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Occurrence and significance of elevated D-dimer levels in different types of osteomyelitis: a clinical study

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Abstract. – OBJECTIVE: Plasma D-dimer levels >0.5 mg/L are encountered in various conditions besides venous thromboembolism (VTE). Recent studies use them as a prognostic indicator for systemic and inflammatory diseases. The clinical significance of abnormal levels is unclear in osteomyelitis patients with baseline elevation. Our study reviews the occurrence and significance of >0.5 mg/L D-dimer levels in different types of osteomyelitis.

PATIENTS AND METHODS: This study involved 125 individuals, out of which 94 were male and 31 were female. The patients were divided into two groups based on the results of bacterial culture testing. Group A comprised those who tested positive for bacterial culture, while group B included those who tested negative. Out of 68 samples tested, 56% were found to have *Staphylococcus aureus*. All 125 patients underwent blood testing, which included measuring the D-dimer levels, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), and MHR monocyte to high-density lipoprotein cholesterol (HDL-C) ratio in different types of osteomyelitis. The statistical analysis of these tests was carried out.

RESULTS: Although there were no significant differences in white blood cell (WBC) count, Neutrophil count, Lymphocyte count, or erythrocyte sedimentation rate (ESR) as well as the NLR, PLR, LMR, MHR, HDL-C ratio. The C-reactive protein (CRP) levels were significantly higher in group A (26.13±50.30) than in group B (10.76±18.70) ($p<0.05$). D-dimer levels were elevated in 40.8% of patients with bacterial culture-positive osteomyelitis, negative culture osteomyelitis, implants with fractures, and no trauma osteomyelitis. No correlation was found between the increase in D-dimer levels and the presence of bacterial culture or implant-related osteomyelitis in patients.

CONCLUSIONS: No significant correlation was found between D-dimers and osteomyelitis, including positive bacterial cultures, implant-related osteomyelitis, or osteomyelitis without trauma. However, 40% of the patients had higher D-dimer levels.

Key Words:
Osteomyelitis, D-dimers, Orthopedic implants, Bacterial culture, Fractures.

Introduction

Osteomyelitis is a bone inflammatory condition caused by an infection, which can be acute or chronic. Symptoms of acute osteomyelitis include fever, pain, and edema. Chronic osteomyelitis is characterized by necrotic bone and fistulous tracts. The condition is classified as hematogenous or non-hematogenous. Diagnosis involves imaging, laboratory findings, bone biopsy, and microbial cultures. Diabetes mellitus and cardiovascular disease increase the overall risk of osteomyelitis[1-3]. Osteomyelitis pathogens vary with age. *Staphylococcus aureus* is the most common cause of acute and chronic hematogenous osteomyelitis in both adults and children. Group A streptococcus, *Streptococcus pneumoniae*, and *Kingella kingae* are children's next most common pathogens. Group B streptococcal infection primarily affects newborns, while *S. aureus* is the most common pathogen in adults. Methicillin-resistant *Staphylococcus aureus* (MRSA) is increasingly isolated in patients with osteomyelitis. Fungal and mycobacterial infections are uncommon and generally found in patients with impaired immune function[4-6]. D-dimer is a protein fragment in plasma that can indicate the presence of venous thromboembolism (VTE), with levels above 500 ng/mL being considered "positive". Normal levels rule

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out VTE, while high levels can suggest VTE or other conditions such as cancer, sepsis, infection, trauma, and massive bleeding. Further evaluation is necessary to determine the underlying cause of elevated D-dimer levels[7-13]. D-dimer levels increase due to infection-induced inflammation in sepsis[14]. Systemic inflammation is increasingly recognized as a key factor in the development of atherosclerosis; several biomarkers, including neutrophil to lymphocyte ratio (NLR), MHR, and platelet to lymphocyte ratio (PLR), have been identified as important indicators of this process[15-21]. Leukocyte subtypes, such as NLR, PLR, lymphocyte-to-monocyte ratio (LMR), and MHR indexes, are useful markers of systemic inflammation[22]. Our study aimed to analyze D-dimer levels in different groups of patients diagnosed with osteomyelitis and determine the clinical significance of D-dimer levels in various types of disease. Our primary hypothesis is whether there is any significant correlation between the levels of D-dimers and different types of osteomyelitis.

