Follow us @BoneJointOpen

Freely available online OPEN ACCESS

KNEE

Diagnosing periprosthetic joint infection

A VALIDATION STUDY OF BLOOD CELL RATIO COMBINATIONS

S. Denyer,
C. Eikani,
M. Sheth,
D. Schmitt,
N. Brown

From Loyola University Medical Center, Maywood, Illinois, USA

Aims

The diagnosis of periprosthetic joint infection (PJI) can be challenging as the symptoms are similar to other conditions, and the markers used for diagnosis have limited sensitivity and specificity. Recent research has suggested using blood cell ratios, such as platelet-to-volume ratio (PVR) and platelet-to-lymphocyte ratio (PLR), to improve diagnostic accuracy. The aim of the study was to further validate the effectiveness of PVR and PLR in diagnosing PJI.

Methods

A retrospective review was conducted to assess the accuracy of different marker combinations for diagnosing chronic PJI. A total of 573 patients were included in the study, of which 124 knees and 122 hips had a diagnosis of chronic PJI. Complete blood count and synovial fluid analysis were collected. Recently published blood cell ratio cut-off points were applied to receiver operating characteristic curves for all markers and combinations. The area under the curve (AUC), sensitivity, specificity, and positive and negative predictive values were calculated.

Results

The results of the analysis showed that the combination of ESR, CRP, synovial white blood cell count (Syn. WBC), and polymorphonuclear neutrophil percentage (PMN%) with PVR had the highest AUC of 0.99 for knees, with sensitivity of 97.73% and specificity of 100%. Similarly, for hips, this combination had an AUC of 0.98, sensitivity of 96.15%, and specificity of 100.00%.

Conclusion

This study supports the use of PVR calculated from readily available complete blood counts, combined with established markers, to improve the accuracy in diagnosing chronic PJI in both total hip and knee arthroplasties.

Cite this article: *Bone Jt Open* 2023;4-11:881–888.

Keywords: Periprosthetic joint infection, Total knee arthroplasty, Total hip arthroplasty

Introduction

Periprosthetic joint infection (PJI) is a severe complication following total hip arthroplasty (THA) or total knee arthroplasty (TKA), with reported rates as high as 2%.[1-3] Currently, the International Consensus Meeting has put out a guideline on PJI diagnosis,[4] but there is still no gold standard of diagnosis for PJI due to its complexity, similarity to other conditions, and lack of visibility on imaging. Common biomarkers used for the diagnosis of PJI include ESR, CRP, and synovial fluid analysis, including white blood cell count (Syn. WBC) and polymorphonuclear neutrophil percentage (PMN%). However, the use of these biomarkers has yielded variable sensitivity and specificity results.[5–7]

Previous research has evaluated a number of other biomarkers to be used as an adjunct in PJI diagnosis including synovial alpha defensin, synovial CRP, and D-dimer.[8–10] Of these, alpha defensin has become the most promising synovial fluid marker.[11,12] Despite this, there has been limited adoption of alpha defensin due to its high cost, time to obtain results (given

Correspondence should be sent to Steven Denyer; email: Steven.denyer@luhs.org

doi: 10.1302/2633-1462.411.BJO-2023-0094.R1

Bone Jt Open 2023;4-11:881–888.

the test is typically performed at an external lab), and recent studies questioning its accuracy.[13,14] Therefore, there is an immense need for a low-cost and widely available marker for the diagnosis of PJI.

Blood cells, including neutrophils, monocytes, and platelets, play a critical role in the immune response to inflammation and infection. Neutrophils, for instance, are among the first white blood cells to respond to sites of injury or infection, where they phagocytose and eliminate invading pathogens. Similarly, monocytes differentiate into macrophages, which phagocytose, and clear pathogens and cellular debris. Platelets are also involved in inflammation, promoting the recruitment of neutrophils to sites of injury or infection.[15] By measuring changes in the ratios of different blood cell types, we can gain valuable insights into the overall state of the immune response and the extent of ongoing inflammation or infection.

Platelet-to-volume ratio (PVR), defined as the ratio of platelet count to mean platelet volume (MPV), and platelet-to-lymphocyte ratio (PLR) have therefore been suggested as potential markers for PJI.[16,17] Tirumala et al[17] found that both PLR and PVR when combined with ESR, CRP, Syn. WBC, and PMN% achieved a high sensitivity and specificity for diagnosing PJI following TKA (PLR: 99.03% and 98.80%; PVR: 98.54% and 97.89%). Similarly, Klemt et al[16] showed a high sensitivity and specificity when combining PLR or PVR with the aforementioned established inflammatory and synovial markers for diagnosing PJI following THA (PLR: 97.9% and 98.5%; PVR: 94.2% and 94.5%).

