

## CLINICAL ARTICLE

# The Potential Value of Monocyte to Lymphocyte Ratio, Platelet to Mean Platelet Volume Ratio in the Diagnosis of Periprosthetic Joint Infections

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**Objective:** To explore the possibility of obtaining more accurate information from routine blood tests for the diagnosis of periprosthetic joint infection (PJI).

**Methods:** This is a retrospective study. Between 2017 and 2018, a total of 246 patients who underwent total hip or knee revision surgery were included in this study. There were 146 females and 100 males, and the mean age of the patients was  $62.1 \pm 12.75$  years. Laboratory parameters erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), D-dimer, plasma fibrinogen, serum white blood cell (WBC), and calculable ratio markers were collected. Based on leukocytes (monocyte count, neutrophil count, lymphocyte count), platelet count, and mean platelet volume Inflammation-related ratio markers were calculated, which including monocyte to lymphocyte ratio (MLR), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and platelet to mean platelet volume ratio (PMR). Follow-up of all studied cases for at least 1 year. The diagnostic value of the markers based on the receiver operating characteristic (ROC) analysis. The most optimal combinations of blood markers were selected by the prediction models. Statistical analyses and prediction models were performed using R software.

**Results:** Of the 246 patients, 125 were diagnosed with PJI and 121 with aseptic loosening. A higher rate of patients underwent revision surgery due to hip prosthesis loosening in the aseptic loosening group (74.4%) compared to the PJI group (45.6%,  $P < 0.001$ ). ROC curves showed that the area under the curve (AUC) for classical markers, fibrinogen was 0.853 (95% confidence interval [CI], 0.805–0.901), ESR was 0.836 (95% CI, 0.785–0.887) and CRP was 0.825 (95% CI, 0.773–0.878). Followed by the PMR, PLR, NLR and MLR, which showed promising diagnostic performance with AUCs of 0.791, 0.785, 0.736, and 0.733. The AUCs of the ratio markers were higher than those of D-dimer (0.691; 95% CI, 0.6243–0.7584) and serum WBC (0.622; 95% CI, 0.552–0.691). After the predictive model calculation, AUC was up to 0.923 (95% CI, 0.891–0.951) when plasma fibrinogen combined with MLR and PMR and interpreted excellent discriminatory capacity with a sensitivity of 86.40% and a specificity of 84.17%. The new combination significantly increases the accuracy and reliability of the diagnosis of PJI ( $P < 0.001$ ). The AUC increased to 0.899 (95% CI, 0.861–0.931;  $P = 0.007$ ) and 0.916 (95% CI, 0.880–0.946;  $P < 0.001$ ), followed by CRP and ESR, respectively. All plasma fibrinogen, ESR, and CRP combined with both PMR and MLR achieved the highest specificity (89.17%) and PPV (85.34%).

**Conclusion:** The diagnostic performance greatly improved when plasma fibrinogen, ESR, and CRP combined with ratio markers.

**Key words:** Biomarkers; Diagnostic test; Inflammation; Peripheral blood; Periprosthetic joint infection

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## Introduction

Periprosthetic joint infection (PJI) is a rare but severe complication after total joint replacement (TJA)<sup>1,2</sup>. It is a huge economic burden not only for the individual patient but also for the global healthcare system. For primary total joint arthroplasty, the incidence of infection ranges between 1 and 3%<sup>2</sup>. The current study indicated the infection ranges after revision total joint (hips and knees) arthroplasty 3% to 8%<sup>3</sup>. However, the diagnosis of infection is still the main challenge after TJA<sup>4</sup>. Besides, accurate differentiation between septic and aseptic failure is essential to determine treatment protocols<sup>5</sup>. There is currently lacking a single gold-standard test for diagnosing PJI. Based on the 2018 International Consensus Conference on Musculoskeletal infection, Surgeons rely on a combination of a series of laboratory tests in peripheral blood and synovial fluid, microbial culture, and histopathological examinations to diagnose PJI<sup>6</sup>. Recent studies have shown that potential novel markers that need to perform joint aspiration for the diagnosis of PJI, include synovial alpha-defensin, synovial leukocyte test strips, synovial C-reactive protein<sup>7-9</sup>. However, these potential synovial markers may increase the financial burden of patients. Moreover, surgeons are often facing a lack of synovial fluid or “dry tap”, and joint aspiration is an invasive procedure with an increased risk of deep infection. Improvements in diagnostic tools, mainly to obtain more accurate diagnostic information from blood tests, are necessary.

