



CLINICAL ARTICLE

Exciting Performance of Plasma Fibrinogen in Periprosthetic Joint Infection Diagnosis

Jin-cheng Huang, MD, PhD^{1†} , Xiao Chen, MD^{2†}, Shuo Qiang, MD^{1†}, Wen-di Zheng, MD¹, Jia Zheng, MD¹ , Yi Jin, MD, PhD¹

¹Department of Orthopaedics, Henan Provincial People's Hospital and ²Department of Orthopaedics, People's Hospital of Zhengzhou University, Zhengzhou, China

Objective: To test the significance of serum C-reactive protein (CRP), the erythrocyte sedimentation rate (ESR), the platelet count/mean platelet volume ratio (PC/MPV), plasma fibrinogen, and D-Dimer in periprosthetic joint infection (PJI) diagnosis.

Methods: We retrospectively analyzed the clinical data of 149 patients diagnosed from July 2016 to December 2019 with primary osteoarthritis (OA group, average age 63.18 years [range, 53–82 years] 18 males, 46 females), PJI (PJI group, average age 63.74 years [range, 52–81 years], 16 males, 31 females), and aseptic loosening (aseptic group, average age 63.18 years [range, 53–80 years], 12 male, 26 female) in our department. Demographic data and the sensitivity and specificity of preoperative CRP, ESR, PC/MPV, fibrinogen, and D-Dimer in PJI diagnosis were compared.

Results: There were no significant differences when the demographic data of the three groups were compared. The expression level of CRP (50.67 ± 58.98 mg/L), ESR (50.55 ± 25.81 mm/h), PC/MPV (35.79 ± 18.00), and fibrinogen (4.85 ± 1.33 μ g/mL) in the PJI group were higher than in the OA group (CRP: 4.09 ± 9.68 mg/L; ESR: 13.44 ± 9.32 mm/1 h; PC/MPV: 24.97 ± 7.58 ; fibrinogen: 3.09 ± 0.55 μ g/mL) and the aseptic group (CRP: 7.01 ± 11.83 mg/L; ESR: 22.47 ± 17.53 mm/1 h; PC/MPV: 25.18 ± 11.48 ; fibrinogen: 3.39 ± 0.80 μ g/mL), respectively. The expression level of plasma D-dimer (1.60 ± 1.29 mg/L) in the PJI group was higher than in the OA group (0.49 ± 0.42 mg/L) but similar to that in the aseptic group (1.21 ± 1.35 mg/L). Receiver operating characteristic (ROC) curve analysis demonstrated that the areas under the ROC curve (AUC) for CRP, ESR, PC/MPV, fibrinogen, and D-dimer were 0.892 (95% confidence interval, 0.829–0.954), 0.888 (0.829–0.947), 0.686 (0.589–0.784), 0.873 (0.803–0.943), and 0.835 (0.772–0.899), respectively. When PC/MPV > 31.70, fibrinogen > 4.01 μ g/mL, and D-dimer > 1.17 mg/L were set as the threshold values for the diagnosis of PJI, the sensitivity of PC/MPV in PJI diagnosis was lower than that of ESR and plasma fibrinogen. In contrast, there was no significant difference when comparing the specificity of CRP, ESR, PC/MPV, fibrinogen, and D-dimer in PJI diagnosis.

Conclusion: Plasma fibrinogen is a good new auxiliary diagnostic marker for PJI.

Key words: D-dimer; Diagnosis; Fibrinogen; Periprosthetic joint infection; Platelets

Introduction

Periprosthetic joint infection (PJI) is a terrible complication for both patients and clinical surgeons. Although

one-stage or two-stage revision surgery combined with antibiotic treatment have favorable clinical effects in PJI patients, it is not easy for clinicians to make an accurate PJI diagnosis

Address for correspondence Jia Zheng and Yi Jin, Department of Orthopedics, Henan Provincial People's Hospital, People's Hospital of Zhengzhou University, People's Hospital of Henan University, Zhengzhou, China, 450003. Tel: +86 13837140761, Fax: +86 13837140761; Email: henanzhengjiaguke@163.com (Zheng); hnjinymd@163.com (Jin)

[†]Co-first authors.