Patients and Methods

Study Design

This study was designed as a prospective observational study. Initially, 233 patients were selected between September 2019 and January 2023, out of which 125 were diagnosed with osteomyelitis, making them eligible for the study. The data was collected from the hospital's database. Patients were observed according to the hospital protocols. Out of the 125 selected patients, 17 had osteomyelitis due to trauma and fractures, while the remaining 108 had osteomyelitis without any related trauma. We retrospectively reviewed clinical, laboratory, and imaging data of inpatients to identify clinical identifiers associated with high plasma D-dimer levels. Patients were categorized into four groups based on plasma D-dimer levels and clinical diagnoses. The medical records of all patients were reviewed 60 days after discharge to identify new clinical diagnoses related to elevated plasma D-dimer levels and patient mortality. Furthermore, the patients were divided into bacterial culture-positive and negative osteomyelitis. Repeat plasma D-dimer levels were not obtained as part of routine follow-up. All study patients completed the post-discharge follow-up through in-person clinic follow-up or telephone.

Inclusions

All of the patients included in the study were between the ages of 18 and 65 and met the diagnostic criteria for osteomyelitis. Radiological studies, such as X-rays and CT scans, as well as complete blood reports, pathological and histological studies, and bacterial cultural studies, were evaluated. Additionally, patients with trauma fractures who underwent open reduction and internal fixation implant procedures were also included.

Exclusions

Patients with pediatric orthopedic trauma, patients above 65 years of age, patients with cardiac implants and congenital or ischemic heart diseases, neurosurgery-related patients with brain implants and stroke patients, patients with congenital vascular diseases or patients who use anticoagulants, and patients with lung or kidney diseases were excluded from the study.

Statistical Analysis

The study presented numerical data as both numbers and proportions. Continuous variables were expressed as mean values accompanied by their standard deviation. To compare categorical and continuous variables, we employed statistical methods such as χ^2, Student's *t*-test (for normally distributed data), and Mann-Whitney U test (for non-normally distributed data). A statistically significant value was $p<0.05$. All data analysis and figures were processed using GraphPad Prism 9.5.1. (San Diego, CA, United States).

Results

Demographics

In this study, a total of 125 patients were included, out of which 94 were male and 31 were female. Eight of them were diagnosed with diabetes mellitus, four had congenital heart diseases, eight had hypertension, and two were smokers. The patients were then divided into two groups: bacterial culture-positive (group A) and bacterial culture-negative (group B). Group A had 68 patients with positive bacterial culture results, while group B had 57 patients with negative results. The average age of patients in group A was 46.50±14.80, and in group B was 45.14±15.86. The gender composition, average age, and body mass index (BMI) of the two groups showed no significant differences, except that group A

Table I. Patients' characteristics.

	Bacterial culture positive	Bacterial culture negative	t/χ^2	*p*
Num.	68	57		
Male/Female	55/13	39/18	2.58	0.108
Age	46.50 ± 14.80	45.14 ± 15.86	0.49	0.621
BMI	22.43 ± 2.93	23.09 ± 3.07	-1.23	0.153
Systematic disease (%)				
DM	8 (12)	0 (0)		
CHD	2 (3)	2 (4)		
Hypertension	3 (4)	5 (9)		
Smoke	2 (3)	0 (0)		
Location (%)				
Patella	1 (1)	0 (0)		
Femoral	14 (21)	12 (21)		
Tibial	29 (43)	25 (44)		
Fibular	5 (7)	0 (0)		
Metatarsal	3 (4)	3 (5)		
Calcaneus	8 (12)	7 (12)		
Pelvic	1 (1)	1 (2)		
Humeral	2 (3)	3 (5)		
Radial	2 (3)	0 (0)		
Metacarpal	0 (0)	1 (0)		
Clavicle	1 (1)	2 (4)		
Vertebral	2 (3)	3 (5)		
With/Without Implants	42/31	26/26		0.468

Body mass index (BMI), Diabetes mellitus (DM), congenital heart diseases (CHD).

had 12% diabetic patients while the comparative group had none. Both groups showed a similar proportion of location of osteomyelitis, with the femur and tibia being the most susceptible (65% and 66%, respectively). For bacterial culture-positive patients, 42 of them had implants, while 31 of them did not. The same was observed for patients with positive culture osteomyelitis, where 26 patients had implants and 26 patients did not, as seen in Table I.

