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Association of pre-biopsy inflammatory indices with prosthetic joint infection after megaprosthetic reconstruction for osteosarcoma

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ABSTRACT

Aims: Prosthetic joint infection (PJI) is a challenging disease associated with substantial patient disability and high treatment costs. This study aimed to evaluate the association between inflammatory markers measured in pre-biopsy blood samples and PJI in patients with osteosarcoma.

Methods: This retrospective study included 48 patients with osteosarcoma who underwent neoadjuvant chemotherapy followed by resection prosthesis at a tertiary care centre between January 2020 and October 2023. PJI was observed in 7 patients (14.6%) during the 12-month follow-up period, and the diagnosis was established in accordance with the 2018 Musculoskeletal Infection Society criteria. Blood samples collected before biopsy were analyzed for a comprehensive set of inflammatory markers, including white blood cell count, erythrocyte sedimentation rate, C-reactive protein, mean platelet volume, red blood cell distribution width, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), Systemic Immune-Inflammation Index (SII), Systemic Inflammation Response Index (SIRI), and pan-immune-inflammation value.

Results: PJI occurred in 7 patients (14.6%), while 41 patients (85.4%) did not develop PJI. There were no significant differences between the two groups in terms of age, body-mass index, gender, affected extremity, or prosthesis location ($p>0.05$). Patients with PJI had significantly higher NLR (3.9±0.8 vs. 2.0±0.7, $p<0.001$), PLR (227.5±131.7 vs. 150.0±60.1, $p=0.024$), SII (1172.1±435.2 vs. 561.1±228.1, $p<0.001$), SIRI (2.2±0.6 vs. 1.3±0.6, $p=0.001$), and pan-immune-inflammation value (PIV) (923.9±124.0 vs. 424.4±133.3, $p<0.001$) compared to patients without PJI. In receiver operating characteristic analysis for PIV value, a cutoff of >570.6 was associated with PJI, with a sensitivity of 100% and specificity of 97.6% (AUC 0.979, 95% CI 0.889-0.999; $p<0.001$).

Conclusion: Pre-biopsy blood levels of NLR, PLR, SII, SIRI, and PIV were significantly associated with PJI in patients undergoing limb-sparing resection and prosthetic reconstruction for osteosarcoma; PIV and NLR showed the highest apparent sensitivity and specificity, without a significant difference between them. Given the small number of events, these findings should be considered hypothesis-generating and require validation in larger, prospective, multicentre cohorts before clinical application.

Keywords: Prosthetic joint infection, PJI, inflammatory indices, inflammatory markers, osteosarcoma, limb-sparing surgery

INTRODUCTION

Over the past decades, advances in surgical techniques, chemotherapy, imaging modalities, and preoperative planning have led to substantial improvements in the survival of patients with primary bone tumors.[1] Currently, limb-sparing procedures are the preferred surgical approach in orthopedic oncology.[2] Resection of the tumor-bearing bone followed by reconstruction with a megaprosthesis is a commonly employed approach.[3] Although megaprostheses used in tumor surgery facilitate early postoperative mobilization and rapid rehabilitation, they have been reported to carry a 5- to 10-fold higher risk of infection compared to conventional prostheses.[4,5] The incidence of infection following tumor resection prosthesis ranges from 8% to 19%, while the rate of amputation due to prosthetic infection has been reported to be considerably high, between 23.5% and 87%.[5-7] Several factors are known to raise this risk. These include a large surgical surface area, long operative times, extensive soft-tissue dissection, tumor-induced immunosuppression, and immune dysregulation.[7,8]

Tumors are known to be associated with chronic inflammation in the tumor microenvironment, which may be initiated by the presence of malignant cells.[9,10] Malignant cells trigger the release of proinflammatory mediators. Dysregulated immune cells then infiltrate the tumor in large numbers. This creates

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an immunosuppressive microenvironment that promotes angiogenesis and tumor progression. Immune dysregulation is closely associated with chronic inflammation and impaired anti-tumor immune responses. It has been increasingly recognized as one of the key factors in cancer development, progression, and prognosis.[11-13]

Recently, beyond conventional inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), novel inflammatory indices (NLR, PLR, SII, SIRI, and PIV) have been introduced and widely studied in various medical fields. They have been investigated in a wide range of conditions, including prognostic evaluation in cancer,[11-16] assessment of disease activity in rheumatologic disorders,[17] and outcome assessment in various inflammatory conditions.[18,19] Several studies have also investigated the association between preoperative inflammatory markers and the development of periprosthetic joint infection (PJI) following primary total knee arthroplasty or total hip arthroplasty.[19-21] However, we found no previous study specifically evaluating the association between pre-biopsy inflammatory markers and prosthetic joint infection after megaprosthetic reconstruction in patients with osteosarcoma. This conclusion was based on a literature search performed in PubMed, Scopus, and Web of Science (last searched in July 2026).