The blood test provides surgeons with important information on inflammatory markers due to its simplicity, accessibility, and short waiting time. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are minor diagnostic criteria in 2018 ICM criteria. The reliability and usefulness of ESR and CRP for diagnosing PJI have been well studied. In a meta-analysis, the researchers noted the sensitivity and specificity were 0.860 (95% CI, 0.825–0.890) and 0.723 (95% CI, 0.704–0.742) for ESR, and for CRP were 0.869 (95% CI, 0.835–0.899) and 0.786 (95% CI, 0.769–0.803) according to the diagnostic criteria for ICM<sup>10</sup>. However, McArthur *et al.* indicated that both ESR and CRP are negative according to current diagnostic criteria, there are still cases involving false negatives for diagnosing PJI<sup>11</sup>. One study has also shown that the false-negative rate is 9.2 and 5.3% for ESR and CRP, respectively, combined ESR and CRP the false-negative rates up to 11.1%<sup>12</sup>. Controversy still exists due to their unclear thresholds and a negative serum ESR and CRP test result does not exclude the possibility of infection, so it is essential to obtain more accurate diagnostic information from the blood test results.

In addition to the classical inflammatory markers CRP and ESR, coagulation-related markers also showed high diagnostic efficacy in the diagnosis of PJI. Plasma fibrinogen and D-dimer have been studied by researchers for use to diagnose PJI<sup>13</sup>. Fibrinogen is a positive acute reactive protein produced by the liver and an essential component of the coagulation system. Li *et al.* demonstrated that the diagnostic efficacy of plasma fibrinogen was comparable to that of ESR and CRP<sup>14</sup>. Similarly, D-dimer is a fibrin degradation

product, which is used as a screening tool for thrombosis and is also related to inflammation<sup>15</sup>. Some researchers noted that D-dimer showed better diagnostic efficacy than ESR and CRP levels<sup>5,16</sup>. In addition to classic blood markers, several studies have documented that platelets and mean platelet volume (MPV) play an essential role in the inflammatory process<sup>13,17,18</sup>. Recent literature has shown that the combination of MPV/PC with CRP and ESR significantly improves the efficacy of diagnosing PJI<sup>19</sup>. Moreover, Huang *et al.* reported that peripheral blood dynamic ratio neutrophil/lymphocyte ratio (NLR) and MLR correlate with inflammatory body status<sup>20</sup>. It provides a new potential method for getting sufficient information for diagnosing PJI through a single blood test. However, more studies are needed to confirm the accuracy of ratio markers in the diagnosis of PJI and there is still a need to determine the diagnostic performance of the combination of coagulation-related markers with peripheral blood ratio markers.

In most institutions, it is usually possible to obtain a routine complete blood count by blood testing, including monocyte count, neutrophil count, lymphocyte count, platelet count, and MPV. Ratio valuables are also easy to calculate. Besides, a routine blood test can perform on all patients, particularly for those patients with “dry tap”. To the best of our knowledge, there are no studies that have evaluated the use of the combination of coagulation-related markers with peripheral blood dynamic ratio for the diagnosis of PJI.

Therefore, we hypothesized that peripheral blood indicators, coagulation-related markers combined with ratio markers maybe increase the accuracy of PJI diagnosis. The main purpose of the present study was to: (i) access the diagnostic value of ESR, CRP and coagulation-related markers; (ii) select useful ratio markers and examine the differences between bacterial species for ratio markers; and (iii) evaluate whether combined measurement provides surgeons additional information in order to diagnose PJI more accurately.

## Materials and Methods

### Inclusion and Exclusion Criteria

The inclusion criteria were: (i) patients diagnosed with chronic PJI or aseptic loosening (AL); (ii) patient underwent revision hip or knee arthroplasty; (iii) patients divided into two groups according to the 2014 MSIS criteria<sup>21</sup>; (iv) the major evaluation peripheral blood inflammatory biomarkers included CRP, ESR, plasma fibrinogen, d-dimer, WBC, PLR, PMR, NLR, MLR; and (v) this study is a retrospective study.

The exclusion criteria were: (i) acute PJI (defined as infection occurs within 3 months after the surgery); (ii) inflammation-related diseases include rheumatoid arthritis, systemic lupus erythematosus, and ankylosing spondylitis; (iii) revision due to periprosthetic fracture or dislocation; (iv) severe liver dysfunction or the presence of malignant tumors; and (v) insufficient serum marker data.

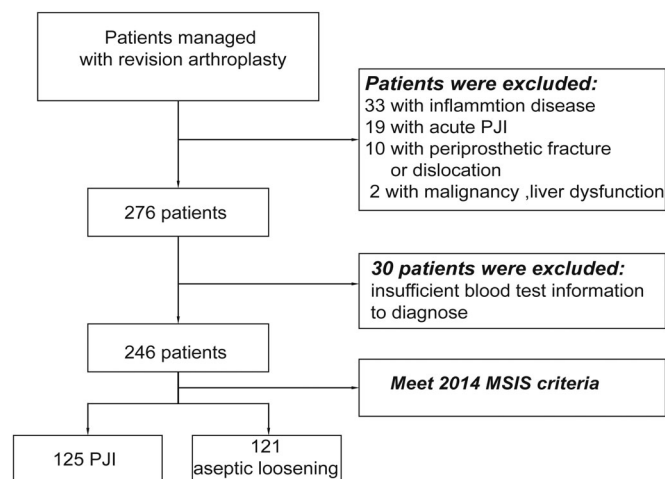
### Demographics

Our institution's research ethics board approved this retrospective observational study. We enrolled patients who were managed with revision surgery after hip or knee arthroplasty from January 2017 to December 2018 at a single institution. Ultimately, 246 patients were included, of which 125 were diagnosed with PJI, and 121 were aseptic loosening (Fig. 1). The clinical records of the patient's information that included age, Body mass index (BMI), gender, surgery type (knee or hip), Charlson comorbidity index (CCI) were showed in Table 1.

