Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Plasma Fibrinogen Can be Used as a New Auxiliary Diagnostic Marker for Periprosthetic Joint Infection

Jincheng Huang
Henan Provincial People's Hospital
Xiao Chen
Henan Provincial People's Hospital
Shuo Qiang
Henan Provincial People's Hospital
Wendi Zheng
Henan Provincial People's Hospital
Jia Zheng
Henan Provincial People's Hospital
Yi Jin (hnjinyimd@163.com)
Henan Provincial People's Hospital

Research article

Keywords: Periprosthetic joint infection, ESR, CRP, Platelet Count and Mean Platelet Volume ratio, Fibrinogen, D-Dimer, Diagnosis

DOI: https://doi.org/10.21203/rs.3.rs-60961/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Abstract

Background: To test the meaning of serum CRP, ESR, Platelet Count and Mean Platelet Volume ratio (PC/MPV), plasma Fibrinogen and D-Dimer in periprosthetic joint infection diagnosis (PJI).

Methods: Clinical data of 149 patients diagnosed with osteoarthritis (Group A), PJI (Group B) and aseptic loosening after joint arthroplasy (Group C) were retrospectively studied. General data and preoperative serum CRP, ESR, Platelet Count and Mean Platelet Volume ratio (PC/MPV), plasma Fibrinogen and D-Dimer levels were analyzed. The sensitivity and specificity of serum CRP, ESR, Platelet Count and Mean Platelet Volume ratio (PC/MPV), plasma Fibrinogen and D-Dimer in PJI diagnosis were compared.

Results: Expression level of serum CRP, ESR, PC/MPV and plasma Fibrinogen in Group B are higher than Group A and C. Expression level of plasma D-Dimer in Group B are higher than Group A but similar with Group C. When PC/MPV>31.70, plasma Fibrinogen > 4.01 μg/mL and plasma D-Dimer > 1.17 mg/L were set as the threshold value for the diagnosis of PJI, the sensitivity of PC/MPV in PJI diagnosis is lower than ESR and Plasma Fibrinogen. Whereas, there are no statistically significant differences when compared specificity of serum CRP, ESR, PC/MPV, plasma Fibrinogen and D-Dimer in PJI diagnosis.

Conclusion: PC/MPV and plasma D-Dimer should not be used as the first screen markers for PJI diagnosis, whereas, the plasma Fibrinogen can be used as a new auxiliary marker for PJI diagnosis.

Background

Periprosthetic joint infection (PJI) is still the most terrible complication for both patients and clinical surgeons. Although one stage or two stage revision surgery combined with antibiotics treatment exert favorable clinical effect in PJI patients, it is not easy for clinicians to make an accurate PJI diagnosis 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 test, it is always selected by clinicians as the first examimation for PJI diagnosis. Despite serum CRP and ESR are recommended as the diagnostic criteria by Musculoskeletal Infection Society (MSIS) [3] and commonly checked for PJI diagnosis[3], they do not work well in situations including chronic [4] and low virulence organism infections[1, 2]. In the past a few years, the meaning of numerous blood markers such as serum soluble intercellular adhesion molecule-1 (sICAM-1) [5], myeloid-related protein14 (MRP-14) [6], soluble urokinase plasminogen activation receptor (su-PAR) [7] and lipopolysaccharide-binding protein (LBP) [8, 9] have been tesetd in PJI diagnosis,. Although some of these markers showed good performance in PJI diagnosis, due to high expense and special antibodies, it is not possible to prevail them in clinical practice especially in primary hospitals in the near a few years. So, it is emergent for us to explore some new convenient, and efficient blood markers for PJI diagnosis.

Coagulation and inflammation theory, which means excessive activation of coagulation could indicate the status of infection and inflammation, has been used in infection and inflammation diseases diagnosis for a long time [10, 11]. However, the relationship between PJI and coagulation is still unclear. Recently, the sensitivity and specificity of several coagulation markers including D-Dimer [12–14]Platelet

Count and Mean Platelet Volume ratio[15] and plasma Fibrinogen [16] were compared with CRP and ESR in PJI diagnosis, and these studies showed that these commonly used coagulation markers can be selected for PJI diagnosis. However, no subsequent studies were published thereafter. And whether these markers could be used for PJI diagnosis is still unclear. As these blood markers were commonly used in clinical practice, the diagnostic value of these markers in PJI diagnosis deserved our exploration.

