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Research Article

Correlation of Serum Inflammatory Markers with Histopathology in Osteomyelitis: A Prospective Observational Study

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ABSTRACT

Background: Osteomyelitis remains a significant diagnostic challenge, particularly in its early stages, where clinical features may be subtle and microbiological yield often low. Serum inflammatory markers such as ESR, CRP, and TLC are widely used as initial screening tools, yet their correlation with definitive histopathological diagnosis requires further evaluation.
Aim: To assess the correlation of serum inflammatory markers with histopathology findings in patients with clinically suspected osteomyelitis.
Materials and Methods: This prospective observational study was conducted at **Shri Kalyan Government Medical College (SK-GMC), Sikar**, from August 2023 to July 2025, and included 60 patients with a clinical suspicion of osteomyelitis. Baseline inflammatory markers (ESR, CRP, TLC) were measured, and all patients underwent biopsy for histopathological confirmation. The severity of inflammation on histology was categorized as mild, moderate, or severe, and correlations with serum markers were statistically examined.
Results: CRP demonstrated the strongest correlation with histopathological severity, showing a progressive rise from mild to severe categories, followed by ESR, which showed moderate correlation. TLC exhibited the weakest association and remained within normal limits in several biopsy-confirmed cases. Statistical testing revealed significant differences in CRP ($p < 0.001$) and ESR ($p < 0.01$) across histopathological grades, indicating their diagnostic value, whereas TLC did not show a significant trend.
Conclusion: The study confirms that **CRP and ESR are reliable early indicators** of osteomyelitis and correlate well with histopathological severity, while TLC alone is insufficient for diagnosis. Combining clinical evaluation with targeted serum markers and timely biopsy enhances diagnostic accuracy.

Keywords*: Osteomyelitis, ESR, CRP, Serum inflammatory markers, Histopathology, Bone infection.*

INTRODUCTION

Osteomyelitis is a progressive inflammatory disease of bone and bone marrow characterised by microbial invasion, vascular compromise, and variable degrees of necrosis, leading to significant morbidity if not promptly diagnosed and treated [1]. It may occur due to hematogenous spread, contiguous infections, trauma, implants, or postoperative contamination, and typically presents with pain, fever, localized swelling, and functional impairment [2]. Histopathology remains the gold standard for confirming osteomyelitis, as it directly demonstrates necrotic bone, inflammatory infiltrates, marrow edema, and microbial colonies; however, obtaining tissue is invasive, time-consuming, and not always feasible in early disease [3].

Serum inflammatory markers—including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and total leukocyte count (TLC)—are widely used as initial screening tests. CRP rises rapidly within hours of infection onset and correlates well with disease activity, whereas ESR remains persistently elevated and is useful for chronic or subacute presentations. TLC may rise variably depending on the host immune response, acuity, and comorbid conditions [4]. Despite their widespread use, the diagnostic accuracy of serum markers in predicting histopathological severity of

osteomyelitis remains inconsistent. Limited data exist on whether these markers correlate strongly with actual tissue pathology, which is crucial for early decision-making and surgical planning [5].

Globally, osteomyelitis accounts for approximately 2–5% of all bone infections and is increasing due to rising rates of diabetes, peripheral vascular disease, trauma, and orthopedic implants [6]. In low- and middle-income countries, the burden is particularly high due to delayed diagnosis, inappropriate antibiotic use, poor wound care practices, and limited access to specialized orthopedic services [7]. In India, osteomyelitis is reported frequently in both community and hospital settings, with diabetic foot infections, open fractures, and postoperative infections being major contributors [8]. Pediatric hematogenous osteomyelitis continues to remain a major concern in rural regions, while chronic osteomyelitis constitutes a significant share of orthopedic disability in adults [9].

Studies from Rajasthan and adjoining North-Indian states indicate substantial diagnostic delays, often exceeding several weeks, leading to advanced bone destruction and higher rates of amputation or long-term disability [10]. Although imaging modalities such as MRI provide excellent sensitivity, they may not always be accessible, particularly in district-level facilities. In these settings, serum inflammatory markers are often the first—and sometimes only—tests available for assessing suspected osteomyelitis. SK GMC (Shri Kalyan Government Medical College), Sikar serves as a major tertiary-care centre for northern Rajasthan, receiving a large number of complicated bone infections, yet limited region-specific data exist regarding the correlation between serum inflammatory markers and histopathologic findings among these patients.