### Laboratory Tests

#### Blood Testing and Details

As part of our routine preoperative testing, blood samples are collected the morning after admission and then sent to the Medical Laboratory Center for testing. In addition to record ESR, CRP, fibrinogen, D-dimer, WBC as main peripheral markers; we also recorded lymphocyte count, neutrophil count, platelet count, and MPV to calculate PLR, PMR, NLR, MLR as adjunct ratio markers for diagnosing PJI. The CRP level was analyzed with a special protein analyzer PA-990 (Sysmex). The ESR was measured with an automated sedimentation rate screener SRS 100/II (Greiner Bio-One). WBC count, platelet, and MPV were determined with an automated hematology analyzer, the Sysmex XN-20 modular system (Sysmex). Plasma fibrinogen and D-dimer were quantified with an STA R Max Evolution analyzer (Diagnostica Stago). A BACT/ALERT 3D blood culture system (BioMerieux) was used for culture, and a matrix-assisted laser desorption ionization-time of flight mass spectrometry system, VITEK-MS (BioMerieux), was used for microorganism identification.



**Fig 1** Flowchart of included and excluded cases. PJI, periprosthetic joint infection; MSIS, Musculoskeletal Infection Society.

### Other Tests

Other tests include cultures, synovial leukocyte (WBC) counts, percentage of polymorphonuclear neutrophils (PMN %), and histological analysis. During the surgical procedure, about 3–5 samples (synovial fluid, deep tissue, and bone) were obtained for aerobic and anaerobic, and fungal cultures. The samples were sent to the medical laboratory center and each sample was inoculated for 14 days unless microorganisms were detected. Culture results were used for correlation analysis with ratio markers.

### Statistical Analysis

All the statistical analyses were performed with the statistical software packages R (<http://www.R-project.org>, The R Foundation). Categorical variables were expressed as frequencies and percentages, and continuous variables were expressed as mean  $\pm$  standard deviation. A comparison of the clinical characteristics between the PJI group and AL group was performed using the independent t-test or the chi-square test. The diagnostic value of each marker for PJI assessment was determined by receiver operating characteristic ROC curve analysis. Curves are considered valuable when  $AUC \geq 0.7$ . The Youden index was used to determine the optimal threshold for classical markers (fibrinogen, ESR, CRP, D-dimer) and ratio markers (PLR, PMR, NLR, MLR). Predictive models were utilized to screen the best combination of indicators. The statistical significance was defined as  $P < 0.05$ .

### Results

#### General Results

Demographic information is shown in Table 1. This study included 246 patients, of whom 125 (50.8%) diagnosed with PJI and 121 (49.1%) with aseptic loosening. Of these, 99 patients underwent total knee revisions, and 147 patients undergone hip revisions. The mean ages of the PJI group and AL group were  $62.8 \pm 12.7$  years and  $61.2 \pm 12.8$  years ( $P = 0.251$ ). There were no significant statistical differences between gender ( $P = 0.570$ ), BMI ( $P = 0.471$ ), and CCI ( $P = 0.266$ ). The aseptic loosening group had more hip joints than the PJI group (90 [74.4%] vs 57 [45.6%];  $P < 0.001$ ).

#### Clinical Results

##### Routine Blood Tests

The concentration of blood markers plasma fibrinogen, CRP, ESR, D-dimer, serum WBC, neutrophil count, monocyte count, the platelet count in the PJI group higher than the aseptic loosening group, except for lymphocyte count and mean platelet volume with statistically significant differences ( $P < 0.001$ ) (Table 2).

##### ROC Curves Analysis for Various Laboratory Markers

Utilizing ROC curves to analyze the ability of major blood markers and adjunct ratio markers to diagnose PJI (Fig. 2). And calculating the AUC and the specificity, sensitivity,

**TABLE 1 Characteristics of the study group**

Variables	PJI group (n = 125)	Aseptic loosening group (n = 121)	P value
Age (year)	62.8 ± 12.7	61.2 ± 12.8	0.251
BMI (kg/m <sup>2</sup> )	25.7 ± 3.9	25.2 ± 3.7	0.417
Gender (%)			0.570
Female	72 (57.6%)	74 (61.2%)	
Male	53 (42.4%)	47 (38.8%)	
Joint			<0.001
Knee	68 (54.4%)	31 (25.6%)	
Hip	57 (45.6%)	90 (74.4%)	
CCI (%)			0.266
<4	94 (72.8%)	106 (87.6%)	
≥4	31 (27.2%)	15 (12.4%)	

BMI, body mass index; CCI, Charlson comorbidity index; PJI, periprosthetic joint infection.

