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Comparative Diagnostic Value of Serological and Synovial Tests for Periprosthetic Joint Infections

A Comprehensive Analysis

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Background: Prompt diagnosis of periprosthetic joint infections (PJIs) is crucial for providing optimal care. Currently, there are no gold-standard tests available. An ideal test would be simple to implement, cost-effective, and readily available. We aimed to determine the best single or combined serological or synovial markers for diagnosing PJIs.

Methods: There were 177 of 313 patients who had PJIs between April 2012 and March 2023 and a control group of 60 patients who were included in this retrospective review. The PJIs were diagnosed using Musculoskeletal Infection Society (MSIS) and European Bone and Joint Infection Society (EBJIS) criteria. Serum (C-reactive protein [CRP], white blood-cell [WBC] count, neutrophil-lymphocyte ratio [NLR], polymorphonuclear neutrophil percentage [PMN%]), and synovial fluid (WBC, NLR, PMN%) parameters were compared between the 2 groups. We determined the sensitivity, specificity, area under the curve (AUC), and cutoff values (COV) for each marker. We determined the best combination of markers to diagnose PJIs. There was no statistical significance between the demographic data of the control and treatment groups.

Results: The S-CRP had the highest AUC of 0.912 with a COV of 16.15 mg/dL (Sensitivity 79.6%, Specificity 97.8%). The combination of tests, S-CRP, synovial fluid (SF-WBC), and S-NLR demonstrated the highest AUC of 0.946 (Sensitivity 93%, Specificity 90.9%). The COV for SF-WBC was 5.75 cells/μL (AUC 0.803; Sensitivity 70.3%, Specificity 97.1%); S-NLR COV was 3.659 (AUC 0.803; Sensitivity 67.3%, Specificity 88%).

Conclusion: We found the combination of S-CRP, SF-WBC, and S-NLR to be valuable in diagnosing PJI with high sensitivities and specificities. It can be easily implemented by clinicians without additional cost or equipment. It is important to use this with a thorough clinical and physical examination as well as other modalities (i.e., MSIS/EBJIS criteria).

Level of Evidence: Retrospective Comparative Study–Level III evidence. See Instructions for Authors for a complete description of levels of evidence.

Background

Prompt and accurate diagnosis remains a challenging aspect of PJI management. A PJI diagnostic criteria relies on clinical, radiographic, and laboratory findings, which have many limitations in terms of sensitivity and specificity[4,17-20,22,23,27]. Controversy exist about the ultimate cutoff value (COV) with the highest sensitivity and specificity for CRP[16,24,27], synovial–white blood cell (WBC)[13,22,27], and serum–neutrophil-lymphocyte ratio (NLR)[3,10]. Studies have tried to determine the ideal combination of tests to accurately diagnose PJIs[9]. These combinations either involve a large number of tests, which limits practicality, or lack high sensitivity and specificity. Therefore, further research is warranted to address this deficiency in the literature to accurately and easily diagnose PJIs.

The American Academy of Orthopaedic Surgeons has recently released recommendations regarding the diagnosis of PJI[10,32]. Serum erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and interleukin-6 received strong

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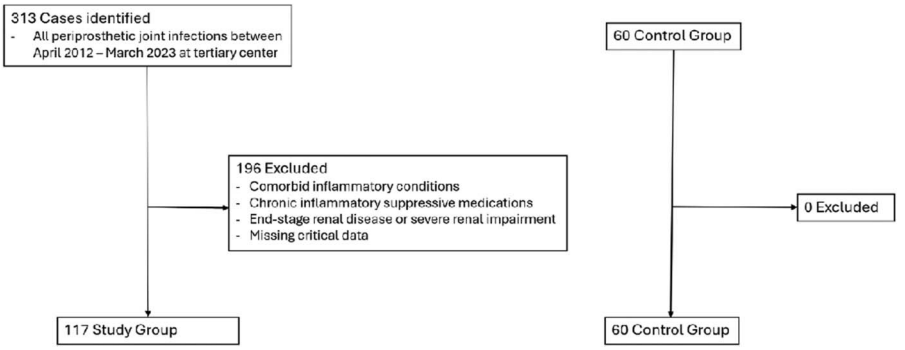

Fig. 1

Patient inclusion and exclusion flowchart.

recommendations, while the synovial fluid (SF) tests, including CRP, polymorphonuclear neutrophil percentage (PMN%), cultures, leukocyte esterase, and polymerase chain reaction assay only received moderate recommendations[10]. Multiple newer tests have been described for the diagnosis of PJI, including D-dimer, calprotectin, alpha-2 macroglobulin, adenosine, and alpha defensin; however, they have also been described to have limitations which make them difficult to apply to clinical practice[24]. Therefore, there is currently no gold-standard diagnostic test, and there is large threshold variability between a growing number of tests[5,6,12,13]. An ideal test would be easily available and currently part of the routine workup with no additional cost.

Recent literature has focused on serum and SF NLR, proposing that inflammatory and infective processes can be described by the ratio between neutrophils and lymphocytes obtained from a simple complete blood count or a more invasive SF aspiration[3,14,31]. This does make inherent sense seeing that neutrophils tend to increase and lymphocytes tend to decrease at the initial stages of infection[10,12]. Serum ratios in particular, including monocyte-lymphocyte ratio, platelet/mean platelet volume ratio, and platelet-lymphocyte ratio, are advantageous since they require no laboratory or equipment costs and therefore are easy to implement[6,13]. However, there has been conflicting evidence on its diagnostic capabilities compared with previously established measurements such as S-PMN% or S-WBC[3,10,24,28-30].

Given the need to further clarify if serum and/or SF NLR is a reliable PJI diagnostic marker, we conducted a retrospective chart review to test the sensitivity and specificity of serum NLR as a specific diagnostic marker for PJI. Second, we aimed to determine the optimal serological and SF marker for the diagnosis of PJI. Our third objective was to determine if there is an optimal combination of tests that yields the highest diagnostic value.

Patients and Methods

Following University of Saskatchewan Research Ethics Board approval (BIO-3178, October 18, 2023), we conducted a single-center, retrospective review of patients presenting to a tertiary center with periprosthetic joint infections (PJIs) of hip and knee between April 2012 and March 2023 as diagnosed using Musculoskeletal Infection Society (MSIS)[22] and European Bone and Joint Infection Society criteria (EBJIS)[20]. PJI cases were only included if both the MSIS and EBJIS criteria confirmed infection. A total of 313 patients with PJIs were identified through our Discharge Abstract Database using procedure codes. All patients identified through the database did undergo either a debridement, antibiotic, and implant retention procedure or a 1-stage or 2-stage revision. A further 60 patients were identified who underwent aseptic revisions using procedure codes.

