Original Article

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Diagnostic Performance of Neutrophil-to-lymphocyte, Platelet-to-lymphocyte, and Monocyte-to-lymphocyte Ratios in Aseptic Loosening after Hip and Knee Arthroplasty

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Abstract

Aim: Aseptic loosening remains one of the leading causes of late failure after hip and knee arthroplasty, and its diagnosis is often challenging because imaging and conventional inflammatory markers have limited specificity. We aimed to evaluate and compare the diagnostic performance of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) in detecting aseptic loosening following hip and knee arthroplasty.

Methods: This single-center, retrospective diagnostic accuracy study included 291 patients who underwent three-phase bone scintigraphy for suspected prosthetic loosening between 2020 and 2025. Patients were classified into aseptic loosening and control groups based on scintigraphic findings supported by clinical evaluation. Hematological parameters were obtained from complete blood counts, and NLR, PLR, and MLR were calculated. Diagnostic performance was assessed using receiver operating characteristic curve analysis, and optimal cut-off values were determined using the Youden index.

Results: In knee arthroplasty, MLR was significantly higher and the white blood cell count was significantly lower in patients with aseptic loosening, whereas NLR and PLR showed no significant differences. In hip arthroplasty, both PLR and MLR were significantly elevated in the loosening group. Receiver operating characteristic analysis demonstrated the low-to-moderate discriminatory ability of MLR in both knee (AUC=0.61) and hip (AUC=0.64) arthroplasty, whereas PLR achieved the highest diagnostic performance in the hip group (AUC=0.68) with high sensitivity. Neutrophil-to-lymphocyte ratio consistently demonstrated limited diagnostic value across both joint types.

Conclusion: Monocyte-to-lymphocyte ratio and PLR demonstrate modest diagnostic utility in the evaluation of aseptic loosening after hip and knee arthroplasty, with joint-specific differences in performance. These hematological markers should be considered adjunctive tools rather than standalone diagnostic tests and may contribute to clinical decision-making when interpreted alongside imaging findings and clinical assessment.

Keywords: Aseptic loosening, prosthesis failure, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio, biomarkers, radionuclide imaging

Introduction

Degenerative joint diseases represent a major and growing public health burden worldwide, largely driven by population aging and increased life expectancy. Osteoarthritis, the most prevalent form, is a leading cause of chronic pain, disability, and loss of functional independence in individuals over 60 years of age (1-3). Total knee arthroplasty (TKA) and total hip arthroplasty

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(THA) are well-established and highly effective surgical treatments for end-stage joint degeneration, providing substantial improvements in pain relief and quality of life (4). However, the increasing volume of primary arthroplasty procedures has been accompanied by a parallel rise in revision surgeries, among which aseptic loosening remains one of the most common late failure mechanisms (5).

Accurate diagnosis of aseptic loosening is clinically challenging. Conventional diagnostic approaches rely on a combination of clinical assessment and imaging modalities, including plain radiographs, three-phase bone scintigraphy (TPBS), single-photon emission computed tomography combined with computed tomography (SPECT/CT), and magnetic resonance imaging (6). Although these techniques are widely used, they may be limited by cost, availability, metal-related artifacts, and suboptimal sensitivity for early loosening (7). Consequently, there is growing interest in simple, minimally invasive, and cost-effective biomarkers that could support clinical decision-making. In this context, inflammatory indices derived from routine complete blood count parameters—such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR)—have attracted attention in orthopedic research. While these markers have been extensively investigated in the differentiation of periprosthetic joint infection from aseptic failure, their diagnostic value specifically in non-infectious aseptic loosening remains insufficiently defined, with inconsistent and heterogeneous results across studies (8).

Most previous investigations have focused on either hip or knee arthroplasty populations in isolation and have rarely compared multiple hematological markers within the same methodological framework. We hypothesized that inflammatory cell ratios, particularly MLR, differ between patients with and without aseptic loosening and that they demonstrate joint-specific diagnostic performance for hip and knee arthroplasty. This study aimed to compare the diagnostic accuracy of NLR, PLR, and MLR in patients with suspected aseptic loosening following TKA and THA using a uniform diagnostic approach, thereby clarifying their relative clinical utility across joint types and supporting more informed adjunctive use of readily available hematological parameters in the diagnostic evaluation of prosthetic loosening.

