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SYSTEMATIC REVIEW

Is D-dimer a reliable biomarker compared to ESR and CRP in the diagnosis of periprosthetic joint infection?

A SYSTEMATIC REVIEW AND META-ANALYSIS

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Aims

The diagnosis of periprosthetic joint infection (PJI) has always been challenging. Recently, D-dimer has become a promising biomarker in diagnosing PJI. However, there is controversy regarding its diagnostic value. We aim to investigate the diagnostic value of D-dimer in comparison to ESR and CRP.

Methods

PubMed, Embase, and the Cochrane Library were searched in February 2020 to identify articles reporting on the diagnostic value of D-dimer on PJI. Pooled analysis was conducted to investigate the diagnostic value of D-dimer, CRP, and ESR.

Results

Six studies with 1,255 cases were included (374 PJI cases and 881 non-PJI cases). Overall D-dimer showed sensitivity of 0.80 (95% confidence interval (CI) 0.69 to 0.87) and specificity of 0.76 (95% CI 0.63 to 0.86). Sub-group analysis by excluding patients with thrombosis and hyper-coagulation disorders showed sensitivity of 0.82 (95% CI 0.70 to 0.90) and specificity of 0.80 (95% CI 0.70 to 0.88). Serum D-dimer showed sensitivity of 0.85 (95% CI 0.76 to 0.92), specificity of 0.83 (95% CI 0.74 to 0.90). Plasma D-dimer showed sensitivity of 0.67 (95% CI 0.60 to 0.73), specificity of 0.58 (95% CI 0.45 to 0.72). CRP showed sensitivity of 0.78 (95% CI 0.72 to 0.83), specificity of 0.81 (95% CI 0.72 to 0.87). ESR showed sensitivity of 0.68 (95% CI 0.63 to 0.73), specificity of 0.83 (95% CI 0.78 to 0.87).

Conclusion

In patients without thrombosis or a hyper-coagulation disorder, D-dimer has a higher diagnostic value compared to CRP and ESR. In patients with the aforementioned conditions, D-dimer has higher sensitivity but lower specificity compared to ESR and CRP. We do not recommend the use of serum D-dimer in patients with thrombosis and hyper-coagulation disorders for diagnosing PJI. Serum D-dimer may perform better than plasma D-dimer. Further studies are needed to compare serum D-dimer and plasma D-dimer in arthroplasty patients.

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Keywords: D-dimer, Periprosthetic joint infection

Article focus

- Investigate the diagnostic value of D-dimer in the diagnosis of periprosthetic joint infection (PJI). Compare the diagnostic value of serum D-dimer and plasma D-dimer.
- Compare the diagnostic value between D-dimer, CRP, and ESR.
- Investigate how D-dimer, CRP, and ESR perform in patients without thrombosis and hyper-coagulation disorder.

Key messages

- D-dimer has higher sensitivity and lower specificity when compared with that of CRP and ESR.

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- Serum D-dimer showed higher sensitivity and specificity compared with plasma D-dimer.
- In patients without thrombosis and hyper-coagulation disorder, D-dimer has the highest area under the receiver operating characteristic (ROC) curve (AUC) and diagnostic odds ratio (DOR), suggesting better diagnostic performance compared with CRP and ESR.

Strengths and limitations

- PJI is a low-incidence complication following arthroplasty surgeries, and the sample sizes are relatively small in studies investigating D-dimer in PJI diagnosis. Our analysis gathered available data and provided with results based on a relatively large sample size.
- Subgroup analysis was conducted to rule out patients with thrombosis and hyper-coagulation disorder. Subgroup analysis was conducted to compare diagnostic value of serum and plasma D-dimer.
- Patients from Asia and the USA were included, which may influence our analysis. Subgroup analysis based on different races was not feasible due to insufficient number of studies.

Introduction

The need for arthroplasty surgeries continues to grow rapidly worldwide.[1] Periprosthetic joint infection (PJI) is a devastating complication following arthroplasty surgeries. The reported prevalence of PJI varies greatly in different literatures: 1% to 4% after total knee arthroplasty (TKA) and 1% to 2% after total hip arthroplasty (THA), causing great social and economic burden in the healthcare system.[2,3]

The diagnosis of PJI has always been challenging and there is no 'gold standard' so far. Different techniques and biomarkers have been explored to improve diagnostic accuracy.[4–6] The Musculoskeletal Infection Society (MSIS) criteria integrate laboratory and clinical findings and showed high reliability in clinical practice. In 2018, Parvizi et al[7] updated the MSIS criteria by adding D-dimer as a minor criteria. Two points are scored if a patient has an elevated CRP or D-dimer, suggesting equal diagnostic value between CRP and D-dimer. Since 2018, several studies have looked into the diagnostic value of D-dimer:[5] Huang et al[8] suggested D-dimer is not suitable for distinguishing between PJI and aseptic loosening; Li et al[9] and Xiong et al[10] reported limited diagnostic value of D-dimer; and Shahi et al[11] reported that D-dimer outperformed ESR and CRP in the diagnosis of PJI. Because PJI is a low-incidence complication following arthroplasty, there is still controversy over the diagnostic value of D-dimer. We aimed to gather existing evidence from published literature and conduct a meta-analysis based on large samples for the first time. The aim of this meta-analysis and systematic review is to: 1) investigate the diagnostic value of D-dimer as a biomarker in diagnosing PJI; 2) compare the diagnostic value of D-dimer, ESR, and CRP; and 3) explore potential causes influencing the diagnostic value of D-dimer.