Patients who had clinical or investigative suspicion of PJI received serological tests and SF aspiration during the medical encounter as part of their routine workup. The serological and synovial thresholds used to determine infection includes the following: S-CRP >10 mg/dL, SF-WBC >3,000 cells/μL, and synovial polymorph nuclear cells (SF-PMN) >80%[20,22]. All data obtained

TABLE I Summary of the Significance Level of Differences Between the Control Group and the Study Group, as Well as Statistical Power of the Test*

	p	Power
Age	0.164	0.370
Height	0.106	0.370
Weight	0.147	0.280
BMI	0.474	0.080
SF WBC	<0.001	1,000
SF Neutrophil	<0.001	0.990
SF Lymphocyte	0.016	0.680
SF NLR	<0.001	0.920
SF PMN	0.118	0.350
S WBC	<0.001	1,000
S CRP	<0.001	1,000
S Neutrophil	<0.001	1,000
S Lymphocyte	0.006	0.830
S NLR	<0.001	0.990
S PMN	<0.001	0.990

*For each variable, Student *t*-test for independent group was used.
BMI = body mass index, CRP = C-reactive protein, NLR = neutrophil-lymphocyte ratio, PMN = polymorphonuclear, SF = synovial fluid, and WBC = white blood cells.

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TABLE II Asymptotic Significance Shows How Sure We Are That Our Classification Is Nonrandom, p < 0.05 is Considered Significant Here*

	Area Under the Curve	Asymptotic Significance	Cutoff Value	Max K-S†
Synovial fluid				
SF-PMN%	0.774	<0.001	0.81	0.613
SF-NLR	0.810	<0.001	9.354	0.604
SF-ALC (%)	0.594	0.084	0.472	0.349
SF-ANC (%)	0.792	<0.001	4.15	0.580
SF-WBC (cells × 10^9/L)	0.803	<0.001	5.75	0.675
Serum				
S-PMN%	0.736	<0.001	0.718	0.488
S-NLR	0.803	<0.001	3.659	0.553
S-ALC (%)	0.278	<0.001	0.36	0.001
S-ANC (%)	0.736	<0.001	5.62	0.457
S-CRP (mg/dL)	0.912	<0.001	16.15	0.774
S-WBC (cells × 10^9/L)	0.694	<0.001	8.9	0.412

*The maximum Kolmogorov-Smirnov (K-S) metric is used to determine the cutoff value. Generally, higher values are better. Area under the curve is one the most important values in ROC analysis. Values close to 0.5 indicate that the classification is random. Area of 0.7 or higher is generally considered acceptable, 0.8 or higher is good, and 0.9 or higher is great. †The maximum Kolmogorov-Smirnov (K-S) metric. ALC = absolute lymphocyte count, ANC = absolute neutrophil count, CRP = C-reactive protein, NLR = neutrophil-lymphocyte ratio, PMN = polymorphonuclear, S = serum, SF = synovial fluid, and WBC = white blood cells.

from medical records included a WBC count, absolute neutrophil count (ANC), and absolute lymphocyte count (ALC) from both SF and serum. The NLR was calculated by dividing the ANC by the ALC[30]. The PMN% was calculated by dividing the ANC by the WBC[7].

There were 196 patients from the study group who were excluded based on our exclusion criteria: (1) comorbid inflammatory conditions to avoid potential confounding inflammatory marker elevation, e.g., rheumatoid arthritis and ankylosing spondyloarthritis; (2) chronic inflammatory suppressive medications, e.g., corticosteroids and disease modifying antirheumatic drugs (DMARDs); and (iii) end-stage renal disease or severe renal impairment (Estimated Glomerular Filtration Rate <30). No patients were excluded from the control group. This left 117 and 60 patients in the study and control groups, respectively, to be analyzed (Fig. 1). The study group included all comers who fulfilled the criteria for PJIs according to the EBJIS and MSIS criteria (MSIS). We have propensity matched the treatment and control group in regard to age and body mass index (BMI).

The study protocol adhered to the Declaration[1] of Helsinki and Strengthening the Reporting of Observational Studies in Epidemiology guidelines[11].

TABLE III Combination of the Variables*

Variables	AUC	Significance
S-CRP + SF NLR	0.903	<0.001
S-CRP + SF WBC	0.937	<0.001
S-CRP + S-NLR	0.933	<0.001
S-CRP + SF NLR + SF WBC	0.913	<0.001
S-CRP + SF WBC + S-NLR	0.946	<0.001
S-CRP + SF NLR + S-NLR	0.898	<0.001
S-CRP + SF NLR + SF WBC + S-NLR	0.916	<0.001

*S-CRP = serum CRP, SF NLR = synovial neutrophil lymphocyte ratio, SF WBC = synovial fluid white blood cell count, and S-NLR = serum neutrophil-lymphocyte ratio.

TABLE IV Patient Demographics of the Control Group and the Treatment Group*

Group	N	Mean	Std. Deviation	Std. Error Mean	p
Age (yrs)					
Control	60	67	7.86	1.01	
Treatment	253	65	10.70	0.67	0.164
Height (m)					
Control	40	1.64	0.10	0.01	
Treatment	91	5.51	22.64	2.37	
Weight (kg)					
Control	47	94.89	27.48	4.00	
Treatment	97	102.33	30.99	3.14	
BMI (kg/m^2)					
Control	40	36.19	9.96	1.57	0.474
Treatment	85	34.75	11.32	1.22	

*BMI = body mass index.

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Control Group

We used a control group of 60 patients who underwent revision surgery for aseptic reasons. All patients in the control group were thoroughly investigated preoperatively with serological markers and sterile aspirations to exclude infection. Cultures were collected in aerobic and anaerobic culture bottles and cultured for 14 days. All patients included in the control group were deemed to be "not infected" by the MSIS[22] or "infection unlikely" by the EBJIS[20].

Data Analyses

This study used Student t-tests to compare immune cell composition between diseased and nondiseased individuals, with statistical power calculated using sample size, effect size, and a significance level of 0.05[2]. Receiver operating characteristic analyses assessed the diagnostic value of immune cell composition in blood serum and SF for PJI (Table I). Area under the curve (AUC) values were critical, with ≥0.7 deemed acceptable, ≥0.8 good, and ≥0.9 excellent (Table II)[8,15]. Cutoff values were determined through Kolmogorov-Smirnov tests[2,21]. Factor analyses, including principal component analysis, enhanced predictive capabilities (Table III). Statistical blinding was not applied.

Results

Patient Demographics

We included 60 patients in the control group and 117 patients in the treatment group. The mean age in the control group was 67 years (range, 59.2-74.9) and 65 years in the treatment group (range, 54.6-75.7) (p = 0.164) (Table IV). The mean body mass index (BMI) in the control group was 36.2 (range, 26.2-46.1) and in the treatment group 34.8 (range, 23.4-46) (p = 0.474). There was 57% of the patients in the treatment group were men (p = 1.0). The treatment group consisted of 60.7% total knee arthroplasty and 38.3% total hip arthroplasty.

