Meta-analysis of serum and/or plasma D-dimer in the diagnosis of periprosthetic joint infection

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Abstract

Background

The purpose of this meta-analysis was to evaluate the diagnostic value of D-dimer in detecting periprosthetic joint infection (PJI).

Methods

A systematic search and screen of relevant studies was performed in the PubMed, Web of Science and Embase databases using the following medical subject headings (MeSH) or keywords: “arthroplasty or joint prosthesis or joint replacement or periprosthetic joint or prosthetic joint”, “infection or infectious or infected”, and “D-dimer or serum D-dimer or plasma D-dimer or fibrin degradation products”. Then, the data were analysed and processed by Meta-Disc software.

Results

A total of 7 studies with 1285 patients were included in this meta-analysis. The pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR) were 0.75 (95% confidence interval [CI]: 0.70 to 0.79), 0.69 (95% CI: 0.66 to 0.72), 3.01 (95% CI: 1.84 to 4.93), 0.32 (95% CI: 0.19 to 0.53) and 10.20 (95% CI: 3.63 to 28.64), respectively. Subgroup analyses showed that use of serum D-dimer had better sensitivity and specificity than plasma D-dimer for the diagnosis of PJI (0.86, 0.84 vs. 0.67, 0.60, respectively).

Conclusion

Serum D-dimer had a better diagnostic value than plasma D-dimer for the diagnosis of PJI.

Background

Periprosthetic joint infection (PJI) is the most challenging complication of arthroplasty because the gold standard for diagnosing PJI is unclear [1]. How to diagnose the infection is a difficult issue and the key to the successful management of PJI. Preoperative diagnoses are a preliminary screening of suspected infection cases in the earlier stage and provide valuable information to the further diagnostic procedure or help to rule out infection. Systemic inflammation markers and synovial fluid biomarkers have been a hot research topic in recent years [2, 3]. Compared with blood tests, synovial fluid tests are more dependent on doctors’ personal operational experience; some test results were decided by the tester’s subjective judgement, and the procedures of joint aspiration can easily affect the final result [4–7]. Therefore, blood tests may be easier to use, more stable, more cost-effective and easier to popularize for diagnosing PJI. Serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are the most commonly used and first-line blood examinations in the diagnosis of PJI, and they are included in the American Academy of Orthopedic Surgeons (AAOS) guidelines and in one of the minor criteria of the Musculoskeletal Infection Society (MSIS) guidelines [8]. However, CRP, ESR, and the combination of CRP and ESR have a high sensitivity but low specificity for the diagnosis of PJI [9]. Moreover, the levels of ESR and CRP could be shown as normal in the case of low-virulence organisms [10]. New complementary or alternative serum biomarkers to CRP or ESR are needed to further improve the diagnostic accuracy. D-dimer is usually used for the exclusion of suspected venous thromboembolic disease in the area of orthopaedics [11, 12]. Shahi A et al. [13] found that serum D-dimer seems to be a promising biomarker for the diagnosis of PJI, with a higher sensitivity and specificity than ESR or CRP. Nevertheless, recent studies have been controversial regarding the diagnostic value of D-dimer [14, 15], and although both serum and plasma D-dimer were used for diagnosing PJI [16, 17], their diagnostic value has not yet been assessed. The purpose of the present meta-analysis was to determine the accuracy of serum and/or plasma D-dimer in diagnosing PJI.

Methods

Search strategy

We searched electronic databases including PubMed, Embase, and Web of Science for articles that were published on the diagnostic method of D-dimer in detecting PJI. The first article was published in 2017. Therefore, the search time was set between 2017 and 2019. The search strategy is presented in Table 1. In addition, the reference lists of the included studies and relevant literature on D-dimer were also manually searched to identify potential studies until no additional articles could be found. Duplicated articles were removed in Endnote version X9 reference manager software (Thomson Reuters, New York City, NY).