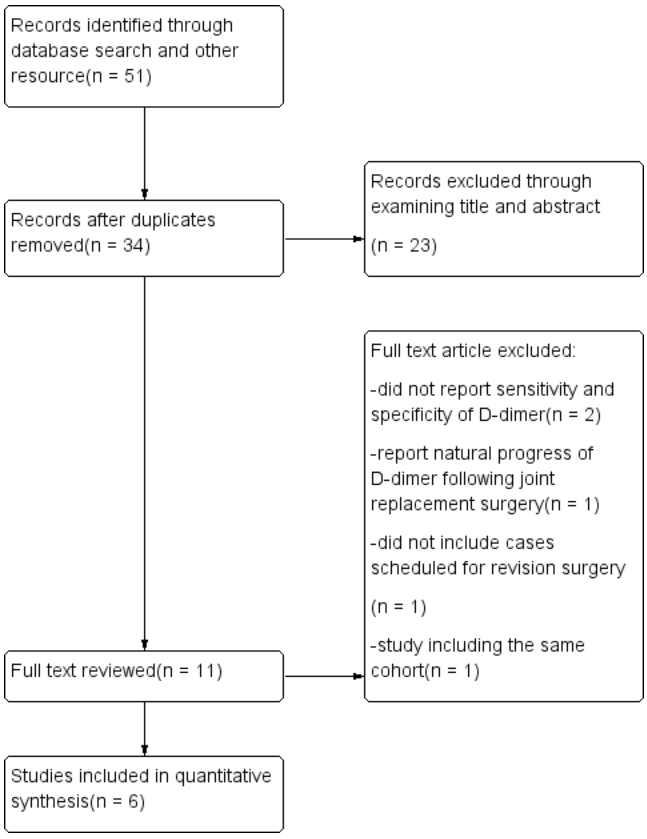

Fig. 1

Flow diagram of the method for searching and screening relevant studies.

Methods

Search strategy. PubMed, Embase, and the Cochrane Library were comprehensively searched in February 2020. Related search terms included: D-dimer, fibrin fragment D, joint, periprosthetic, arthroplasty, and infection. The search terms used in PubMed are as follows: (("fibrin fragment D"[Supplementary Concept] OR "fibrin fragment D"[All Fields] OR "d dimer"[All Fields]) OR "fibrin fragment D"[Supplementary Concept]) AND ((periprosthetic[All Fields] AND ("infection"[MeSH Terms] OR "infection"[All Fields])) OR (periprosthetic[All Fields] AND ("joints"[MeSH Terms] OR "joints"[All Fields] OR "joint"[All Fields]) AND ("infection"[MeSH Terms] OR "infection"[All Fields]))). All articles published before 2 February 2020 were screened. Additional studies were identified from references of retrieved articles.

Inclusion and exclusion criteria. Clinical trials were included if they: 1) included patients with previous history of arthroplasty surgery of the hip and knee; 2) applied clear and well-recognized diagnostic criteria for PJI; 3) investigated the diagnostic value of D-dimer in diagnosing PJI; 4) reported sensitivity, specificity, and other

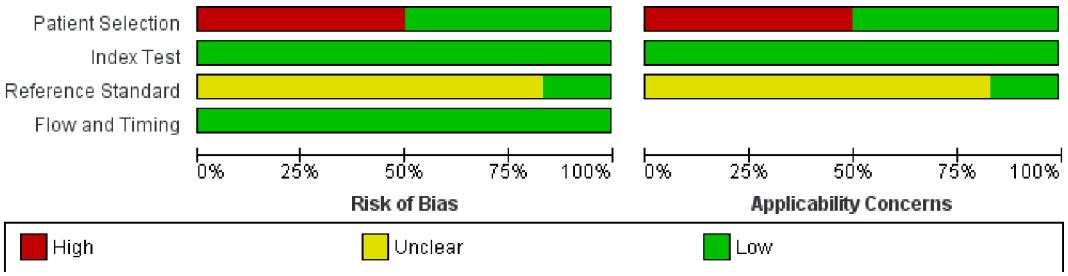

Fig. 2

Quality assessment of all included studies using Quality Assessment of Diagnostic Accuracy Studies Version 2 (QUADAS-2).

Table I. Study characteristics. All studies focused on both hip and knee arthroplasty.