Serum and Synovial Fluid

Serum-CRP had the highest AUC of 0.91 with a COV of 16.15 mg/dL (sensitivity = 79.6%, specificity = 97.8%) (Please see Table II and Figs. 2–7 for complete results). Other measurements that achieved "good results" included SF-NLR with an AUC of 0.810 (COV = 9.354; Sensitivity = 71.9%, Specificity = 88.5%), SF-WBC (AUC = 0.803, COV = 5.75 cells × 10^9; Sensitivity = 70.3%, Specificity = 97.1%), and serum NLR (AUC = 0.803, COV = 3.659; Sensitivity = 67.3%, Specificity = 88.0%). "Acceptable" results included SF-ANC (AUC = 0.792, COV = 4.15%; Sensitivity

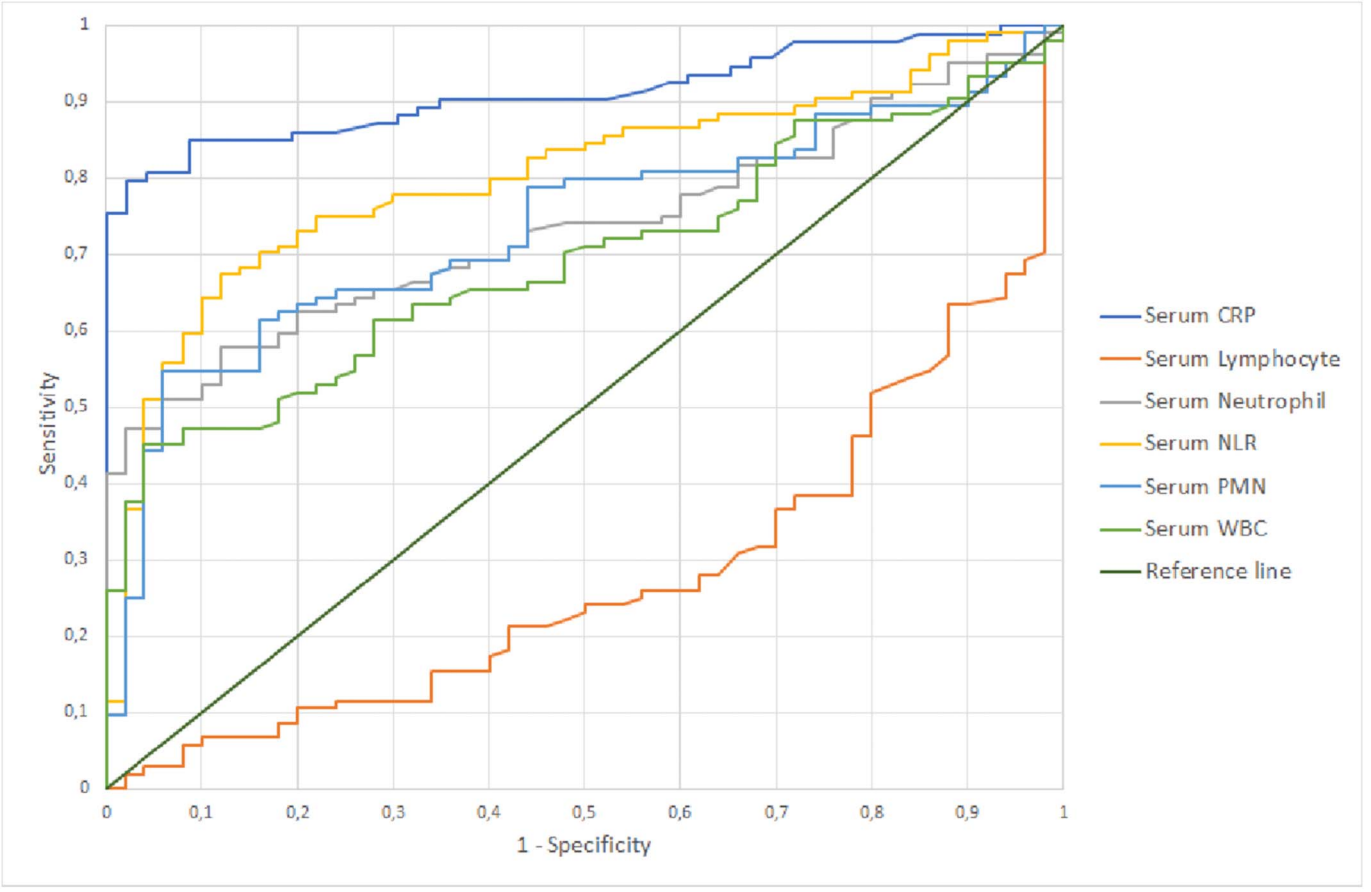

Fig. 2

ROC: individual markers. CRP = C-reactive protein test, NLR = neutrophil-lymphocyte ratio, PMN = polymorphonuclear leucocytes, ROC = receiver operating characteristic curve, and WBC = white blood cells.

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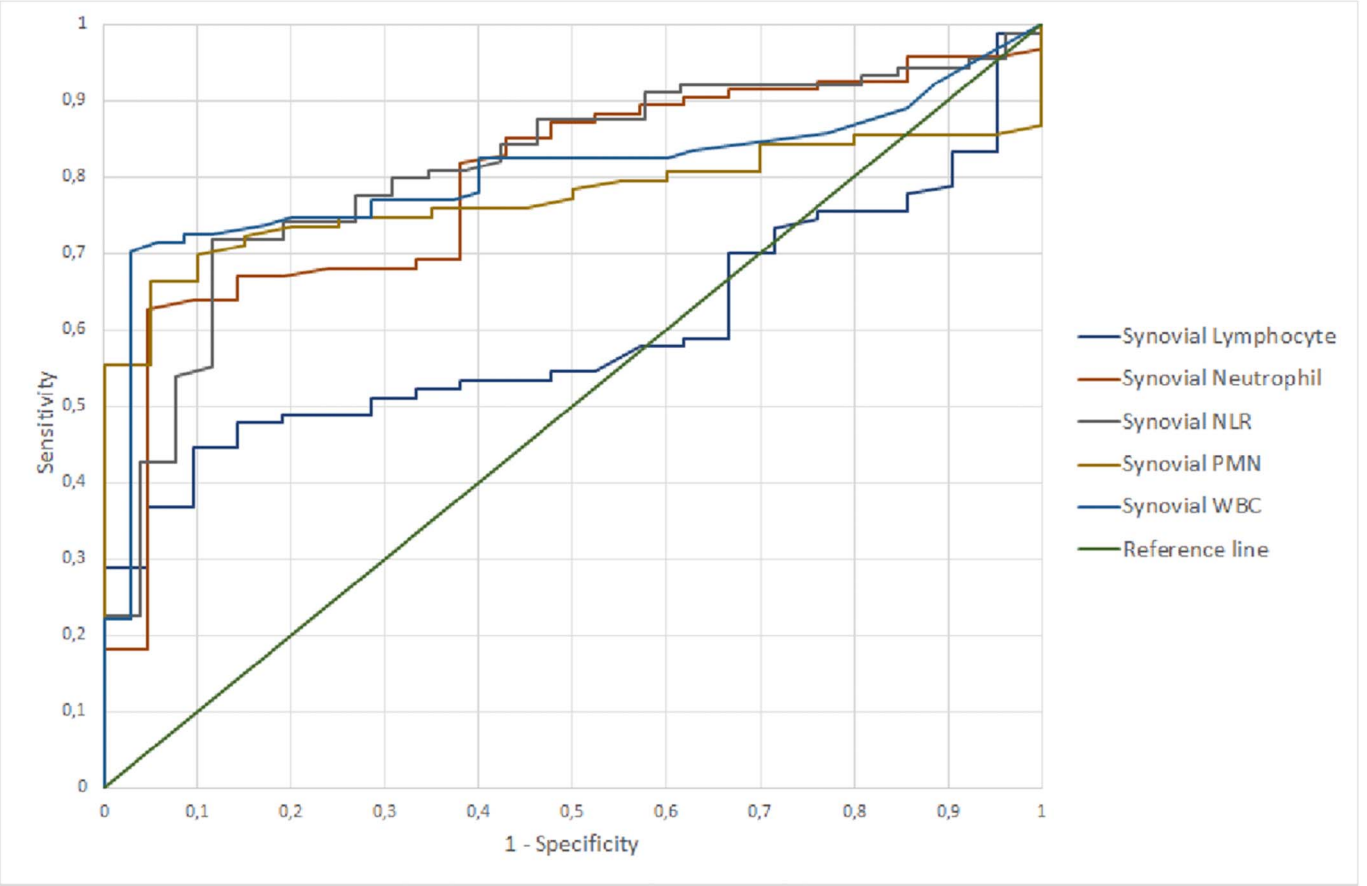

Fig. 3

ROC: individual markers. NLR = neutrophil-lymphocyte ratio, PMN = polymorphonuclear leucocytes, ROC = receiver operating characteristic curve, and WBC = white blood cells.