Identifying factors associated with infection in tumor prostheses is clinically important, as the number of limb-salvage procedures using tumor endoprostheses has progressively increased. Our hypothesis is that preoperative inflammatory markers may reflect a state of immune dysregulation associated with the potential development of postoperative prosthetic infection. Therefore, the aim of this study is to evaluate the relationship between inflammatory markers measured in peripheral blood prior to biopsy and the occurrence of prosthetic infection in patients who underwent tumor resection and reconstruction with a megaprosthesis due to osteosarcoma.

METHODS

Ethics

The ethical approval study protocol was approved by the Gaziantep City Hospital Non-interventional Clinical Researches Ethics Committee (Date: 21.05.2025, Decision No: 224/2025). The study was performed in accordance with the Declaration of Helsinki.

Study Design

The study was performed by retrospectively reviewing the records of patients who underwent tumor resection and megaprosthetic reconstruction for osteosarcoma between January 2020 and October 2023. To ensure a homogeneous study group, only patients diagnosed with osteosarcoma who received neoadjuvant chemotherapy prior to tumor resection were included. Blood samples were obtained at initial presentation, at the time patients first presented with the mass, before both biopsy and the initiation of neoadjuvant chemotherapy; this therefore represents a single, chemotherapy-naïve, pre-biopsy time point for all patients, with no repeated measurements.

The inclusion criteria were as follows: a diagnosis of osteosarcoma, receipt of neoadjuvant chemotherapy prior to tumor resection, and limb-salvage reconstruction using tumor endoprostheses. The exclusion criteria were as follows: local or systemic infection within two weeks prior to biopsy; open soft-tissue defects before biopsy; soft-tissue complications during tumor resection (such as the need for flap coverage due to inability to achieve primary wound closure); absence of neoadjuvant chemotherapy; missing postoperative follow-up data; and a follow-up period of less than one year after prosthetic surgery. All patients underwent tumor resection and megaprosthetic reconstruction following completion of a standard institutional neoadjuvant chemotherapy protocol; as noted above, the inflammatory markers analyzed in this study were obtained before chemotherapy was initiated, not immediately before surgery. Hospital records of 76 patients were retrospectively reviewed for the designated study period; 48 patients meeting the criteria were included in the study, while 28 patients who failed to attend follow-up appointments or whose data could not be obtained were excluded.

All surgeries were performed by senior orthopedic surgeons experienced in orthopedic oncology, and standardized perioperative antibiotic and rehabilitation protocols were applied. Patients were classified into two groups; those with postoperative PJI and those without PJI. PJI was diagnosed according to the 2018 Musculoskeletal Infection Society criteria defined by Parvizi et al.[22] Patients were considered infected if at least one major criterion (the presence of a sinus tract communicating with the prosthesis or two positive cultures) was met, or if the aggregate minor criteria score was ≥6. PJI was diagnosed at a mean of 6-12 months postoperatively. All patients received standardized antibiotic prophylaxis, consisting of 2 g intravenous cefazolin administered 45-60 minutes before surgical incision, followed postoperatively by intravenous ampicillin-sulbactam 2 g four times daily for 3 days. Patients diagnosed with PJI underwent surgical debridement, followed by pathogen-directed antibiotic therapy once culture and sensitivity results were available; patients who did not improve after debridement and targeted antibiotic therapy underwent revision surgery.

Patient demographics and blood parameters were obtained from the hospital data recording system. The inflammatory markers analyzed correspond to the first complete blood count obtained at the patient's initial presentation with a mass, prior to both chemotherapy and biopsy; no patient had received any chemotherapy before this sample was drawn, and only a single pre-treatment value was available and used for each patient (i.e., no repeated pre-biopsy measurements were performed or averaged). Pre-biopsy blood parameters including white blood cell count (WBC, 10^9/L; reference 4.5-11), ESR, mm/h; reference 0-15, CRP, mg/L; reference 0-5, mean platelet volume (MPV, fL; reference 9.2-12.1), red blood cell distribution width (RDW, %; reference 11.5-14.5), NLR (neutrophil-to-lymphocyte ratio), platelet-to-lymphocyte ratio (PLR), Systemic Immune-Inflammation Index (SII: neutrophil count×platelet count/lymphocyte count), Systemic Inflammation Response Index (SIRI: neutrophil count×monocyte count/lymphocyte count), and pan-immune-inflammation value (PIV: neutrophil count×platelet

count×monocyte count/lymphocyte count) were calculated and recorded. These values were compared between patients who developed PJI and those who did not. Additionally, patient characteristics at initial presentation-including affected extremity (upper or lower limb), location of the resection prosthesis (distal femur, proximal femur, proximal tibia, or femoral intercalary), gender, and body-mass index (BMI)-were recorded and compared between groups with and without PJI.