Author name	Country	Pub year	PJI, n	Non-PJI, n	Diagnostic criteria
Huang J	China	2019	31	70	MSIS
Li R	China	2019	76	363	ICM
Qin L	China	2020	55	67	MSIS
Shahi	USA	2017	23	86	MSIS
Xiong L	China	2019	26	54	MSIS
Xu H	China	2019	129	189	MSIS

ICM, International Consensus Meeting; MSIS, Musculoskeletal Infection Society; PJI, periprosthetic joint infection; Pub, publication.

quantitative data; 5) reported patients for the first stage of revision surgery; and 6) were published in English. Studies were excluded if they: 1) were conference abstracts, animal studies, cadaveric studies, in vitro studies, or articles published in a form other than clinical trials; 2) had no quantitative data; or 3) only reported D-dimer as a biomarker for persistent infection during two-stage revision for PJI.

Data extraction and quality assessment. Two researchers (SZ, YW) extracted data and assessed the quality of included study independently. The corresponding author (WQ) was sought to resolve any disagreement. Inclusion and exclusion criteria of the included studies were recorded. Data including sample size, sensitivity, specificity, cut-off value, pathogens, true positives (TP), true negatives (TN), false positives (FP), and false negatives (FN) for D-dimer, CRP, and ESR were recorded. Study characteristics including patient population, publication year, and techniques for measuring serum or plasma D-dimer were recorded. Quality Assessment of Diagnostic Accuracy Studies Version 2 (QUADAS-2) was used to assess the quality of included studies.[12] The initial search yielded 51 studies; no additional studies were identified through the references of relevant articles. After careful screening, six studies were included in our analysis (Figure 1).

Statistical analysis. Stata 16 (StataCorp, College Station, Texas, USA) and Review Manager 5.3 I (New York, New York, USA) were used to conduct statistical analysis. A bivariate effect model was used to estimate sensitivity and specificity, and mean logit of sensitivity and specificity with their SD and 95% confidence intervals (CIs), while adjusting for sources of bias and variability. The logit-transformed sensitivity and specificity is assumed to follow bivariate distribution. Summarized sensitivity, specificity diagnostic odds ratios (DORs), and summary receiver operating curve (ROC) were obtained. Positive and negative likelihood ratio was also obtained using the same approach. A summary ROC and DOR would not be generated if there were less than four studies included. Heterogeneity was assessed with I^2 and bivariate boxplot. Multivariate meta-regression and subgroup analyses were used to explore and reduce potential cause of heterogeneity. Publication bias was assessed by Deek's Funnel Plot.

Results

Study characteristics. Basic characteristics of included studies are listed in Table I. Clear exclusion criteria were applied in five studies[8–11,13] to rule out other confounding factors such as thrombosis and hyper-coagulation disorder, which may influence the interpretation of index results. The cut-off value of D-dimer ranged from 0.76 mg/l to 1.25 mg/l. All studies were published within the last three years. Blood sample was acquired after admission and prior to surgeries. Four studies tested serum D-dimer,[8,10,11,13] and two studies tested plasma D-dimer.[9,14] Measuring techniques were not specified (Table I). Quality of included studies was assessed using QUADAS-2 and is shown in Figure 2.

Diagnostic value of D-dimer. Six studies were all included in our analysis, with 374 PJI cases and 881 non-PJI cases. Pooled sensitivity for D-dimer was 0.80 (95% CI 0.69 to 0.87) and pooled specificity was 0.76 (95% CI 0.63 to 0.86) (Figure 3). The area under the ROC curve (AUC) was 0.85 (95% CI 0.81 to 0.88) (Figure 4). The DOR for D-dimer was 12.06 (95% CI 3.96 to 36.74). Different exclusion criteria were applied in five studies,[8–11,13] which all excluded patients with thrombosis and hyper-coagulation disorders. A sub-group analysis was conducted including these five studies, the results are as follows: sensitivity 0.82 (95% CI 0.70 to 0.90), specificity 0.80 (95% CI 0.70 to 0.88), AUC 0.88 (95% CI 0.85 to 0.90), DOR 17.76 (95% CI 4.54 to 69.51). Pooled analysis for CRP and ESR were also conducted. Results from this analysis were recorded in Table II.

Sensitivity analysis. I^2 analysis showed substantial heterogeneity in sensitivity (I^2 = 87.68, 95% CI 79.26 to 96.09)