In our study of 68 samples, *Staphylococcus aureus* was found in 56%, making it the most common cause of bacterial osteomyelitis. Clinical patterns have unique characteristics, risk factors, presentation, and etiology. Regardless of the mechanism, *Staphylococcus aureus* is the most common organism causing osteomyelitis[23-25], Table II, Figure 1.

The study used a Student *t*-test to analyze the white blood cells (WBC), Neutrophils, Lymphocytes, Monocytes, HDL-C, NLR, PLR, LMR, and MHR. The Mann-Whitney U test was used to examine erythrocyte sedimentation rate (ESR) and C-reaction protein (CRP). Similarly, no significant differences were found in the WBC, Neutrophils, Lymphocytes, Monocytes, or ESR. Although the mean NLR, PLR, and LMR were higher in the bacterial culture-positive group, none of these ratios showed any significant differences between the two groups. However, the CRP level of the bacterial culture positive group (26.13±50.30) was found to be significantly higher than that of the bacterial culture negative group (10.76±18.70), with a *p*-value of less than 0.05 (Table III, Figure 2a-b).

According to this study, 25% of patients (31 patients) with bacterial culture-positive osteomyelitis, 16% of patients (20 patients) with negative culture osteomyelitis, 22% of patients (28

Table II. Bacterial culture results.

Bacteria	No. (%)
Staphylococcus aureus	38 (56)
Pseudomonas aeruginosa	9 (13)
Klebsiella pneumoniae	6 (9)
Staphylococcus epidermidis	6 (9)
E. coli	3 (4)
Staphylococcus haemolyticus	1 (1)
Enterococcus avium	1 (1)
Enterococcus faecalis	1 (1)
Acinetobacter baumannii	1 (1)
Citrobacterium freudii	1 (1)
Tuberculosis	1 (1)

Staphylococcus aureus shows the highest value in the culture outcome (56% out of 68).

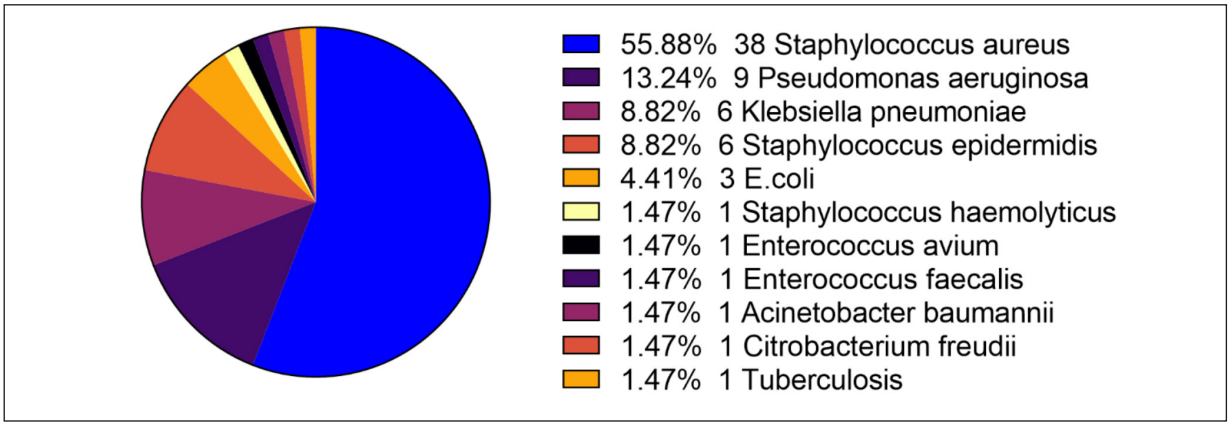

Figure 1. Pie chart showing bacterial culture proportion out of 68 cultured samples.

Table III. Blood test of osteomyelitis patients.

