





REVIEW ARTICLE

Role of D-dimer and Fibrinogen in the Diagnosis of Periprosthetic Joint Infection: A Systematic Review and Meta-Analysis

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The diagnostic potential of D-dimer and fibrinogen to detect periprosthetic joint infection (PJI) of the hip and knee is not well-understood. The aim of this study was to determine whether D-Dimer and fibrinogen can be used as effective biomarkers to screen PJI. A systematic review of the literature indexed in Web of Science, PubMed, Cochrane Library, Embase, and Google Scholar databases was performed. All studies using D-dimer levels in serum or plasma, or fibrinogen levels in plasma, for the diagnosis of PJI were included. Meta-analysis estimates, including sensitivity, specificity, diagnostic odds ratios (DOR), and the area under the summary receiver operating characteristic curve (AUSROC), were calculated using a random-effects model, and used to assess the diagnostic accuracy of these biomarkers. A total of nine studies were analyzed, and their quality was considered to be acceptable. D-dimer gave a limited diagnostic value if serum and plasma combined: sensitivity (0.77, 95% confidence interval [CI] [0.63 to 0.87]), specificity (0.67, 95% CI [0.54 to 0.78]), DOR (6.81, 95% CI [2.67 to 17.37]), and AUSROC (0.78, 95% CI [0.74 to 0.82]). Plasma D-dimer levels were associated with less satisfactory sensitivity (0.65, 95% CI 0.57 to 0.71), specificity (0.58, 95% CI 0.50 to 0.66), DOR (2.52, 95% CI 1.64 to 3.90), and AUSROC (0.65, 95% CI 0.61 to 0.69). Serum D-dimer levels showed higher corresponding values of 0.89 (95% CI 0.79 to 0.94), 0.76 (95% CI 0.55 to 0.89), 24.24 (95% CI 10.07 to 58.32), and 0.91 (95% CI 0.88 to 0.93). Plasma fibrinogen showed acceptable corresponding values of 0.79 (95% CI 0.70 to 0.85), 0.73 (95% CI 0.57 to 0.85), 10.14 (95% CI 6.16 to 16.70), and 0.83 (95% CI 0.79 to 0.86). Serum D-dimer may be an effective marker for the diagnosis of PJI in hip and knee arthroplasty patients, and it may show higher diagnostic potential than plasma fibrinogen. Plasma D-dimer may have limited diagnostic potential.

Key words: D-dimer; Fibrinogen; Meta-analysis; Periprosthetic joint infection; Plasma; Serum

Introduction

Total joint arthroplasty (TJA) is a successful surgical treatment for advanced hip and knee diseases^{1, 2}. However, periprosthetic joint infection (PJI) that occurs after TJA is a catastrophic complication, leading to prolonged treatment, increased hospital expenses, and even higher morbidity and mortality rates^{3, 4}. The incidence rate of PJI is estimated to

range between 0.7% and 2.4%^{5, 6}, and is expected to increase rapidly with an increase in prevalence of primary TJA. The number of revision knee arthroplasties is expected to grow at a high rate of nearly 90% each year and is expected to reach 47,313 cases by 2050, which is mainly due to the increase in PJI⁷. An early and accurate diagnosis of PJI is important for patients and surgeons. This helps plan and execute an

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optimal therapy scheme, manage patients' emotions and expectations, and ensure retention of the implanted prosthesis as well as joint function⁸. PJI screening is of prime importance, especially for those patients with chronic infection (which occurred after 3 months of the index procedure) caused by low-virulence pathogens. Markers in blood, serum, or plasma are first-line screening tools and play a critical role in PJI screens, since they are convenient, fast, and inexpensive to assay. C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR) have been used to identify PJI in the clinic, as recommended by the Musculoskeletal Infection Society (MSIS) workgroup⁹. However, these indices have been associated with a high rate of false negatives, since they can fall within the normal range when the patient has an infection with a weakly virulent organism¹⁰, such as *Cutibacterium acnes*¹¹. Therefore, it is very important to find and evaluate new indicators to diagnose PJI to improve the diagnostic accuracy and avoid missed diagnosis of PJI.

Recent studies report that D-dimer and fibrinogen could be useful for PJI screening, and serum D-dimer has been adopted as a PJI marker by the 2018 criteria of the International Consensus Meeting (ICM)¹². However, the sample sizes of these studies are limited and there are inconsistencies in the diagnostic accuracy of D-dimer^{13, 14}; more importantly, the D-dimer reported in some studies was tested from serum^{13, 14}, while others were tested from plasma^{15, 16}. In addition, plasma fibrinogen needs further discussion before it can be applied for diagnosing PJI in clinic. Hence, this systematic review and meta-analysis were conducted to: (i) synthesize the available information on the use and diagnostic accuracy of D-dimer levels in serum and plasma as well as fibrinogen levels in plasma for PJI screening; and (ii) more importantly, compare the diagnostic accuracy of D-dimer between serum and plasma for PJI screening.

Methods

Study Design

This systematic review and meta-analysis was performed to the aim to evaluate the diagnostic values of D-dimer and fibrinogen, following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement. It has also been registered at the International Prospective Register of Systematic Reviews (CRD42020170438). The serum D-dimer means the values were tested in post-coagulation serum, while the values of plasma D-dimer and fibrinogen were tested in plasma.