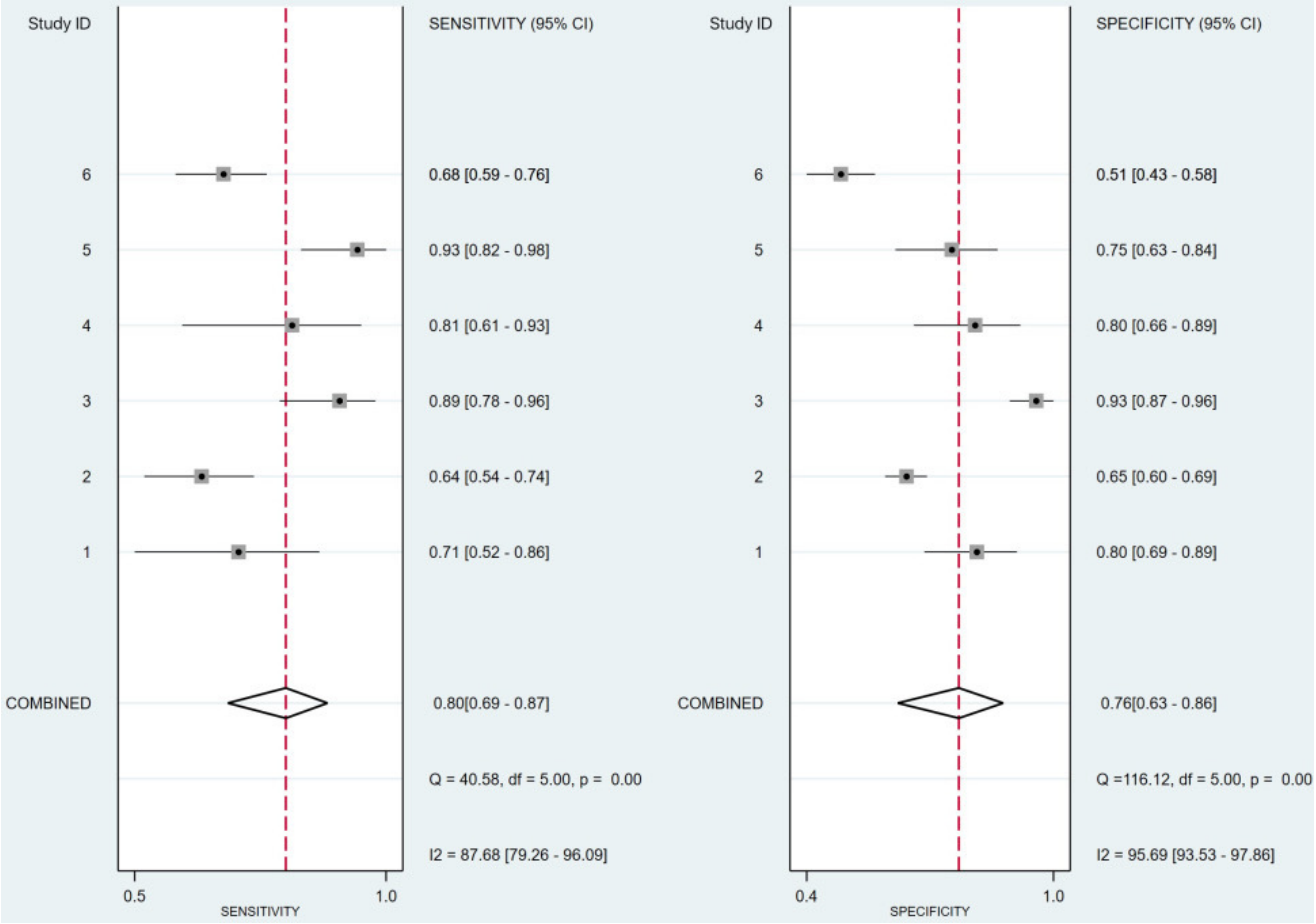

Fig. 3

Forest plot of the accuracy of D-dimer in the diagnosis of prosthetic joint infection. All p-values were calculated using bivariate effect model with logit transition. CI, confidence interval.

and specificity (I^2 = 95.69, 95% CI 95.53 to 97.86). The correlation (mixed model) was 0.83 and the proportion of heterogeneity likely due to threshold effect was 0.69, suggesting that threshold effect could be one of the causes for heterogeneity. Bivariate box plot (Figure 5) was then drawn to identify source of heterogeneity, which showed that five studies were within the 95% CI; using Stata 16 we were able to identify the one study[11] outside the 95% CI zone. Sensitivity analysis was conducted by excluding the source of heterogeneity identified, which yielded the following results: sensitivity 0.80 (95% CI 0.66 to 0.89), specificity 0.73 (95% CI 0.66 to 0.80), and AUC 0.81 (95% CI 0.77 to 0.84). The result was consistent with previous analysis except for a small climb in specificity.

To further address a potential source of heterogeneity, multivariate meta-regression was performed to combine results from multiple studies with attention to between-study variation. Covariates including country, comorbidity, and serum/plasma test were analyzed (Table II). The results showed that serum or plasma testing method is a major cause of heterogeneity (p = 0.01). Sub-group analysis of serum and plasma D-dimer was conducted and results are listed in Table II. There are not enough studies to generate a summary ROC and DOR for plasma D-dimer.

Publication bias. Publication bias was assessed with Deek's Funnel Plot Asymmetry Test (Figure 6). The p-value was 0.19; no significant publication bias was found.