	Bacterial culture positive	Bacterial culture negative	*t/u*	*p*
WBC (*10^3/L)	7.08 ± 2.18	6.34 ± 2.05	1.93	0.056
Neutrophil (%)	61.77 ± 10.97	58.14 ± 9.19	1.96	0.052
Lymphocyte (%)	26.65 ± 12.06	26.10 ± 11.75	0.21	0.836
Monocyte (%)	7.61 ± 3.02	8.32 ± 3.19	1.017	0.312
ESR (mm/h)	26.55 ± 28.72	18.69 ± 24.03	1466	0.094
CRP (mg/L)	26.13 ± 50.30	10.76 ± 18.70	1407	0.012
HDL-C (mmol/L)	1.14 ± 0.12	1.11 ± 0.12	1.055	0.295
NLR	2.71 ± 2.45	2.247 ± 0.92	1.10	0.276
PLR	115.7 ± 52.07	98.91 ± 44.42	1.55	0.126
LMR	4.50 ± 2.99	4.00 ± 1.78	0.895	0.373
MHR	0.44 ± 0.19	0.45 ± 0.21	0.346	0.730

NLR: neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, LMR: Lymphocyte to monocyte ratio, MHR: monocyte to high-density lipoprotein cholesterol HDL-C ratio.

patients) with implants with fractures, and 18% of patients (23 patients) without any trauma osteomyelitis had elevated levels of D-dimers. The data was analyzed using the Chi-square test, and it found there is no correlation between the increase in D-dimer levels and bacterial culture or implant-related osteomyelitis patients. Out of 125 osteomyelitis patients, 51 patients showed D-dimer levels above 0.5 mg/L, as shown in Table IV and Figure 3.

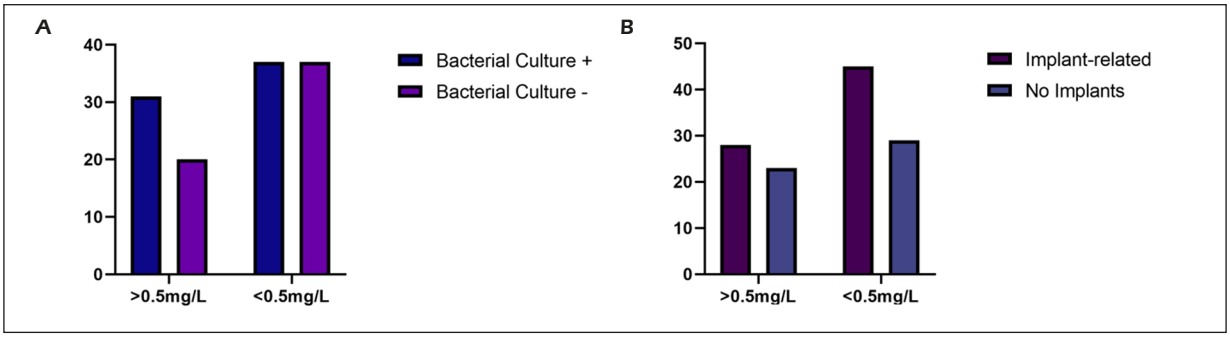

Figure 2. **A**, The D-dimer ratio in a bacterial culture osteomyelitis patients' group. **B**, The D-dimer ratio in implant-related osteomyelitis patients' group.

Table IV. The ratio of D-dimer values in positive culture osteomyelitis and negative culture osteomyelitis.

	D-D			
	> 0.5 mg/L	< 0.5 mg/L	χ^2	*p*
			1.416	0.117
Bacterial culture positive	31	37		
Bacterial culture negative	20	37		

The D-D of osteomyelitis patients were tested according to bacterial culture results. The Chi-square test showed that the rise of the D-D value had no correlation with bacterial culture.