These findings suggest that the combination of blood cell ratios may have improved diagnostic accuracy compared to the use of individual markers alone. Nevertheless, both of these studies were carried out in the same institution and their findings have not been validated on a new data set at a different institution. This is important, given that there are multiple variables, including the interval between blood sample collection and measurement, and the type of anticoagulant used, which can influence the reliability of these findings. The aim of this study was to confirm the effectiveness of PVR and PLR as an adjunct to the diagnosis of PJI in a distinct cohort of patients, who presented to a tertiary medical centre with a diverse patient population.

Methods

Data collection. In this comprehensive retrospective chart review, we systematically examined a cohort of patients who sought medical care at our esteemed university hospital between 1 January 2005 and 31 December 2022, due to the presence of a painful prosthetic joint. Our investigation specifically focused on individuals who underwent a knee aspiration procedure, encompassing those who were evaluated for PJI or underwent PJI exclusion measures before proceeding with aseptic revision for TKA. Our study was reviewed by the Institutional Review Board and received ethical approval. There was no informed consent for this study. Chronic PJI was identified through a manual chart review of medical records, using the definition established by the Infectious Diseases Society of America (IDSA, 2013) for the classification of chronic PJI.[18] All patients included in this study were diagnosed with chronic PJI based on IDSA standards and had a complete blood count drawn within 60 days of their revision procedure, and underwent a revision procedure if placed in the PJI group. Patients with a diagnosis of acute PJI were excluded from the study and defined per the International Consensus Meeting 2013 guidelines of diagnosis within 90 days of index procedure.[19] The study population included patients with a history of primary arthroplasty, septic revisions, and aseptic revisions. Septic revisions included debridement, antibiotics, and implant retention (DAIR), and one-stage and two-stage reimplantation. Aseptic revisions included revisions for instability, loosening, malalignment, and fracture. Patients with a past medical history of rheumatoid arthritis, systemic lupus erythematosus, and metastatic cancer were also excluded from the study. Complete blood counts were obtained to collect neutrophil, lymphocyte, monocyte, and platelet counts, and to calculate the monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR), PLR, and PVR. Patients with cell counts and inflammatory markers beyond four weeks before revision or workup for PJI were also excluded. Syn. WBC and PMN% were also collected.

Patient demographics. A total of 283 patients with a TKA were included in the study (Table I). The non-PJI group consisted of 159 patients (53.5% female, 82.4% between the ages of 50 and 79 years, 67.3% white, 85.5% with a BMI of less than 40 kg/m^2) and the PJI group consisted of 124 patients (56.5% female, 79.8% between the ages of 50 and 79 years, 74.2% white, 76.6% with a BMI of less than 40 kg/m^2). The PJI group included various *Staphylococcus* species, *Streptococcus* species, *Pseudomonas* species, *Proteus mirabilis*, *Mycobacterium avium* complex, and *Cutibacterium acnes.* There was no significant difference between the two groups with regard to sex, age, race, and BMI. In terms of prior knee surgeries, the majority of patients in both groups had only had a primary TKA (87.1% in the PJI group and 94.3% in the non-PJI group).

A total of 289 patients with a THA were included in the study. The non-PJI group consisted of 167 patients (48.5% female, 72.5% between the ages of 50 and 79 years, 81.4% white, 90.4% with a BMI of less than 40 kg/m^2) and the PJI group consisted of 122 patients (44.3% female, 81.1% between the ages of 50 and 79 years, 87.7% white, 82% with a BMI of less than 40 kg/m^2). There was no significant difference between the two

Table I. Demographics for patients with a total knee arthroplasty.

Demographic	Knee PJI				Demographic	Hip PJI			
	No		Yes			No		Yes	
	N	%	N	%		N	%	N	%
Total patients	162	56.6	124	43.4	Total patients	167	57.8	122	42.2
Age					**Age**				
< 50 yrs	18	11.1	9	7.3	< 50 yrs	16	9.6	10	8.2
50 to 79 yrs	134	82.7	99	79.8	50 to 79 yrs	121	72.5	99	81.1
80 to 99 yrs	10	6.2	16	12.9	80 to 99 yrs	30	18	13	10.7
Sex					**Sex**				
Female	87	53.7	70	56.5	Male	86	51.5	68	55.7
Male	72	44.4	54	43.5	Female	81	48.5	54	44.3
Unknown	3	1.9	-	-	**Race**				
Race					White	136	81.4	107	87.7
White	110	67.9	92	74.2	Asian	2	1.2	1	0.8
Asian	2	1.2	-	-	Black	20	12	13	10.7
Black	39	24.1	24	19.4	Other	7	4.2	1	0.8
Other	8	4.9	8	6.5	Unknown	2	1.2	-	-
Unknown	3	1.9	-	-	**BMI (kg/m²)**				
BMI (kg/m²)					< 40	151	90.4	100	82
< 40	139	85.8	95	76.6	≥ 40	16	9.6	22	18
≥ 40	23	14.2	29	23.4	**Prior surgeries**				
Prior surgeries					DAIR THA	2	1.2	10	8.2
DAIR TKA	1	0.6	5	4	RTHA	9	5.4	3	2.5
MUA TKA	-	-	1	0.8	THA	156	92.8	109	88.5
RTKA	7	4.3	4	3.2					
Replant TKA	1	0.6	6	4.8					
TKA	150	92.6	108	87.1					
UKA	3	1.7	-	-					