Discussion

D-dimer is a fibrin degradation product produced in the coagulation process. Some studies have shown a correlation between coagulation and inflammation: coagulation-related biomarkers have a proinflammatory effect and persistent inflammatory response contributes to a hyper-coagulable state.[15–17] Therefore, coagulation biomarkers including D-dimer may be elevated in infectious disease. Studies have reported D-dimer as diagnostic marker in infectious and inflammatory diseases including rheumatoid arthritis, bacteraemia, endocarditis, pneumonia caused by *Mycoplasma pneumoniae*, and spontaneous bacterial peritonitis.[18–22]

Our analysis included six studies and 1,255 cases; pooled analysis of D-dimer showed sensitivity of 80% and specificity of 76%. Summary ROC curve suggested

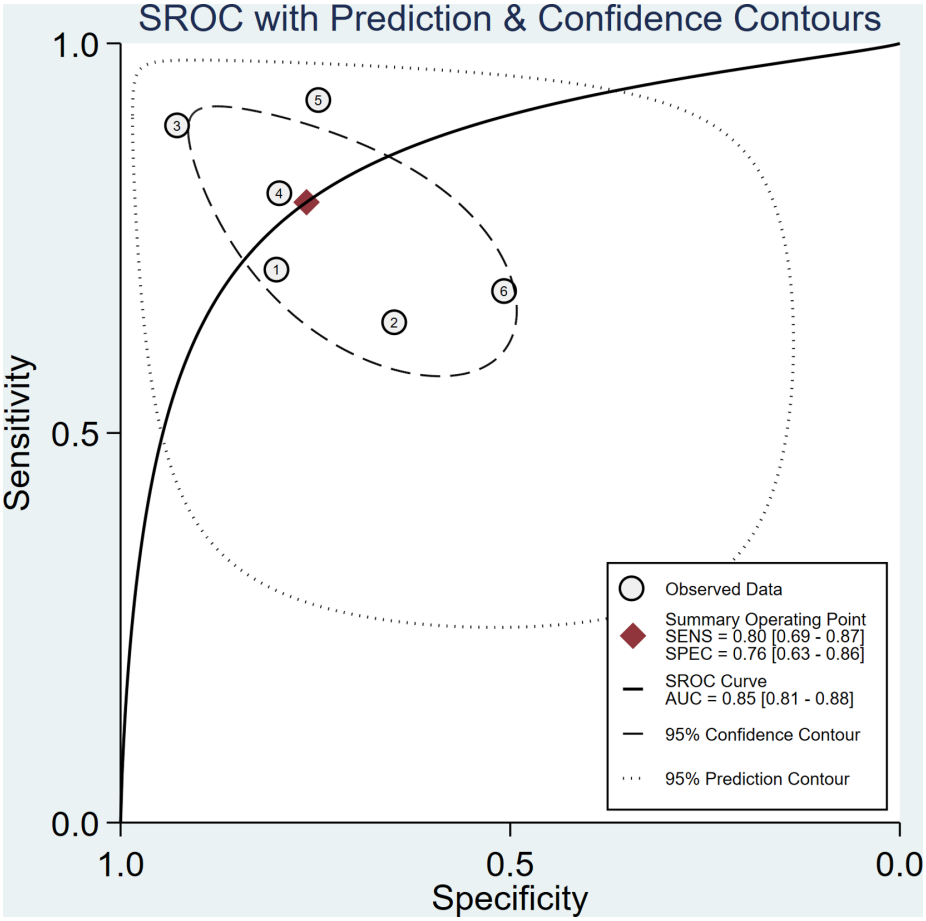

Fig. 4

Summary receiver operating characteristic (SROC) area under the curve (AUC) for the diagnostic value of D-dimer in prosthetic joint infection. SENS, sensitivity; SPEC, specificity.

Table II. Diagnostic value of D-dimer, CRP, and ESR. Values are displayed as estimates and 95% confidence intervals.

Overall diagnostic accuracy of D-dimer, CRP, and ESR	**Sensitivity**	**Specificity**	**SROC AUC**	**DOR**
D-dimer	0.80 (0.69 to 0.87)	0.76 (0.63 to 0.86)	0.85 (0.81 to 0.88)	12.06 (3.96 to 36.74)
CRP	0.78 (0.72 to 0.83)	0.81 (0.72 to 0.87)	0.84 (0.81 to 0.87)	15.17 (11.14 to 20.66)
ESR	0.68 (0.63 to 0.73)	0.83 (0.78 to 0.87)	0.72 (0.68 to 0.76)	10.03 (6.67 to 15.10)
In patients without thrombosis and hyper-coagulation disorder				
D-dimer	0.82 (0.70 to 0.90)	0.80 (0.70 to 0.88)	0.88 (0.85 to 0.90)	17.76 (4.54 to 69.51)
CRP	0.77 (0.69 to 0.84)	0.79 (0.68 to 0.87)	0.84 (0.80 to 0.87)	13.38 (9.29 to 19.27)
ESR	0.68 (0.62 to 0.74)	0.83 (0.77 to 0.88)	0.71 (0.67 to 0.75)	10.38 (5.99 to 17.99)
Diagnostic performance of D-dimer				
Serum	0.85 (0.76 to 0.92)	0.83 (0.74 to 0.90)	0.91 (0.88 to 0.93)	28.25 (9.60 to 83.15)
Plasma	0.67 (0.60 to 0.73)	0.58 (0.45 to 0.72)	N/A	N/A