Search Strategy

We searched the related literature using electronic databases, including PubMed, Web of Science, the Cochrane Library, Embase, and Google Scholar. Relevant literature was examined from database inception to August 2020 with no language restrictions. The vocabulary and syntax of search strings were adjusted for each database as necessary. The

following search strategy were used for searches: (((((infection[MeSH Terms]) OR infection) OR infections)) AND (((fibrinogen[MeSH Terms]) OR fibrinogen) OR D-dimer)) AND ((((((arthroplasty[MeSH Terms]) OR arthroplasty) OR arthroplasties) OR replacement[MeSH Terms]) OR replacement) OR replacements). The search strategy in Pubmed was shown in Supplementary Table S1. All references cited in these studies and relevant review articles were analyzed manually. Furthermore, unpublished and gray literature found in established orthopaedic journals (e.g., *The Journal of Bone and Joint Surgery*, *Clinical Orthopaedics and Related Research*, *The Journal of Arthroplasty*, and *The Bone & Joint Journal*) between January 2016 and August 2020 was also evaluated.

Inclusion and Exclusion Criteria

Two reviewers (XH and XJW) independently screened the literature, and all disagreements were resolved after discussion with a third reviewer (YJL). The studies that evaluated the diagnostic values of D-dimer and fibrinogen for identifying PJI in patients who underwent revision knee or hip arthroplasty in comparison with the diagnostic results of reference standard were included. Inclusion criteria: (i) Participants: patients who had undergone revision knee or hip arthroplasty due to PJI or aseptic mechanical failure; (ii) Interventions: not applicable; (iii) Comparisons: not applicable; (iv) Outcomes: diagnostic values of plasma

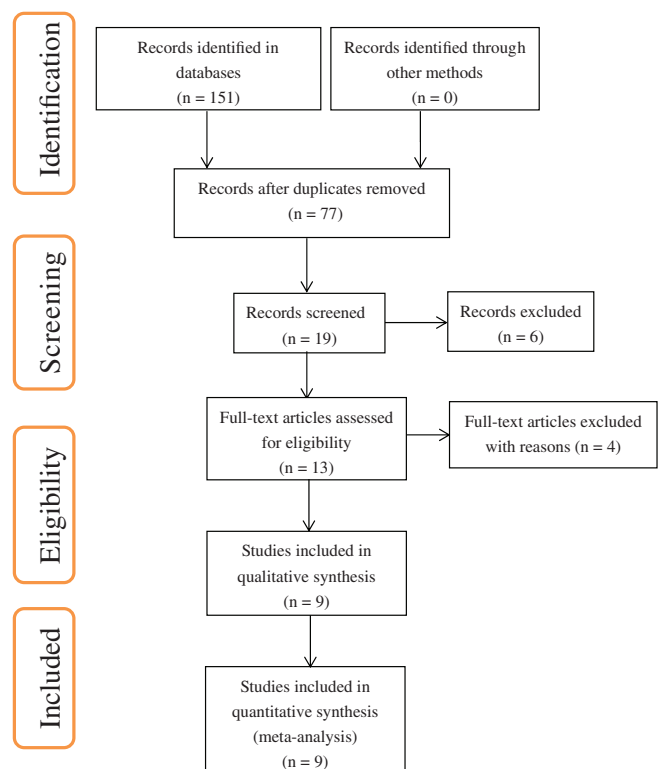


Fig. 1 PRISMA flow diagram of the literature screening process.