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in some situations due to the absence of a gold standard for PJI diagnosis^{1,2}. Owing to the low-risk and rapidity of blood tests, they are always selected by clinicians as the first assessment for PJI diagnosis. Despite serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) being recommended as diagnostic criteria by the Musculoskeletal Infection Society (MSIS)³ and commonly being used in PJI diagnosis³, they do not work well in certain situations, including cases of chronic⁴ and low virulence organism infections^{1,2}.

In the past a few years, the value of numerous blood markers, such as serum soluble intercellular adhesion molecule-1 (sICAM-1)⁵, myeloid-related protein 14 (MRP-14)⁶, soluble urokinase plasminogen activation receptor (su-PAR)⁷, and lipopolysaccharide-binding protein (LBP)^{8,9}, has been tested in PJI diagnosis. Although these markers have shown good performance in PJI diagnosis, due to high expense and the existence of special antibodies, it is often not possible to access them in clinical practice, especially in primary hospitals. Therefore, it is important to explore some new convenient and efficient blood markers for PJI diagnosis.

Coagulation and inflammation theory, which involves considering how excessive activation of coagulation could indicate the status of infection and inflammation, has been used in the diagnosis of infection and inflammation diseases for almost 20 years^{10,11}. However, the relationship between PJI and coagulation remains unclear. Recently, the sensitivity and specificity of several coagulation markers, including D-dimer¹²⁻¹⁴, platelet count and mean platelet volume ratio¹⁵, and plasma fibrinogen¹⁶, have been compared with CRP and ESR in PJI diagnosis; these studies show that these commonly used coagulation markers can be applied for PJI diagnosis. However, no subsequent studies were published. Whether these markers could be used for PJI diagnosis remains unclear. As these blood markers are commonly used in clinical practice, the diagnostic value of these markers in PJI diagnosis deserved our exploration.

The purpose of this study is to test the value of serum CRP, ESR, platelet count/mean platelet volume ratio (PC/MPV), plasma fibrinogen, and D-dimer in PJI diagnosis. We hypothesize that: (i) the expression levels of CRP, ESR, PC/MPV, fibrinogen and D-dimer in PJI patients should be higher than in primary osteoarthritis and aseptic loosening patients; (ii) the sensitivity of CRP, ESR, PC/MPV, fibrinogen, and D-dimer in PJI diagnosis should be different; and (iii) the specificity of CRP, ESR, PC/MPV, fibrinogen, and D-dimer in PJI diagnosis should be different.

Materials and Methods

Inclusion and Exclusion Criteria

This study was conducted in accordance with the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) and was approved by the ethics board of Henan Provincial People's Hospital.

Inclusion Criteria

The inclusion criteria were: (i) patients had been diagnosed with primary osteoarthritis, PJI, and aseptic loosening and received corresponding treatment (primary arthroplasty, resection arthroplasty, spacer insertion surgery, and revision arthroplasty) in our department from July 2016 to December 2019; (ii) patients whose data were available for preoperative serum CRP, ESR, PC/MPV, plasma fibrinogen, and D-dimer expression level; (iii) comparisons of sensitivity and specificity of preoperative CRP, ESR, PC/MPV, fibrinogen, and D-dimer in PJI diagnosis had been made among patients from the three different groups; (iv) different expression of CRP, ESR, PC/MPV, fibrinogen, and D-dimer among patients from the three different groups and sensitivity and specificity of CRP, ESR, PC/MPV, fibrinogen, and D-dimer in PJI diagnosis should be expected; and (v) the study design was a retrospective study.

Exclusion Criteria

The exclusion criteria include the following: patients with (i) any type of skin ulcer or hematoma; (ii) a history of recent dislocation or trauma (within 2 weeks); (iii) visible ecchymosis; (iv) a prosthetic heart valve; (v) a history of hyper-coagulation disorder; (vi) systemic inflammatory disease (such as rheumatoid arthritis, psoriasis, systemic lupus erythematosus, polymyalgia rheumatica, hepatitis B and C, inflammatory bowel disease, sarcoidosis, gout, myelodysplastic syndrome, lymphocytic leukemia, and multiple myeloma); (vii) tumors.