**TABLE 2 Distribution of blood markers in PJI and aseptic loosening group**

Markers	PJI group		Aseptic loosening group		P value
	Mean ± SD	Median (Min-Max)	Mean ± SD	Median (Min-Max)	
CRP (mg/L)	36.74 ± 48.05	19.22 (0.94–257.00)	5.77 ± 11.78	1.92 (0.50–81.00)	<0.001
ESR (mm/h)	42.36 ± 28.33	36.00 (2.00–113.00)	13.02 ± 11.42	10.00 (0.20–63.00)	<0.001
D-dimer (µg/mL)	1.80 ± 1.19	1.63 (0.15–6.99)	1.33 ± 1.58	0.84 (0.16–11.36)	<0.001
Plasma Fibrinogen (g/L)	5.74 ± 8.18	4.82 (2.40–95)	3.3 ± 0.79	3.1 (1.73–5.50)	<0.001
WBC (10 <sup>9</sup> /L)	6.88 ± 2.30	6.36 (2.16–18.00)	5.97 ± 1.42	5.75 (2.63–9.50)	<0.001
Neutrophil count (10 <sup>9</sup> /L)	4.65 ± 2.05	4.24 (1.49–14.87)	3.57 ± 1.09	3.33 (1.53–6.55)	<0.001
Lymphocyte count (10 <sup>9</sup> /L)	1.54 ± 0.55	1.51 (0.20–2.86)	1.77 ± 0.48	1.70 (0.75–2.85)	<0.001
Monocyte count (10 <sup>9</sup> /L)	0.47 ± 0.20	0.43 (0.20–1.66)	0.37 ± 0.12	0.36 (0.17–0.74)	<0.001
Platelet count (10 <sup>9</sup> /L)	293.43 ± 79.79	279 (106–511)	224.28 ± 52.19	22 (104–364)	<0.001
Mean Platelet Volume (fl)	9.97 ± 1.01	9.90 (7.00–15.70)	10.67 ± 1.06	10.55 (8.30–14.20)	<0.001
NLR	3.52 ± 2.82	2.72 (1.06–25.47)	2.14 ± 0.81	2.01 (0.85–5.32)	<0.001
MLR	0.36 ± 0.22	0.28 (0.12–1.14)	0.22 ± 0.08	0.21 (0.03–0.50)	<0.001
PLR	236.60 ± 195.11	185.01 (108.12–1712.74)	135.19 ± 46.57	123.99 (55.08–290.47)	<0.001
PMR	29.73 ± 8.68	27.96 (10.00–56.09)	21.36 ± 6.01	21.68 (7.70–37.62)	<0.001

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MLR, monocyte to lymphocyte ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PMR, platelet to mean platelet volume ratio; WBC, white blood cell.

PPV, NPV of Blood markers. The AUC of plasma fibrinogen was 0.853 (95% CI, 0.805–0.901), followed by ESR 0.836 (95% CI, 0.785–0.887) and CRP 0.825 (95% CI, 0.773–0.878), respectively. While the AUCs of adjunct ratio markers were NLR 0.736 (95% CI, 0.674–0.798), MLR 0.733 (95% CI, 0.671–0.796), PLR 0.785 (95% CI, 0.729–0.840) and PMR 0.792 (95% CI, 0.736–0.847), which were more accurate than D-dimer 0.691 (95% CI, 0.624–0.758) and serum WBC 0.622 (95% CI, 0.552–0.692), respectively.

#### Comparison of Sensitivity and Specificity in PJI Group with AL Group

The plasma fibrinogen optimal threshold (4.13 g/L) demonstrated a sensitivity and specificity of 75.20 and 86.78%, respectively. CRP and ESR had optimal cutoff of 7.34 mg/L (75.19% sensitivity, 84.30% specificity) and 26.0 mm/h. (69.60% sensitivity, 88.43% specificity), respectively. PLR had an optimal threshold of 129.33 (83.20 and 57.02%). The optimal threshold of MLR at 0.26 (60.00% sensitivity, 81.82% specificity) and the optimal threshold of PMR at