Statistical Analysis

The normality of numerical variables was assessed using the Shapiro-Wilk test. Student's t-test was used to compare normally distributed variables between two groups, whereas the Mann-Whitney U test was applied for non-normally distributed variables. Because only 7 patients developed PJI, the Mann-Whitney U test was applied to all continuous variables instead. This is a more conservative, distribution-free approach for a small subgroup. Results are still reported as mean±SD, together with the median (interquartile range), to remain consistent with prior literature on inflammatory indices. Associations between categorical variables were evaluated using the Chi-square test. Receiver operating characteristic (ROC) curve analysis was employed to determine optimal cutoff values, calculate the area under the curve (AUC), and compare diagnostic performances of variables. ROC analysis and all pairwise AUC comparisons using the DeLong method were performed for all five inflammatory indices (NLR, PLR, SII, SIRI, and PIV), regardless of statistical significance, for completeness and transparency. Sensitivity and specificity 95% confidence intervals (CIs) were calculated using the Clopper-Pearson exact (binomial) method. Optimal cut-off values were determined using the Youden Index. Statistical analyses were performed using SPSS version 22.0 for Windows and MedCalc version 20.115. A p-value <0.05 was considered statistically significant. Only 7 PJI events occurred, which is too few for a standard multivariable logistic regression model with several covariates. We therefore estimated age- and BMI-adjusted associations separately for Each Inflammatory Index, using Firth's penalized (bias-reduced) logistic regression. This method reduces small-sample bias and lowers the risk of non-convergence. Each of the five composite indices (NLR, PLR, SII, SIRI, PIV) was standardized (z-score) and entered in a separate model together with age and BMI. This was necessary because the indices are mathematically inter-related; entering them together would have caused severe multicollinearity. Results are reported as odds ratios (OR) with 95% Wald CIs per 1-SD increase in each marker.

RESULTS

Of the patients included, 33 (68.75%) were male and 15 (31.25%) were female, with a mean age of 17.9 years. Prosthetic joint infection (PJI) developed in 7 patients (14.58%) (3 methicillin-resistant *Staphylococcus aureus* (MRSA), 2 *Staphylococcus epidermidis*, 1 *Escherichia coli*, and 1 *Salmonella* species) (Table 1). There was no statistically significant difference in age between patients with and without PJI. PJI showed no statistically significant association with gender (p=1.000, Fisher's exact test), affected extremity (p=1.000, Fisher's exact test), or the anatomical location of the resection prosthesis (p=0.953, exact Monte Carlo test) Similarly, no significant relationship was observed between BMI and PJI (p=0.389) (Table 2).

Table 1. Summary of the seven prosthetic joint infection cases

Patient(s)	Organism	Diagnostic criterion met (MSIS)	Initial treatment
1-3	MRSA (n=3)	Sinus tract and/or 2 positive cultures	Surgical debridement followed by pathogen-directed antibiotic therapy
4-5	*Staphylococcus epidermidis* (n=2)	Sinus tract and/or 2 positive cultures	Surgical debridement followed by pathogen-directed antibiotic therapy
6	*Escherichia coli* (n=1)	Sinus tract and/or 2 positive cultures	Surgical debridement followed by pathogen-directed antibiotic therapy
7	*Salmonella* spp. (n=1)	Sinus tract and/or 2 positive cultures	Surgical debridement followed by pathogen-directed antibiotic therapy

PJI was diagnosed at a mean of 6-12 months postoperatively, based on MSIS major criteria (sinus tract communicating with the prosthesis and/or two positive cultures of the same organism). All patients with PJI initially underwent surgical debridement followed by culture/sensitivity-directed antibiotic therapy; patients who did not improve after debridement and targeted antibiotic therapy underwent revision surgery. MSIS: Musculoskeletal Infection Society, MRSA: Methicillin-resistant *Staphylococcus aureus*, PJI: Prosthetic joint infection

Table 2. Demographics and patient characteristics

		Prosthetic joint infection		
		Yes (n=7)	No (n=41)	p-value
Age (year)		17.1 (±3.4)	18.1 (±2.9)	0.343
Gender	Female	2 (28.6%)	13 (31.7%)	1.000
	Male	5 (71.4%)	28 (68.3%)	
BMI (kg/m²)		24.23 (±3.61)	24.90±2.75	0.389
Prosthetic location	Distal femur	4 (57.1%)	19 (46.3%)	0.953
	Proximal femur	1 (14.3%)	5 (12.2%)	
	Proximal humerus	1 (14.3%)	6 (14.6%)	
	Proximal tibia	1 (14.3%)	9 (22.0%)	
	Femur intercalary	0	2 (4.9%)	
Extremity	Lower	6 (85.7%)	34 (82.9%)	1.000
	Upper	1 (14.3%)	7 (17.1%)	

The Mann-Whitney U test was used to compare numerical data. Because of the small expected cell counts in this cohort (n=7 PJI events), Fisher's exact test was used for the 2x2 comparisons (gender, extremity) and an exact Monte Carlo-simulated Chi-square test (200.000 permutations) was used for the multi-category comparison (prosthetic location); p-values have been updated accordingly. Values are presented as mean±standard deviation or number (%). A p-value <0.05 was considered statistically significant. BMI: Body-mass index