General Information of Participants

According to the above inclusion and exclusion criteria, the clinical data of 149 patients who had been diagnosed with primary osteoarthritis, PJI, and aseptic loosening from July 2016 to December 2019 were analyzed. These patients were divided into three groups according to the diagnosis: an OA group (primary osteoarthritis), a PJI group (PJI) and an aseptic group (aseptic loosening). For each patient, demographic information (gender and age) and preoperative serum CRP, ESR, PC/MPV, plasma fibrinogen, and D-dimer expression levels were recorded.

Definition of Periprosthetic Joint Infection and Aseptic Loosening

Periprosthetic joint infection was defined using the MSIS criteria³. Aseptic loosening was defined using the criteria in our previous published paper¹⁷.

Measuring Methods

Preoperative serum CRP, ESR, PC/MPV, plasma fibrinogen, and D-dimer expression levels were measured preoperatively. The sensitivity and specificity of preoperative CRP, ESR, PC/MPV, fibrinogen, and D-dimer in PJI diagnosis were compared among the three different groups.

TABLE 1 Demographic data

Characteristics	OA group	PJI group	Aseptic group	Statistics
Age (years)	63.18 ± 9.46	63.74 ± 12.67	66.79 ± 8.24	$F = 1.547$; $P = 0.216$
Gender (M/F)	18/46	16/31	12/26	$\chi^2 = 0.457$; $P = 0.796$
The average (\pm standard deviation) age and proportion of gender showed no statistical difference among the three groups ($P > 0.05$).				

TABLE 2 Expression of serum CRP, ESR, PC/MPV, plasma fibrinogen, and D-Dimer level in patients from the three different groups

Group	CRP (mg/L)	ESR (mm/1 h)	PC/MPV	Fibrinogen (μ g/mL)	D-Dimer (mg/L)
A	4.09 ± 9.68	13.44 ± 9.32	24.97 ± 7.58 ^a	3.09 ± 0.55	0.49 ± 0.42
B	50.67 ± 58.98	50.55 ± 25.81	35.79 ± 18.00 ^b	4.85 ± 1.33	1.60 ± 1.29
C	7.01 ± 11.83	22.47 ± 17.53	25.18 ± 11.48 ^c	3.39 ± 0.80	1.21 ± 1.35
Statistics	$F = 28.498$, $P = 0.000$, $P^{ab} = 0.000$, $P^{bc} = 0.000$, $P^{ac} = 0.677$	$F = 59.300$, $P = 0.000$, $P^{ab} = 0.000$, $P^{bc} = 0.000$, $P^{ac} = 0.016$	$F = 11.596$, $P = 0.000$, $P^{ab} = 0.000$, $P^{bc} = 0.000$, $P^{ac} = 0.933$	$F = 11.596$, $P = 0.000$, $P^{ab} = 0.000$, $P^{bc} = 0.000$, $P^{ac} = 0.123$	$F = 16.416$, $P = 0.000$, $P^{ab} = 0.000$, $P^{bc} = 0.086$, $P^{ac} = 0.001$
Expression of serum CRP, ESR, PC/MPV, and plasma fibrinogen in the (A) PJI group are higher than in the (B) OA group and the (C) aseptic group, while expression plasma D-Dimer in the PJI group is similar to that in the aseptic group. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PC/MPV, platelet count/mean platelet volume ratio; PJI, periprosthetic joint infection.					

Statistical Analysis

Quantitative data were recorded as mean \pm standard deviation. Single factor analysis of variance was used for comparison among multiple groups and SNK test was used for comparison between any two means. The χ^2 -test was used for comparison of counting data among groups. A P -value less than 0.05 was considered significant difference. If the difference was significant, partition of χ^2 was used for comparison between any two means and a P -value less than 0.017 was regarded as significant difference. Receiver operating characteristic (ROC) curves were used to examine the relationships between the true-positive rate (sensitivity) and the false-positive rate (1-specificity) and the areas under the ROC curve (AUC). All statistical analyses were carried out using IBM SPSS Statistics (version 19, IBM SPSS Software).