DAIR, debridement, antibiotics, and implant retention; MUA, manipulation under anaesthesia; PJI, periprosthetic joint infection; RTHA, revision total hip arthroplasty; RTKA, revision total knee arthroplasty; THA, total hip arthroplasty; TKA, total knee arthroplasty; UKA, unicompartmental knee arthroplasty.

groups with regard to sex, age, race, and BMI. In terms of prior surgeries, the majority of patients in both groups only had a primary THA (92.8% in the PJI group and 91% in the non-PJI group). A small proportion of patients in both groups had had TKA (0.8% in the PJI group and 0.7% in the non-PJI group) and revision THA (2.5% in the PJI group and 5.4% in the non-PJI group) as their prior surgery.

Statistical analysis. Descriptive statistics such as mean, standard deviation (SD), and distribution were calculated for all serum and synovial markers. An independent-samples *t*-test was employed to compare the aseptic cohort (negative control group) with the septic cohort. Cut-off points for ESR, CRP, Syn. WBC, and PMN%, as determined by the Musculoskeletal Infection Society (MSIS) 2018 criteria for PJIs, were used.[4] Additionally, the recently published blood cell ratio cut-off points for PJI in knees and hips by Tirumala et al[17] and Klemt et al,[16] respectively, were applied in the analysis. Receiver operating characteristic curves for all markers were analyzed to calculate the area under the curve (AUC), as well as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The utility of combining cell ratios with serum markers and aspirate results was further evaluated using AUC, sensitivity, specificity, PPV, and NPV. A p-value of less than 0.05 was considered statistically significant for all tests. All statistical analyses were conducted using SAS software (SAS Institute, USA).

Results

Marker accuracy for diagnosing PJI following knee arthroplasty. The means and SDs of preoperative serum and synovial markers for patients with knee PJI (Knee PJI) and those without (Knee non-PJI group) are shown in Table II. The Knee non-PJI group had a mean ESR of 21.80 mm/h, CRP of 3.21 mg/l, Syn. WBC of 787.51 cells/ul, synovial PMN% of 27.05, platelet count of 238.90, MPV of 8.60, lymphocyte count of 1.8, monocyte count of 0.64, neutrophil count of 4.43, MLR of 0.35, NLR of 2.75, PVR of 27.69, and PLR of 148.50. The Knee PJI group had a mean ESR of 72.69 mm/h, CRP of 25.33 mg/l, Syn. WBC of 6,0612.13 cells/ul, synovial PMN% of 88.66, platelet count of 303.38, MPV of 8.23, lymphocyte count of 1.36, monocyte count of 0.83, neutrophil count of 7.72, MLR of 1, NLR of 12.54, PVR of 37.37, and PLR of 329.81. All of these markers were found to

Table II. Serum and synovial markers for periprosthetic joint infection and aseptic cohorts.