AUC, area under the curve;DOR, diagnostic odds ratio; N/A, not available; SROC, summary receiver operating characteristic.

all studies were within the 95% prediction contour. The AUC was 0.85. Within the range of 0.5 to 1, the diagnostic value increases as AUC increases. The DOR was 12.06, exhibiting high diagnostic value. DOR reflects the connection between index result and the disease. In the case of DOR > 1, the diagnostic value increases as DOR increases. A Fagan nomogram (Figure 7) shows us the likelihood of a patient having PJI when the index test result is positive or negative through likelihood ratio and post-test probabilities. Given the pre-test probabilities of

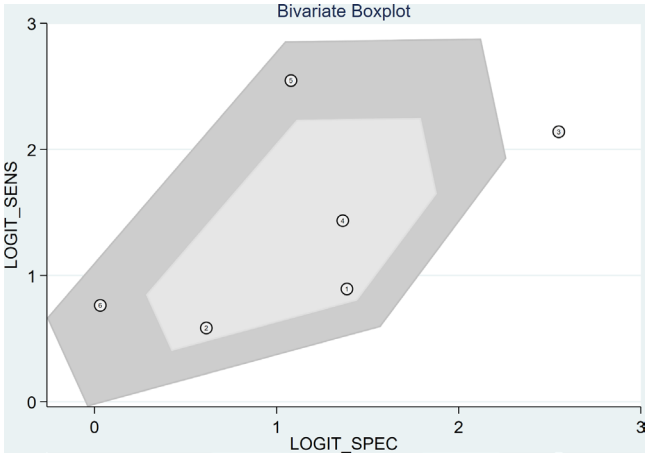

Fig. 5

Bivariate box plot to assess heterogeneity among studies.

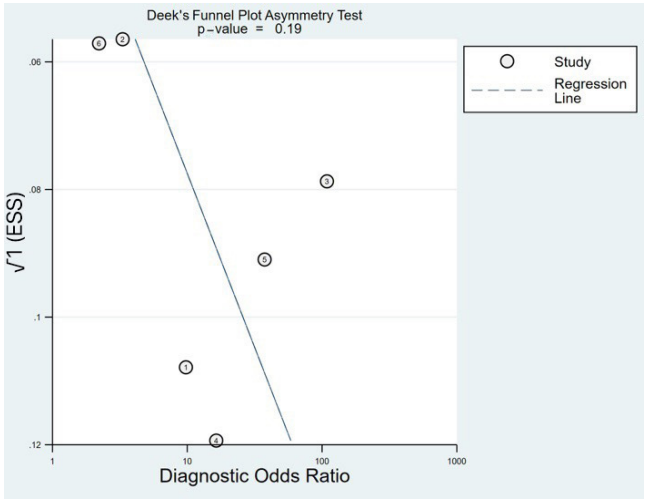

Fig. 6

Deek's Funnel Plot to assess publication bias. ESS, effective sample size.

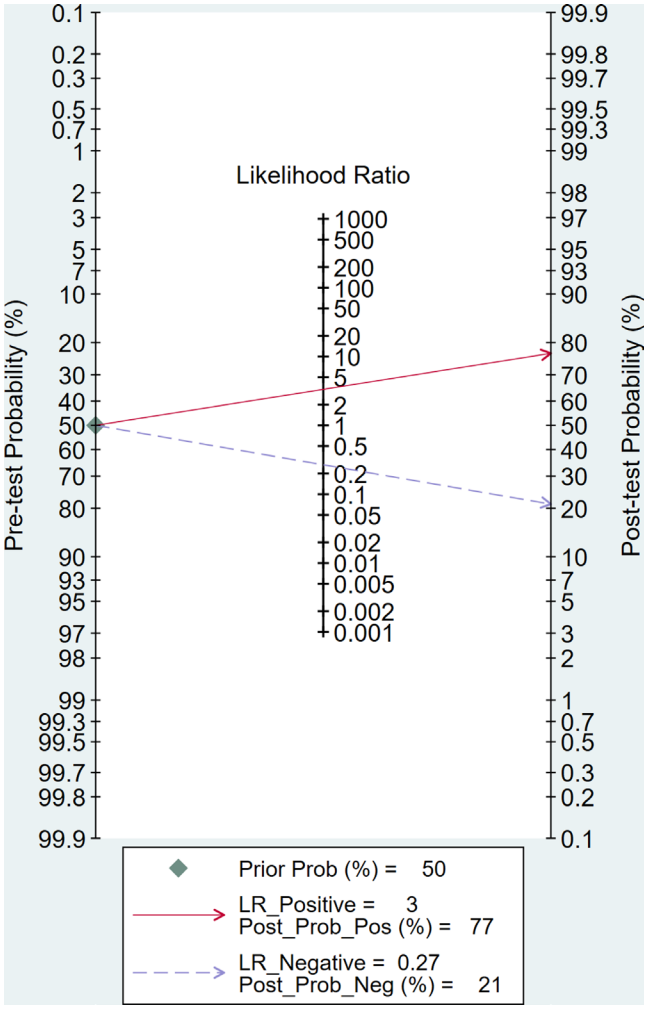

Fig. 7

Fagan nomogram of D-dimer. LR, likelihood ratio

50%, the post-test probabilities of a positive result was 77%, and the probabilities of a negative result was 21%. The positive likelihood ratio of 3 suggests that a patient with PJI is three-times more likely to have a positive test result than patients who do not have PJI.