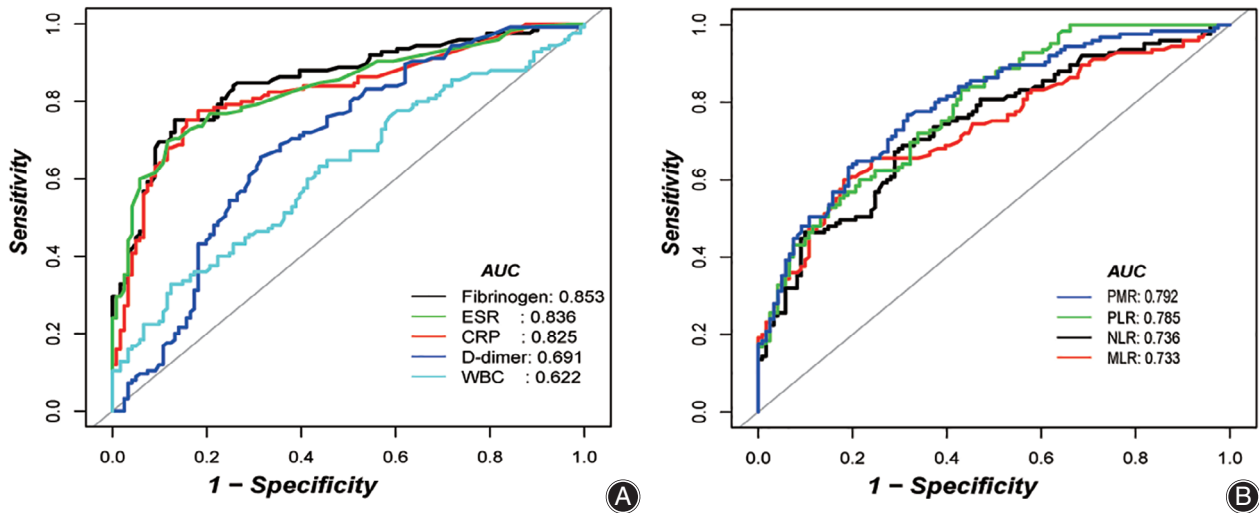
23.42 (79.80% sensitivity, 68.33% specificity). The WBC and D-dimer were unable to demonstrate comparable diagnostic efficacy to the adjunct ratio indicators (Table 3).

#### Distribution of Ratio Markers between Bacterial Species

Differences between Gram-positive and Gram-negative bacteria in inflammatory predictive markers were presented in Table 4. This result highlights no significant differences in peripheral blood markers between microorganisms.

#### Results of the Prediction Model

The combination of PMR and MLR was selected as the best ratio indicators combination among all ratio markers based on the prediction model calculation (Table 5, Fig. 3). The result of single main variables combined with both PMR and MLR are as follows, plasma fibrinogen achieved the highest AUC of 0.923 (95% CI, 0.891–0.951), which resulted in a sensitivity, specificity, PPV, and NPV of 0.864, 0.841, 0.850, and 0.856, respectively. Similarly, PMR, MLR combined with



**Fig 2** ROC curves for the diagnosis of PJI. (A) ROC curve analyses for classic inflammatory markers and coagulation-related markers. (B) ROC curve analyses for ratio markers. The black line depicts 50% sensitivity and specificity. NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PMR, platelet to mean platelet volume ratio; MLR, monocyte to lymphocyte ratio.

**TABLE 3** ROC analysis for main and ratio markers

Test	AUC (95%CI)	Best threshold	Specificity	Sensitivity	Positive-pv	Negative-pv
Plasma Fibrinogen (g/L)	0.8531 (0.8051–0.9011)	4.1300	0.8678	0.7520	0.8545	0.7721
CRP (mg/L)	0.8252 (0.7725–0.8780)	7.3350	0.8430	0.7519	0.8319	0.7669
ESR (mm/h)	0.8359 (0.7852–0.8865)	26.00	0.8843	0.6960	0.8614	0.7379
D-dimer ( $\mu\text{g/mL}$ )	0.6913 (0.6243–0.7584)	1.2350	0.6860	0.6560	0.6833	0.6587
Serum WBC ( $10^9/\text{L}$ )	0.6219 (0.5521–0.6917)	7.5500	0.8760	0.3280	0.7321	0.5579
NLR	0.7358 (0.6739–0.7977)	2.4185	0.7107	0.6720	0.7059	0.6772
MLR	0.7332 (0.6707–0.7957)	0.2550	0.8182	0.6000	0.7732	0.6644
PLR	0.7846 (0.7292–0.8399)	129.3250	0.5702	0.8320	0.6667	0.7667
PMR	0.7918 (0.7362–0.8473)	23.4150	0.6833	0.7980	0.7164	0.7387

MLR, monocyte to lymphocyte ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PMR, platelet to mean platelet volume ratio.

ESR and CRP, the AUC raised to 0.91 (95% CI, 0.880–0.946), 0.899 (95% CI, 0.861–0.931), respectively. When multiple variables including all peripheral main markers (plasma fibrinogen, CRP, ESR, D-dimer, serum WBC) and ratio markers (NLR, PLR, MLR, PMR) were placed in the prediction model, the best combination was plasma fibrinogen, ESR, and CRP, PMR, and MLR. The new combination results in good sensitivity, specificity, PPV, and NPV are 0.824, 0.892, 0.888, and 0.823, respectively (Fig. 4). Compared with the use of plasma fibrinogen, CRP, and ESR alone, the combined use of ratio markers shows a good diagnostic value ( $P < 0.001$ ). A combination of single ratio markers with single main markers shown in Table S1.