Preoperative marker – Knees	Knee non-PJI					Knee PJI					p-value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
ESR, mm/h	21.80	21.51	15.00	1.50	129.00	72.69	33.55	74.00	2.00	140.00	< 0.001
CRP, mg/l	3.21	9.04	0.70	0.10	59.00	25.33	43.32	12.00	0.10	252.00	< 0.001
Synovial WBC, cells/ul	787.51	1,145.62	340.00	0.00	4,500.00	60,612.13	77,916.17	37,200.00	510.00	511,639.00	< 0.001
Synovial PMN%	27.05	22.12	27.00	1.00	73.00	88.66	13.03	91.00	13.00	100.00	< 0.001
Platelet count	238.90	82.04	243.00	3.30	596.00	303.38	129.70	295.00	47.00	732.00	< 0.001
Mean platelet volume	8.60	1.13	8.50	6.60	12.00	8.23	0.90	8.30	6.20	10.00	0.03
Lymphocyte count	1.80	0.64	1.70	0.60	3.90	1.36	0.84	1.30	0.10	5.40	< 0.001
Monocyte count	0.64	0.62	0.50	0.10	6.40	0.83	0.36	0.80	0.20	2.00	0.002
Neutrophil count	4.43	2.02	3.90	0.40	11.00	7.72	4.17	6.80	0.00	24.00	< 0.001
Monocyte-to-lymphocyte ratio	0.35	0.20	0.29	0.02	1.33	1.00	1.06	0.63	0.13	5.67	< 0.001
Neutrophil-to-lymphocyte ratio	2.75	1.80	2.18	0.31	14.83	12.54	25.28	5.06	0.00	205.00	< 0.001
Platelet-to-volume ratio	27.69	12.23	26.63	0.37	82.78	37.37	18.48	31.60	13.91	97.01	< 0.001
Platelet-to-lymphocyte ratio	148.50	69.20	145.00	1.50	405.56	329.81	345.13	226.11	53.59	2,980.00	< 0.001
Preoperative marker – Hips	**Hip non-PJI**					**Hip PJI**					**p-value**
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
ESR, mm/h	26.75	24.09	19.00	3.00	114.00	67.43	33.43	67.00	7.00	140.00	< 0.001
CRP, mg/l	3.30	7.76	1.00	0.10	42.00	22.88	48.11	8.35	0.10	344.00	< 0.001
Synovial WBC, cells/ul	3,949.32	8,980.83	242	5	36,000.00	64,782.56	92,807.47	26,600.00	4	444,600.00	0.0016
Synovial PMN%	54.46	33.31	53.00	4.00	98.00	85.75	21.02	93.00	2.00	100.00	< 0.001
Platelet count	249.67	91.84	241.50	69.00	727.00	308.31	143.27	286.00	38.00	929.00	< 0.001
Mean platelet volume	8.58	0.99	8.50	6.40	11.00	8.12	0.97	8.05	6.20	10.00	0.0031
Lymphocyte count	1.56	0.74	1.40	0.30	4.10	1.34	0.65	1.20	0.20	3.10	0.0125
Monocyte count	0.69	0.41	0.60	0.20	4.00	0.79	0.37	0.70	0.20	2.30	0.0406
Neutrophil count	5.21	2.31	4.90	1.20	13.00	7.14	3.93	6.30	1.40	21.00	< 0.001
Monocyte-to-lymphocyte ratio	0.57	0.54	0.41	0.10	4.00	0.78	0.67	0.55	0.14	4.33	0.0067
Neutrophil-to-lymphocyte ratio	5.11	6.18	3.22	0.59	40.00	8.16	9.69	4.61	0.61	67.00	0.0041
Platelet-to-volume ratio	29.18	11.76	27.71	9.88	76.57	40.14	20.61	36.37	9.20	131.19	< 0.001
Platelet-to-lymphocyte ratio	203.88	142.87	167.65	40.59	826.00	290.62	228.45	205.56	63.33	1,363.33	< 0.001

PJI, periprosthetic joint infection; PMN%, polymorphonuclear neutrophil percentage; SD, standard deviation; WBC, white blood cell count.

Table III. Receiver operating characteristic curve analysis for serum and synovial makers.

Type of PJI	NLR	MLR	PVR	PLR	ESR (> 30 mm/h)	CRP (> 10 mg/l)	Syn. WBC (> 3,000 cells/ul)	PMN% (> 80)
Knee								
AUC	0.80	0.80	0.63	0.75	0.83	0.76	0.90	0.95
Cut-off point	3.62	0.44	30.82	234.13	30.00	10.00	3,000.00	80.00
Sensitivity, %	74.31	65.79	36.11	62.28	87.93	58.62	89.89	89.53
Specificity, %	75.59	82.95	90.00	87.20	78.10	93.33	89.74	100.00
PPV	72.32	77.32	74.29	81.61	81.60	90.67	95.24	100.00
NPV	77.42	73.29	63.78	71.71	85.42	67.12	79.55	80.43
Hip								
AUC	0.64	0.64	0.69	0.64	0.77	0.70	0.81	0.73
Cut-off point	3.46	0.41	27.80	237.90	30.00	10.00	3,000.00	80.00
Sensitivity, %	49.12	66.38	53.03	80.17	84.17	46.67	82.54	82.54
Specificity, %	77.37	58.82	78.70	41.61	69.47	92.55	80.00	62.50
PPV	64.37	57.89	60.34	53.76	77.69	88.89	91.23	85.25
NPV	64.63	67.23	73.28	71.25	77.65	57.62	64.52	57.69

AUC, area under the curve; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; NPV, negative predictive value; PJI, periprosthetic joint infection; PLR, platelet-to-lymphocyte ratio; PMN%, polymorphonuclear neutrophil percentage; PPV, positive predictive value; PVR, platelet-to-volume ratio; Syn. WBC, synovial white blood cell count.

Table IV. Receiver operating characteristic curve analysis for marker combinations.