When comparing D-dimer to CRP and ESR, D-dimer showed the highest sensitivity (similar to CRP), and the lowest specificity. The more false positives in D-dimer might be subjected to comorbidity of included patients. Five studies excluded patients with thrombosis and hyper-coagulable disorders, and subgroup analysis including these five studies yielded increased sensitivity (82%), specificity (80%), and the highest AUC and DOR compared to ESR and CRP. The result from our analysis did not perform as well as Shahi et al,[11] which may be due to patient population: Shahi et al[11] and Parvizi et al[7] included patients in the USA, and reported positively about the diagnostic value of D-dimer, while other studies[8–10,13,14,23] in our analysis included an Asian population and the results were less optimal. We also found that serum D-dimer outperformed plasma D-dimer in sensitivity and specificity. Paniccia et al[24] found that serum D-dimer is higher than plasma D-dimer in both pregnant and non-pregnant women. Our analysis showed that serum D-dimer outperforms plasma D-dimer in diagnostic value. Further studies are needed to compare serum and plasma D-dimer in arthroplasty patients.

The diagnosis of chronic PJI and PJI caused by low-virulence pathogens is more challenging. Positive culture is always difficult to acquire; it has been reported that the responsible pathogens are not identified in up to 50% of sepsis patients.[25] Other auxiliary tests become critical when the major criteria are not met. CRP and ESR are the two most common biomarkers used in diagnosing PJI, but their limited diagnostic value have been reported in both chronic PJI and low-virulence-pathogen-related PJI.[26,27] Qin et al[13] found higher sensitivity (92.73%) of D-dimer compared to ESR and CRP in patients who had PJI-related symptoms for more than six weeks. Shahi et al[11] reported five cases with elevated D-dimer, two of

which had a positive culture from samples taken during revision surgery; ESR and CRP were normal in these two patients. Lee et al[28] investigated the natural progression of D-dimer, CRP, and ESR; they found that D-dimer showed a more rapid rise and fall in early postoperative two weeks, which can be effective in early detection of PJI.

The diagnostic threshold for D-dimer varied among studies. Measured in mg/l, the threshold was 0.85 for Huang et al,[8] 1.25 for Li,[9] 1.17 for Qin,[13] 0.85 for Shahi,[11] 0.76 for Xiong,[10] and 1.02 for Xu.[14] An appropriate threshold is critical, as any change in threshold may have a substantial impact on its diagnostic value. An increase in FN results might lead to failure to recognize patients with PJI, especially in cases of low-virulence pathogens. Likewise, an increase in FPs might lead to unnecessary use of antibiotics and traumatic exams including joint aspiration.

The limitations of our study are as follows: firstly, the test result of D-dimer was interpreted as positive or negative with different thresholds, and the level of D-dimer may change according to the severity of infection. Secondly, serum/plasma testing methods and comorbidity may cause heterogeneity. However, subgroup analysis was conducted to investigate the diagnostic value of D-dimer in serum samples, plasma samples, and in patients without thrombosis and hyper-coagulation disorder. Thirdly, most of our included studies were retrospective due to the nature of our research. Finally, patients from Asia and the USA were all included in our analysis, which could be a source of bias.

The strengths of our study are as follows: firstly, PJI is a low-incidence complication following arthroplasty surgeries, and the sample sizes in studies investigating D-dimer in PJI diagnosis are relatively small. Our analysis gathered available data and provided results based on a relatively large sample size. Secondly, we further investigated any potential factors that might influence the diagnostic accuracy. We found that D-dimer has higher diagnostic value in patients without thrombosis and hyper-coagulation disorders, and also that serum D-dimer may perform better than plasma D-dimer.

In summary, in patients without thrombosis or a hyper-coagulation disorder, D-dimer has a higher diagnostic value compared to CRP and ESR. In patients with the aforementioned conditions, -dimer has higher sensitivity but lower specificity compared to ESR and CRP. We do not recommend the use of serum D-dimer in patients with thrombosis and hyper-coagulation disorders for diagnosing PJI. Serum D-dimer may perform better than plasma D-dimer. Further studies are needed to compare serum D-dimer and plasma D-dimer in arthroplasty patients.