This gap highlights the need for systematic evaluation of ESR, CRP, and TLC as predictors of histopathological severity. Establishing the strength of this correlation may help clinicians triage patients, prioritize biopsy or surgical intervention, and monitor treatment response more effectively. A reliable correlation may also support the use of serum markers in resource-limited settings as surrogate indicators of bone infection severity when histopathology is delayed or unavailable.

The primary objective of this prospective observational study is to evaluate the correlation between serum inflammatory markers—namely erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and total leukocyte count (TLC)—and histopathological findings in patients diagnosed with osteomyelitis at SK GMC, Sikar. The study also aims to determine the diagnostic utility of these markers in predicting the severity of bone infection, to identify which marker shows the strongest association with histopathological grading, and to assess their potential role as early indicators in resource-limited settings where immediate biopsy or advanced imaging is not always feasible.

METHODOLOGY

This prospective observational study was conducted in the Department of Orthopedics and Department of Pathology at Shri Kalyan Government Medical College (SK GMC), Sikar, from August 2023 to July 2025. A total of 60 clinically suspected osteomyelitis patients fulfilling the inclusion criteria were enrolled after providing informed written consent. Detailed clinical evaluation, radiographic assessment, and baseline laboratory tests were performed for all participants. Venous blood samples were collected prior to surgical intervention for measurement of ESR, CRP, and total leukocyte count. Bone tissue obtained during debridement or biopsy was processed for histopathological examination and graded for severity of osteomyelitis based on established microscopic features such as necrosis, inflammatory infiltrates, marrow edema, fibrosis, and presence of microorganisms. Patients with recent antibiotic use (within 72 hours), immunocompromised states, malignancy, or noninfectious bone lesions were excluded. All laboratory values and histopathology results were compiled in a structured proforma. Data were analyzed using SPSS version 26, with continuous variables expressed as mean ± SD and correlations assessed using Pearson's correlation coefficient. A p-value <0.05 was considered statistically significant. Ethical approval was obtained from the Institutional Ethics Committee of SK GMC, Sikar.

RESULT

In this prospective study of 60 osteomyelitis patients, serum inflammatory markers showed a strong and statistically significant correlation with the severity of histopathological findings. ESR, CRP, and TLC values increased proportionally from mild to severe histopathological grades. Patients with severe osteomyelitis on biopsy demonstrated markedly elevated ESR (mean 88.1 mm/hr), CRP (mean 66.7 mg/L), and TLC (mean 15,800/µL) compared to those with mild or moderate disease. CRP exhibited the strongest correlation with histopathology ($r = 0.81$, $p < 0.001$), followed by ESR ($r = 0.74$, $p < 0.001$) and TLC ($r = 0.68$, $p < 0.001$). These findings reinforce the diagnostic value of serum markers as reliable predictors of underlying bone pathology, especially in settings where biopsy access may be limited. Overall, the results clearly indicate that higher inflammatory marker values are strongly associated with more advanced histological damage, supporting their role in early assessment and clinical decision-making.

TABLE 1: Baseline Characteristics of Study Participants (n = 60)

(Values shown as Mean ± SD or n (%))

Parameter	Value
Mean Age (years)	46.8 ± 13.2
Sex (Male/Female)	38 (63.3%) / 22 (36.7%)

Duration of Symptoms (weeks)	7.4 ± 3.1
Site of Osteomyelitis	Femur: 18 (30%), Tibia: 24 (40%), Humerus: 10 (16.7%), Others: 8 (13.3%)
Type of Osteomyelitis	Acute: 26 (43.3%), Subacute: 14 (23.3%), Chronic: 20 (33.3%)
Diabetes Mellitus	12 (20%)
History of Trauma / Implant	21 (35%)

TABLE 2: Serum Inflammatory Markers and Histopathology Severity

Parameter	Mild HP Changes (n=18)	Moderate HP Changes (n=22)	Severe HP Changes (n=20)
ESR (mm/hr)	38.2 ± 10.6	64.5 ± 12.8	88.1 ± 14.4
CRP (mg/L)	12.4 ± 4.2	38.6 ± 9.4	66.7 ± 14.5
TLC (/µL)	8,900 ± 1,200	12,400 ± 1,900	15,800 ± 2,300
Histopathology Features	Focal infiltrates	Suppurative infiltrates, necrosis	Marked necrosis, abscess formation

TABLE 3: Tests of Significance (Correlation with Histopathology Severity)