## Discussion

PJI is a devastating complication after TJA. It is estimated that the rate of PJI approximately 1% to 3% of patients who undergo primary TJA, and it will increase the mental and financial burden of patients<sup>2,4,22,23</sup>. Recent

**TABLE 4** Comparison between Gram positive PJI and Gram-negative PJI

Types	Gram-positive (N = 91)	Gram-negative (N = 9)	P value
PMR	29.21 $\pm$ 8.52	27.21 $\pm$ 11.39	0.227
PLR	235.09 $\pm$ 191.99	318.98 $\pm$ 320.20	0.608
MLR	0.35 $\pm$ 0.19	0.47 $\pm$ 0.36	0.529
NLR	3.34 $\pm$ 1.86	6.54 $\pm$ 8.03	0.468

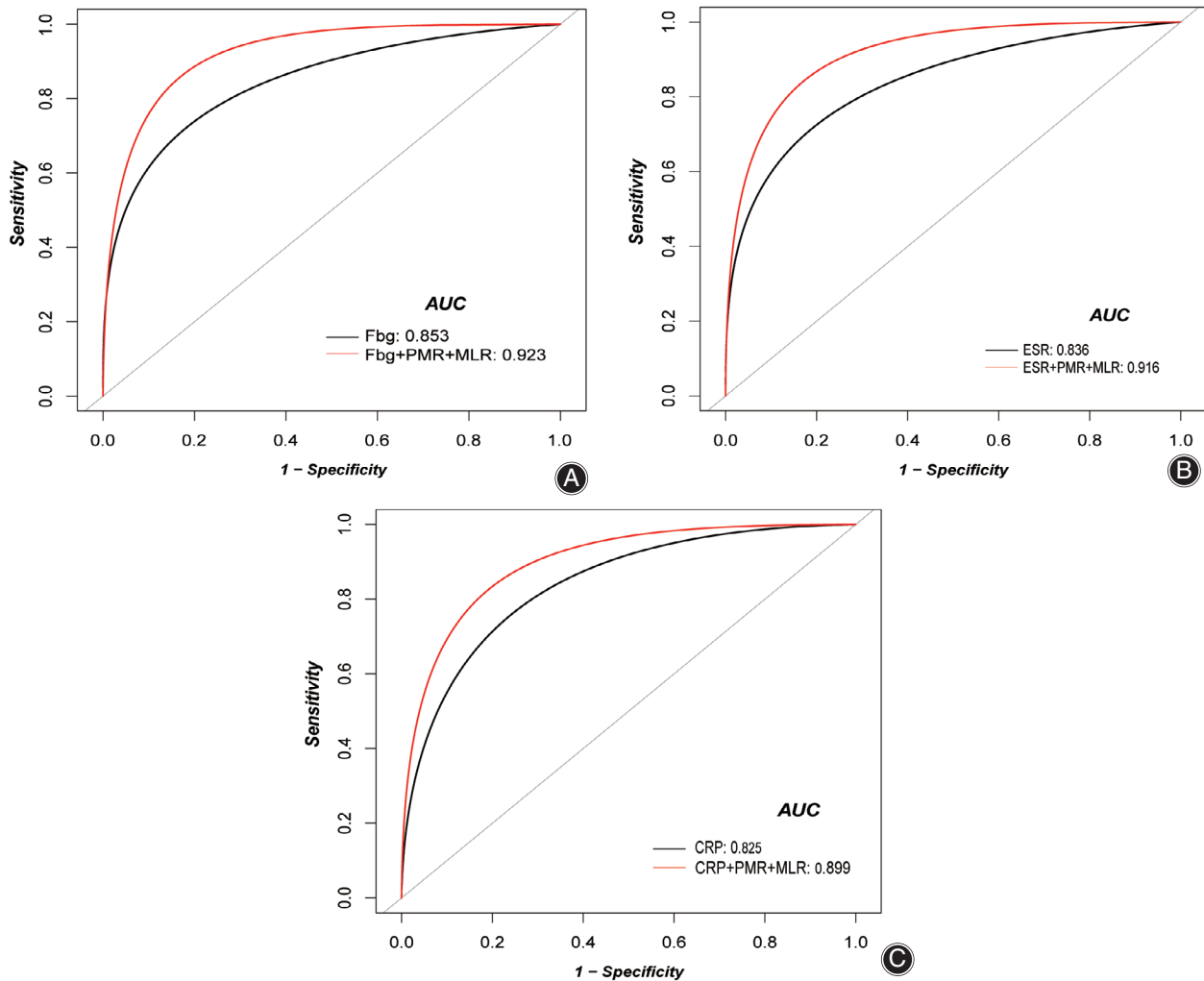
MLR, monocyte to lymphocyte ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PMR, platelet to mean platelet volume ratio.

studies indicate that novel tests such as leukocyte esterase (LE), alpha-defensin, and next-generation genome sequencing show very promising diagnostic efficacy, but these tests are expensive, require specialized equipment, and cannot be implemented in all institutions<sup>7–9,24,25</sup>. Also, these tests