= 62.8%; Specificity = 95.2%), SF-PMN% (AUC = 0.774, COV = 0.81%; Sensitivity = 66.3%, Specificity = 95.0%), S-PMN% (AUC = 0.736, COV = 0.718%; Sensitivity = 54.8%, Specificity = 94.0%), and S-ANC (AUC = 0.736, COV = 5.62 × $10e^9$/L; Sensitivity = 57.7%, Specificity = 88.0%). The SF-ALC demonstrated the least benefit of diagnosing PJI (AUC = 0.594, COV = 0.472%; Sensitivity = 44.4%, Specificity = 90.5%), while S-ALC indicate reverse dependency where a higher value might demonstrate the absence of infection (AUC = 0.278, COV = 0.36 cells × 10^9; Sensitivity = 98.2%, Specificity = 2.0%).

When we combined the individual variables (Fig. 4) with the highest AUC, we found the combination of S-CRP + SF WBC + S-NLR to have the highest AUC (AUC = 0.946, $p \leq 0.001$; Sensitivity = 93%, Specificity = 90.9%). This was followed by in decreasing order: S-CRP + SF WBC (AUC = 0.937, $p \leq 0.001$; Sensitivity = 89.2%, Specificity = 92.6%), S-CRP + S NLR (AUC = 0.933, $p \leq 0.001$; Sensitivity = 82.4%, Specificity = 94.7%), S-CRP + SF NLR + SF WBC + S-NLR (AUC = 0.916, $p \leq 0.001$; Sensitivity = 92.3%, Specificity = 81.8%), S-CRP + SF NLR + SF WBC (AUC = 0.913, $p \leq 0.001$; Sensitivity = 83.6%, Specificity = 93.3%), and S-CRP + SF NLR (AUC = 0.903, $p \leq 0.001$; Sensitivity = 81.1%, Specificity = 90%). Please see Table V for complete results.

Discussion

We found higher values of the serological and synovial markers in patients who have septic compared with aseptic total joint failures. This was a similar finding from multiple other studies and underlines the increasing role of these parameters in diagnosing PJI[3,5,12]. For individual markers, S-CRP demonstrated the highest AUC, while the combination of S-CRP + SF-WBC + S-NLR had the highest AUC for all the markers.

C-Reactive Protein

The CRP is an acute phase reactant that is produced by the liver in response to inflammation, infection, or neoplasm[6]. Its levels usually peak around 3 days after surgery and then return to normal 3 to 6 weeks later[6,24]. Multiple studies highlighted the accuracy of S-CRP in diagnosing PJI[6,25]. Controversy still exists about the ultimate COV with the highest sensitivity and specificity[16,27]. The MSIS group used an S-CRP value greater than 1 mg/dL[22] while the EBJIS uses 10 mg/dL as their cutoff value. In a recent meta-analysis[27] and systematic review evaluating 45,316 patients, it was found that a higher S-CRP value of 13.5 mg/dL demonstrated the best sensitivity (84%) and specificity (83%). Our data suggests a sensitivity of 79.6% and specificity of 97.8% with a COV of 16.15 mg/dL for optimal CRP

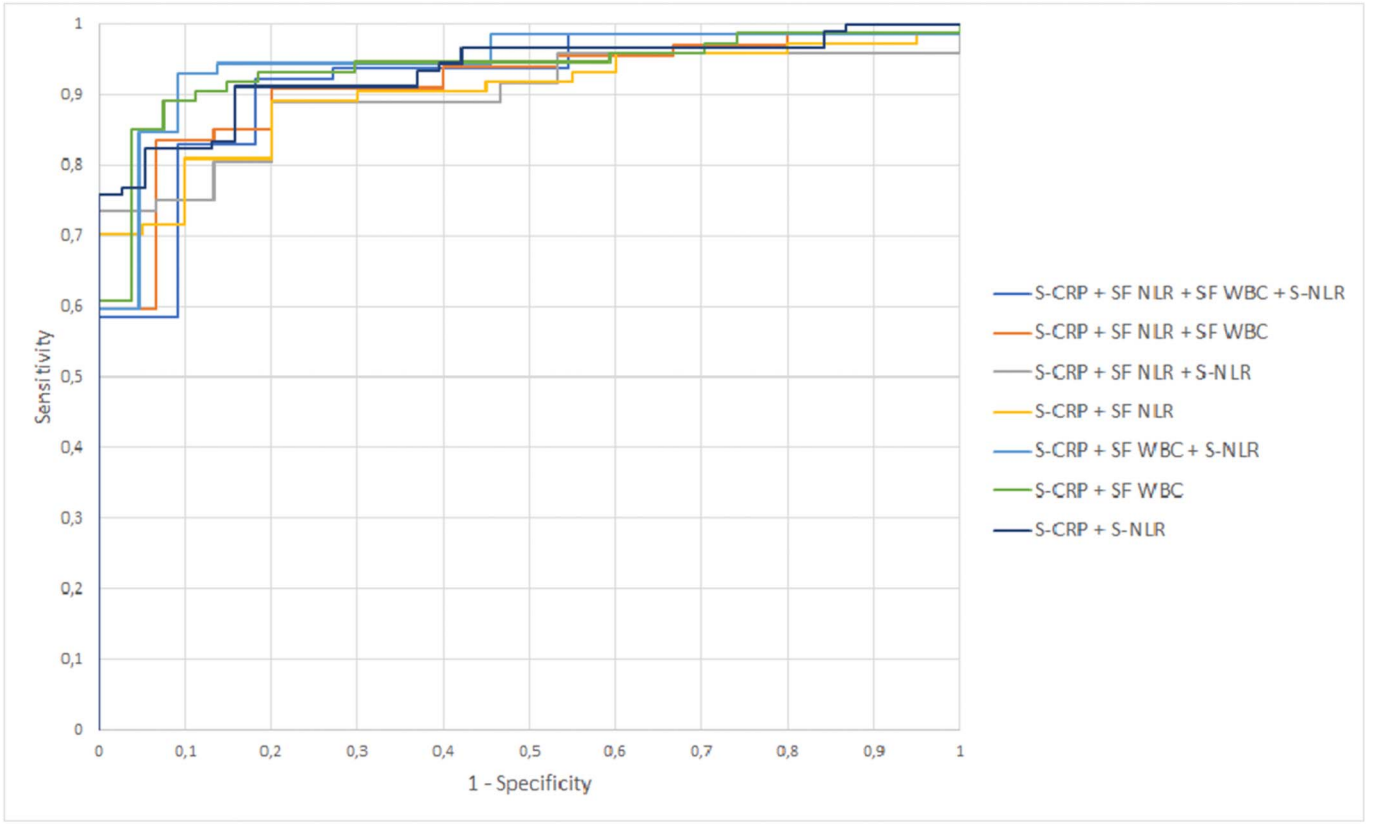

Fig. 4

ROC: combined markers. CRP = C-reactive protein test, NLR = neutrophil-lymphocyte ratio, ROC = receiver operating characteristic curve, S = serum, SF = synovial fluid, and WBC = white blood cells.