Number	Medical subject headings (MeSH) or text keywords	Web of Science/ PubMed/ EMbase (items found)
#1	arthroplasty or joint prosthesis or joint replacement or periprosthetic joint or prosthetic joint	14,141 / 16,517 / 18,358
#2	infection or infectious or infected	202,428 / 206,267 / 281,637
#3	D-dimer or serum D-dimer or plasma D-dimer or fibrin degradation products	1519 / 1764 / 3454
#4	#1 AND #2 AND #3	19 / 20 / 18

Table 1. Search strategy and results between 2017 and 2019

Eligibility criteria

Articles were selected according to the following inclusion criteria: (1) the diagnosis of PJI was confirmed by the International Consensus Meeting (ICM), Infectious Diseases Society of America (IDSA), MSIS, or European Bone and Joint Infection Society (EBJIS) criteria or any other definition, including clinical signs of infection, presence of sinus tract or purulence around the prosthesis, histopathological examination of periprosthetic tissue indicating acute inflammation or positive culture result from synovial fluid, periprosthetic tissue samples or sonication fluid [1, 8, 18–20]; (2) the number of true positive (TP), true negative (TN), false positive (FP), and false negative (FN) values were clearly described or could be calculated by their corresponding sensitivity and specificity in each study; (3) each of the selected studies contained at least 15 infected cases; and (4) publications in English.

Quality assessment

The search results were screened independently in accordance with the inclusion criteria by two investigators. All included studies were assessed according to the QUADS-2 guidelines [21], and any disagreement in the evaluation of the studies was adjudicated by a third author.

Data extraction

Data extraction was completed independently by two investigators and then rechecked by the other investigators. The following information was abstracted from the articles: first author, year of publication, country, enrolment period, study design, number of total cases and infected cases, type of prosthetic joint, acquisition time, cut-off, diagnostic criteria, potentially influencing elements, the use of antibiotics, and the sensitivity and specificity of D-dimer.

Statistical analysis

For the analysis of the diagnostic value of D-dimer, all statistical analyses were performed using Meta-Disc software (version 1.4, Unit of Clinical Biostatistics team, Madrid, Spain) [22]. The pooled sensitivity, specificity, PLR, NLR, and DOR were calculated by a bivariate random-effects regression model. The I^2 statistic was used to assess the heterogeneity of the included studies, with a range of values from 0 to 100%. Significant heterogeneity exists when the I^2 value is greater than 50%, and a value of 0% indicates no observed heterogeneity. If heterogeneity existed, subgroup analysis and meta-regression were performed to explain the potential source of heterogeneity, including the study design, type of blood sample, cut-offs, etc.

Results

Literature search results

From the selected databases, a total of 57 articles were obtained, and 31 were ruled out because of multiple indexing in different databases. After reviewing the abstracts and full articles, 7 articles met the inclusion criteria and were included in this meta-analysis [13–17, 23, 24]. The flow diagram of the selection process is shown in Fig. 1.

Characteristics of the eligible studies and quality of the included studies

A total of 1285 hip and knee cases were included in the present meta-analysis. The first study was published in 2017 by authors in the USA, and the remaining 6 papers came from China in 2019. Among these 7 studies, 3 were conducted retrospectively, and the others were prospective studies. Only two studies described the situation of antibiotic use. The detailed characteristics of the included studies are summarized in Tables 2 and 3. The QUADAS-2 assessments for each study are shown in Table 4, and the results indicated that the included studies were of good quality.

Table 2. Characteristics of included studies for meta-analysis

Study	Country	Enrollment period	Total cases	Infected cases	Study design	Location	Cut off (ng/mL)	Sen	Spe	Standard	Received antibiotics	Exclusion c
[13]	USA	From April 2015 to August 2016	195	57	Prospective study	Hip,knee	850	89.47%	92.75%	ICM criteria (2014)	Yes	1,9,10,11, 13
[16]	China	From October 2016 to October 2017	30	15	Prospective study	Hip,knee	850	66.67%	60.00%	MSIS criteria (2011)	NA	3,4,12,15
[14]	China	From June 2016 to December 2018	101	31	Retrospective study	Hip,knee	850	71%	80%	ICM criteria (2014)	NA	1,2,4,9,10,1
[24]	China	From January 2016 to December 2017	439	76	Retrospective Study (Multicenter)	Hip,knee	1250	64.5%	65%	ICM criteria (2014)	NA	2,4,5,6,15
[17]	China	From April 2017 to August 2018	80	26	Prospective study	Hip,knee	756	80.77%	79.63%	MSIS criteria (2011)	NA	1,5,9,11, 15
[23]	China	From January 2013 to December 2018	318	129	Retrospective Study	Hip,knee	1020	68.29%	50.70%	ICM criteria (2014)	Yes	8,9,14
[15]	China	From January 2015 to December 2018	122	55	Prospective study	Hip,knee	1170	92.73%	74.63%	ICM criteria (2014)	NA	3,4,5,7,11,1