Results

Demographic Data

In this study, 149 patients were included and grouped as follows: the OA group, which included 64 primary osteoarthritis patients (received primary arthroplasty); the PJI group, which included 47 PJI patients (received resection arthroplasty and antibiotic cement spacer insertion surgery); and the aseptic group, which included 38 aseptic loosening patients (received revision surgery). Patient demographics are presented in Table 1 and there were no significant differences among the three groups.

Different Performance of Serum C-Reactive Protein, Erythrocyte Sedimentation Rate, Platelet Count/Mean Platelet Volume Ratio, Plasma Fibrinogen, and D-Dimer in Periprosthetic Joint Infection Diagnosis

As shown in Table 2, expression of serum CRP (50.67 \pm 58.98 mg/L), ESR (50.55 \pm 25.81 mm/1 h), PC/MPV (35.79 \pm 18.00), and fibrinogen (4.85 \pm 1.33 μ g/mL) in the PJI group are higher than in the OA group (CRP: 4.09 \pm 9.68 mg/L; ESR: 13.44 \pm 9.32 mm/h; PC/MPV: 24.97 \pm 7.58; fibrinogen: 3.09 \pm 0.55 μ g/mL) and the aseptic group (CRP: 7.01 \pm 11.83 mg/L; ESR: 22.47 \pm 17.53 mm/1 h; PC/MPV: 25.18 \pm 11.48; fibrinogen: 3.39 \pm 0.80 μ g/mL), respectively. The expression level of plasma D-dimer (1.60 \pm 1.29 mg/L) in the PJI group is higher than in the OA group (0.49 \pm 0.42 mg/L) but similar to that in the aseptic group (1.21 \pm 1.35 mg/L). These data indicate that elevated CRP, ESR, PC/MPV, and plasma fibrinogen may predicate PJI, while plasma D-dimer cannot distinguish PJI from aseptic loosening.

All the above data show that plasma D-dimer cannot predicate PJI, whereas PC/MPV and plasma fibrinogen may play vital roles in PJI diagnosis. Recently, papers published by Li¹⁶ and Paziuk¹⁵ showed when PC/MPV > 31.70 and fibrinogen > 4.01 μ g/mL were set as the optimum threshold values for PJI diagnosis, PC/MPV and plasma fibrinogen are effective for PJI diagnosis. However, no subsequent related studies have been undertaken. Therefore, we decided to compare the sensitivity and specificity of CRP, ESR, PC/MPV, fibrinogen, and D-dimer in PJI diagnosis among patients

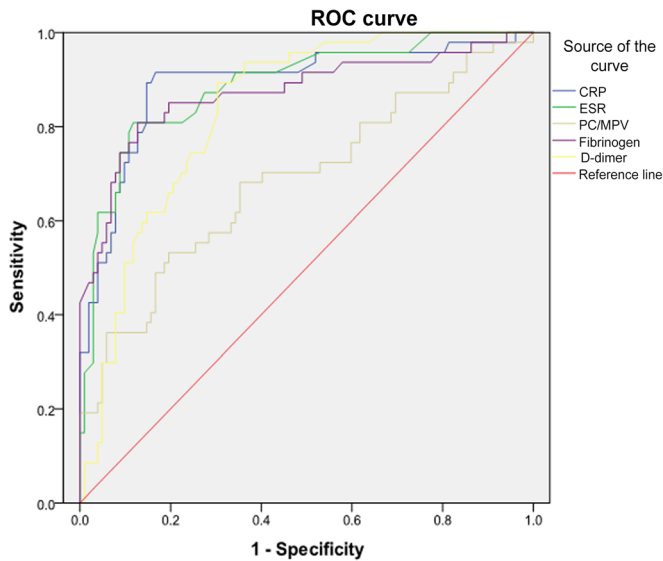


Fig. 1 Receiver operating characteristic (ROC) curves of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), platelet count/mean platelet volume ratio (PC/MPV), fibrinogen, and D-dimer.