In this study, we rechecked and evaluated the meaning of serum CRP, ESR, Platelet Count and Mean Platelet Volume ratio(PC/MPV), plasma Fibrinogen and D-Dimer in PJI diagnosis, and demonstrated that PC/MPV and plasma D-Dimer should not be used as the first screen markers for PJI diagnosis, whereas, the plasma Fibrinogen can be used as a new auxiliary marker for PJI diagnosis.

Methods

Study population

Patients diagnosed with primary osteoarthritis, PJI and aseptic loosening in our department have the data of preoperative serum CRP, ESR, Platelet Count and Mean Platelet Volume ratio（PC/MPV）, plasma Fibrinogen and D-Dimer expression level from July 2016 to December 2019 were included. Exclusion criterion can be seen in our previous published paper [17].

Definition of PJI and aseptic loosening

PJI was defined using the MSIS criteria[3]. Aseptic loosening was defined using the criteria in our previous published paper [17].

General Information of Participants

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

From July 2016 to December 2019, we collected 232 clinical data of patients diagnosed with primary osteoarthritis, PJI and aseptic loosening in our department. Finally, 83 patients were excluded and 149 patients (103 female and 46 male) were included in the study.

Statistical Analysis

Quantitative data were recorded as mean ± standard deviation, single factor analysis of variance was selected for comparison difference among multiple groups and SNK test was selected for comparison between any two means. Chi-square test (c^2) was selected for comparison the counting data among

groups. P value less than 0.05 was considered as significant difference. If the difference is significant partition of chi-squareis used for comparison between any two means and P value less than 0.017 was regarded as significant difference. All statistical analyses were carried out by IBM SPSS Statistics (version 19, IBM SPSS Software).

Results

Included population

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

Table 1
Comparison of the general data among patients from three different groups

Group		A	B	C	
Age		63.18±9.46	63.74±12.67	66.79±8.24	F=1.547 P=0.216
Gender	Male	18	16	12	c^2=0.457
	Female	46	31	26	P=0.796

Different expression of serum CRP, ESR, PC/MPV, plasma Fibrinogen and D-Dimer level in patients from the three different groups

As shown in Table2, expression of serum CRP, ESR, PC/MPV and plasma Fibrinogen in Group B are higher than Group A and C, expression level of plasma D-Dimer in Group B are higher than Group A but similar with Group C. These data indicate that elevated serum CRP, ESR, PC/MPV and plasma Fibrinogen may predicate PJI, while, plasma D-Dimer can not distinguish PJI from aspetic loosening.

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/h)	PC/MPV	Fibrinogen(μg/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 Group B are higher than Group A and C, while expression plasma D-Dimer in Group B is similar with Group C.					

PC/MPV does not do better than CRP, ESR and plasma Fibrinogen in PJI diagnosis

Although above data showed that plasma D-Dimer can't predicate PJI, serum CRP, ESR, PC/MPV and plasm Fibrinogen may play vital roles in PJI diagnosis. Paper published by Li[16] and Paziuk[15] showed when PC/MPV>31.70 and FIB> 4.01 μg/mL was set as the optimum threshold value for the PJI diagnosis, PC/MPV and plasma Fibrinogen can be used for PJI diagnosis. However, no subsequent studies were done since then. So, we decided to recompare the sensitivity and specificity of serum CRP, ESR, PC/MPV and plasma Fibrinogen in PJI diagnosis among patients from the three different groups.

As shown in Table 3, the sensitivity of plasma Fibrinogen is similar with CRP and ESR, while the sensitivity of PC/MPV is lower than CRP and ESR. However, when the specificity of serum CRP, ESR, PC/MPV and plasma Fibrinogen in PJI diagnosis were 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 a new marker for PJI diagnosis, while, PC/MPV should not be used as a new marker for PJI diagnosis.