TABLE 1 Characteristics of studies included in meta-analysis

Study	Location	Study design	Reference standard	Inclusion criteria	Origin and values of cutoffs	Patients: All (PJI/Non-PJI)	Age (years), and sex (Male/Female)
Serum D-dimer Shahi et al. ¹³ (2017)	Thomas Jefferson Univ., Philadelphia, USA	P	MSIS (2013)	Patients undergoing primary and revision hip or knee arthroplasty	Youden index; 850 ng/mL	195 (57/138)	PJI: 59.7 (49–76)*, (24/33); Non-PJI: NR (44–81)*, (77/61)
Xiong et al. ¹⁸ (2019)	The First Affiliated Hospital of Nanchang Univ., Nanchang, China	P	MSIS (2011)	Patients with suspected infections after TJA, and those prepared for revision arthroplasty	Youden index; 756 ng/mL	80 (26/54)	PJI: (65.42 ± 10.8) # (7/19); Non-PJI: (59.76 + 12.53) # (25/29)
Huang et al. ¹⁹ (2019)	People's Hospital of Zhengzhou Univ., Zhengzhou, China	R	MSIS (NR)	Patients with primary OA or secondary to hip congenital, PJI, and aseptic loosening	Reference to previous studies; 850 ng/mL	101 (31/70)	NR
Qin et al. ²⁰ (2020)	The First Affiliated Hospital of Chongqing Medical Univ., Chongqing, China	P	MSIS (2013)	Patients presenting with pain after TJA for surgical revision	Youden index; 1170 ng/mL	122 (55/67)	PJI: (65.89 ± 10.72) #, (28/27); Non-PJI: (64.66 ± 10.39) #, (25/42)
Pannu et al. ¹² (2020)	Cleveland Clinic Florida, Weston, USA	R	MSIS (2013)	Patients with revision TJA	Youden index; 850 ng/mL	111 (49/62)	PJI: (70 ± 10) #, (22/27); Non-PJI: (68 ± 10) #, (27/35)
Plasma D-dimer Li et al. ²¹ (2019)	Chinese PLA General Hospital and Beijing Jishuitan Hospital, Beijing, China	R	MSIS (2013)	Patients managed with revision hip or knee arthroplasty	Youden index; 1.25 mg/mL	565 (95/470)	PJI: 63.7 (18–89) *, (43/52); Non-PJI: 61.3(23–86) *, (205/265)
Pei et al. ²² 2019	West China Hospital, Sichuan Univ., Chengdu, China	R	MSIS (2013)	Patients who have undergone revision hip or knee arthroplasty	Youden index; 1.02 mg/L	224 (82/142)	NR
Plasma fibrinogen Klim et al. ²³ (2018)	Medical Univ. of Graz, Graz, Austria.	P	MSIS (2011)	Patients scheduled to have revision hip or knee arthroplasty	NR; 519 mg/dL (equal to 5.19 g/L)	84 (55/29)	PJI: (65.7 ± 15.8) #, NR; Non-PJI: (65.1 ± 14.6) #, NR
Li et al. ²¹ (2019)	Chinese PLA General Hospital and Beijing Jishuitan Hospital, Beijing, China	R	MSIS (2013)	Patients managed with revision hip or knee arthroplasty	Youden index; 4.01 g/L	565 (95/470)	PJI: 63.7 (18–89) *, (43/52); Non-PJI: 61.3 (23–86) *, (205/265)
Xu et al. ²⁴ (2019)	West China Hospital, Sichuan Univ., Chengdu, China	R	MSIS (2013)	Patients who have undergone revision hip or knee arthroplasty	Youden index; 3.57 g/L	439 (196/243)	NR

MSIS, Musculoskeletal Infection Society; NR, not reported; OA, osteoarthritis; P, Prospective; PJI, Periprosthetic joint infection defined by their reference standard; R, Retrospective; TJA, Total joint arthroplasty.; * Age is presented as mean (range); # Age is presented as mean ± standard deviation.

TABLE 2 Quality assessment of studies included in meta-analysis

Study	Risk of bias														Applicability concerns			
	Patient selection				Index test			Reference standard			Flow and timing				Patient selection Q12	Index test Q13	Reference standard Q14	
	Q1	Q2	Q3	F	Q4	Q5	F	Q6	Q7	F	Q8	Q9	Q10	Q11				F
Serum D-dimer																		
Shahi <i>et al.</i> ¹³ (2017)	Y	Y	Y	L	Y	N	H	Y	Y	L	Y	Y	Y	Y	L	L	L	L
Xiong <i>et al.</i> ¹⁸ (2019)	Y	Y	Y	L	Y	N	H	Y	Y	L	Y	Y	Y	Y	L	L	L	L
Huang <i>et al.</i> ¹⁹ (2019)	Y	Y	Y	L	U	Y	U	Y	Y	L	Y	Y	Y	Y	L	L	L	L
Qin <i>et al.</i> ²⁰ (2020)	Y	Y	Y	L	Y	N	H	Y	Y	L	Y	Y	Y	Y	L	L	L	L
Pannu <i>et al.</i> ¹² (2020)	Y	Y	Y	L	Y	N	H	Y	Y	L	Y	Y	Y	Y	L	L	L	L
Plasma D-dimer																		
Li <i>et al.</i> ²¹ (2019)	Y	Y	Y	L	U	N	H	Y	Y	L	Y	Y	Y	Y	L	L	L	L
Pei <i>et al.</i> ²² (2019)	Y	Y	Y	L	Y	N	H	Y	Y	L	Y	Y	Y	Y	L	L	L	L
Plasma fibrinogen																		
Klim <i>et al.</i> ²³ (2018)	Y	Y	Y	L	Y	U	U	Y	Y	L	Y	Y	Y	Y	L	L	L	L
Li <i>et al.</i> ²¹ (2019)	Y	Y	Y	L	U	N	H	Y	Y	L	Y	Y	Y	Y	L	L	L	L
Xu <i>et al.</i> ²⁴ (2019)	Y	Y	Y	L	Y	N	H	Y	Y	L	Y	Y	Y	Y	L	L	L	L