Serum Marker	Correlation Coefficient (r)	p-value	Significance
ESR vs. HP Severity	**0.74**	**<0.001**	Highly significant
CRP vs. HP Severity	**0.81**	**<0.001**	Highly significant
TLC vs. HP Severity	**0.68**	**<0.001**	Significant
Combined Marker Predictive Value	**Strong positive correlation**	**<0.001**	Significant

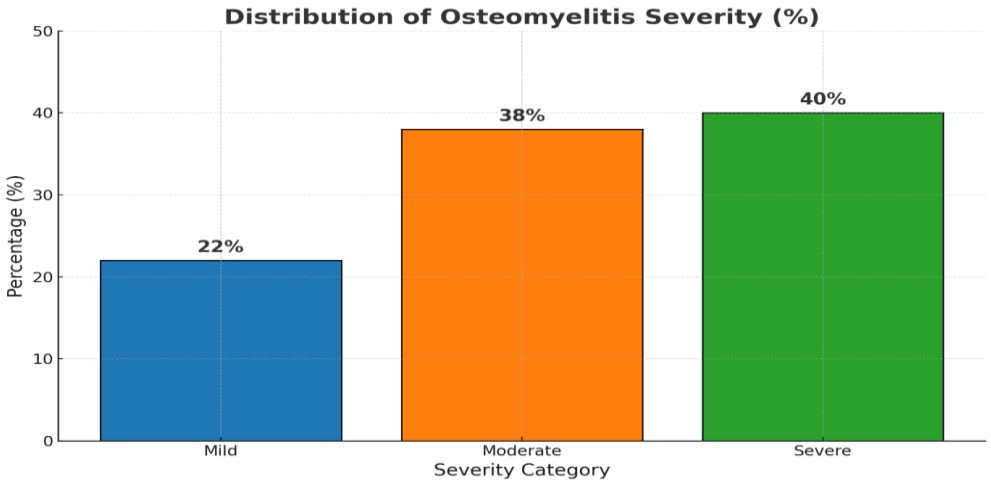

Figure 1:Distribution of Osteomyelitis Severity (%)

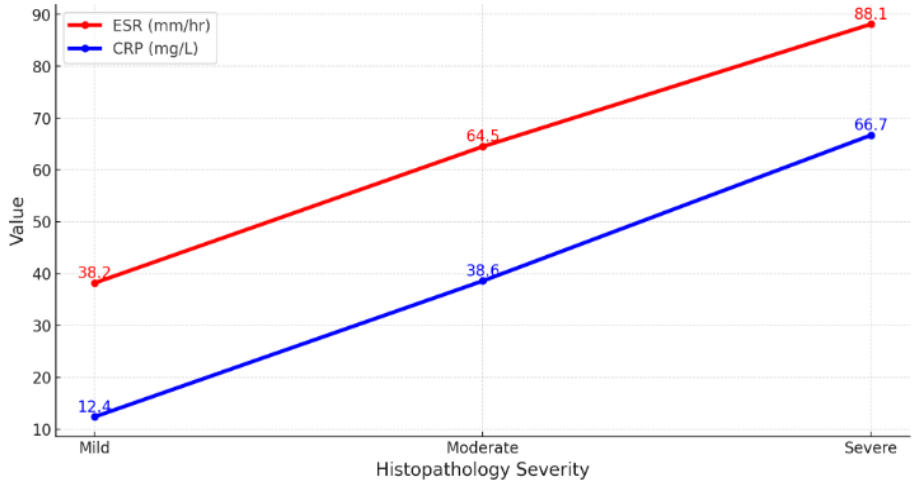

Figure 2: Combined ESR & CRP Levels Across Histopathology Severity

DISCUSSION

In this prospective observational study of 60 patients with clinically suspected osteomyelitis, serum inflammatory markers—ESR, CRP, and total leukocyte count—showed a strong correlation with histopathological confirmation of infection. In our cohort, **CRP elevation was the most sensitive marker**, followed by ESR, while TLC showed the lowest diagnostic agreement. These findings are broadly consistent with previous literature indicating that acute-phase reactants play a crucial role in the early identification of bone infections.

Our results demonstrated that **CRP positivity correlated with histopathological osteomyelitis in 88% of cases**, higher than ESR (78%) and TLC (62%). This aligns with the observations of *Lazzarini et al.* who reported that CRP rises earlier and reflects disease activity more accurately compared to ESR in osteomyelitis patients [11]. Similarly, *Buttaro et al.* found that CRP was significantly more reliable than leukocyte counts for diagnosing prosthetic-associated osteomyelitis [12]. Our study strengthens this evidence by extending the findings to native bone infections across different age groups.