Inflammatory markers obtained from pre-biopsy laboratory evaluations-including WBC, ESR, CRP, MPV, RDW, NLR, PLR, SII, SIRI, and PIV-were analyzed and compared between groups (Table 3). No statistically significant differences were found for WBC, ESR, CRP, MPV, or RDW (p=0.971, p=0.775, p=0.474, p=0.161, and p=0.864, respectively). In contrast, significant differences were observed for NLR, PLR, SII, SIRI, and PIV (p=0.001, p=0.024, p=0.001, p=0.001, and p=0.001, respectively Patients with PJI had significantly higher NLR (3.9±0.8 vs. 2.0±0.7, p<0.001), PLR (227.5±131.7 vs. 150.0±60.1, p=0.024), SII (1172.1±435.2 vs. 561.1±228.1, p<0.001), SIRI (2.2±0.6 vs. 1.3±0.6, p=0.001), and PIV (923.9±124.0 vs. 424.4±133.3, p<0.001) compared to patients without PJI (Table 3). Box-plot comparisons of NLR, SII, SIRI, and PIV in patients with and without prosthetic joint infection are presented in Figure 1-4.

Table 3. Comparison of pre-biopsy inflammatory markers between patients with and without prosthetic joint infection

	Prosthetic joint infection				
	Yes		No		
	Mean (±SD)	Median (25%-75%)	Mean (±SD)	Median (25%-75%)	p-value
WBC (×10³/μL)	7.57 (±1.48)	7.4 (6.8-8.1)	7.59±1.32	7.48 (6.65-8.2)	0.971
ESR (mm/h)	5.57 (±3.1)	5.0 (3.0-6.0)	5.56±2.52	5.0 (4-7)	0.775
CRP (mg/L)	3.97 (±2.58)	2.8 (2.1-6.9)	3.06±1.9	2.8 (1.7-3.9)	0.474
MPV (fL)	9.11 (±0.84)	9.1 (8.6-9.6)	9.69±1.01	9.6 (9.2-10.3)	0.161
RDW (%)	13.41(±1.1)	13.0 (12.8-14.1)	13.43±1.0	13.3 (12.8-13.9)	0.864
NLR	3.93 (±0.83)	3.9 (3.3-4.1)	2.05±0.7	1.87 (1.65-2.42)	**<0.001**
PLR	227.50 (±131.77)	210.0 (152.8-215.0)	150.01±60.1	142.5 (114.2-168.5)	**0.024**
SII	1172.1 (±435.29)	1132.0 (847.6-1659.0)	561.18±228.13	530.2 (440-610.5)	**<0.001**
SIRI	2.24±0.65	2.5 (1.7-2.6)	1.37±0.67	1.24 (0.96-1.51)	**<0.001**
PIV	923.93±124.09	946.2 (815.3-1027.0)	424.40±133.3	403.8 (361.4-470.5)	**<0.001**

The Mann-Whitney U test was used for the comparison of numerical data. Statistically significant p-values (p<0.05) are shown in bold. SD: Standard deviation, WBC: White blood cell count, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, MPV: Mean platelet volume, RDW: Red cell distribution width, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammation response Index, PIV: Pan-immune-inflammation value

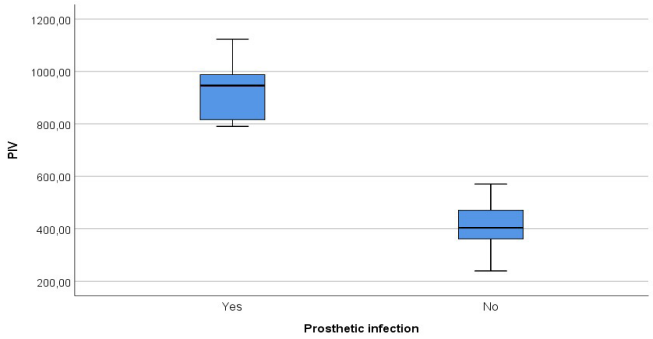


Figure 1. Box-plot comparison of PIV in patients with and without prosthetic infection

PIV: Pan-immune-inflammation value

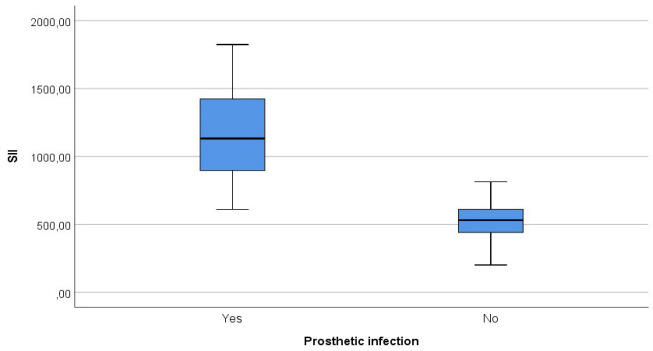


Figure 2. Box-plot comparison of SII in patients with and without prosthetic infection

SII: Systemic Immune-Inflammation Index

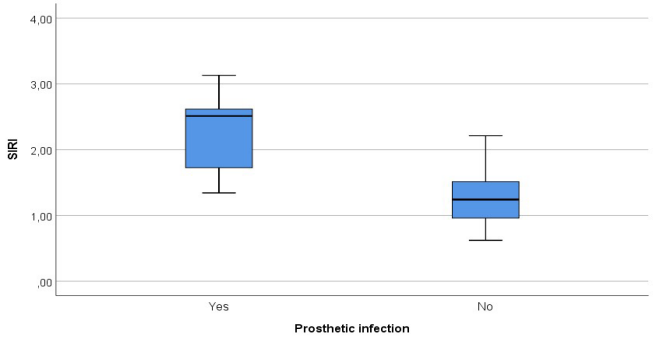


Figure 3. Box-plot comparison of SIRI in patients with and without prosthetic infection