Y indicates “yes”, N indicates “No” and U indicates “unclear” for the signaling questions of each domain. **F**, final judgment of risk of bias or clinical applicability of each domain. **L** indicates “low risk of bias”, **H** indicates “high risk of bias” and **U** indicates “unclear” for the risk of bias of each domain or clinical applicability of the first three domains. Q1, Was a consecutive or random sample of patients enrolled? Q2, Was a case-control design avoided? Q3, Did the study avoid inappropriate exclusions? Q4, Were the index test results interpreted without knowledge of the results of the reference standard? Q5, If a threshold was used, was it pre-specified? Q6, Is the reference standard likely to correctly classify the target condition? Q7, Were the reference standard results interpreted without knowledge of the results of the index test? Q8, Was there an appropriate interval between index test(s) and reference standard? Q9, Did all patients receive a reference standard? Q10, Did all patients receive the same reference standard? Q11, Were all patients included in the analysis? Q12, Is there concern that the included patients do not match the review question? Q13, Are there concerns that the index test, its conduct, or interpretation differ from the review question? Q14, Are there concerns that the target condition as defined by the reference standard does not match the review question?

fibrinogen and D-dimer tested in serum or plasma for identifying PJI. Exclusion criteria: (i) Studies that tested unrelated biomarkers and studies reporting insufficient information to calculate sensitivity and specificity were excluded; (ii) Case reports, commentaries, expert opinions, and reviews were also excluded. A PRISMA flow diagram of the literature screening process used in this study was constructed (Fig. 1).

Data Extraction and Quality Assessment

Two reviewers (XH and XJW) independently extracted relevant data from the included studies using a standardized form. Data included sensitivity, specificity, positive and negative predictive values; numbers, age range, sex ratio, and inclusion criteria of patients; cutoff values for the markers being tested and their origin, whether derived from the Youden index or predetermined by the authors; reference standards; study design; and location and name of study site.

The quality assessment of the included studies was conducted using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool¹⁷. This tool uses 14 questions based on the following four key domains to assess the risk of bias: patient selection, index test, reference standard, as well as flow and timing. On the one hand, the information is recorded based on the signaling questions, which are answered as “yes,” “no,” or “unclear” and phrased such that

“yes” indicates low risk of bias, and used to determine the risk of bias for each domain, which is judged as “low,” “high,” or “unclear” according to the answers to all signaling questions. On the other hand, review authors record the information on which the judgment of applicability concerns is determined and then rate their concern that the study does not match the review question. The applicability concerns are rated as “low,” “high,” or “unclear,” focusing on the first three domains.

Statistical Analyses

The bivariate model retains the two-dimensional property of the original data and considers the negative correlation between sensitivity and specificity, which is based on a random effects model and takes heterogeneity among included studies into consideration. The comprehensive evaluation value of sensitivity and specificity and the negative correlation value between them can be obtained by fitting the model. Therefore, the bivariate model is used to synthesize the entire pooled dataset to ensure the reliable estimation of diagnostic accuracy^{18, 19}.

Pooled values for sensitivity, specificity, positive and negative likelihood ratios (LRs), and diagnostic odds ratios (DORs) were calculated along with 95% confidence intervals (CIs). What’s more, the summarized receiver operating characteristic (SROC) curves were constructed, and the area