Materials and Methods

Compliance with Ethical Standards

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Due to its retrospective design and the use of anonymized data obtained from routine clinical records, formal written informed consent was waived. Ethical approval was granted by the Kutahya Health Sciences University Non-Interventional Clinical Research Ethics Committee (approval no.: 2024/14-11, date: 16.12.2024). No additional diagnostic or therapeutic procedures were performed for research purposes.

Study Design

This single-center retrospective diagnostic accuracy study evaluated hematological inflammatory ratios for identifying aseptic loosening after total hip and knee arthroplasty. The study included patients who underwent TPBS for suspected prosthetic loosening between January 2020 and May 2025. The patient selection process and study flow are summarized in Figure 1.

Study Population and Patient Selection

All eligible consecutive patients who underwent TPBS for suspected prosthetic loosening during the study period were screened to minimize selection bias. We excluded 21 patients because of incomplete records or diagnoses other than aseptic loosening, resulting in a final cohort of 291 patients.

Group 1 (loosening): One hundred and eleven (73 TKA, 38 THA) with scintigraphic findings suggestive of aseptic loosening confirmed by clinical evaluation. Clinical evaluation included assessment of prosthesis stability, pain score, and plain radiographs; when ambiguity persisted, SPECT/CT was performed using a Siemens Symbia Intevo scanner to obtain reference uptake indices.

Group 2 (control): One hundred and eighty (112 TKA, 68 THA) with TPBS performed for suspected prosthetic

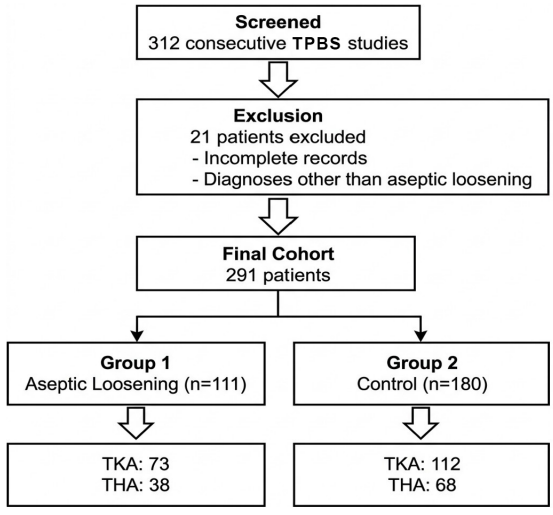

Figure 1. Study flow diagram illustrating patient selection and group allocation
TKA: Total knee arthroplasty, THA: Total hip arthroplasty, TPBS: Three-phase bone scintigraphy

loosening but reported as "normal" or "not in favor of loosening." Because the number of eligible control patients exceeded that of the loosening group, controls were selected by simple random sampling from an anonymized list using a computer-generated random number table to minimize selection bias.

Imaging Protocol

In this study, TPBS was performed in patients evaluated for suspected loosening after total joint arthroplasty. Scintigraphic imaging was performed using a Mediso gamma camera system. Prior to imaging, patients were intravenously administered 20-25 mCi (740-925 MBq) of technetium-99m labeled methylene diphosphonate. The TPBS protocol included a dynamic blood flow phase during the first minute post-injection, followed by a blood pool phase at 3-5 minutes, and delayed static images acquired approximately 3 hours after injection. In interpreting the scans, the absence of increased activity or hyperemia in the blood flow and pool phases was considered indicative of the absence of infection. However, in the delayed phase, increased tracer uptake in the periprosthetic bone compared with adjacent healthy bone, particularly in areas under mechanical stress, was interpreted as suggestive of aseptic loosening. Based on this imaging protocol, the final diagnosis of aseptic loosening was established by integrating scintigraphic findings with clinical and laboratory data.

Diagnostic Definition of Aseptic Loosening

Aseptic loosening was diagnosed based on increased periprosthetic tracer uptake during the delayed phase of TPBS in the absence of clinical, laboratory, or imaging findings suggestive of infection. Importantly, histopathological confirmation and intraoperative cultures were not routinely available, and the diagnosis relied on the integration of imaging and clinical data. The absence of histopathological confirmation may have led to misclassification bias, a methodological limitation of the study.