Sen, Sensitivity; Spe, Specificity; ICM, International Consensus Meeting; MSIS, Musculoskeletal Infection Society

Table 3

The potentially influence element of D-dimer result

Number	Inclusion or exclusion criteria
1	Hematoma
2	Systemic inflammatory diseases, such as systemic lupus erythematosus, psoriasis, polymyalgia rheumatica, sarcoidosis, inflammatory bowel disease, gout, hepatitis B and C, lymphocytic leukemia, myelodysplastic syndrome, and multiple myeloma
3	Obesity (body mass index [BMI] > 30 kg/m2), heavy smoking
4	Malignancies
5	Venous thrombosis
6	Cardiovascular and cerebrovascular diseases
7	Infection in other regions of the body
8	Reimplantation surgery
9	History of recent trauma or dislocation (within 2 weeks)
10	Any type of skin ulcer
11	Visible ecchymosis,or a history of hypercoagulation disorder
12	Viral infections
13	Prosthetic heart valve
14	Periprosthetic fracture or joint dislocation
15	Inflammatory arthritis

Table 4
The results of the QUADAS-2 evaluation

STUDY	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
STUDY 1	J	J	?	J	J	Λ	?
STUDY 2	J	J	J	J	J	J	J
STUDY 3	J	J	J	J	J	J	J
STUDY 4	J	?	J	J	J	J	J
STUDY 5	J	?	J	J	J	J	J
STUDY 6	J	?	J	J	J	Λ	J
STUDY 7	J	?	J	J	J	J	J

ϑ: Low Risk; Λ: High Risk; ?: Unclear Risk.

Diagnostic value of D-dimer for PJI

Significant heterogeneity was found in the sensitivity (I^2 = 78.4%), specificity (I^2 = 93%), PLR (I^2 = 92.1%), NLR (I^2 = 83.9%) and DOR (I^2 = 90.7%). Thus, a random-effects model was used. The pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR) estimates for the detection of PJI using D-dimer were 0.75 (95% CI: 0.70 to 0.79), 0.69 (95% CI: 0.66 to 0.72), 3.01 (95% CI: 1.84 to 4.93), 0.32 (95% CI: 0.19 to 0.53) and 10.20 (95% CI: 3.63 to 28.64), respectively (Figs. 2, 3, 4, 5, and 6). The summary receiver operating characteristic (SROC) plot showed the sensitivity and specificity as well as the 95% confidence intervals and prediction regions, with an area under the curve (AUC) of 0.8344 (standard error, 0.0621) (Fig. 7). The subgroup analysis of serum and plasma D-dimer is shown in Table 5.

Table 5
The results of subgroup analysis

Subgroup analyses	No.of papers	No.of patients	Sen	Spe	PLR	NLR	DOR	SROC(SE)
Overall studies	7	1285	0.75(0.70–0.79)	0.69(0.66–0.72)	3.01(1.84–4.93)	0.32(0.19–0.53)	10.2(3.63–28.64)	0.8344(0.0621)
Type of blood sample								
Plasma	3	787	0.67(0.60–0.73)	0.60(0.56–0.64)	1.59(1.28–1.99)	0.59(0.48–0.72)	2.69(1.92–3.77)	0.6918(0.0361)
Serum	4	498	0.86(0.80–0.91)	0.84(0.80–0.88)	4.91(2.85–8.48)	0.19(0.09–0.37)	28.25(9.60-83.15)	0.9085(0.0403)

Sen, Sensitivity; Spe, Specificity; PLR, Positive likelihood ratio; NLR, Negative likelihood ratio; DOR, Diagnostic odds ratio; SROC, Summary receiver operating characteristic; SE, Standard error