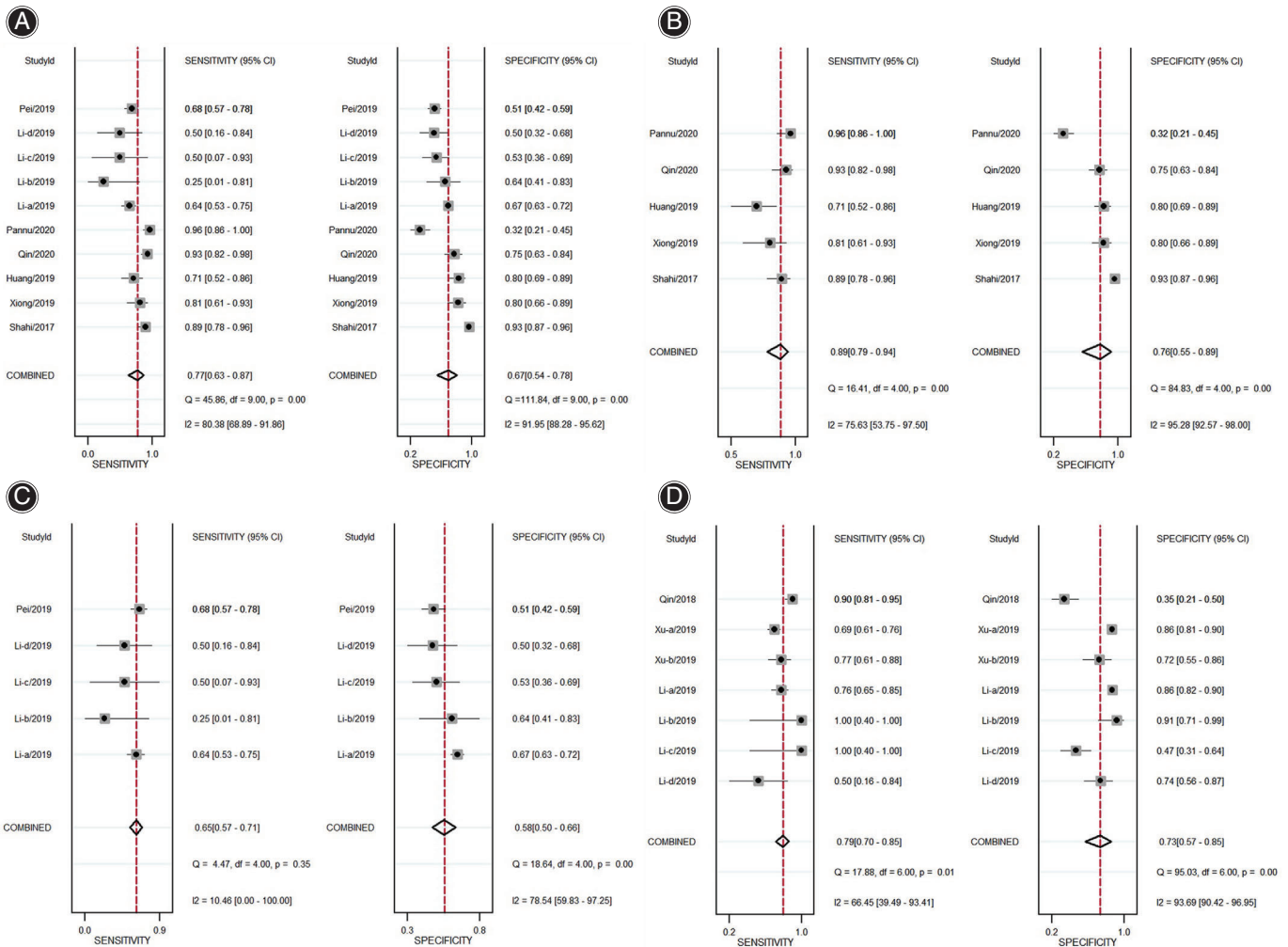


Fig. 2 Sensitivity and specificity of markers used for PJI screening: (A) D-dimer (serum and plasma combined); (B) serum D-dimer; (C) plasma D-dimer; (D) plasma fibrinogen.

under the SROC curves (AUSROCs) was used to evaluate the diagnostic potential of the markers. Spearman’s correlation coefficients between sensitivity and specificity were used to determine threshold effects, and a *P* value <0.05 was defined to indicate a significant threshold effect. A visual

analysis of the SROC curve of sensitivity and specificity was used to assess the threshold effect across studies: a “shoulder-arm” pattern suggests the existence of a diagnostic threshold bias²⁰. To assess the diagnostic accuracy of D-dimer, data for serum or plasma D-dimer were analyzed first

TABLE 3 Summary results of key diagnostic characteristics for potential markers

Potential marker	AUSROC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR(95% CI)	Negative LR(95% CI)	DOR(95% CI)
D-dimer (serum and plasma combined)	0.78 (0.74 to 0.82)	0.77 (0.63 to 0.87)	0.67 (0.54 to 0.78)	2.34 (1.53 to 3.57)	0.34 (0.19 to 0.61)	6.81 (2.67 to 17.37)
Serum D-dimer	0.91 (0.88 to 0.93)	0.89 (0.79 to 0.94)	0.76 (0.55 to 0.89)	3.56 (1.85 to 7.24)	0.15 (0.08 to 0.27)	24.24 (10.07 to 58.32)
Plasma D-dimer	0.65 (0.61 to 0.69)	0.65 (0.57 to 0.71)	0.58 (0.50 to 0.66)	1.54 (1.24 to 1.91)	0.61 (0.48 to 0.77)	2.52 (1.64 to 3.90)
Plasma fibrinogen	0.83 (0.79 to 0.86)	0.79 (0.70 to 0.85)	0.73 (0.57 to 0.85)	2.95 (1.85 to 4.72)	0.29 (0.23 to 0.37)	10.14 (6.16 to 16.70)

AUSROC, area under the summary receiver operating characteristic curve; DOR, diagnostic odds ratio; LR, likelihood ratio.