Data Collection and Laboratory Measurements

Demographic variables (age, sex), arthroplasty type (hip or knee), and time interval between primary surgery and scintigraphic evaluation were recorded. Laboratory parameters, including white blood cell, neutrophil, lymphocyte, monocyte, and platelet counts, and C-reactive protein (CRP) levels, were retrieved from the hospital information system. To minimize temporal variability, laboratory measurements obtained closest to the scintigraphic examination (within ±7 days) were included in the analysis. When multiple measurements were available, the value closest to the imaging date was used.

Derived inflammatory ratios were calculated as follows:

- NLR = Neutrophil-to-lymphocyte ratio
- PLR = Platelet-to-lymphocyte ratio
- MLR = Monocyte-to-lymphocyte ratio

Outcome Measures

The primary outcome was the diagnostic performance of NLR, PLR, and MLR in distinguishing patients with aseptic loosening from controls, assessed using receiver operating characteristic (ROC) curve analysis.

The secondary outcomes included:

- Comparison of hematological parameters between loosening and control groups stratified by joint type (hip vs. knee),
- Determination of optimal cut-off values using the Youden index,
- Evaluation of sensitivity and specificity for each marker.

Statistical Analysis

Statistical analyses were performed using the SPSS, version 25.0 (IBM Inc., Armonk, NY, USA). Normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Normally distributed variables were expressed as mean ± standard deviation and compared using independent samples t-tests. Categorical variables were compared using the chi-square test.

Receiver operating characteristic curve analysis was used to assess diagnostic accuracy, and area under the curve (AUC) values were calculated with 95% confidence intervals (CIs). Optimal cut-off values were determined using the Youden index.

Given the exploratory nature of this study and the evaluation of multiple biomarkers and subgroup analyses, no formal correction for multiple comparisons was applied; the results should be interpreted accordingly. A p-value <0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics

A total of 291 patients were included in the analysis, comprising 111 patients with aseptic loosening and 180 controls. In the loosening group, 73 patients had TKA and 38 patients had THA. Baseline demographic characteristics, including age, sex distribution, and the time interval from primary surgery to scintigraphic evaluation, were comparable between the loosening and control groups for both joint types (Table 1).

Hematological Findings in Knee Arthroplasty

In the TKA cohort, patients with aseptic loosening demonstrated significantly higher MLR values compared with controls (0.26±0.12 vs. 0.21±0.06, p=0.024). The white blood cell count was significantly lower in the loosening group (9.34±3.67 vs. 14.45±4.87 $\times 10^9$/L, p=0.031). No significant differences were observed for neutrophil count, lymphocyte count, platelet count, NLR, or PLR (Table 2).

Receiver operating characteristic analysis showed that MLR had low-to-moderate discriminative ability for detecting aseptic loosening in the knee cohort (AUC=0.61, 95% CI: 0.53-0.69). NLR and PLR demonstrated poor diagnostic performance (AUC <0.60) (Figure 2).

Hematological Findings in Hip Arthroplasty

In the THA cohort, both PLR and MLR were significantly higher in patients with aseptic loosening compared with controls (PLR: p=0.033; MLR: p=0.017). No significant differences were observed in white blood cell count, neutrophil count, lymphocyte count, platelet count, NLR, or CRP levels (Table 2).

Receiver operating characteristic analysis revealed that PLR had the highest diagnostic accuracy in the hip cohort (AUC=0.68, 95% CI: 0.58-0.78), followed by MLR (AUC=0.64, 95% CI: 0.53-0.75). NLR again showed limited discriminative value (AUC=0.56; Figure 2).