from the three different groups. First, the receiver operating characteristic (ROC) curve was used to analyze the areas under the ROC curve (AUC) for CRP, ESR, PC/MPV, fibrinogen, and D-dimer. As shown in Fig. 1, the AUC for CRP, ESR, PC/MPV, fibrinogen, and D-dimer is 0.892 (95% confidence interval, 0.829–0.954), 0.888 (0.829–0.947), 0.686 (0.589–0.784), 0.873 (0.803–0.943), and 0.835 (0.772–0.899), respectively (Fig. 1). Second, when CRP > 10 mg/L, ESR > 30 mm/h, PC/MPV > 31.70, fibrinogen > 4.01 $\mu\text{g/mL}$, and D-dimer > 1.17 mg/L are set as the optimum threshold values for the PJI diagnosis, the sensitivity of fibrinogen (0.78) is similar to that of CRP (0.74) and ESR (0.81), while the sensitivity of PC/MPV (0.55) is lower than that of CRP (0.74) and ESR (0.81) (Table 3). However, when the specificity of serum CRP (0.91), ESR (0.88), PC/MPV (0.81), and plasma fibrinogen (0.88) in PJI diagnosis are compared among patients from three different groups, the differences are not statistically significant (Table 4). All these data indicate that plasma fibrinogen can be used as an auxiliary marker for PJI diagnosis, while PC/MPV should not be used as an auxiliary marker for PJI diagnosis.

Discussion

In this study, our results showed that plasma fibrinogen can be used as an auxiliary marker for PJI diagnosis.

Platelet Count/Mean Platelet Volume Ratio and Plasma Fibrinogen May Indicate the Status of Periprosthetic Joint Infection

Despite numerous efforts having been made to increase the accuracy of PJI diagnosis, there is still no consensus on the superiority of one marker over another. Although CRP and

TABLE 3 Comparison of the sensitivity of serum CRP, ESR, PC/MPV, plasma fibrinogen, and plasma D-Dimer in the diagnosis of PJI among patients from three different groups

	True positive	False negative	Sensitivity
CRP (>10 mg/L)	35	12	0.74 ^a
ESR (>30 mm/1 h)	38	9	0.81 ^b
PC/MPV (>31.70)	26	21	0.55 ^c
Plasma fibrinogen (>4.01 $\mu\text{g/mL}$)	37	10	0.78 ^d
Plasma D-dimer (>1.17 mg/L)	28	19	0.60 ^e

$\chi^2 = 11.988$, $P = 0.017$. $P^{ab} = 0.458$; $P^{ac} = 0.052$, $P^{ad} = 0.626$, $P^{ae} = 0.125$, $P^{bc} = 0.008$, $P^{bd} = 0.797$, $P^{be} = 0.024$, $P^{cd} = 0.016$, $P^{ce} = 0.677$, $P^{de} = 0.044$. There are statistically significant differences when comparing the sensitivity of serum CRP, ESR, PC/MPV, plasma fibrinogen, and plasma D-Dimer in the diagnosis of PJI among patients from three different groups. The differences in sensitivity of ESR and PC/MPV and PC/MPV and plasma fibrinogen in PJI diagnosis were significant when a P -value of less than 0.017 was set as the cutoff for significant difference. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PC/MPV, platelet count/mean platelet volume ratio; PJI, periprosthetic joint infection.

TABLE 4 Comparison of the specificity of serum CRP, ESR, PC/MPV, and plasma fibrinogen in diagnosis of PJI among patients from three different groups

	True negative	False positive	specificity
CRP (>10 mg/L)	93	9	0.91
ESR (>30 mm/1 h)	90	10	0.88
PC/MPV (31.70)	83	19	0.81
Plasma fibrinogen (4.01 $\mu\text{g/mL}$)	90	12	0.88
Plasma dimer (1.17 mg/L)	87	15	0.85

$\chi^2 = 4.914$, $P = 0.296$. There are no statistically significant differences when comparing specificity of serum CRP and PC/MPV, ESR and PC/MPV, and PC/MPV, plasma fibrinogen and plasma D-Dimer in the diagnosis of PJI among patients from three different groups. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PC/MPV, platelet count/mean platelet volume ratio; PJI, periprosthetic joint infection.