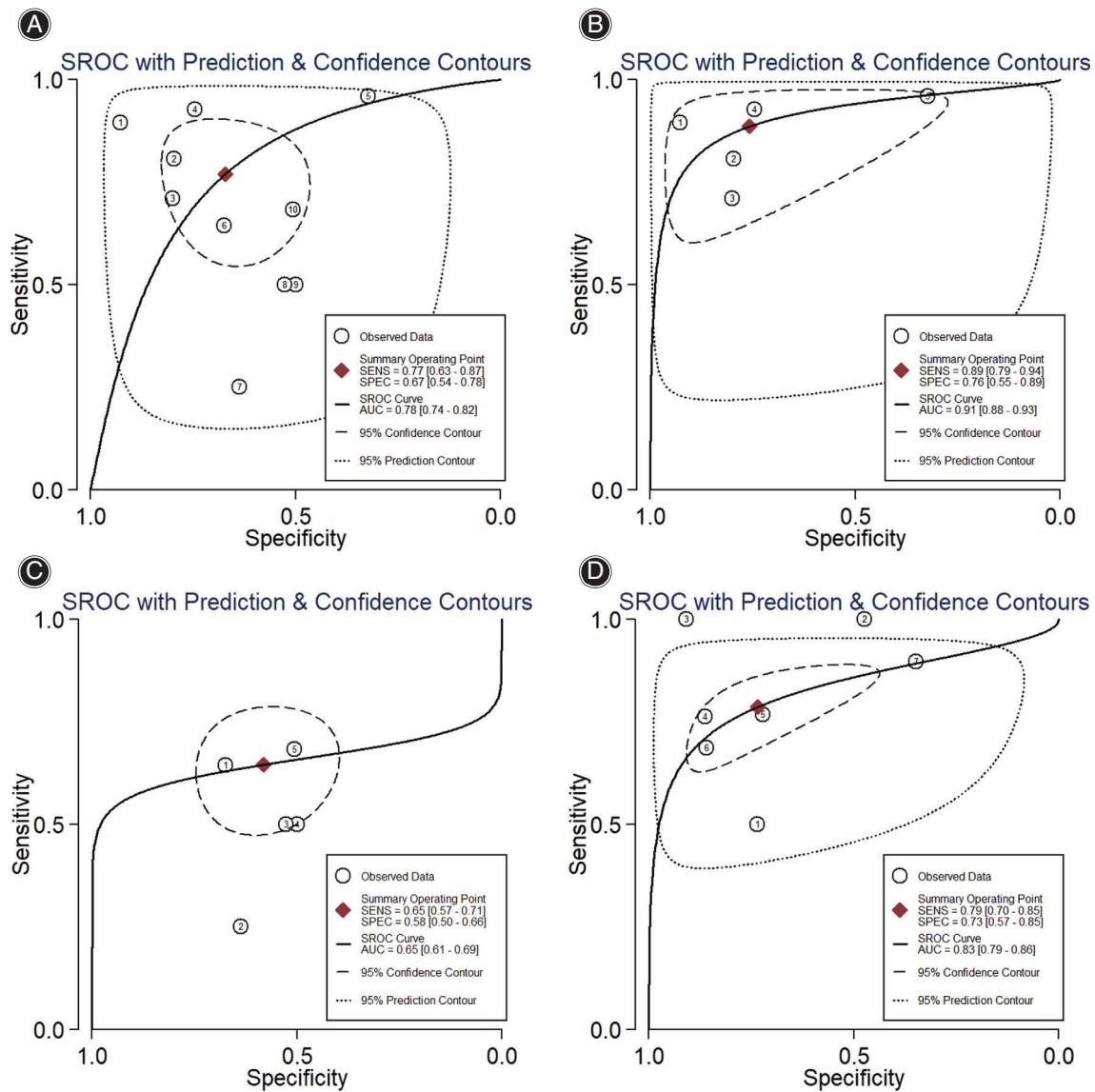


Fig. 3 Summary receiver operating characteristic (SROC) curves with prediction and confidence contours for sensitivity (SENS) and specificity (SPEC) of markers: (A) D-dimer (serum and plasma combined); (B) serum D-dimer; (C) plasma D-dimer; (D) plasma fibrinogen.

together, then separately. All statistical analyses were performed using MIDAS commands in Stata 11 (StataCorp., College Station, Texas).

Results

Of a total of 151 records identified from various databases, nine unique studies were found to satisfy the

TABLE 4 Diagnostic potential of serum D-dimer (cutoff value = 850 ng/mL)

Study	Patients: All (PJI/Non-PJI)	AUC	Sensitivity	Specificity	PPV	NPV	Positive LR	Negative LR	Accuracy
Shahi <i>et al.</i> ¹³ (2017)	195 (57/138)	NR	89.47%	92.75%	83.61%	95.52%	12.34	0.11	91.79%
Huang <i>et al.</i> ¹⁹ (2019)	101 (31/70)	NR	70.97%	80.00%	61.12%	86.17%	3.55	0.36	77.23%
Pannu <i>et al.</i> ¹² (2020)	111 (49/62)	0.742	95.92%	32.26%	52.81%	90.91%	1.42	0.13	60.36%

AUC, area under the curve; LR, likelihood ratio; NPV, negative predictive value; NR, not reported; PPV, positive predictive value.

inclusion criteria and were therefore included in the synthesis and meta-analysis (Fig. 1). Five studies^{13, 14, 21–23} evaluated the diagnostic potential of serum D-dimer against a reference standard in 609 patients, including 218 with PJI and 391 without PJI. Two studies^{15, 16} assessed the diagnostic accuracy of plasma D-dimer in 789 patients, including 177 with PJI and 612 without PJI. One of these studies¹⁶ evaluated the diagnostic accuracy of both plasma D-dimer and fibrinogen, and we analyzed the data for each marker separately. The diagnostic potential of plasma fibrinogen was also evaluated by three studies^{16, 24, 25}, in 1088 patients, including 346 with PJI and 742 without PJI. The details of all studies included are summarized in Table 1.

Among the included studies, the study of Li *et al.*¹⁶ classified patients into two groups based on the presence of comorbidities found while evaluating the diagnostic value of plasma D-dimer and fibrinogen; moreover, comorbidities were further divided into three categories, which included malignancy, autoimmune disease, and cardiovascular and cerebrovascular disease. Similarly, the study of Xu *et al.*²⁵ also divided their patients into two groups based on whether they found comorbidities while evaluating the diagnostic accuracy of plasma fibrinogen. All patients with comorbidities in both studies were included and analyzed. Almost all studies included ($n = 7$) used the Youden index to derive cutoff values. One exception was a study in which Huang *et al.*²² determined the cutoff based on previous studies^{14, 26}, and the another study in which Klim *et al.*²⁴ used two cutoff values, of which we chose to use the value closest to the largest value based on the Youden index during our analyses.