Marker combination	AUC	Sensitivity, %	Specificity, %	PPV	NPV
Knee PJI					
ESR + CRP	0.88	91.15	75.49	80.47	88.51
Syn. WBC + PMN%	0.98	89.53	100.00	100.00	80.00
ESR + CRP + Syn. WBC + PMN%	0.99	94.87	100.00	100.00	87.50
ESR + CRP + Syn. WBC + PMN% + NLR	0.99	95.45	100.00	100.00	87.50
ESR + CRP + Syn. WBC + PMN% + MLR	0.99	97.10	100.00	100.00	91.67
ESR + CRP + Syn. WBC + PMN% + PVR	0.99	97.73	100.00	100.00	91.67
ESR + CRP + Syn. WBC + PMN% + PLR	0.99	97.10	100.00	100.00	91.67
Hip PJI					
ESR + CRP	0.83	89.83	65.96	76.81	83.78
Syn. WBC + PMN%	0.82	83.61	79.17	91.07	65.52
ESR + CRP + Syn. WBC + PMN%	0.88	79.66	85.00	94.00	58.62
ESR + CRP + Syn. WBC + PMN% + NLR	0.87	90.20	76.47	92.00	72.22
ESR + CRP + Syn. WBC + PMN% + MLR	0.87	90.57	76.47	92.31	72.22
ESR + CRP + Syn. WBC + PMN% + PVR	0.98	96.15	100.00	100.00	87.50
ESR + CRP + Syn. WBC + PMN% + PLR	0.90	90.57	76.47	92.31	72.22

CRP and ESR measured in mg/l and mm/h, respectively.
MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; NPV, negative predictive value; PJI, periprosthetic joint infection; PLR, platelet-to-lymphocyte ratio; PMN%, polymorphonuclear neutrophil percentage; PPV, positive predictive value; PVR, platelet-to-volume ratio; Syn. WBC, synovial white blood cell count.

have a significant difference between the two groups ($p < 0.05$).

ROC analysis for serum and synovial markers in patients with knee PJIs are shown in Table III. The cut-off points used for the blood cell ratios (NLR, MLR, PVR, and PLR) were described by Tirumala et al,[17] while the cut-offs for ESR, CRP, Syn. WBC, and PMN% were described by MSIS criteria. NLR had a cut-off of 3.62, sensitivity of 61.47%, specificity of 87.90%, and AUC of 0.80. MLR had a cut-off of 0.44, sensitivity of 65.79%, specificity of 82.54%, and AUC of 0.80. PVR had a cut-off of 30.82, sensitivity of 36.11%, specificity of 89.77%, and AUC of 0.63. PLR had a cut-off of 234.13, sensitivity of 62.28%, specificity of 86.89%, and AUC of 0.75. ESR had a cut-off of 30.00, sensitivity of 87.93%, specificity of 77.67%, and AUC of 0.83. CRP had a cut-off of 10.00, sensitivity of 58.62%, speicificty of 93.20%, and AUC of 0.76. Syn. WBC had a cut-off of 3,000.00, sensitivity of 89.89%, specificity of 89.74%, and AUC of 0.90. PMN% had a cut-off of 80.00, sensitivity of 89.53%, specificity of 100.00%, and AUC of 0.95.

We then performed a ROC analysis for marker combinations for knee PJIs, shown in Table IV. ESR, CRP, Syn. WBC, PMN%, and NLR combination had an AUC of 0.99,

sensitivity of 95.45%, and specificity of 100%. ESR, CRP, Syn. WBC, PMN%, and MLR combination had an AUC of 0.99, sensitivity of 97.10%, and specificity of 100%. ESR, CRP, Syn. WBC, PMN%, and PVR combination had an AUC of 0.99, sensitivity of 97.73%, and specificity of 100%. ESR, CRP, Syn. WBC, PMN%, and PLR combination had an AUC of 0.99, sensitivity of 97.10%, and specificity of 100%. Less significant combinations are shown in Supplementary Table i.

Marker accuracy for diagnosing PJI following hip arthroplasty. Similarly, Table II shows the preoperative serum and synovial markers for patients with a hip PJI (hip PJI group) and those without (hip non-PJI group). The hip non-PJI group had a mean ESR of 26.75 mm/h, CRP of 3.3 mg/l, Syn. WBC of 3,949.32 cells/ul, synovial PMN% of 54.46, platelet count of 249.67, platelet volume of 8.58, lymphocyte count of 1.56, monocyte count of 0.69, neutrophil count of 5.21, MLR of 0.57, NLR of 5.11, PVR of 29.18, and PLR of 203.88. In contrast, the hip PJI group had a mean ESR of 67.43 mm/h, CRP of 22.88 mg/l, Syn. WBC of 64,782.56 cells/ul, synovial PMN% of 85.75, platelet count of 308.31, platelet volume of 8.12, lymphocyte count of 1.34, monocyte count of 0.79, neutrophil count of 7.14, MLR of 0.78, NLR of 8.16, PVR of 40.14, and PLR of 290.62. All of these markers were found to have significant differences between the two groups ($p < 0.05$).