ESR are still widely used as first-line screening markers for PJI, they are non-specific blood inflammatory markers and could be influenced by many factors¹⁸. Therefore, many researchers are evaluating the value of other blood markers for PJI diagnosis. Although coagulation markers such as PC/MPV¹⁹, D-dimer²⁰, and fibrinogen²¹ have been demonstrated to play vital roles in diagnosis of inflammation and infectious diseases^{10,11}, the roles of these markers in PJI diagnosis remain unclear. Several recent studies have tested the value of these coagulation markers in PJI diagnosis^{12–16} and demonstrated that D-dimer >1170 ng/m¹⁴, PC/MPV >31.70¹⁵, and FIB >4.01 $\mu\text{g/mL}$ ¹⁶ can be used as the optimum threshold value for PJI diagnosis; however, no subsequent related studies have been published. Therefore, in this study, we analyzed the expression level of PC/MPV,

fibrinogen, and D-dimer in patients from the three different groups and found that PC/MPV and plasma fibrinogen were highly expressed in PJI patients and might predicate PJI, while plasma D-dimer cannot.

Fibrinogen Can Be Used as a New Marker for Periprosthetic Joint Infection Diagnosis

To further define the role of PC/MPV and fibrinogen in PJI diagnosis, we compared the sensitivity and specificity of CRP, ESR, platelet count/mean platelet volume ratio (PC/MPV), D-dimer, and fibrinogen in PJI diagnosis. Similar to a study by Li¹⁶, we found that the sensitivity and specificity of plasma fibrinogen in PJI diagnosis were similar to those of CRP and ESR, which means that fibrinogen can be used as a new auxiliary marker for PJI diagnosis. However, different from Paziuk *et al.*¹⁵, our data demonstrated that the sensitivity of PC/MPV in PJI diagnosis is lower than ESR and the specificity of PC/MPV in PJI diagnosis is similar to that of CRP and ESR. In addition, different from Qin *et al.*¹⁴, we found the sensitivity and specificity of D-dimer in PJI diagnosis to be similar to those for CRP and ESR. Because there was no significant difference when the expression level of D-dimer in PJI and aseptic loosening patients were compared, we determined that D-dimer should not be selected as the first option for PJI diagnosis. Based on our data, fibrinogen could be used as a new marker for PJI diagnosis.

Possible Reasons for the Discrepancy Between Our Results and Those of Other Published Papers

Although our results differ from those in the published literature, we believe our conclusion still stands, partly because: (i) we used the MSIS criteria³ for the optimum threshold value for PJI diagnosis of ESR > 30 mm/h and CRP > 10 mg/L (in contrast to Paziuk's ESR > 46 mm/h and CRP > 1.5 mg/L); (ii) consistent with Guangxu *et al.*²² and Cheng *et al.*²³, we again showed that plasma D-dimer has limited performance for the diagnosis of PJI. As a result, our findings are more robust than those of Paziuk *et al.* and Qin *et al.* in terms of clinical utilization.

Limitations

There are several limitations in our study: (i) the number of included patients in our study is only 149, much less than in Paziuk's study (4938 patients), which indicates that our conclusion may be less reliable than Paziuk's; (ii) we also excluded patients with rheumatologic disease, which constitute almost 10% of patients in our department, which to some extent limited the practicability of our conclusion in clinical PJI evaluation. Larger high-quality studies are needed to evaluate the value of CRP, ESR, PC/MPV, fibrinogen, and D-dimer in PJI diagnosis in the future.

Conclusion

Overall, in this study, our data showed that plasma fibrinogen can be used as an auxiliary marker for PJI diagnosis.

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