomy with removal of all accessible rice bodies was performed (Figure 3b).[6] Because of its size, location, and proximity to critical neurovascular structures, osteochondroma was not considered for arthroscopic excision and was left in situ for planned second stage open resection.[7]

Histopathological examination confirmed the diagnosis of synovial chondromatosis. Immediate postoperative rehabilitation emphasized edema control and gentle assisted exercises while avoiding forceful stretching. Functional range of motion exercises progressively advanced from the second postoperative week onward.

A planned second stage open resection through anteromedial and posterolateral approaches was performed 8 weeks after the index procedure. Following completion of both surgical stages, the patient achieved normal elbow motion, pain relief, and return to competitive sporting activity.

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DISCUSSION

The elbow's constrained anatomy makes it particularly susceptible to mechanical impingement by space occupying lesions. Synovial chondromatosis typically presents with pain, swelling, mechanical locking, and restricted motion, whereas osteochondroma commonly presents as a painless bony prominence and is rarely encountered in an intraarticular location around the elbow.[1,2] The simultaneous occurrence of the two pathologies is exceptionally uncommon, making diagnosis and management challenging.[2,3] In athletes subjected to repetitive valgus and axial loading, microtrauma has been hypothesized to induce synovial metaplasia.[4]

In the present case, the coexistence of numerous intraarticular rice bodies with a large distal humeral osteochondroma resulted in significant functional limitation and a mechanical block to elbow motion. Some reports have described delayed diagnosis because symptoms are often attributed to sports related overuse injuries or repetitive microtrauma.[4]

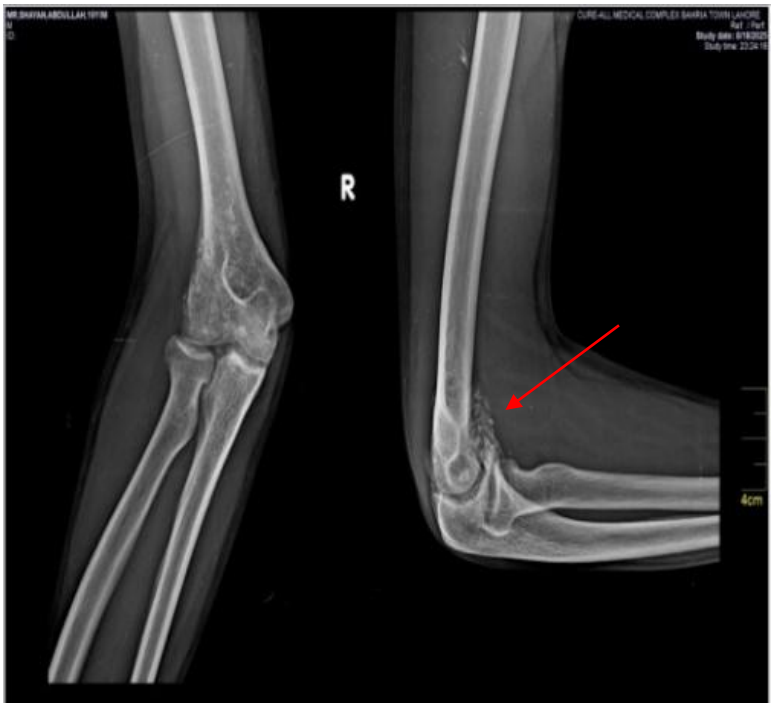

Figure 1: Anteroposterior and Lateral Radiographs of the Right Elbow showing a Radiopaque Mass Arising from the Anterior Distal Humerus, Consistent with Osteochondroma

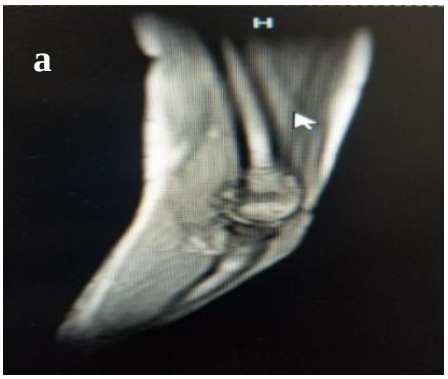

Figure 2a: Sagittal T2-Weighted MRI Demonstrating Multiple Intraarticular Rice Bodies and an Anterior Distal Humeral