Table 1. Demographic and clinical characteristics of patients with suspected aseptic loosening following hip and knee arthroplasty

Group (n=291)	Number of men (n=159)	Number of women (n=132)	Age (Mean ± SD)	Follow-up period (Mean ± SD years)
Knee patient (73)	41	32	68.3±12.7	11.3±7.2
Knee control (112)	61	51	70.6±9.8	10.2±8.3
Hip patient (38)	21	17	65.4±16.2	13.1±8.9
Hip control (68)	36	32	69±11.6	12.1±4.1

Values are presented as mean ± standard deviation or number of patients
SD: Standard deviation

Table 2. Comparison of demographic, clinical, and hematological parameters between patients with and without aseptic loosening after knee and hip arthroplasty

	Variables	Group 1		Group 2	p
Knee	Gender	Male	41	61	0.825
		Sex/female	32	51	
	Age		68.3±12.7	70.6±9.8	0.642
	Follow-up period (year)		11.3±7.2	10.2±8.3	0.562
	Hematological parameters	NLR	2.35±1.71	1.93±0.84	0.282
		PLR	141.12±70.37	136.00±81.65	0.167
		MLR	0.26±0.12	0.21±0.06	**0.024**
		CRP	7.3±5.4	9.8±10.8	0.072
		White blood cell	9.34±3.67	14.45±4.87	**0.031**
Hip	Gender	Male	21	36	0.218
		Sex/female	17	32	
	Age		65.4±16.2	69.0±11.6	0.432
	Follow-up period (year)		13.1±8.9	12.1±4.1	0.136
	Hematological and biochemistry parameters	NLR	2.04±1.27	2.43±1.69	0.07
		PLR	143.42±13.58	131.00±28.42	**0.033**
		MLR	0.22±0.19	0.14±0.09	**0.017**
		CRP	9.6±6.1	8.5±4.8	0.231
		White blood cell	10.71±3.92	11.44±6.72	0.855

Values are presented as mean ± standard deviation or number of patients. Group 1: patients with aseptic loosening; Group 2: controls. Comparisons between groups were performed using the independent-samples t-test for continuous variables and the chi-square test for categorical variables. Bold p-values indicate statistically significant differences (p<0.05). Age is given in years, CRP in mg/L, and white blood cell count in $\times 10^9$/L
NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, CRP: C-reactive protein

Optimal Cut-off Values

Optimal cut-off values derived using the Youden index are summarized in Table 3. In knee arthroplasty, an MLR threshold of 0.268 yielded a sensitivity of 43.8% and a specificity of 86.6%. In hip arthroplasty, a PLR cut-off of 122.85 provided high sensitivity (97.4%) with low specificity (44.1%), whereas an MLR cut-off of 0.278 demonstrated high specificity (94.1%) with moderate sensitivity (55.3%).

Subgroup and Sensitivity Analyses

Subgroup analyses stratified by sex and follow-up duration (>10 years vs. ≤10 years) did not reveal significant interactions affecting MLR or PLR performance (p for interaction >0.1). Sensitivity analyses excluding patients with CRP levels >10 mg/L yielded comparable AUC values, supporting the robustness of the findings.

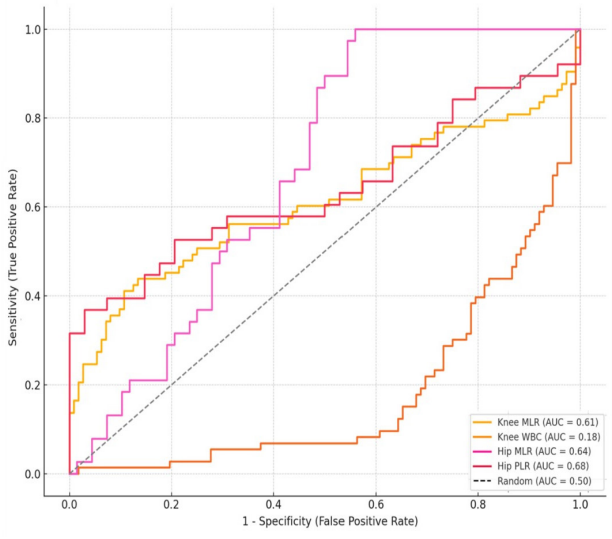

Figure 2. Receiver operating characteristic curves demonstrating the diagnostic performance of hematological parameters in the detection of aseptic loosening following hip and knee arthroplasty

MLR: Monocyte-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, *AUC: Area under the curve, WBC: White blood cell*

Discussion

In this single-center retrospective study, we evaluated the diagnostic performance of routinely available hematological inflammatory ratios in patients with suspected aseptic loosening following total hip and knee arthroplasty. The main finding of this study is that the MLR demonstrated modest but consistent diagnostic performance in both joint types, whereas the NLR showed limited value in the non-infectious setting. In contrast, the PLR exhibited joint-specific behavior, showing clinically relevant performance only in hip arthroplasty (9,10).