ROC analysis for serum and synovial markers in patients with hip PJI is shown in Table III. The cut-off points used for the blood cell ratios (NLR, MLR, PVR, and PLR) were described by Klemt et al,[16] while the cut-offs for ESR, CRP, Syn. WBC, and PMN% are described by the MSIS criteria. NLR had a cut-off of 3.46, sensitivity of 49.12%, specificity of 77.37%, and AUC of 0.64. MLR had a cut-off of 0.41, sensitivity of 66.38%, specificity of 58.82%, and AUC of 0.64. PVR had a cut-off of 27.80, sensitivity of 53.03%, specificity of 78.70%, and AUC of 0.69. PLR had a cut-off of 237.90, sensitivity of 80.17%, specificity of 41.61%, and AUC of 0.64. ESR had a cut-off of 30.00, sensitivity of 84.17%, specificity of 69.47%, and AUC of 0.77. CRP had a cut-off of 10.00, sensitivity of 46.67%, specificity of 92.55%, and AUC of 0.70. Syn. WBC had a cut-off of 3,000.00, sensitivity of 82.54%, specificity of 80.00%, and AUC of 0.81. PMN% had a cut-off of 80.00, sensitivity of 82.54%, specificity of 62.50%, and AUC of 0.73.

In Table IV, the ROC analysis for marker combinations for patients with hip PJIs is presented. The combination of ESR + CRP + Syn. WBC + PMN% + NLR had an AUC of 0.87, sensitivity of 90.20%, and specificity of 76.47%. The combination of ESR + CRP + Syn. WBC + PMN% + MLR had an AUC of 0.87, sensitivity of 90.57%, and specificity of 76.47%. The combination of ESR + CRP + Syn. WBC + PMN% + PVR had an AUC of 0.98, sensitivity of 96.15%, and specificity of 100.00%. Finally, the combination of ESR + CRP + Syn. WBC + PMN% + PLR had an AUC of 0.90, sensitivity of 90.57%, and specificity of 76.47%. These results suggest that the combination of markers may improve diagnostic accuracy for hip PJI.

Discussion

Despite numerous innovative techniques employed for diagnosing PJI, a consensus has not been reached regarding the optimal diagnostic approach. Various assays, such as D-dimer, synovial alpha defensin, synovial leucocyte esterase, and synovial CRP, have been investigated in recent literature but have not been widely implemented due to their potential for high cost, lengthy turnaround times, and often variable results.[7,12–14,20–22] Blood cell ratios, namely PLR, NLR, MLR, and PVR, obtained during routine complete blood count, have been proposed in recent studies to enhance the accuracy of PJI diagnosis, offering a cost-effective and time-efficient alternative.[23] Moreover, two recent studies demonstrated that the use of PVR or PLR combined with established serum and synovial markers (CRP, ESR, Syn. WBC, and PMN%) increased the accuracy for diagnosing PJI.[16,17] However, these studies were conducted in a single institution and have not been validated. Thus, we sought to evaluate the effectiveness of the proposed cut-off points for PVR and PLR in diagnosing PJI in both knees and hips using a distinct patient population.

In our study population, the combination of serum markers, synovial markers, and the addition of PVR in the knee cohort was found to have an AUC of 1.00, a sensitivity of 97.73%, and a specificity of 100%. Similarly, adding PLR to these markers yielded a high AUC of 0.99, a sensitivity of 97.10%, and a specificity of 100%. Furthermore, the hip cohort showed similar results with the combination of serum markers, synovial markers, and PVR having an AUC of 0.98, a sensitivity of 96.15%, and a specificity of 100%. Conversely, the addition of PLR yielded slightly less confirmatory results with an AUC of 0.90, a sensitivity of 90.57%, and a specificity of 76.47%.