Quality Assessment

The quality of the included studies was assessed using the QUADAS-2 tool. Risk of bias and applicability concerns were shown in Table 2. In general, the quality of the included studies was considered to be acceptable. Regarding patient selection, reference standard domain, and flow and timing domain, all included studies had low risk of bias. Regarding the index test domain, the included studies had high risk of bias due to seven studies determining the cutoffs based on the Youden index instead of pre-specified cutoffs. In addition, there was a low risk for concern applicability for all included studies.

Diagnostic Potential of D-Dimer for PJI Screening

Our first step was to assess the diagnostic accuracy of D-dimer used for PJI screening by combining the data available on serum and plasma D-dimer. Pooling results for serum and plasma D-dimer gave a sensitivity of 0.77 (95% CI 0.63–0.87) and specificity of 0.67 (95% CI 0.54–0.78) (Fig. 2A). The pooled positive and negative LR were 2.34 (95% CI 1.53–3.57) and 0.34 (95% CI 0.19–0.61), respectively (Table 3). The DOR and AUSROC values were 6.81 (95% CI 2.67–17.37) and 0.78 (95% CI 0.74–0.82), respectively (Table 3, Fig. 3A).

Next the diagnostic potential of D-dimer level was assessed separately for serum or plasma. Serum D-dimer gave a pooled sensitivity of 0.89 (95% CI 0.79–0.94) and specificity of 0.76 (95% CI 0.55–0.89) (Fig. 2B) for serum D-dimer. Plasma D-dimer showed lower pooled sensitivity (0.65, 95% CI = 0.57–0.71) and specificity (0.58, 95% CI = 0.50–0.66) than serum D-dimer (Fig. 2C). Serum D-dimer showed higher pooled positive LR (3.56, 95% CI 1.85–7.24) and lower negative LR (0.15, 95% CI 0.08–0.27) than plasma D-dimer, which gave the corresponding values of 1.54 (95% CI 1.24–1.91) and 0.61 (95% CI 0.48–0.77; Table 3). Serum D-dimer had a higher DOR (24.24, 95% CI 10.07–58.32) and AUSROC (0.91, 95% CI 0.88–0.93) than plasma D-dimer, which gave the corresponding values of 2.52 (95% CI 1.64–3.9) and 0.65 (95% CI 0.61–0.69) (Table 3, Fig. 3B and C).

Diagnostic Potential of Plasma Fibrinogen for PJI Screening

We found that the diagnostic potential of plasma fibrinogen used for PJI screening was lower than that of serum D-dimer, but higher than plasma D-dimer. The pooled values for diagnostic sensitivity and specificity of plasma fibrinogen were 0.79 (95% CI 0.70–0.85) and 0.73 (95% CI 0.57–0.85), respectively, (Fig. 2D). Pooled positive and negative LR were 2.95 (95% CI 1.85–4.72) and 0.29 (95% CI 0.23–0.37) (Table 3), DOR was 10.14 (95% CI 6.16–16.70), and AUSROC was 0.83 (95% CI 0.79–0.86) (Table 3, Fig. 3D).

Threshold Effect of Tested Markers and Optimal Cutoff Value for Serum D-Dimer

No significant correlation was observed between sensitivity and specificity for any of these markers: Spearman's correlation coefficient was 0.237 ($P = 0.510$) for serum and plasma D-dimer combined, -0.7 ($P = 0.188$) for serum D-dimer, -0.103 ($P = 0.870$) for plasma D-dimer, and 0.126 ($P = 0.788$) for plasma fibrinogen, and all P values >0.05 . Furthermore, no “shoulder-arm” pattern between sensitivity and specificity was observed in the SROC curves of these markers, confirming that there was no threshold effect. In addition, a cutoff value of 850 $\mu\text{g/mL}$ of serum D-dimer was used in three of five studies; the cutoff values for two studies^{16, 20} were calculated based on the Youden index, while the cutoff value in the third study¹⁸ was based on previous studies (Table 4). However, no additional estimates were calculated due to the lack of sufficient studies.

Discussion

This appears to be the first systematic review and meta-analysis evaluating the diagnostic accuracy of D-dimer and fibrinogen to identify PJI in revision hip or knee arthroplasty patients. Firstly, the evidences of plasma fibrinogen, serum or plasma D-dimer for screening PJI were synthesized, and then the diagnostic accuracy of D-dimer between serum and plasma were assessed separately to compare their diagnostic values. Our results suggest that serum

D-dimer has a higher diagnostic accuracy for identifying PJI before revision hip or knee arthroplasty, and the diagnostic value of plasma fibrinogen is inferior to serum D-dimer, while plasma D-dimer has limited diagnostic potential.