The relatively better performance of MLR may be explained by the underlying pathophysiology of aseptic loosening. Chronic low-grade inflammation induced by wear debris leads to macrophage activation and periprosthetic osteolysis, processes in which monocytes play a central role (7,11). As monocytes are precursors of macrophages, MLR may better reflect these biological mechanisms compared with NLR, which is more closely associated with acute infectious responses (12). This distinction likely explains why NLR, despite its established utility in periprosthetic joint infection, failed to demonstrate diagnostic relevance in the present aseptic cohort (13,14).

An important finding of this study is the differential diagnostic performance of PLR in hip versus knee arthroplasty. While PLR did not show significant value in knee arthroplasty, it demonstrated high sensitivity in hip arthroplasty, suggesting a potential role as a rule-out marker in this subgroup (15,16). Differences in joint biomechanics, implant characteristics, and local inflammatory responses may contribute to this finding, although the exact mechanism remains unclear. Given its low specificity, PLR should not be used as a standalone diagnostic parameter but may provide supportive information when combined with more specific markers such as MLR.

Although several hematological parameters reached statistical significance, their clinical implications should be interpreted with caution. The values of the area under the ROC curve for MLR and PLR ranged from 0.61 to 0.68, indicating fair but limited discriminatory ability. These findings suggest that hematological ratios alone are insufficient for definitive diagnosis and should be interpreted as adjunctive tools alongside clinical assessment and imaging modalities (17,18).

Table 3. Optimal cut-off values, sensitivity, and specificity of inflammatory markers for the diagnosis of aseptic loosening based on Youden index analysis

Parameter	Cut-off value	Sensitivity	Specificity
Knee MLR	0.268	0.438	0.866
Hip PLR	122.85	0.974	0.441
Hip MLR	0.278	0.553	0.941

Cut-off values were derived from receiver operating characteristic curve analysis. Sensitivity and specificity values reflect the diagnostic performance of each parameter in knee and hip arthroplasty cohorts
MLR: Monocyte-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

Previous studies have primarily focused on differentiating periprosthetic joint infection from aseptic failure or have evaluated hip and knee arthroplasty populations separately (19,20). By contrast, the present study simultaneously analyzed both joint types using a uniform diagnostic methodology and directly compared multiple inflammatory ratios within the same cohort. This approach provides a more comprehensive assessment of the potential role of hematological markers in the diagnostic work-up of aseptic loosening.

Study Limitations

This study has several limitations. Its retrospective, single-center design may limit generalizability and introduce selection bias. Aseptic loosening was diagnosed based on clinical assessment and TPBS, without histopathological confirmation or intraoperative cultures; this may have resulted in misclassification bias. In addition, multiple biomarkers were analyzed without formal adjustment for multiple comparisons, and multivariate modeling was not performed.

Despite these limitations, the study benefits from a relatively large cohort, the inclusion of both hip and knee arthroplasty patients, and the evaluation of simple, widely available hematological markers using a standardized diagnostic approach.

Conclusion

Monocyte-to-lymphocyte ratio and PLR showed modest diagnostic value for assessing aseptic loosening after hip and knee arthroplasty, with joint-specific differences in performance. MLR demonstrated higher specificity across both joint types, whereas PLR showed high sensitivity, mainly in hip arthroplasty. Given the moderate discriminatory ability of these markers (AUC: 0.61-0.68), they should be considered adjunctive tools rather than standalone diagnostic tests. Future prospective multicenter studies with surgical or histopathological confirmation are warranted to validate these findings.

Ethics

Ethics Committee Approval: Ethical approval was granted by the Kutahya Health Sciences University Non-Interventional Clinical Research Ethics Committee (approval no.: 2024/14-11, date: 16.12.2024).

Informed Consent: Since the study was designed retrospectively, individual informed consent was waived.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.A., Concept: B.A., A.A.U., A.B., Design: B.A., E.A., A.B., Data Collection or Processing: B.A., A.A.U., Analysis or Interpretation: B.A., E.A., Literature Search: B.A., A.A.U., Writing: B.A., A.B.

Conflict of Interest: The authors declared that there were no conflicts of interest.

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