SIRI: Systemic Inflammation Response Index

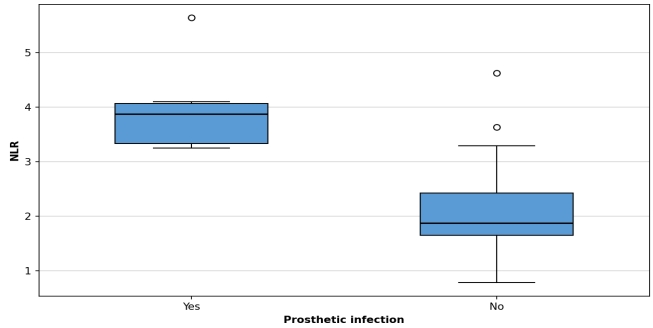


Figure 4. Box-plot comparison of NLR in patients with and without prosthetic infection

NLR: Neutrophil-to-lymphocyte ratio

ROC curve analysis was conducted for NLR, PLR, SII, SIRI, and PIV values (Table 4), which also reports 95% CIs for sensitivity and specificity, calculated using the Clopper-Pearson exact method given the small number of events. In ROC analysis, a PIV cutoff value of >570.6 was associated with PJI, with a sensitivity of 100% and specificity of 97.6% (AUC 0.979, 95% CI 0.889-0.999; p<0.001) (Figure 5). For SII, ROC analysis demonstrated a cutoff value of >813, with a sensitivity of 85.7% and a specificity of 92.7% (AUC 0.927, 95% CI 0.814-0.982; p<0.001) (Figure 5). For SIRI, ROC analysis showed that a cutoff value of >1.6 was associated with PJI, with a sensitivity of 85.7% and a specificity of 78% (AUC 0.861, 95% CI 0.730-0.944; p<0.001) (Figure 5). For NLR, ROC analysis showed that a cutoff value of >3.0 was associated with PJI, with a sensitivity of 100% and specificity of 92.7% (AUC 0.962, 95% CI 0.910-1.000; p<0.001). For PLR, ROC analysis showed that a cutoff value of >209.2 was associated with PJI, with a sensitivity of 57.1% and specificity of 92.7% (AUC 0.767, 95% CI 0.556-0.977; p=0.013); PLR's sensitivity and AUC were numerically the lowest of the five indices. All exact 95% CIs for sensitivity and specificity are reported in Table 3; given the small number of PJI events, several of these intervals are wide (e.g., sensitivity 95% CI 59.0-100.0% for NLR and PIV) and should temper confidence in the point estimates. (Figure 5, Table 4).

Table 4. ROC analysis of NLR, PLR, SII, SIRI, and PIV for association with PJI

Marker	AUC (95% CI)	p-value	Cut-off	Sensitivity% (95% CI)	Specificity% (95% CI)
NLR	0.962 (0.910-1.000)	<0.001	>3.0	100.0 (59.0-100.0)	92.7 (80.1-98.5)
PLR	0.767 (0.556-0.977)	0.013	>209.2	57.1 (18.4-90.1)	92.7 (80.1-98.5)
SII	0.927 (0.814-0.982)	<0.001	>813	85.7 (42.1-99.6)	92.7 (80.1-98.5)
SIRI	0.861 (0.730-0.944)	<0.001	>1.6	85.7 (42.1-99.6)	78.0 (62.4-89.4)
PIV	0.979 (0.889-0.999)	<0.001	>570.6	100.0 (59.0-100.0)	97.6 (87.1-99.9)

AUC 95% confidence intervals were calculated using the DeLong method; sensitivity and specificity 95% CIs were calculated using the Clopper-Pearson exact (binomial) method, given the small number of events (n=7 PJI, n=41 no PJI). Optimal cut-off values were determined using the Youden Index. All AUCs differed significantly from 0.5 (p<0.05); however, given the small number of events, all cut-off, sensitivity, and specificity estimates should be regarded as exploratory and unvalidated. ROC: Receiver operating characteristic, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammation Response Index, PIV: Pan-immune-inflammation value, PJI: Prosthetic joint infection, AUC: Area under the curve, CI: Confidence interval

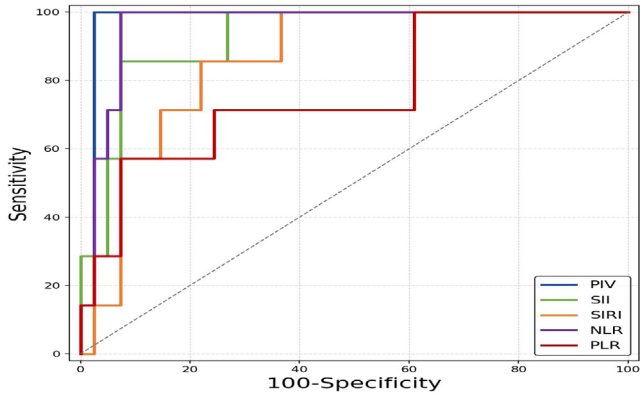


Figure 5. ROC curves for association with prosthetic joint infection using PIV, SII, SIRI, NLR, and PLR