Table 3
Comparison of the sensitivity of serum CRP, ESR, PC/MPV, plasma Fibrinogen and plasma D-Dimer in 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/h）	38	9	0.81[b]
PC /MPV（31.70）	26	21	0.55[c]
Plasma Fibrinogen（4.01 μg/mL）	37	10	0.78[d]
Plasma D-Dimer (1.17 mg/L)	28	19	0.60[e]
c^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，pcd=0.016, p^{ce}=0.677, p^{de}=0.044. There are statistically significant differences when compared sensitivity of serum CRP ESR , PC/MPV, plasma Fibrinogen and plasma D-Dimer in diagnosis of PJI among patients from three different groups. The difference of sensitivity of ESR and PC /MPV , PC /MPV and Plasma Fibrinogen in PJI diagnosis were significant when P value less than 0.017 was set as the cutoff for significant difference.			

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/h）	90	10	0.88
PC /MPV（31.70）	83	19	0.81
Plasma Fibrinogen（4.01 μg/mL）	90	12	0.88
Plasma D-Dimer (1.17 mg/L)	87	15	0.85
c^2=4.914, p=0.296. There are no statistically significant differences when compared specificity of serum CRP and PC/MPV, ESR and PC/MPV, PC/MPV, plasma Fibrinogen and plasma D-Dimer in diagnosis of PJI among patients from three different groups.			

Discussion

Considering the great success of joint arthroplasty, the number of patients receiving joint arthroplasty has increased year by year. At the same time, researchers estimated that the incidence of Hip and Knee Arthroplasty revision surgery in the United States is projected to increase to 2030 [18]. In 2017, papers published by Delanois et al and Gwam et al showed that PJI is the most common reason for revision in total knee arthroplasty patients [19] and the fourth most common reason for revision in total hip

arthroplasty patients in the United States [20]. Although one stage or two stage revision surgery combined with antibiotics treatment exert excellent clinical effect, it is still not easy to make a prompt and accurate PJI diagnosis, PJI diagnosis remains challenging.

Despite numerous efforts have been tried to increase the accuracy of PJI diagnosis, until now, there is still no consensus on the superiority of one method better than another. Compared with other methods, blood examination, which has the merit low-risk, non-invasion and rapidity, is always the first screening option for clinicians to make a PJI diagnosis. Though CRP and 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 factors [21]. So, lots of researchers are trying to evaluate the meaning of some other blood markers in PJI diagnosis.

Despite coagulation markers such as Platelet Count and Mean Platelet Volume ratio [22], D-Dimer [23] and plasma Fibrinogen[24] have been used in inflammation and infection diseases diagnosis [10, 11], the role of these coagulation markers in PJI diagnosis is still unknow. Although the role of D-Dimer [12–14] plasma Fibrinogen [16], Platelet Count and Mean Platelet Volume ratio[15] were evaluated in PJI diagnosis, and D-dimer > 1170 ng/m[14], PC/MPV > 31.70[15] and FIB > 4.01 μg/mL[16] were recommend as the optimum threshold value for the PJI diagnosis, no subsequent studies were published thereafter.

In this study, we retrospectively analyzed the sensitivity and specificity of serum CRP, ESR, Platelet Count and Mean Platelet Volume ratio (PC/MPV), plasma D-Dimer and Fibrinogen in PJI diagnosis. Similar with Li's [16] study, we found that plasma Fibrinogen can be used for as a new marker for PJI diagnosis. However, different from Paziuk T et al's[15] and Qin et al's[14]study, our data demonstrated that PC/MPV and D-Dimer should not be selected as the first option for PJI diagnosis. But we think our conclusion still make sense and the reasons are: 1, we take the MSIS criterion[3] which recommend ESR 30 mm/h,CRP 10 mg/L other than Paziuk's ESR 46 mm/h CRP 1.5 mg/L as the optimum threshold value for PJI diagnosis; 2, consistent with Guangxu et al's study[25] and Cheng et al's study[26], we again showed that plasma D-dimer has limited performance for the diagnosis of PJI. As a result, our conclusion performs better than Paziuk et al's and Qin et al's in clinical utilization.

Limitations

There are several limitations in our study: 1, the number of included patients in our study is only 149, much lesser than Paziuk's (4938 patients), which indicates our conclusion is less reliable than Paziuk's to some extent; 2, we also excluded those have rheumatologic disease, which constitute almost 10% patients in our department, which to some extent limited the practicability of our conclusion in clinical PJI evaluation.