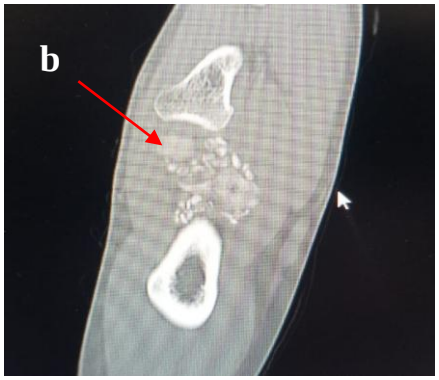

Figure 2b: Sagittal CT Image Demonstrating Multiple Intraarticular Rice Bodies within the Anterior Compartment of the

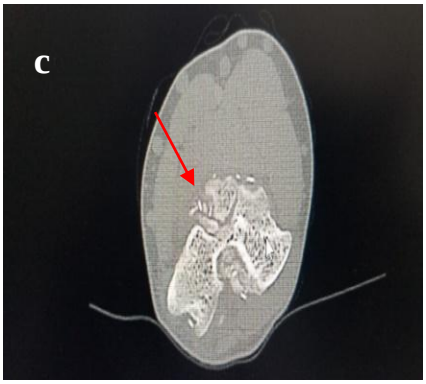

Figure 2c: (c) Axial CT Image Demonstrating the Distal Humeral Osteochondroma and Associated Intraarticular Rice Bodies Elbow

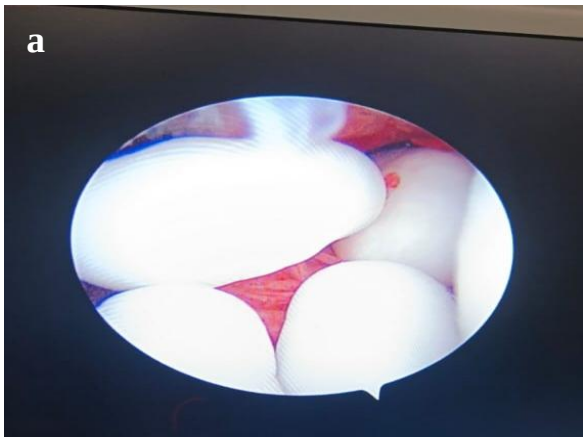

Figure 3a: Arthroscopic View of the Elbow Joint showing Rice Bodies

Figure 3b: Rice Bodies Removed from the Elbow Joint

Arthroscopic synovectomy with removal of rice bodies is considered the standard treatment for synovial chondromatosis because it provides superior visualization, lower morbidity, and faster rehabilitation.[1,6] A study described the arthroscopic management of elbow synovial chondromatosis and highlighted the advantages of arthroscopy, including shorter rehabilitation and improved patient satisfaction. However, long term surveillance is necessary, as recurrence of synovial chondromatosis has been reported in a small proportion of patients.[6]

Management of osteochondromas around the elbow depends on lesion size, location, symptoms, and proximity to neurovascular structures. Larger osteochondromas are associated with an increased risk of incomplete excision and iatrogenic neurovascular injury, whereas arthroscopic excision is generally reserved for carefully selected cases.[7] A study published in 2024 reported successful surgical treatment of intraarticular elbow osteochondroma with favourable functional outcomes, supporting the role of complete lesion excision in symptomatic patients.[8] Given the confined anatomy of the elbow, surgical planning must balance complete tumor resection with preservation of surrounding neurovascular structures.[7]

Arthroscopic soft tissue clearance followed by planned open osteochondroma excision was selected, as arthroscopic management may not be suitable for all intraarticular osteochondromas, particularly when lesion characteristics raise concerns regarding complete and safe resection.[9]

CONCLUSION

The concurrent occurrence of synovial chondromatosis and distal humeral osteochondroma of the elbow is exceptionally rare and may cause significant pain, mechanical blockage, and restricted motion in young athletes. Accurate radiological assessment is essential for diagnosis and treatment planning. In this case, arthroscopic synovectomy with removal of rice bodies provided effective initial management, while staged open excision of the osteochondroma was planned to ensure safe and complete resection. This case highlights the importance of individualized surgical planning and rehabilitation in achieving optimal functional recovery and return to sporting activity.

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