ROC: Receiver operating characteristic, PIV: Pan-immune-inflammation value, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammation Response Index, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

Table 4 presents all pairwise comparisons of areas under the curve (AUCs) derived from ROC analysis of NLR, PLR, SII, SIRI, and PIV for prosthetic joint infection (Figure 5). Of the ten pairwise comparisons, one was nominally significant (PIV vs. SIRI, p=0.034) and one was borderline (PIV vs. PLR, p=0.048); none of the remaining eight comparisons reached significance. Because these ten comparisons were not corrected for multiple testing, and because the indices being compared are themselves mathematically inter-related, these two findings should be interpreted with caution and are not taken as evidence that PIV is superior to the other indices (Table 5).

Given the small number of PJI events (n=7) in this cohort, these ROC-derived cut-off values and the corresponding sensitivity/specificity estimates should be regarded as exploratory. They were generated and evaluated within the same dataset without external or internal (e.g., bootstrap or cross-validation) validation, and are therefore susceptible to optimism bias and overfitting; the reported diagnostic performance may not generalize to independent cohorts.

To check whether these associations were independent of age and BMI, we ran a limited sensitivity analysis. For Each Inflammatory Index, we estimated an age- and BMI-adjusted odds ratio using Firth's penalized (bias-reduction) logistic regression, implemented in Python with a custom, NumPy-based version of the Firth algorithm; 95% CIs came from a Wald-type approximation based on the penalized information matrix. We chose age and BMI because they were the only clinical variables in our dataset that were not themselves part of the inflammatory indices and were unlikely to be strongly collinear with them. With only 7 events, we could not add further covariates. Results are shown in Table 6. After adjustment for age and BMI, NLR (OR 9.12 per 1-SD, 95% CI 2.13-39.08, p=0.003), SII (OR 4.20, 95% CI 1.63-10.84, p=0.003), SIRI (OR 2.49, 95% CI 1.14-5.46, p=0.022), and PIV (OR 7.50, 95% CI 2.37-23.76, p=0.001) remained significantly associated with PJI, whereas PLR did not (OR 2.05, 95% CI 0.96-4.38, p=0.064). Neither age nor BMI was independently associated with PJI in any model (all p>0.29). These sensitivity analyses suggest that the association between NLR, SII, SIRI, and PIV and PJI is not simply explained by age or BMI. However,

Table 5. Pairwise comparison of AUCs derived from ROC analysis of NLR, PLR, SII, SIRI, and PIV for prosthetic joint infection

Comparison	Difference between AUCs	SE	95% CI	z	p-value
PIV~NLR	0.017	0.027	-0.036 to 0.070	0.642	p=0.521
PIV~SII	0.052	0.048	-0.033 to 0.138	1.196	p=0.232
PIV~SIRI	0.118	0.056	0.009 to 0.228	2.116	p=0.034
PIV~PLR	0.213	0.107	0.002 to 0.423	1.980	p=0.048
NLR~SII	0.035	0.042	-0.047 to 0.117	0.836	p=0.403
NLR~SIRI	0.101	0.062	-0.020 to 0.222	1.638	p=0.101
NLR~PLR	0.195	0.108	-0.016 to 0.407	1.809	p=0.070
SII~SIRI	0.066	0.067	-0.065 to 0.197	0.989	p=0.322
SII~PLR	0.160	0.088	-0.013 to 0.333	1.818	p=0.069
SIRI~PLR	0.094	0.096	-0.095 to 0.283	0.976	p=0.329

All pairwise AUC comparisons were performed using the DeLong method. None of the comparisons were significant after accounting for the exploratory, non-multiplicity-adjusted nature of these analyses (see Discussion and Limitations); the single nominally significant comparison (PIV vs. SIRI, p=0.034) and borderline comparison (PIV vs. PLR, p=0.048) should be interpreted with caution given the number of comparisons performed. Abbreviations: AUC: Area under the curve, ROC: Receiver operating characteristic, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammation Response Index, PIV: Pan-immune-inflammation value, SE: Standard error, CI: Confidence interval

because of the small number of events, we could only adjust for two covariates at a time. This analysis should therefore be seen as a limited, exploratory sensitivity check, not as proof of a fully independent, multivariable-adjusted predictive value. Residual confounding by unmeasured operative, nutritional, or chemotherapy-related factors cannot be excluded.