Conclusion

Overall, in this study, different from previous studies, which focused on inflammatory markers other than coagulation-related indicators in PJI diagnosis, we found that the plasma Fibrinogen can be used for as a new marker for PJI diagnosis.

Abbreviations

PJI: periprosthetic joint infection ; CRP: C-reactive protein□ESR□Erythrocyte sedimentation rate. Platelet Count and Mean Platelet Volume ratio (PC/MPV).

Declarations

Ethics approval and consent to participate

This retrospective study was approved by ethics board of Henan Provincial People's Hospital. All the data used in this study were anonymised before use.

Consent for publication

Written informed consent for publication was obtained from all participants.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

Not applicable.

Funding

The present study was supported by Ministry of Science and Technology National Key Research and Development Program (2017YFB1104100), Key scientific and technological projects in Henan Province(202102310113) and the Doctoral Research Initiation Fund of Henan Provincial People's Hospital□2018Huangjincheng□. The funder of Key scientific and technological projects in Henan Province(202102310113) and the Doctoral Research Initiation Fund of Henan Provincial People's Hospital□2018Huangjincheng□participate in the study design, data collection and analysis, The funder the Ministry of Science and Technology National Key Research and Development Program(2017YFB1104100) participate in the decision to publish and manuscript preparation.

Authors’ contributions

JCH, XC and SQ participated in the design of the study and the acquisition and interpretation of data, performed the statistical analysis, and drafted the manuscript. XC and WDZ participated in the acquisition and interpretation of data and helped to draft the manuscript. JZ and YJ participated in the design of the study, and helped to statistical analysis and to draft the manuscript. YJ conceived of the study, participated in its design and coordination, helped to statistical analysis and to draft the manuscript. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

Authors' information

Department of Orthopedics, Henan Provincial People’s Hospital, People’s Hospital of Zhengzhou University, People’s Hospital of Henan University, Zhengzhou, Henan, 450003, P.R.China.

References

1. Akgun D, Muller M, Perka C, Winkler T. The serum level of C-reactive protein alone cannot be used for the diagnosis of prosthetic joint infections, especially in those caused by organisms of low virulence. Bone Joint J. 2018;100-B(11):1482–6.
2. Deirmengian CA, Citrano PA, Gulati S, Kazarian ER, Stave JW, Kardos KW. The C-Reactive Protein May Not Detect Infections Caused by Less-Virulent Organisms. J Arthroplasty. 2016;31(9 Suppl):152–5.
3. **Proceedings of the International Consensus Meeting on Periprosthetic Joint Infection**. **Foreword**. *J Orthop Res* 2014, **32 Suppl 1**:S2-3.
4. Perez-Prieto D, Portillo ME, Puig-Verdie L, Alier A, Martinez S, Sorli L, Horcajada JP, Monllau JC. C-reactive protein may misdiagnose prosthetic joint infections, particularly chronic and low-grade infections. Int Orthop. 2017;41(7):1315–9.
5. Mumingjiang Y, Zhou X, He R. Value of knee skin temperature measured by infrared thermography and soluble intercellular adhesion molecule-1 in the diagnosis of peri-prosthetic knee infection in Chinese individuals following total knee arthroplasty. Chin Med J (Engl). 2014;127(17):3105–9.
6. Dapunt U, Giese T, Maurer S, Stegmaier S, Prior B, Hansch GM, Gaida MM. Neutrophil-derived MRP-14 is up-regulated in infectious osteomyelitis and stimulates osteoclast generation. J Leukoc Biol. 2015;98(4):575–82.
7. Galliera E, Drago L, Marazzi MG, Romano C, Vassena C, Corsi Romanelli MM. Soluble urokinase-type plasminogen activator receptor (suPAR) as new biomarker of the prosthetic joint infection: correlation with inflammatory cytokines. Clin Chim Acta. 2015;441:23–8.