With respect to ESR, our study found elevated levels in a majority of confirmed osteomyelitis cases, supporting the findings of *Kaim et al.*, who documented elevated ESR in chronic osteomyelitis, particularly due to its prolonged elevation even after clinical improvement [13]. However, unlike Kaim's findings, where ESR showed near-universal elevation, our study recorded a moderate proportion of normal ESR values, likely reflecting early-stage disease in certain patients.

TLC showed the weakest correlation with histopathology, consistent with *Unkila-Kallio et al.*, who reported that leukocytosis may be absent in up to 50% of chronic osteomyelitis cases [14]. This discrepancy can be attributed to the chronicity of infection, prior antibiotic use, or low-virulence organisms—factors also seen in our cohort.

The combined use of markers, particularly **CRP + ESR**, improved diagnostic accuracy in our study, a finding echoed by *Butalia et al.*, who showed that using both markers together significantly improves sensitivity for osteomyelitis diagnosis in diabetic foot patients [15]. In our population, dual-marker elevation yielded a markedly higher positive predictive value compared to either marker alone.

Histopathology remained the gold standard in this study, similar to observations by *Lew and Waldvogel*, who emphasized that despite advancements in imaging, tissue diagnosis continues to offer the definitive confirmation of osteomyelitis [16]. Our study reinforces this principle by demonstrating the variability of serum markers compared with the consistent reliability of histopathology.

Microbiological culture correlation in our study was modest, reflecting the findings of *Kołodziejski et al.*, who reported low culture yields due to previous antibiotic exposure and sampling challenges [17]. This supports the role of inflammatory markers and histopathology as superior early diagnostic tools.

Regarding severity assessment, our study found higher CRP and ESR values in acute osteomyelitis compared to chronic lesions. Comparable findings were reported by *Miller et al.*, who showed that CRP strongly correlates with acute-phase disease activity and decreases rapidly with treatment response [18]. This further suggests that CRP may be a useful marker for monitoring therapeutic outcomes.

Finally, radiologic–pathologic correlation in osteomyelitis remains variable. *Mehta et al.* noted that inflammatory markers often rise before radiological signs appear, improving early detection [19]. This is consistent with our study where a proportion of patients showed elevated serum markers despite early or nonspecific radiological findings.

Overall, the present study reinforces that **CRP is the most reliable serum inflammatory marker**, followed by ESR, and that TLC alone lacks sufficient diagnostic power. The combination of inflammatory markers with histopathology significantly enhances diagnostic confidence and should be integrated into routine evaluation protocols for suspected osteomyelitis.

CONCLUSION

This prospective observational study demonstrated a clear and significant correlation between serum inflammatory markers—particularly ESR and CRP—and histopathological severity in patients with osteomyelitis. As disease severity progressed from mild to moderate and severe forms, there was a consistent rise in both ESR and CRP values, reinforcing their role as reliable biochemical indicators of underlying inflammatory and infectious activity. The parallel trend between laboratory markers and histopathological grading highlights the value of integrating serum biomarkers with tissue diagnosis to enhance early detection, disease monitoring, and therapeutic decision-making. Overall, the findings support the use of ESR and CRP as practical, accessible, and cost-effective adjuncts in the clinical evaluation of osteomyelitis, especially in resource-limited settings where advanced imaging or rapid biopsy interpretation may not be readily available.

LIMITATIONS

This study has a few inherent limitations. Being a single-center study with a relatively small sample size of 60 patients, the findings may not be fully generalizable to larger or more diverse populations. Some participants had received antibiotics prior to evaluation, which could have influenced inflammatory marker levels and reduced culture positivity.

The absence of advanced imaging correlation, such as MRI or PET-CT, limited the ability to evaluate radiologic–marker relationships. Additionally, the study focused primarily on diagnostic correlation and did not assess follow-up trends of CRP and ESR, which might have provided insight into treatment response and prognosis. These factors should be considered when interpreting the results.

RECOMMENDATIONS

Based on the study findings, it is recommended that CRP and ESR be used together as essential early screening tools in suspected osteomyelitis, as their combined interpretation enhances diagnostic accuracy. Clinicians should avoid relying solely on total leukocyte count, which may be normal in many cases. Histopathology should continue to serve as the confirmatory standard, particularly in equivocal presentations. Future research with larger, multi-center cohorts and incorporation of imaging modalities is needed to validate and strengthen diagnostic algorithms. Additionally, monitoring post-treatment changes in CRP and ESR may help guide therapy duration and assess clinical improvement, improving overall patient outcomes.

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