Table 6. Age- and BMI-adjusted associations between pre-biopsy inflammatory indices and prosthetic joint infection (Firth's penalized logistic regression)

Inflammatory Index	Adjusted OR (per 1-SD)	95% CI	p-value
NLR	9.12	2.13-39.08	0.003
PLR	2.05	0.96-4.38	0.064
SII	4.20	1.63-10.84	0.003
SIRI	2.49	1.14-5.46	0.022
PIV	7.50	2.37-23.76	0.001

Each Inflammatory Index was standardized (z-score) and entered in a separate model together with age and BMI, because the indices are mathematically inter-related and could not be entered simultaneously. ORs are expressed per 1-SD increase in the marker. Neither age nor BMI was independently associated with PJI in any model (all p>0.29, not shown). Firth's penalized logistic regression was used to reduce small-sample bias given the limited number of PJI events (n=7). BMI: Body-mass index, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammation Response Index, PIV: Pan-immune-inflammation value, OR: Odds ratio, SD: Standard deviation, CI: Confidence interval

DISCUSSION

Resection arthroplasty performed for sarcomas located adjacent to or involving a joint is associated with significantly higher postoperative infection rates than conventional arthroplasty procedures.[23] In cases of PJI involving megaprostheses, both the risk of amputation and the overall treatment cost substantially increase.[5-7,24] In the present study, we aimed to evaluate the association between inflammatory biomarkers and the development of PJI, a complication that is both morbid and costly. To ensure homogeneity, our study included only patients diagnosed with osteosarcoma who received neoadjuvant chemotherapy and had no soft-tissue coverage complications during surgery. Additionally, patients with any local or systemic infection within two weeks prior to the collection of biomarker samples were excluded. Designing the study with such a narrowly defined patient group allowed us to minimize confounding factors and obtain more reliable results for the parameters being investigated.

In our study, inflammatory indices were evaluated only in the pre-biopsy period, and post-chemotherapy inflammatory indices were not assessed. The absence of post-chemotherapy inflammatory data may be considered a limitation. Our primary aim, however, was different: to test whether inflammatory indices measured before biopsy reflect an underlying, basal immune dysregulation and a susceptibility to postoperative PJI. For this reason, all analyses used only the pre-biopsy inflammatory markers. We did not use post-chemotherapy values because several factors can confound them. These include chemotherapy-induced bone marrow suppression, variation between patients in the timing of blood-count recovery, and the possible need for blood transfusions. For this reason, pre-biopsy inflammatory markers were considered a more homogeneous and interpretable time point in this study. The use of similar chemotherapy protocols across all patients was considered to have contributed to improved intergroup comparability of inflammatory indices obtained in the pre-biopsy period.

ESR and CRP are inflammatory markers widely used in clinical practice and are known to increase in conditions such as infection, trauma, malignancy, and inflammatory diseases.[20,25] Several studies in the field of primary arthroplasty (total knee or total hip) have investigated the association between preoperatively elevated serum inflammatory markers and the development of PJI after arthroplasty; however, there is no consensus in the literature on this issue.[20,21,26,27] In a retrospective analysis of 3,376 primary total knee arthroplasties, Xu et al.[20] demonstrated that elevated preoperative ESR and CRP levels were associated with a significantly increased risk of PJI. In a similar study, Inoue et al.[21] analyzed 1,115 patients who underwent primary total hip arthroplasty and reported that elevated preoperative ESR and CRP levels were risk factors for PJI or surgical site infection. On the other hand, Godoy et al.[26] conducted a retrospective cohort study of 351 patients who underwent primary TKA and found no statistically significant association between postoperative complications and preoperative CRP or ESR levels. In another similar study, Mederake et al.[27] retrospectively analyzed 239 patients who underwent primary total hip arthroplasty and were unable to demonstrate a statistically significant association between preoperative CRP levels and the occurrence of PJI. Similarly, in our study, no association was observed between pre-biopsy ESR and CRP levels and the development of PJI after tumor resection prosthesis. This finding may be attributed to the nonspecific nature of conventional inflammatory markers such as ESR and CRP, which can be influenced by a wide range of factors.

In recent years, beyond conventional inflammatory markers such as ESR and CRP, several novel inflammatory indices derived from hematologic parameters-including NLR, PLR, SII, SIRI, and PIV-have gained increasing research interest. They provide a comprehensive reflection of the activity of neutrophils, monocytes, platelets, and lymphocytes, which play a key role in the inflammatory process.[19,28] These indices have been investigated in multiple clinical contexts, including cancer prognosis, rheumatologic disease activity assessment, and outcome assessment in various inflammatory conditions. Associations of these indices with sarcopenia and nutritional status have also been reported.[29,30] Furthermore, the relationship between preoperative inflammatory markers and the development of PJI following primary total knee or total hip arthroplasty has been explored.[19,21] In a retrospective study conducted by Lyubimova et al.,[19] 6,036 patients who underwent primary hip or knee arthroplasty were evaluated, and PJI was identified in 193 patients. The study showed that SIRI, SII, and Aggregate Index of Systemic Inflammation (AISI, which is calculated using the same formula as the PIV) were significantly higher in patients with PJI. In our study, we evaluated the relationship between inflammatory markers and prosthetic joint infection in patients who underwent tumor resection and megaprosthesis reconstruction due to osteosarcoma-an association that, to our knowledge, based on a literature search performed in PubMed, Scopus, and Web of Science (last searched in July 2026), no previous study