The timely, accurate diagnosis of PJI remains a significant challenge for clinical surgeons²⁷. Although the MSIS workgroup has provided a definition and criteria for identifying PJI, clear-cut clinical diagnoses remain problematic when it comes to clinical practice, especially for patients with occult infections²⁸. Compared with synovial markers, blood/serum/plasma markers are more important for screening infection because they are the earliest referenced indicators that clinicians are exposed to when PJI is clinically suspected. Therefore, an accurate biomarker in blood, serum, or plasma can efficiently reduce the chances of a missed diagnosis and inaccurate management of infection. Additionally, for patients with autoimmune diseases²⁹ or infections caused by weakly virulent organisms¹⁰, the use of CRP and ESR may be ineffective. Fibrinolytic system is strongly associated with inflammatory system³⁰, and fibrinolysis and coagulation indicators, such as D-dimer³¹, fibrinogen degradation products³², fibrinogen³³, and even platelets³⁴, play an important role in inflammatory processes. Scholars have begun to pay attention to the values of these markers for identifying PJI. Moreover, the ICM (2018) Criteria had recommended the serum D-dimer as a marker for identifying PJI¹².

D-dimer, the product of fibrin(ogen) degradation, is familiar to clinicians because it is also used to exclude venous thromboembolism³⁵ and monitor the status of postoperative fibrinolytic response³⁶. However, there is increasing evidence supporting the association between D-dimer and infections^{31, 37}. One of the first studies to evaluate the use of serum D-dimer in PJI screening showed that its diagnostic accuracy was higher than that of ESR and serum CRP¹⁴. Then, several researchers also evaluated the diagnostic values of serum/plasma D-dimer for PJI with their own data. We synthesized these studies and the results showed the serum D-dimer is an excellent marker for screening infection, while plasma D-dimer may be limited. However, the discrepancy is still uncertain. Fibrinogen is first converted into fibrin monomers by the action of thrombin, and the fibrin monomers are polymerized into soluble fibrin dimers, trimers, oligomers, and multimers^{38, 39}. These fibrin polymers are bound by non-covalent bonds and are soluble in urea or chloroacetic acid, also known as soluble fibrin monomer complex (SFMC), which may aggregate into insoluble fibrin as the serum sample coagulates completely *in vitro*^{40, 41}. Hence, these substances containing D-dimer structure are consumed in serum samples due to re-coagulation, leading to soluble D-dimer levels that are lower than the corresponding levels in plasma samples. Conversely, a fibrinolytic response secondary to coagulation *in vitro* may lead to a false increase in the concentration of D-dimer in serum samples⁴². Future studies comparing the diagnostic accuracy of serum and

plasma D-dimer should simultaneously collect serum and plasma samples from the same patients undergoing revision knee or hip arthroplasty.

Plasma fibrinogen is a large, hexameric, homodimeric glycoprotein of 340 kDa⁴³, and it is used as an index of coagulation function during routine preoperative screening. The glycoprotein secreted from the liver is converted into fibrin to stop excessive bleeding, stabilize blood clots, and promote hemostasis after tissue and vascular injury⁴⁴. Plasma fibrinogen is also associated with the activation and mediation of inflammatory processes⁴⁵, and its secretion can be upregulated by inflammatory events⁴³. Our results indicate that plasma fibrinogen may also be a useful biomarker for PJI screening. Furthermore, both the studies of Li *et al.*¹⁶ and Xu *et al.*²⁵ revealed that fibrinogen may be preferable for detecting PJI in patients with coagulation-related comorbidities and inflammatory arthritis, while traditional diagnostic indices, CRP and ESR, may be confusing in such conditions²⁹.

Larger studies should verify and extend our finding that serum D-dimer may be an effective biomarker for periprosthetic joint infection screening, especially since the present study had important limitations. First, the limited number of included studies meant that we were unable to investigate sources of heterogeneity among the studies or assess the presence of publication bias. Second, our study suggested that serum D-dimer and plasma fibrinogen may be useful for screening PJI; however, there is no primary study comparing the diagnostic values between serum D-dimer and plasma fibrinogen. Therefore, future prospective studies are needed to compare the serum D-dimer and plasma fibrinogen in the same subject. Additionally, although the 2018 criteria of the ICM suggest a cutoff value of 860 µg/L of serum D-dimer for diagnosing chronic PJI¹², we could not determine an optimal threshold for serum D-dimer or plasma fibrinogen because of the lack of relevant data. Despite these issues, our study substantiates the clinical applicability of D-dimer and plasma fibrinogen for PJI screening and lays a solid foundation for future research on the optimization of diagnostic criteria for PJI.

Conclusions

The serum D-dimer may be a promising biomarker for screening PJI, and the diagnostic accuracy of plasma fibrinogen was inferior to it; however, plasma D-dimer may be limited for identifying PJI. More large-sample studies on these markers are needed due to the limited number of included studies.

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Author Contributions

HX and **JWX**: screened the literature and extracted relevant data, drafted the work, and revised it critically for important intellectual content. **JLY**: analyzed and interpreted data for the work. **ZYH**: participated in final approval of the version of this paper to be published. **FXP** contributed to the conception and design of the work, and revised the manuscript. All authors read and approved the final manuscript.

Availability of Data and Materials

Please contact author for data requests.

Supporting Information

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

Supplementary Table 1 Search strategy in Pubmed

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