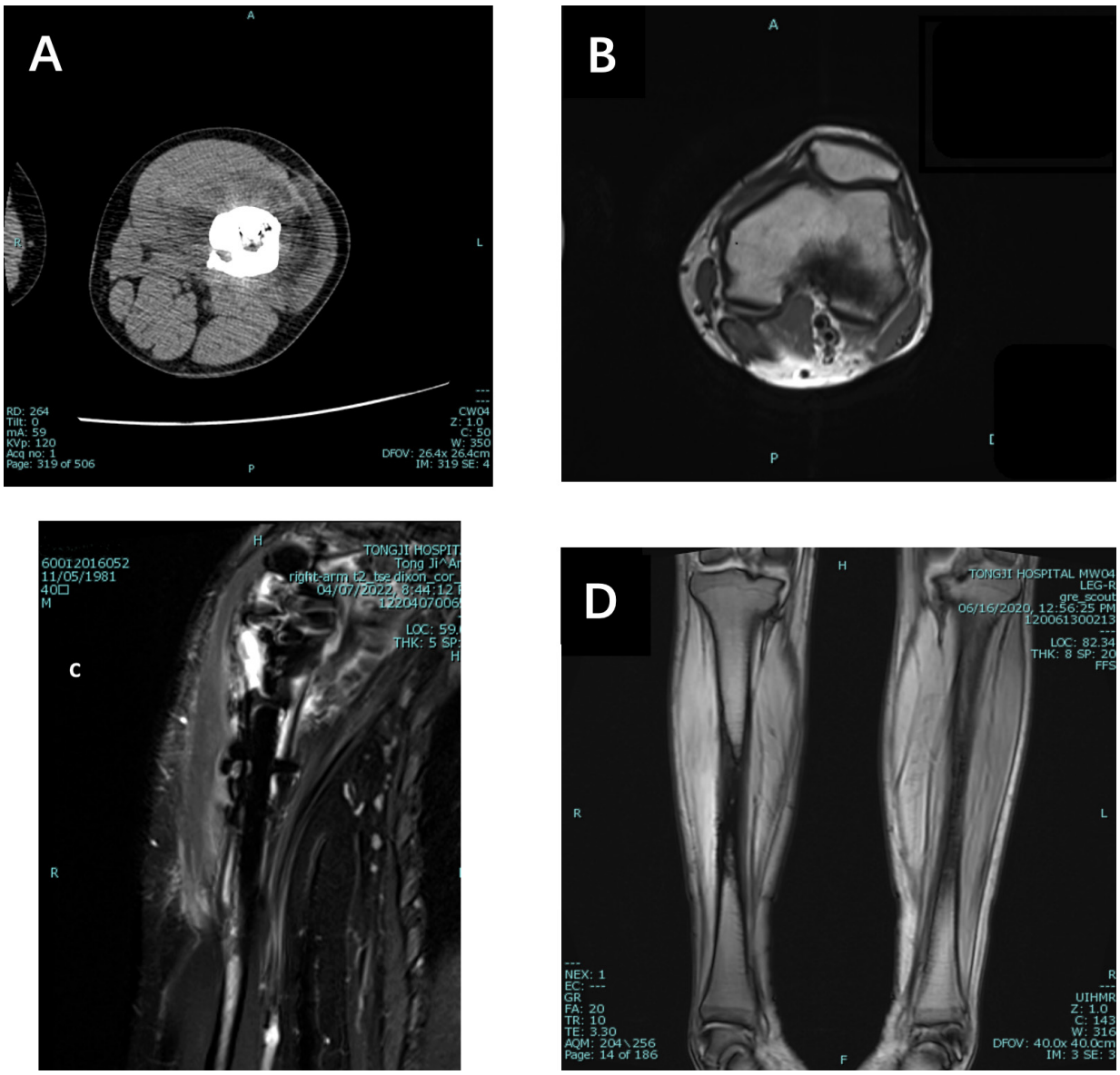

Figure 3. MRI SCANS of patients diagnosed with osteomyelitis (OM). **A**, Positive bacterial culture with Implant (OM). The left femur was irregularly shaped with calluses, striated low-density shadows between metal fixation and thickened bone cortex, and no callus covering was observed in front of local fixation. **B**, (+) Bacterial culture with Implant (OM): an abnormal signal shadow in the distal left femur bone. **C**, (-) bacterial culture with implant (OM): showing Local edema of the right humerus head and neck. **D**, (-) bacterial culture with implant (OM): showing an abnormal flaky signal in the middle of the right tibia.