has specifically evaluated pre-biopsy inflammatory markers for predicting prosthetic joint infection after megaprosthetic reconstruction in osteosarcoma patients. Patients with PJI had significantly higher NLR, PLR, SII, SIRI, and PIV values compared with patients without PJI. We observed that PIV was one of the two parameters most strongly associated with PJI, demonstrating high sensitivity and specificity in this preliminary analysis. PIV and NLR showed the numerically highest apparent AUCs among the indices tested (0.979 and 0.962, respectively). However, their AUCs did not differ significantly (DeLong p=0.521), and the age/BMI-adjusted odds ratio was in fact numerically higher for NLR than for PIV (Table 6). We therefore do not Consider Either Index superior to the other. Both are broad, leukocyte-based composite indices, and both simply showed the strongest discrimination among the markers tested. For completeness, we also evaluated PLR by ROC analysis (**Table 4**). Its AUC (0.767, 95% CI 0.556-0.977, p=0.013) was numerically lower than that of NLR, SII, SIRI, and PIV, and its sensitivity (57.1%) was the lowest of the five indices. This fits with its comparatively weaker discrimination on both univariable and pairwise analysis.

The Higher Inflammatory Index values in patients who developed PJI may reflect a malignancy-associated inflammatory state. Tumors are known to induce chronic inflammation in the tumor microenvironment through the presence of malignant cells. This process promotes the release of proinflammatory mediators and draws in dysregulated immune cells, which together create an immunosuppressive microenvironment. Such immune dysregulation may in turn increase susceptibility to postoperative infections, including PJI.

The incidence of infection after sarcoma surgery has been reported to range between 8% and 19% in the literature, and in our study, we found a similar rate of 14.5%.[31,32] Prior studies have shown that BMI may be a risk factor for prosthetic infection, whereas age and gender are generally not associated with PJI risk.[33] Consistent with these findings, our analysis demonstrated no significant relationship between age, BMI, or gender and PJI development. The absence of an association between BMI and PJI in our study may be explained by the fact that all patients had a BMI under 25. Previous studies have reported a higher risk of PJI in proximal tibial reconstructions.[33] However, our study did not find any significant association between tumor location and PJI. This discrepancy may be explained by the exclusion of patients with soft-tissue defects, which could otherwise influence infection risk.

Limitations

The study has several limitations. First, it was a single-center, retrospective study with a relatively small sample size, which limited statistical power. Osteosarcoma is rare, and PJI is a specific subtopic within it; given this, the small sample size for a single-center study is reasonable. Another limitation is that follow-up was limited to 12 months after surgery. Only 7 PJI events occurred, so a conventional multivariable logistic regression model with several confounders (such as tumor location, nutritional status, operative time, blood loss, and chemotherapy-related variables) could not be reliably fitted; the usual minimum event-per-variable threshold was not met. As a limited sensitivity analysis, we used Firth's penalized logistic regression to test Each Inflammatory Index after adjusting for age and BMI. NLR, SII, SIRI, and PIV remained significantly associated with PJI; PLR did not (p=0.064). We could not adjust for the other candidate confounders listed above, so residual confounding cannot be excluded. NLR, SII, SIRI, and PIV are also mathematically inter-related, since each incorporates overlapping leukocyte subpopulations. We examined multiple correlated indices, regression models, and pairwise AUC comparisons without a formal correction for multiple testing. All p-values in this study should therefore be read as exploratory, not confirmatory. As a result, these associations should not be taken as evidence of a fully independent, validated predictive value. The ROC-derived cut-off values were not tested in an independent validation cohort. Inflammatory indices were also measured at only a single pre-biopsy time point, so we do not know how they behave over the course of treatment. This study used a retrospective convenience sample rather than one based on a formal, a priori power calculation. No patients had missing values for the variables analyzed. Together with the single-center design, these limitations mean the findings should be regarded as hypothesis-generating. Larger, prospective studies with longer follow-up could offer more complete and reliable answers. The study does have notable strengths, however: it is the first to examine the association between inflammatory markers and PJI in patients treated with a resection prosthesis for osteosarcoma, and all surgeries were performed by experienced senior surgeons at a tertiary care center, ensuring high procedural quality.

CONCLUSION

In patients undergoing tumor resection and prosthetic reconstruction for bone sarcoma, pre-biopsy inflammatory markers-NLR, PLR, SII, SIRI, and PIV-were significantly associated with PJI. PIV and NLR showed the highest apparent discrimination, combining high sensitivity and specificity for identifying at-risk patients; these two indices did not differ significantly from one another. These associations remained significant for NLR, SII, SIRI, and PIV (but not PLR) after a limited sensitivity analysis adjusting for age and BMI. However, the small number of events, the single-centre design, and the lack of external validation mean these findings are hypothesis-generating rather than definitive. Larger, prospective, multicentre studies are needed before these indices can be used as validated, clinically actionable biomarkers.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Gaziantep City Hospital Non-interventional Clinical Researches Ethics Committee (Date: 21.05.2025, Decision No: 224/2025).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Author Contributions

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