**TABLE 5 Comparison of ROC curves between single and multiple combined markers**

Main markers vs combination with ratio markers	AUC (95%CI)	Specificity	sensitivity	PPV	NPV	P-value
Plasma fibrinogen vs plasma fibrinogen + PMR + MLR	0.9233 (0.8909–0.9508)	0.8417	0.8640	0.8504	0.8559	<0.001
CRP vs CRP + PMR + MLR	0.8994 (0.8606–0.9307)	0.8167	0.8400	0.8268	0.8305	0.0072
ESR vs ESR+ PMR + MLR	0.9159 (0.8804–0.9456)	0.8250	0.8640	0.8372	0.8534	<0.001
Plasma fibrinogen + ESR + CRP vs plasma fibrinogen + ESR + CRP+ PMR + MLR	0.9269 (0.8909–0.9547)	0.8917	0.8240	0.8879	0.8295	<0.001

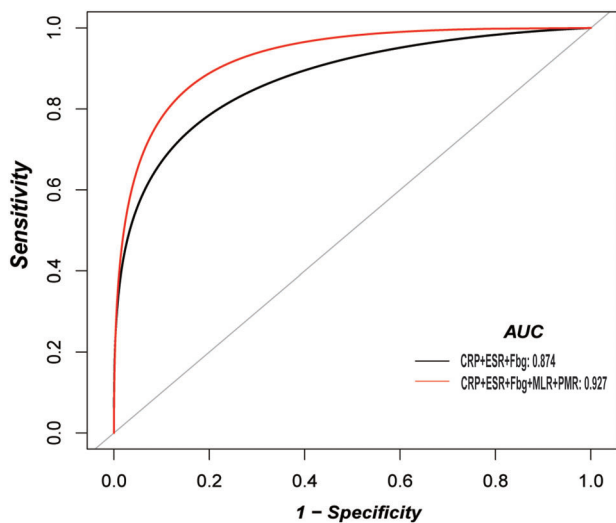
AUC, area under the curve.



**Fig 3** Comparison of receiver operator curves between single and multiple combined markers. ROC for fibrinogen and combined MLR and PLR predicting PJI. (B) ROC for ESR and combined MLR and PLR predicting PJI. (C) ROC for CRP and combined MLR and PLR predicting PJI. Fbg, fibrinogen; PMR, platelet to mean platelet volume ratio; MLR, monocyte to lymphocyte ratio.

cannot be used as a single gold standard for the diagnosis of PJI, and according to the 2018 MSIS criteria combination of various clinical examination approaches is still recommended. Therefore, identifying reliable and accurate

potential markers for the diagnosis of PJI is the key to the preoperative diagnosis and the development of an appropriate treatment plan. The primary purpose of this study was to determine the diagnostic value of ratio markers



**Fig 4** ROC curves of best blood marker combination by the prediction model. Fbg, fibrinogen; PMR, platelet to mean platelet volume ratio; MLR, monocyte to lymphocyte ratio.

and evaluate the performance of the combined diagnosis of PJI with classical inflammatory and coagulation-related markers.

#### Diagnostic Value of ESR, CRP, and Coagulation-related Markers

The results of the classical inflammation-related markers ESR, CRP, and coagulation-related marker plasma fibrinogen were consistent with previous studies, demonstrating promising diagnostic efficacy (AUCs > 0.8)<sup>14</sup>. However, the findings of the D-dimer of the current study do not support the previous research that D-dimer outperformed both the ESR and the CRP<sup>5,16</sup>. There were two possible explanations, one is D-dimer concentration is different in races, another is the previous study use the plasma as the tested sample, but in our study, we use serum sample as a tested sample, which may result in different levels of D-dimer. In our study, the diagnostic power of the inflammation ratio indicators (AUCs > 0.7) was significantly better than the D-dimer (AUC: 0.691). As we find, one of the factors influencing peripheral blood parameters is bacterial species.

#### Differences of Ratio Markers Between Bacterial Species

In a previous study, Abe *et al.*<sup>26</sup> demonstrated that blood inflammation markers CRP and IL-6 had significantly higher Gram-negative bacteremia than Gram-positive bacteremia. These findings suggest that differences in host response and virulence mechanisms to different pathogenic microorganisms should be taken into account when using peripheral blood ratio indicators. The findings of Kalbian *et al.* confirm the prevailing view that Gram-negative PJI is associated with poorer overall results than Gram-positive PJI<sup>27</sup>. Therefore,

determining the diagnostic efficacy of markers is very important, and different bacterial species may influence other indicators. However, our study indicated no significant differences in peripheral blood markers between microorganisms. As a ratio indicator, they may not be significantly affected by Gram-positive *versus* Gram-negative bacteria according to the present result. Another possible explanation for this might be that delayed infections may be associated with low-virulent organisms, and differences between bacterial species cannot be easily detected<sup>28</sup>.