value. When calculating our data and determining the sensitivity and specificity by using the MSIS criteria of > 1 mg/dL or the EBJIS of > 10 mg/dL, we found sensitivities of 98.9 and 84.9% and specificities of 11.0% and 89.1%, respectively. Jiao et al.[16] found S-CRP to be the most valuable test to diagnose PJI with a COV of 14.26 mg/mL (Sensitivity = 71.1%; Specificity = 87.1%). Lower COV might become important in low virulent PJIs where bacteria are embedded in biofilms, which leads to a lower immune response[24]. Thus, using a higher COV could lead to higher false-negative results. In the contrary, using a low COV could lead to higher sensitivity and lower specificity, which could lead to unnecessary surgery and prolonged antibiotic treatment. This emphasizes the importance of not solely using one marker to diagnose infections.

Serum Neutrophil-Lymphocyte Ratio

The S-NLR is an established marker for inflammation and uses neutrophils, which play a critical role in the innate immune response by acting as the first line of defense against bacterial infections, and lymphocytes, which form part of the adaptive immunity and target specific pathogens[24]. Neutrophils reach a peak value by postoperative day 2 (POD) and preoperative values by POD 21, while lymphocytes reach a low by POD 2 and preoperative values by POD 14 to 21[12,24]. This lymphocytopenia occurs because the various anti-inflammatory cytokines released in the bloodstream during the process of sepsis, or disease, can induce immunosuppression, subsequently leading to apoptosis of a large number of lymphocytes, reducing the overall lymphocyte count throughout the body[12]. Therefore, S-NLR might be beneficial in the early detection of PJIs.

We tried to determine the highest specificity at the cost of the sensitivity to use S-NLR as a "rule-in test" rather than a screening test[10]. This is further supported by Festa et al.[12] in their systematic review and meta-analysis who concluded that NLR demonstrated fair diagnostic accuracy and thus was not useful as a screening tool. In our study, we determined the S-NLR cutoff value was 3.659 (Sensitivity = 71.9%, Specificity = 88.5%). Multiple other studies determined COV ranging between 2.1 and 3.82[3,5,10,18,24]. Interestingly, Balato et al.[3] found that the S-NLR ratio showed the highest AUC compared with other ratios studied (Monocyte-Lymphocyte ratio, Platelet-Lymphocyte ratio, and Platelet volume ratio) but was less accurate than S-ESR and S-CRP. We found similarly that S-NLR ratio is considered a valuable test with an AUC of 0.803 but less valuable than S-CRP or SF-WBC individually. Salimi et al.[24] also concluded that S-NLR can be easily adopted by surgeons as a screening tool for PJI. In addition, NLR is cheap and readily available.

The S-NLR ratio as an individual marker, however, does demonstrate conflicting results with different sensitivities and specificities reported in the literature[10]. One reason for the

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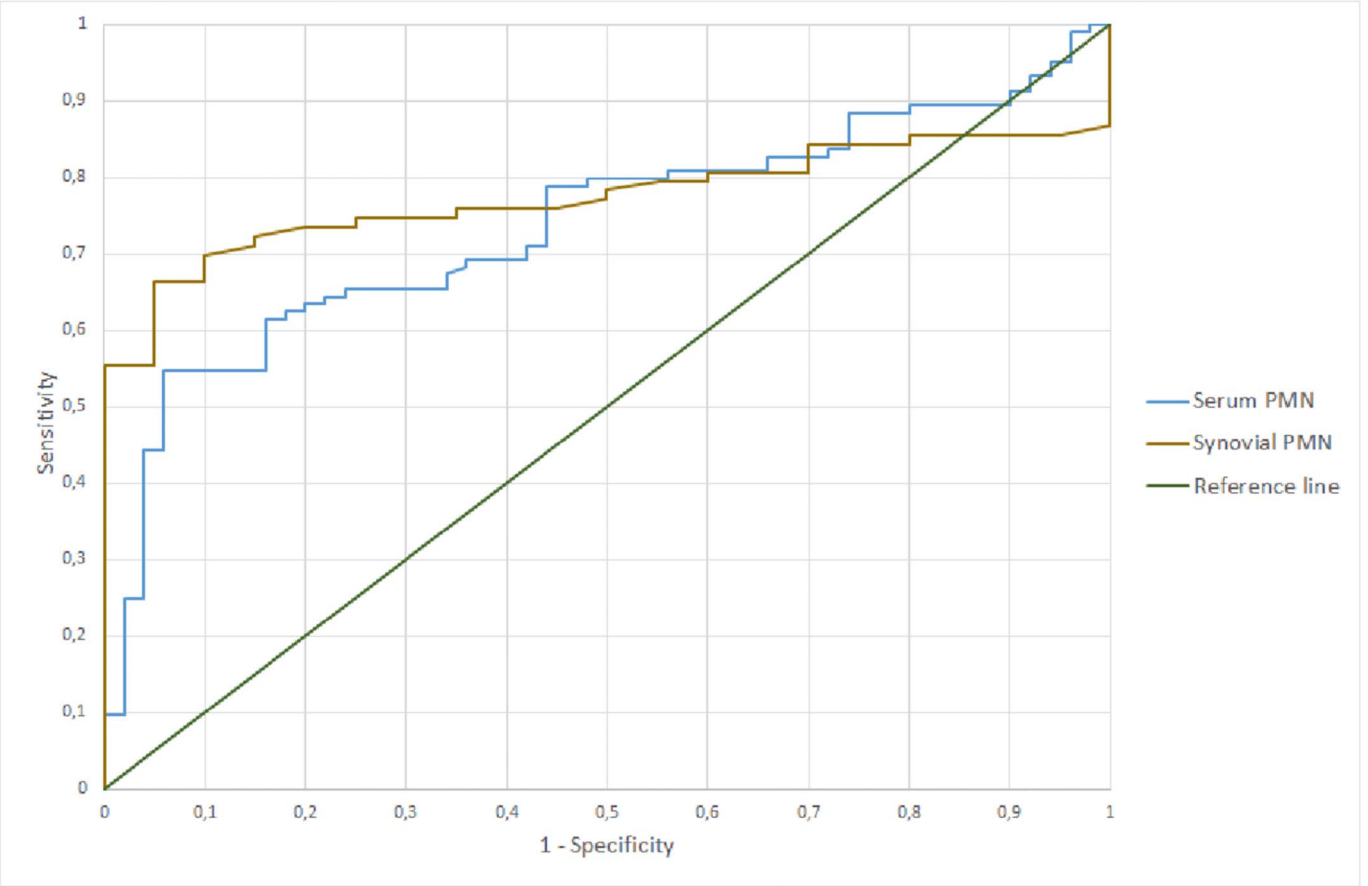

Fig. 5

ROC: combined markers. PMN = polymorphonuclear leucocytes and ROC = receiver operating characteristic curve.

differences can be the acuity of the PJI. In our study, we did not distinguish between acute (<90 days) and chronic (>90 days) infections. Yu et al.[30] determined that S-NLR was a more useful test in diagnosing acute (<90 days) PJI than S-CRP. Their study, however, was a retrospective study evaluating 121 patients and used a COV of 2.13 (AUC = 0.802; Sensitivity = 85%, Specificity = 68.3%). Another reason might be the utilization of different control groups and gender differences. Balato et al.[3] demonstrated that S-NLR achieved improved specificity in men. They proposed that one possible reason could be the expression of different sex hormones. They proposed 2 different cutoffs for men and women (men NLR ≥ 2.51; Women ≥ 2.46). With their optimal COV of 2.46, they had an AUC of 0.70 with a sensitivity of 61.6% and specificity of 78.3%.