References

1. **Maradit Kremers H**, **Larson DR**, **Crowson CS**, **et al**. Prevalence of total hip and knee replacement in the United States. *J Bone Joint Surg Am.* 2015;97-A(17):1386–1397.
2. **Kurtz SM**, **Lau E**, **Watson H**, **Schmier JK**, **Parvizi J**. Economic burden of periprosthetic joint infection in the United States. *J Arthroplasty.* 2012;27(8 Suppl):61–65.
3. **Ahmed SS**, **Haddad FS**. Prosthetic joint infection. *Bone Joint Res.* 2019;8(11):570–572.
4. **Chen M-F**, **Chang C-H**, **Chiang-Ni C**, **et al**. Rapid analysis of bacterial composition in prosthetic joint infection by 16S rRNA metagenomic sequencing. *Bone Joint Res.* 2019;8(8):367–377.
5. **Saleh A**, **George J**, **Faour M**, **Klika AK**, **Higuera CA**. Serum biomarkers in periprosthetic joint infections. *Bone Joint Res.* 2018;7(1):85–93.
6. **Chen M-F**, **Chang C-H**, **Yang L-Y**, **et al**. Synovial fluid interleukin-16, interleukin-18, and CRELD2 as novel biomarkers of prosthetic joint infections. *Bone Joint Res.* 2019;8(4):179–188.
7. **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.
8. **Huang J**, **Zhang Y**, **Wang Z**, **et al**. 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.
9. **Li R**, **Shao H-Y**, **Hao L-B**, **et al**. 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-A(7):613–619.
10. **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.
11. **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-A(17):1419–1427.
12. **Wade R**, **Corbett M**, **Eastwood A**. Quality assessment of comparative diagnostic accuracy studies: our experience using a modified version of the QUADAS-2 tool. *Res Synth Methods.* 2013;4(3):280–286.
13. **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):229–234.
14. **Xu H**, **Xie J**, **Huang Q**, **Lei Y**, **Zhang S**, **Pei F**. Plasma fibrin degradation product and D-dimer are of limited value for diagnosing periprosthetic joint infection. *J Arthroplasty.* 2019;34(10):2454–2460.
15. **Cicala C**, **Cirino G**. Linkage between inflammation and coagulation: an update on the molecular basis of the crosstalk. *Life Sci.* 1998;62(20):1817–1824.
16. **Libby P**, **Simon DI**. Inflammation and thrombosis: the clot thickens. *Circulation.* 2001;103(13):1718–1720.
17. **Chung S**, **Kim J-E**, **Park S**, **Han K-S**, **Kim HK**. Neutrophil and monocyte activation markers have prognostic impact in disseminated intravascular coagulation: in vitro effect of thrombin on monocyte CD163 shedding. *Thromb Res.* 2011;127(5):450–456.
18. **Mikuła T**, **Sapuła M**, **Jabłońska J**, **et al**. Significance of heparin-binding protein and D-dimers in the early diagnosis of spontaneous bacterial peritonitis. *Mediators Inflamm.* 2018;2018:1–6.
19. **Turak O**, **Canpolat U**, **Ozcan F**, **et al**. D-dimer level predicts in-hospital mortality in patients with infective endocarditis: a prospective single-centre study. *Thromb Res.* 2014;134(3):587–592.
20. **Schwameis M**, **Steiner MM**, **Schoergenhofer C**, **et al**. D-dimer and histamine in early stage bacteremia: a prospective controlled cohort study. *Eur J Intern Med.* 2015;26(10):782–786.
21. **Mélé N**, **Turc G**. Stroke associated with recent Mycoplasma pneumoniae infection: a systematic review of clinical features and presumed pathophysiological mechanisms. *Front Neurol.* 2018;9:1109.
22. **Tan L**, **Wang Q**, **Zeng T**, **et al**. Clinical significance of detecting HLA-DR, 14-3-3η protein and D-dimer in the diagnosis of rheumatoid arthritis. *Biomark Med.* 2018;12(7):697–705.
23. **Fu J**, **Ni M**, **Chai W**, **Li X**, **Hao L**, **Chen J**. Synovial fluid viscosity test is promising for the diagnosis of periprosthetic joint infection. *J Arthroplasty.* 2019;34(6):1197–1200.
24. **Paniccia R**, **Prisco D**, **Bandinelli B**, **et al**. Plasma and serum levels of D-dimer and their correlations with other hemostatic parameters in pregnancy. *Thromb Res.* 2002;105(3):257–262.
25. **Martin GS**, **Mannino DM**, **Eaton S**, **Moss M**. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med.* 2003;348(16):1546–1554.
26. **Akgün D**, **Müller 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):1482–1486.

27. Pérez-Prieto D, **Portillo ME**, **Puig-Verdié L**, **et al**. C-reactive protein may misdiagnose prosthetic joint infections, particularly chronic and low-grade infections. *Int Orthop*. 2017;41(7):1315–1319.

28. 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.

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- S Zhu: Conducted the statistical analysis, Extracted the data, Assessed the quality of the included studies.
- Y Wang: Co-wrote the manuscript, Extracted the data.
- W Qian: Designed the study, Oversaw the study's quality control.

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