#### The Role of Ratio Markers in Inflammation-related Diseases

The data of ratio indicators can be obtained from the routine blood test, and these exciting data could be analyzed to increase the diagnostic accuracy without additional cost. Our study showed that NLR, MLR, PLR, and PMR in the PJI group were significantly higher than the aseptic loosening group. It could demonstrate the association of the ratio indicators with the state of inflammation and infection in the body. Several studies have indicated that PLR, NLR, MLR, and PMR are associated with inflammatory status in the body. Djordjevic *et al.* demonstrated that MLR, PLR, and MPV/PC are very effective predictors of the outcome and nature of bacteremia<sup>29</sup>. Naess *et al.* reported that NLR and MLR were higher in hospitalized patients with fever due to bacterial infection<sup>30</sup>. They concluded that both NLR and MLR could be used to diagnose bacterial infections with AUCs of 0.688 and 0.708, respectively. This also accords with our findings, which showed that the AUC for the diagnosis of PJI is 0.736 (95% CI, 0.674–0.797), 0.733 (95% CI, 0.671–0.796), respectively. Yombi *et al.* demonstrated similar findings in a high level of NLR may association with the inflammatory or infectious problem<sup>31</sup>.

#### Ratio Indicators as Promising Biomarkers for the Diagnosis of PJI

Up to now, far too little attention has been paid to utilize MLR in diagnosing PJI. PLR has also been confirmed as the better predictor or diagnostic tool for inflammatory states<sup>32–34</sup>. The diagnostic value of the PC to MPV ratio in PJI patients was evaluated by Paziuk and coworkers<sup>19</sup>. They demonstrated that PC to MPV ratio had a high value on diagnosing PJI when combined with ESR and CRP at the optimal threshold 31.7 (AUC: 0.877, sensitivity: 0.802, specificity: 0.821). In contrast, our data showed (Table S1) lower optimal threshold 23.42 but with higher AUC (0.901; 95% CI, 0.876–0.944) and specificity (0.875).

Diagnostic combination illustrates the additional information that can be obtained from routine blood tests to improve diagnostic accuracy further. In a recent study, Tirumala *et al.* confirmed that a combination of multiple tests for infection biomarkers could be used to diagnose PJI with excellent performance. They reported that PLR and PVR combined with ESR, CRP, synovial WBC, and synovial PMN% increased diagnostic sensitivity and specificity comparable to alpha defensin<sup>35</sup>. They

observed that the ROC analysis showed sensitivities of NLR, MLR, PLR, PMR greater than ESR, and some comparable to CRP. In our study, the diagnostic performance of NLR, MLR, PLR, PMR just only better than D-dimer and serum WBC; the most promising markers still are plasma fibrinogen, ESR, and CRP in our study.

Routine blood tests are paid great attention in our study as the first line and the most important tools to diagnose PJI. One of the reasons is that blood tests can be performed on all patients compared to joint synovial fluids. Moreover, the literature reports that the incidence of “dry tap” ranges up to 46%, especially in the hip, and accurate information obtained from blood tests is crucial in this group of patients<sup>36</sup>. In the present study, we selected more inflammation-related markers, including CRP, ESR, Plasma fibrinogen, D-dimer, serum WBC. Furthermore, a predictive model is performed to select the optimal combination. In contrast to previous studies, in our study, according to the prediction model, not a single ratio indicator was chosen but MLR and PMR as the optimal combination. The combination of CRP, ESR, plasma fibrinogen with MLR and PMR greatly improved the diagnostic value. Among them, plasma fibrinogen combined with MLR and PMR achieved the highest diagnostic efficacy (sensitivity: 0.842, specificity: 0.864, PPV: 0.851, and NPV: 0.856). And ESR, CRP had improved the accuracy when combined with MLR and PMR. Besides, we tested the best combinations in all variables. Finally, the three main indicators CRP, ESR, and plasma fibrinogen with MLR and PMR combinations, showed the highest specificity and PPV of 0.892 and 0.888, respectively.

### Limitations

There are some limitations to this study. First, this was a retrospective study, and was inherently subject to selection

bias. Electronic medical records may contain incorrect or non-existent information for individual patients. Second, Peripheral blood ratio markers are influenced by factors other than bacterial species, as well as medication use, age, and some unnoticed comorbidities. Third, this was a single-center study. The discrepancy between the results of our research and the same type of study may be related to races. Finally, the effect of bacterial species on the ratio indicator may not be detected because of the small sample size. Therefore, a large sample size, cross-national multicenter studies are needed.

### Conclusions

In conclusion, our study confirms that ratio markers (MLR and PMR), when used in combination with fibrinogen, achieve better diagnostic performance, especially for patients with “dry tap” can benefit from it. Routine serologic markers more accurately diagnose potential infections through a new combination of models. Blood tests are easy to obtain, will not increase financial burden, and provide surgeons with the possibility of obtaining more accurate information from a single test.

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### Supporting Information

Additional Supporting Information may be found in the online version of this article on the publisher’s web-site:

**Table S1:** Comparison of ROC curve between markers

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