These findings support the use of PVR or PLR in combination with established synovial and serum markers to improve the diagnosis of periprosthetic infection in knees and hips. While our results help to validate these studies, we have also included patients who have undergone revision or reimplantation in the past to further widen the scope of these markers to test their diagnostic potential. Additionally, we increased the blood collection time to within four weeks prior to revision surgery or aspiration. Furthermore, we are a tertiary medical centre, and it is important to note that some of our patients undergo their initial medical assessments, including laboratory tests, at other medical centres before they are transferred to our institution. Despite these differences, our study showed similar results to those reported by Tirumala et al[17] and Klemt et al.[16]

Recent literature has advocated for the use of synovial alpha defensin and/or leucocyte esterase for the diagnosis of PJI, given their high diagnostic accuracy.[24] A meta-analysis by Chen et al[13] confirmed that synovial alpha defensin and leucocyte esterase are highly accurate in predicting PJI, with a combined sensitivity and specificity of 87% and 96%, and 87% and 97%, respectively. However, the use of these biomarkers is limited by their expense, prolonged testing time, and limited availability. In contrast, Klemt et al,[16] Tirumala et al,[17] and our study found that combining PLR or PVR with serum and synovial markers produces sensitivities and specificities that are similar to those obtained with synovial alpha defensin and leucocyte esterase. This approach offers shorter testing time, lower costs, and wide availability, given that these ratios are obtained from complete blood counts.

It is important to consider the limitations of this study when interpreting the results. As a retrospective chart review, the study may have missing data or be subject to bias. Additionally, we acknowledge that the MPV measurement has not been fully characterized and may be affected by multiple variables, such as the type of anticoagulant used (which was not collected in our study), the timing of blood collection, and the analyzer used. Despite this, previous studies have reported the utility of MPV as a diagnostic marker for PJIs.[25] More importantly, we obtained similar results to Klemt et al[16] and Tirumala et al[17] using a different patient population and broader inclusion criteria. Also, it is important to note that the criteria we are using for diagnosis is also what we are studying, which can introduce some bias.

The results of this study validate previous research showing that combinations of blood cell ratios, with established synovial and serum markers may be useful in the diagnosis of PJI. In our patient population, the addition of PVR or PLR to the combination of ESR and CRP, or ESR, CRP, Syn. WBC, and PMN%, increased the AUC, sensitivity, and specificity for predicting PJI in both total hip and knee arthroplasties. Further research is needed to explore the use of these markers in other populations and settings.

Take home message

- This study reinforces the utility of using platelet-to-volume ratio derived from easily accessible complete blood counts in conjunction with established markers, enhancing diagnostic precision for chronic periprosthetic joint infection in both total hip and total knee arthroplasty.

Supplementary material

Table showing receiver operating characteristic curve analysis for all marker combinations analyzed.