Discussion

Our primary hypothesis, which suggested a strong correlation between different types of osteomyelitis and higher levels of D-dimers, was not supported by the results of our study. However, we did note raised levels of D-dimers among 40% of the patients in our study. This finding suggests that D-dimer levels may be important in osteomyelitis patients and could indicate other systemic conditions or infections. Ma et al[26] found a 4.05% prevalence of venous thromboembolism (VTEs) in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) patients during an active stage but no correlation with D-dimer levels. Borowiec et al[27] found no difference in D-dimer concentrations between VTE patients and non-VTE patients. However, patients with granulomatosis with polyangiitis had elevated D-dimer levels associated with disease activity and inflammation rather than the risk of venous thromboembolism. D-dimer levels were more consistently associated with functioning than inflammatory markers serum amyloid A (SAA), fibrinogen, and CRP[28]. D-dimer levels may reflect unmeasured factors associated with impaired function. This mechanism may also apply to CRP and lower extremity function[29-31]. A high level of plasma D-dimer (>5,000 μg/L) is strongly linked with serious illnesses, such as VTE, cancer, or infection, in 93% of participants, according to a study by Schutte et al[32]. The study participants were diagnosed with VTE (40%), cancer (29%), infection, or sepsis (24%), while other rare conditions were also reported. The study highlights the need for thorough investigation and increased suspicion in patients with elevated D-dimer levels. Six Chinese studies had predominantly East Asian patients. D-dimer levels varied by race, including African American and Caucasian patients. It is suspected that East Asian populations could also have different D-dimer levels, but there is no supporting evidence[33-35]. Li et al[36] found poor diagnostic accuracy of D-dimer in subgroups with thrombosis malignancies, autoimmune diseases, pregnancy, and heart and brain vascular diseases. According to recent studies[37-41] certain biomarkers such as NLR, PLR, LMR, MHR, and HDL-C ratio are associated with systemic inflammatory conditions like atherosclerosis, lower extremity arterial disease, nonalcoholic fatty liver disease, ischemic stroke, and acute coronary syndrome (ACS). These biomarkers have shown positive results in the diagnosis of such inflammatory conditions. In our study, the mean values of NLR, PLR, and LMR were found to be higher in the bacterial culture-positive group, but there were no significant differences in these ratios between patients with bacterial cultured and non-bacterial osteomyelitis. Although our study found raised levels of D-dimers in osteomyelitis patients, there is not sufficient evidence to support the use of D-dimers levels as a reliable diagnostic tool for this condition. Elevated D-dimer levels may indicate the presence of other systemic diseases or bacterial and non-bacterial infections. Further studies are needed to confirm the correlation between osteomyelitis and D-dimers. Large sample size studies are required to compare patients with and without osteomyelitis and the absence of other systemic diseases.

Limitations

The study has some limitations, including a small sample size and the inclusion of patients with other systemic diseases like diabetes mellitus, hypertension, and smokers. These factors may have influenced the levels of d-dimers in the blood. Additionally, the study was limited by variability in race, age range, and sex ratio. It is worth noting that Shahi et al[42] reported that premature antibiotic treatment could also affect the results of D-dimer in the blood.

Conclusions

Our research found that patients with osteomyelitis have increased D-dimer levels, which may indicate bone inflammation. However, high D-dimer levels can also signify other systemic diseases. No correlation between osteomyelitis types and D-dimer levels was established. Despite being an inflammatory disease, our study did not find a significant correlation between D-dimer levels and osteomyelitis patients.

Ethics Approval

The Ethics Committee of Tongji Hospital Wuhan approved this study on January 6th, 2024, with registration number TJ-IRB202401006. The author declares that the methods carried out in this study were based on the relevant guidelines and regulations. The study was conducted in accordance with the Declaration of Helsinki.

Informed Consent
All the research participants went through a comprehensive informed consent, and all the patients agreed to participate in the research study.

Conflict of Interest
The authors declare no conflicts of interest.

Funding
No funding was granted or received for this study.

Availability of Data and Materials
On reasonable request, the corresponding authors can provide further data regarding the study.

Authors' Contributions
The title, abstract, introduction, discussion, and results sections of the study were written by Khan Akhtar Ali; data collection, statistical analysis, and writing of the results section were carried out by Ling Xiaohe, Weikai Zhang assisted with data correction and collection. The study was reviewed by Huang Hui and Wenkai Li, who also served as the corresponding authors.

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