Synovial Fluid White Blood Cell Count

In a recent systematic review and meta-analysis[26], SF-WBC was found to be a valuable test in diagnosing PJIs with a sensitivity of 92.4% and a specificity of 90.1% (Youden index 0.83). The ultimate COV is yet to be determined for acute and chronic PJIs with multiple values proposed ranging from 1,100 to 27,800 cells/microliter[13,22,27]. The MSIS[22] and EBJIS criteria use >3,000 cells/μL for diagnosing PJIs. Intra-articular blood and the inflammatory process of recent surgery can elevate the WBCs in the SF[13]. Not only do SF-WBC counts differ in patients who have acute and chronic PJIs, but it seems that SF-WBC is also joint specific[13]. The COV ranged between 6,130 and 27,800 cells/μL for acute PJI[13]. In this study, we determined a new COV for SF-WBC of 5,750 cells/μL, which produced the highest sensitivity and specificity.

Combination of Tests

Inherently, it makes sense that combining diagnostic tests might improve diagnostic accuracy. Multiple studies have tried to find the ideal combination[9]. Denyer et al.[9] demonstrated a high AUC (0.97) with the combination of S-ESR, S-CRP, SF-WBC, SF-PMN, and platelet volume ratio (Sensitivity = 94.3% and Specificity = 88.9%). Even though they did demonstrate a higher AUC than our current study, it involves multiple tests and calculations to be performed and might be cumbersome to implement in everyday practice. We tried to determine a combination that is easy and quick to determine and apply with high diagnostic accuracy. In our study, combining S-CRP + SF-WBC + S-NLR yielded the highest AUC of 0.946 (Sensitivity = 93.0%, Specificity = 90.9%). To our knowledge, this is the first study to combine S-CRP, SF-WBC, and S-NLR to predict PJI. All these tests are readily available, and it would be easy for clinicians to adopt these COVs to help diagnose PJI and total joint arthroplasty.

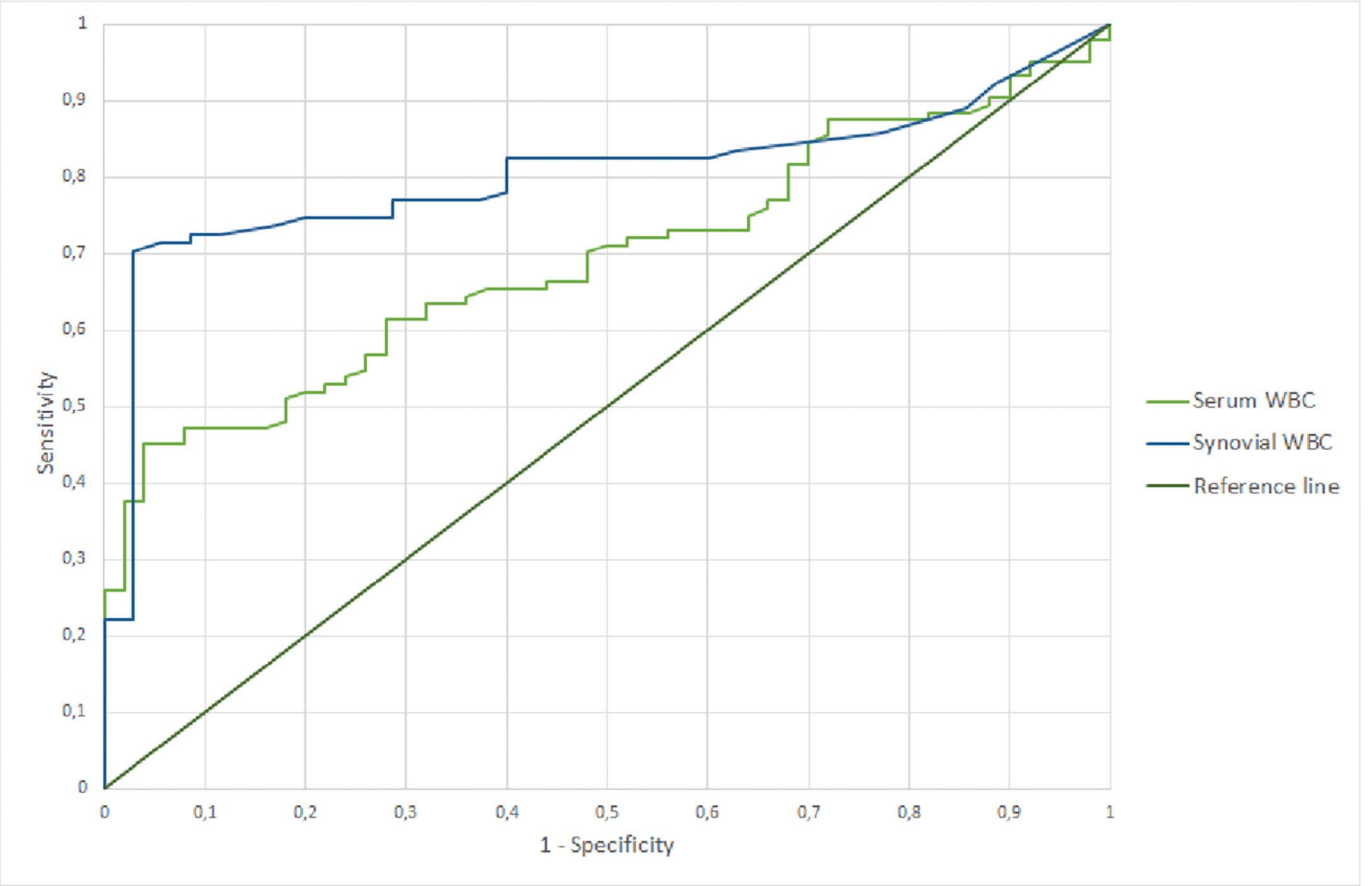

Fig. 6

ROC: individual markers. ROC = receiver operating characteristic curve and WBC = white blood cells.

It is important to note that alternate diagnostic algorithms (MSIS, EBJIS) are not only validated but also demonstrated very high sensitivities and specificities[22]. The goal of this study was not to replace these modalities but to add to the existing literature to enable surgeons in diagnosing PJIs. Some of the alternative modalities do include diagnostic tests (D-Dimer, polymerase chain reaction, Alpha-Defensin) that are expensive and not readily available. By adding easily obtainable and relatively inexpensive tests can aid surgeons in decision making.