References

1. **Jin X**, **Gallego Luxan B**, **Hanly M**, **et al**. Estimating incidence rates of periprosthetic joint infection after hip and knee arthroplasty for osteoarthritis using linked registry and administrative health data. *Bone Joint J*. 2022;104-B(9):1060–1066.
2. **Quinlan ND**, **Werner BC**, **Brown TE**, **Browne JA**. Risk of prosthetic joint infection increases following early aseptic revision surgery of total hip and knee arthroplasty. *J Arthroplasty*. 2020;35(12):3661–3667.
3. **McMaster Arthroplasty Collaborative (MAC)**. Risk factors for periprosthetic joint infection following primary total hip arthroplasty: A 15-year, population-based cohort study. *J Bone Joint Surg Am*. 2020;102-A(6):503–509.
4. **Parvizi J**, **Tan TL**, **Goswami K**, **et al**. The 2018 definition of periprosthetic hip and knee infection: An evidence-based and validated criteria. *J Arthroplasty*. 2018;33(5):1309–1314.e2.
5. **Bingham J**, **Clarke H**, **Spangehl M**, **Schwartz A**, **Beauchamp C**, **Goldberg B**. The alpha defensin-1 biomarker assay can be used to evaluate the potentially infected total joint arthroplasty. *Clin Orthop Relat Res*. 2014;472(12):4006–4009.
6. **Alijanipour P**, **Bakhshi H**, **Parvizi J**. Diagnosis of periprosthetic joint infection: the threshold for serological markers. *Clin Orthop Relat Res*. 2013;471(10):3186–3195.
7. **Xiong L**, **Li S**, **Dai M**. Comparison of D-dimer with CRP and ESR for diagnosis of periprosthetic joint infection. *J Orthop Surg Res*. 2019;14(1):240.
8. **Fernandez-Sampedro M**, **Sanlés-González I**, **García-Ibarbia C**, **Fañanás-Rodríquez N**, **Fakkas-Fernández M**, **Fariñas MC**. The poor accuracy of D-dimer for the diagnosis of prosthetic joint infection but its potential usefulness in early postoperative infections following revision arthroplasty for aseptic loosening. *BMC Infect Dis*. 2022;22(1):91.
9. **Han X**, **Xie K**, **Jiang X**, **et al**. Synovial fluid α-defensin in the diagnosis of periprosthetic joint infection: the lateral flow test is an effective intraoperative detection method. *J Orthop Surg Res*. 2019;14(1):274.
10. **Wang C**, **Li R**, **Wang Q**, **Duan J**, **Wang C**. Leukocyte esterase as a biomarker in the diagnosis of periprosthetic joint infection. *Med Sci Monit*. 2017;23:353–358.
11. **Lee YS**, **Koo K-H**, **Kim HJ**, **et al**. Synovial fluid biomarkers for the diagnosis of periprosthetic joint infection: A systematic review and meta-analysis. *J Bone Joint Surg Am*. 2017;99-A(24):2077–2084.
12. **Miyamae Y**, **George J**, **Klika AK**, **Barsoum WK**, **Higuera CA**. Diagnostic accuracy of the alpha-defensin test for periprosthetic joint infection in patients with inflammatory diseases. *J Arthroplasty*. 2019;34(8):1767–1771.
13. **Chen Y**, **Kang X**, **Tao J**, **Zhang Y**, **Ying C**, **Lin W**. Reliability of synovial fluid alpha-defensin and leukocyte esterase in diagnosing periprosthetic joint infection (PJI): a systematic review and meta-analysis. *J Orthop Surg Res*. 2019;14(1):453.
14. **Amanatullah DF**, **Cheng RZ**, **Huddleston Iii JI**, **et al**. The routine use of synovial alpha-defensin is not necessary. *Bone Joint J*. 2020;102-B(5):593–599.
15. **Semple JW**, **Italiano JE**, **Freedman J**. Platelets and the immune continuum. *Nat Rev Immunol*. 2011;11(4):264–274.
16. **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):1441–1449.
17. **Tirumala V**, **Klemt C**, **Xiong L**, **Chen W**, **van den Kieboom J**, **Kwon Y-M**. Diagnostic utility of platelet count/lymphocyte count ratio and platelet count/mean platelet volume ratio in periprosthetic joint infection following total knee arthroplasty. *J Arthroplasty*. 2021;36(1):291–297.
18. **Osmon DR**, **Berbari EF**, **Berendt AR**, **et al**. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2013;56(1):e1–e25.
19. **Parvizi J**, **Gehrke T**, **Chen AF**. Proceedings of the International Consensus on Periprosthetic Joint Infection. *Bone Joint J*. 2013;95-B(11):1450–1452.
20. **Patel R**, **Alijanipour P**, **Parvizi J**. Advancements in diagnosing periprosthetic joint infections after total hip and knee arthroplasty. *Open Orthop J*. 2016;10:654–661.
21. **Tischler EH**, **Cavanaugh PK**, **Parvizi J**. Leukocyte esterase strip test: matched for musculoskeletal infection society criteria. *J Bone Joint Surg Am*. 2014;96-A(22):1917–1920.
22. **Zeng Y-Q**, **Deng S**, **Zhu X-Y**, **et al**. Diagnostic accuracy of the synovial fluid α-defensin lateral flow test in periprosthetic joint infection: A meta-analysis. *Orthop Surg*. 2021;13(3):708–718.

23. **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.
24. **Bonanzinga T**, **Ferrari MC**, **Tanzi G**, **Vandenbulcke F**, **Zahar A**, **Marcacci M**. The role of alpha defensin in prosthetic joint infection (PJI) diagnosis: a literature review. *EFORT Open Rev*. 2019;4(1):10–13.
25. **Paziuk T**, **Rondon AJ**, **Goswami K**, **Tan TL**, **Parvizi J**. A novel adjunct indicator of periprosthetic joint infection: Platelet count and mean platelet volume. *J Arthroplasty*. 2020;35(3):836–839.

Author information:
- S. Denyer, MD, Orthopaedic Surgery Resident
- C. Eikani, BS, Research Fellow and Medical Student
- M. Sheth, BS, Medical Student
- D. Schmitt, MD, Orthopaedic Surgeon, Board-Certified and Fellowship-Trained
- N. Brown, MD, Orthopaedic Surgeon, Board-Certified and Fellowship-Trained

Department of Orthopaedic Surgery and Rehabilitation, Loyola University Medical Center, Maywood, Illinois, USA.

Author contributions:
- S. Denyer: Conceptualization, Methodology, Formal analysis, Writing – original draft.
- C. Eikani: Data curation, Writing – original draft, Project administration.
- M. Sheth: Data curation, Writing – review & editing.
- D. Schmitt: Conceptualization, Supervision, Methodology, Writing – review & editing.
- N. Brown: Conceptualization, Methodology, Supervision, Visualization, Writing – review & editing.

Funding statement:
- The authors received no financial or material support for the research, authorship, and/or publication of this article.

Data sharing:
- The datasets generated and analyzed in the current study are not publicly available due to data protection regulations. Access to data is limited to the researchers who have obtained permission for data processing. Further inquiries can be made to the corresponding author.

Ethical review statement:
- This project has received approval from the Institutional Review Board.

Open access funding:
- The authors report that the open access funding for their manuscript was self-funded.