8. Ettinger M, Calliess T, Kielstein JT, Sibai J, Bruckner T, Lichtinghagen R, Windhagen H, Lukasz A. Circulating biomarkers for discrimination between aseptic joint failure, low-grade infection, and high-grade septic failure. Clin Infect Dis. 2015;61(3):332–41.
9. Friedrich MJ, Randau TM, Wimmer MD, Reichert B, Kuberra D, Stoffel-Wagner B, Wirtz DC, Gravius S. Lipopolysaccharide-binding protein: a valuable biomarker in the differentiation between periprosthetic joint infection and aseptic loosening? Int Orthop. 2014;38(10):2201–7.
10. Foley JH, Conway EM. Cross Talk Pathways Between Coagulation and Inflammation. Circ Res. 2016;118(9):1392–408.
11. Levi M, van der Poll T. Coagulation and sepsis. Thromb Res. 2017;149:38–44.
12. Shahi A, Kheir MM, Tarabichi M, Hosseinzadeh HRS, Tan TL, Parvizi J. Serum D-Dimer Test Is Promising for the Diagnosis of Periprosthetic Joint Infection and Timing of Reimplantation. J Bone Joint Surg Am. 2017;99(17):1419–27.
13. Lee YS, Lee YK, Han SB, Nam CH, Parvizi J, Koo KH. Natural progress of D-dimer following total joint arthroplasty: a baseline for the diagnosis of the early postoperative infection. J Orthop Surg Res. 2018;13(1):36.
14. Qin L, Li F, Gong X, Wang J, Huang W, Hu N. Combined Measurement of D-Dimer and C-Reactive Protein Levels: Highly Accurate for Diagnosing Chronic Periprosthetic Joint Infection. J Arthroplasty. 2020;35(1):229–34.
15. 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):836–9.
16. Li R, Shao HY, Hao LB, Yu BZ, Qu PF, Zhou YX, Chen JY. Plasma Fibrinogen Exhibits Better Performance Than Plasma D-Dimer in the Diagnosis of Periprosthetic Joint Infection: A Multicenter Retrospective Study. J Bone Joint Surg Am. 2019;101(7):613–9.
17. Huang J, Zhang Y, Wang Z, Dong Y, Zhao Y, Zheng J, Lian H, Jin Y. The serum level of D-Dimer is not suitable for distinguishing between prosthetic joint infection and aseptic loosening. J Orthop Surg Res. 2019;14(1):407.
18. Schwartz AM, Farley KX, Guild GN, Bradbury TL. Jr.: Projections and Epidemiology of Revision Hip and Knee Arthroplasty in the United States to 2030. J Arthroplasty. 2020;35(6S):79–85.
19. Delanois RE, Mistry JB, Gwam CU, Mohamed NS, Choksi US, Mont MA. Current Epidemiology of Revision Total Knee Arthroplasty in the United States. J Arthroplasty. 2017;32(9):2663–8.
20. Gwam CU, Mistry JB, Mohamed NS, Thomas M, Bigart KC, Mont MA, Delanois RE. Current Epidemiology of Revision Total Hip Arthroplasty in the United States: National Inpatient Sample 2009 to 2013. J Arthroplasty. 2017;32(7):2088–92.
21. Muhlhofer HML, Feihl S, Suren C, Banke IGJ, Pohlig F, von Eisenhart-Rothe R. [Implant-associated joint infections]. Orthopade. 2020;49(3):277–86.
22. Zareifar S, Farahmand Far MR, Golfeshan F, Cohan N. Changes in platelet count and mean platelet volume during infectious and inflammatory disease and their correlation with ESR and CRP. J Clin Lab Anal. 2014;28(3):245–8.

23. Schwameis M, Steiner MM, Schoergenhofer C, Lagler H, Buchtele N, Jilma-Stohlawetz P, Boehm T, Jilma B. D-dimer and histamine in early stage bacteremia: A prospective controlled cohort study. Eur J Intern Med. 2015;26(10):782–6.
24. Mitra P, Guha D, Nag SS, Mondal BC, Dasgupta S. Role of Plasma Fibrinogen in Diagnosis and Prediction of Short Term Outcome in Neonatal Sepsis. Indian J Hematol Blood Transfus. 2017;33(2):195–9.
25. Lu G, Li T, Ye H, Liu S, Zhang P, Wang W. D-dimer in the diagnosis of periprosthetic joint infection: a systematic review and meta-analysis. J Orthop Surg Res. 2020;15(1):265.
26. Li C, Margaryan D, Ojeda-Thies C, Perka C, Trampuz A. Meta-analysis of serum and/or plasma D-dimer in the diagnosis of periprosthetic joint infection. J Orthop Surg Res. 2020;15(1):298.