This study acknowledges several limitations in using combined markers for diagnosing PJI across diverse populations and settings. Key challenges include variability in patient populations, marker specificity, cutoff thresholds, and external factors such as medications, age, and comorbidities. Retrospective design biases, missing data, and the tertiary academic center setting limit generalizability. The exclusion of Alpha-defensin and ESR due to institutional policies, and the inability to assess acute vs. chronic PJIs, further constrains findings. In addition, antibiotic usage before testing was not considered. Intraoperative cultures and histological analysis were used to select participants for the study according to MSIS and EBJIS criteria, but the results of the cultures and analysis were not documented. Despite these limitations, diverse surgeon participation enhances the generalizability, supporting study reliability.

Conclusion

The combination of S-CRP, SF-WBC, and S-NLR provides a practical and cost-effective approach for diagnosing PJI with high sensitivity and specificity. However, it should be used in conjunction with a thorough clinical examination and other diagnostic modalities, as no single test offers perfect diagnostic accuracy. It is, however, important to use this in combination with a thorough clinical and physical examination as well as other modalities. ■

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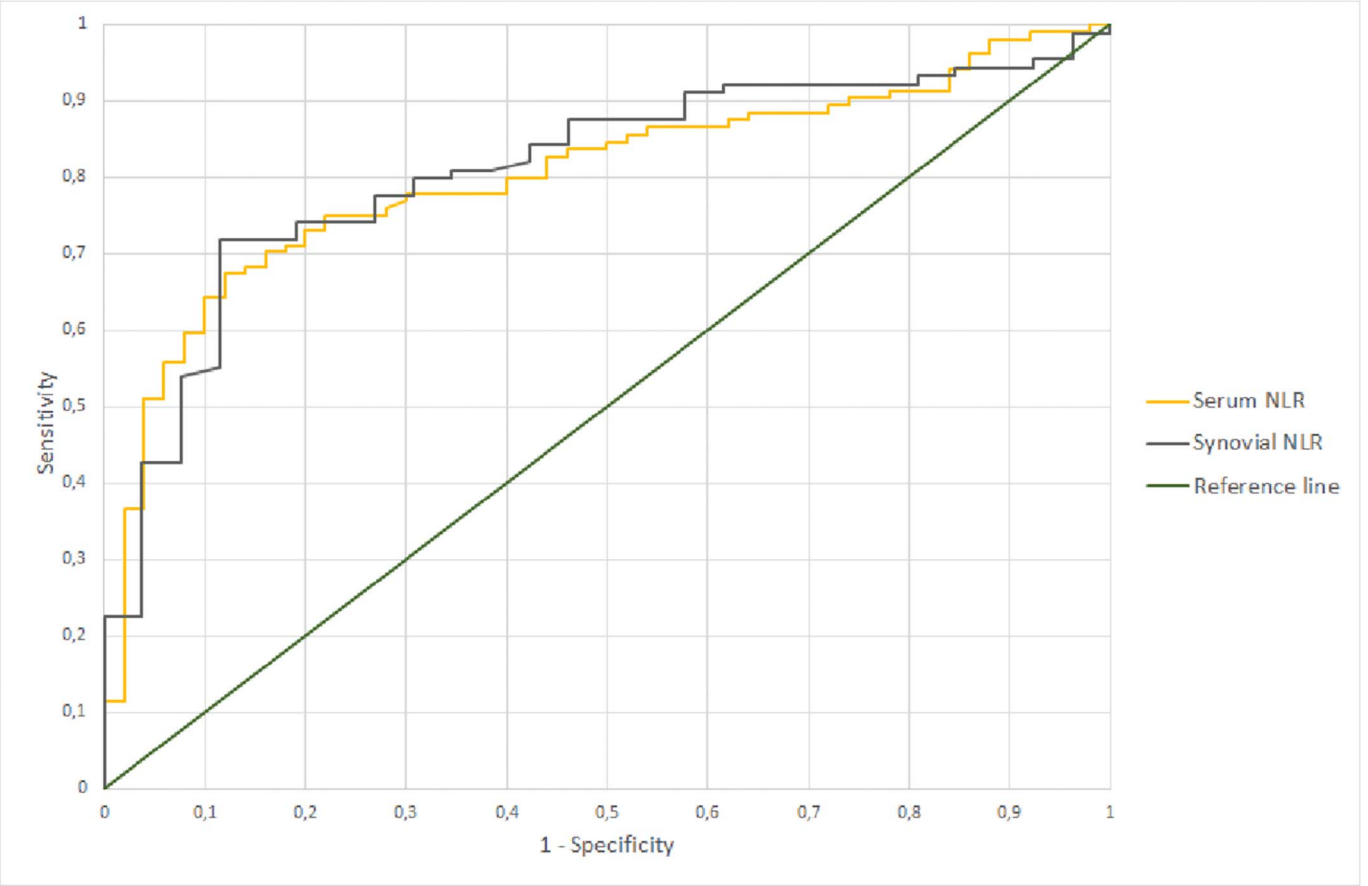

Fig. 7

ROC: combined markers. ROC = receiver operating characteristic curve and NLR = neutrophil-lymphocyte ratio.

TABLE V Combination of the Variables*

Combination	AUC	p	Sensitivity (%)	Specificity (%)
S-CRP + SF-WBC + S-NLR	0.946	≤0.001	93	90.9
S-CRP + SF-WBC	0.937	≤0.001	89.2	92.6
S-CRP + S-NLR	0.933	≤0.001	82.4	94.7
S-CRP + SF-NLR + SF-WBC + S-NLR	0.916	≤0.001	92.3	81.8
S-CRP + SF-NLR + SF-WBC	0.913	≤0.001	83.6	93.3
S-CRP + SF-NLR	0.903	≤0.001	81.1	90

*AUC = area under the receiver operating characteristic curve, S-CRP = serum CRP, SF NLR = synovial neutrophil-lymphocyte ratio, SF WBC = synovial fluid white blood cell count, and S-NLR = serum neutrophil lymphocyte ratio.

References

1. World Medical Association. World medical association declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013; 310(20):2191-4.

2. Aslam M. Introducing Kolmogorov–Smirnov tests under uncertainty: an application to radioactive data. ACS Omega. 2020;5(1):914-7.

3. Balato G, Ascione T, Festa E, Di Gennaro D, Pandolfo G, Pagliano P. The diagnostic accuracy of neutrophils to lymphocytes ratio, platelets to lymphocytes ratio, monocytes to lymphocytes ratio, and platelets to mean platelet volume ratio in diagnosing periprosthetic knee infections. Are gender-specific cutoff values needed? J Arthroplasty. 2023;38(5):918-24.

4. Barton CB, Wang DL, An Q, Brown TS, Callaghan JJ, Otero JE. Two-stage exchange arthroplasty for periprosthetic joint infection following total hip or knee arthroplasty is associated with high attrition rate and mortality. J Arthroplasty. 2020;35(5):1384-9.

5. Berbari E, Mabry T, Tsaras G, Spangehl M, Erwin PJ, Murad MH, Steckelberg J, Osmon D. Inflammatory blood laboratory levels as markers of prosthetic joint infection: a systematic review and meta-analysis. J Bone Joint Surg Am. 2010; 92(11):2102-9.

6. Carli AV, Abdelbary H, Ahmadzai N, Cheng W, Shea B, Hutton B, Sniderman J, Philip Sanders BS, Esmaeilisaraji L, Skidmore B, Gauthier-Kwan OY, Bunting AC, Gauthier P, Crnic A, Logishetty K, Moher D, Fergusson D, Beaulé PE. Diagnostic accuracy of serum, synovial, and tissue testing for chronic periprosthetic joint infection after hip and knee replacements: a systematic review. J Bone Joint Surg Am. 2019;101(7):635-49.

7. Coates T. Laboratory Evaluation of Neutrophil Disorders. UpToDate; 2023. Available at: https://www.uptodate.com/contents/laboratory-evaluation-of-neutrophil-disorders. Accessed April 1, 2024.

8. De Hond AAH, Steyerberg EW, Van Calster B. Interpreting area under the receiver operating characteristic curve. Lancet Digit Health. 2022;4(12):e853-e855.

9. Denyer S, Eikani C, Sheth M, Schmitt D, Brown N. Utility of blood cell ratio combinations for diagnosis of periprosthetic joint infection. Arthroplasty Today. 2023;23:101195.

10. Dilley JE, Seetharam A, Meneghini RM, Kheir MM. Synovial fluid absolute neutrophil count and neutrophil-to-lymphocyte ratio are not superior to polymorphonuclear percentage in detecting periprosthetic joint infection. J Arthroplasty. 2023; 38(1):146-51.

11. Elm EV, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ. 2007;335(7624): 806-8.

12. Festa E, Ascione T, Bernasconi A, Di Gennaro D, Basso MA, Guarino A, Balato G. Diagnostic performance of neutrophil to lymphocyte ratio, monocyte to lymphocyte ratio, platelet to lymphocyte ratio, and platelet to mean platelet volume ratio in periprosthetic hip and knee infections: a systematic review and meta-analysis. Diagnostics. 2022;12(9):2033.

13. Gazendam A, Wood TJ, Tushinski D, Bali K. Diagnosing periprosthetic joint infection: a scoping review. Curr Rev Musculoskelet Med. 2022;15(3):219-29.

14. Golge U, Kaymaz B, Pazarci O, Kilinc S, Öztemür Z, Bulut O. Neutrophil to lymphocyte ratio may be a diagnostic marker for prosthetic joint infection. Ann Clin Anal Med. 2016;7. Available at: https://archive.org/download/neutrophil-to-lymphocyte-ratio-may-be-a-diagnostic-marker-for-prosthetic-joint-infection/3918.pdf. Accessed April 2, 2024.

15. Hajian-Tilaki K. Receiver operating characteristic (ROC) curve analysis for medical diagnostic test evaluation. Caspian J Intern Med. 2013;4(2):627-35.

16. Jiao J, Huang J, Chen X, Jin Y. Albumin to Globulin ratio, neutrophil to lymphocyte ratio, and Globulin levels do not outperform ESR or CRP when diagnosing periprosthetic joint infection. BMC Musculoskelet Disord. 2022;23(1):404.

17. Kapadia BH, Banerjee S, Cherian JJ, Bozic KJ, Mont MA. The economic impact of periprosthetic infections after total hip arthroplasty at a specialized tertiary-care center. J Arthroplasty. 2016;31(7):1422-6.

18. Klemt C, Tirumala V, Smith EJ, Xiong L, Kwon Y-M. Complete blood platelet and lymphocyte ratios increase diagnostic accuracy of periprosthetic joint infection following total hip arthroplasty. Arch Orthop Trauma Surg. 2023;143(3):1441-9.

19. Kurtz SM, Lau E, Watson H, Schmier JK, Parvizi J. Economic burden of periprosthetic joint infection in the United States. J Arthroplasty. 2012;27(8 Suppl):61-5.e1.

20. McNally M, Sousa R, Wouthuyzen-Bakker M, Chen AF, Soriano A, Vogely HC, Clauss M, Higuera CA, Trebše R. The EBJIS definition of periprosthetic joint infection: a practical guide for clinicians. Bone Joint J. 2021;103-B(1):18-25.

21. Mishra P, Singh U, Pandey C, Mishra P, Pandey G. Application of student's t-test, analysis of variance, and covariance. Ann Card Anaesth. 2019;22(4):407-11.

22. Parvizi J, Tan TL, Goswami K, Higuera C, Della Valle C, Chen AF, Shohat N. The 2018 definition of periprosthetic hip and knee infection: an evidence-based and validated criteria. J Arthroplasty. 2018;33(5):1309-14.e2.

23. Premkumar A, Kolin DA, Farley KX, Wilson JM, McLawhorn AS, Cross MB, Sculco PK. Projected economic burden of periprosthetic joint infection of the hip and knee in the United States. J Arthroplasty. 2021;36(5):1484-9.e3.

24. Salimi M, Karam JA, Willman M, Willman J, Lucke-Wold B, Khanzadeh S, Mirghaderi P, Parvizi J. Neutrophil to lymphocyte ratio and periprosthetic joint infection: a systematic review and meta-analysis. J Arthroplasty. 2024;39(3):831-8.

25. Sigmund IK, Holinka J, Staats K, Sevelda F, Lass R, Kubista B, Giurea A, Windhager R. Inferior performance of established and novel serum inflammatory markers in diagnosing periprosthetic joint infections. Int Orthop. 2021;45(4):837-46.

26. Sukhonthamarn K, Tan TL, Xu C, Kuo F-C, Lee MS, Citak M, Gehrke T, Goswami K, Parvizi J. Determining diagnostic thresholds for acute postoperative periprosthetic joint infection. J Bone Joint Surg Am. 2020;102(23):2043-8.

27. Tang H, Xu J, Yuan W, Wang Y, Yue B, Qu X. Reliable diagnostic tests and thresholds for preoperative diagnosis of non-inflammatory arthritis periprosthetic joint infection: a meta-analysis and systematic review. Orthop Surg. 2022;14(11): 2822-36.

28. Varady NH, Schwab P-E, Kheir MM, Dilley JE, Bedair H, Chen AF. Synovial fluid and serum neutrophil-to-lymphocyte ratio: novel biomarkers for the diagnosis and prognosis of native septic arthritis in adults. J Bone Joint Surg Am. 2022;104(17): 1516-22.

29. Ye Y, Chen W, Gu M, Liu Q, Xian G, Pan B, Zheng L, Chen X, Zhang Z, Sheng P. Limited value of serum neutrophil-to-lymphocyte ratio in the diagnosis of chronic periprosthetic joint infection. J Orthop Traumatol. 2021;22(1):37.

30. Yu B-Z, Fu J, Chai W, Hao L-B, Chen J-Y. Neutrophil to lymphocyte ratio as a predictor for diagnosis of early Periprosthetic joint infection. BMC Musculoskelet Disord. 2020;21(1):706.

31. Zhao G, Chen J, Wang J, Wang S, Xia J, Wei Y, Wu J, Huang G, Chen F, Shi J, Lyu J, Liu C, Huang X. Predictive values of the postoperative neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio for the diagnosis of early periprosthetic joint infections: a preliminary study. J Orthop Surg Res. 2020;15(1):571.

32. Available at: https://www.aaos.org/globalassets/quality-and-practice-resources/pji/pji-clinical-practice-guideline-final-2-17-21.pdf. Accessed November 2024.