Discussion

Early diagnosis is the first and most crucial step in the management of PJI. The preoperative test is the front-line to assess an infection, and it provides valuable information for primary differential diagnosis and further clinical decisions. The measurement of CRP or ESR is a preoperative examination that is a fast, convenient, simple and widely used diagnostic method for PJI. However, their diagnostic value is limited due to low diagnostic accuracy, and their levels are especially susceptible to fluctuations in patients with dual taper modular stems, slow-growing organisms, antibiotic treatment, etc. [25–27]. Unfortunately, at present, only CRP and ESR seem to be more suitable for the diagnosis of PJI than other serological tests [28]. Shahi and colleagues [13] first used serum D-dimer (850 ng/mL) for the diagnosis of PJI and showed that it had a higher sensitivity and specificity than ESR and CRP (sensitivity: 89% vs. 73% and 79%; specificity: 93% vs. 78% and 80%, respectively), even when evaluating the sensitivity and specificity of ESR and CRP combined. An earlier animal study by T. Ribera et al. [29] found that the synovial D-dimer concentration was significantly increased in foals with septic joints ($p < 0.001$). A prospective study measured the patient's ESR, CRP, and D-dimer levels before and after primary total hip or knee arthroplasty. D-dimer showed the largest changes during the early postoperative period; the level was sharply increased and peaked on the first day after joint replacement surgery and decreased to the baseline level on the

following day. The author speculates that when D-dimer is combined with ESR and CRP, it might be effective in the early detection of PJI [30]. In the last two years, serum D-dimer was recommended as a promising biomarker for diagnosing PJI, and it was also included in the 2018 ICM criteria for PJI [31].

In the present meta-analysis, the pooled sensitivity and specificity of serum and plasma D-dimer were 0.75 (95% CI: 0.70 to 0.79) and 0.69 (95% CI: 0.66 to 0.72), respectively. The overall diagnostic value of D-dimer had an acceptable sensitivity, whereas the specificity was low. In the subgroup analysis, we found that serum D-dimer had a better sensitivity and specificity than plasma D-dimer (0.86 and 0.84 vs. 0.67 and 0.60, respectively).

In Qin L et al.'s [15] prospective study of revision hip and knee arthroplasty, the serum D-dimer had 92.73% sensitivity and 74.63% specificity with a threshold value of 1170 ng/mL. The diagnostic sensitivity and specificity of serum D-dimer were greater than those of CRP (81% and 66%, respectively) and ESR (64% and 70%, respectively) and their combination (89% and 57%, respectively). These results were similar to Shahi et al.'s previously published results [13], but both studies used different threshold values and differed in whether systemic inflammatory diseases were included. In addition, Qin L and colleagues [15] also demonstrated that the combination of serum D-dimer and CRP could achieve the highest sensitivity compared with each of them alone. However, Huang J et al. [14] found that the sensitivity and specificity of serum D-dimer, CRP, and ESR were not significantly different when using a serum CRP level of 10 mg/L (68% and 93%, respectively), ESR level of 30 mm/h (74% and 87%, respectively) and D-dimer level of 850 ng/mL (71% and 80%, respectively) as the threshold. Xiong L et al. [17] found that the diagnostic value was equivalent among serum D-dimer, CRP and ESR, and their results showed that the AUCs were 0.890, 0.831, and 0.838, respectively. From the studies described above, serum D-dimer had a better or equal diagnostic accuracy to CRP and ESR.

The diagnostic accuracy of plasma D-dimer for the diagnosis of PJI was also tested in recent years. A retrospective cohort study measured the CRP, ESR, interleukin-6 (IL-6), plasma fibrin degradation product (FDP) and D-dimer for diagnosing PJI [23]. The potentially influencing elements included inflammatory disease and antibiotic use. Compared with traditional inflammatory markers, plasma FDP and D-dimer had a lower sensitivity and specificity than CRP, ESR and IL-6. The sensitivity of the combination of D-dimer and any inflammatory marker was decreased compared with any of the indicators used alone, as well as plasma FDP. However, the sensitivity of the combination of D-dimer or any inflammatory marker was elevated compared with any of the indicators used alone, and plasma FDP also had similar results. The authors concluded that compared with traditional inflammatory markers, the diagnostic value of plasma FDP and D-dimer was limited [23]. A prospective study by Fu J and colleagues found that [16] the sensitivity of plasma D-dimer was in the middle of that of CRP and ESR (66.67% vs. 80.00% and 33.33%, respectively), while its specificity was lowest among these three blood tests (60.00%). Li R et al.[24] showed that the diagnostic value of plasma D-dimer was possibly limited, and the AUC of plasma D-dimer was inferior to plasma fibrinogen, ESR and CRP (0.657 vs. 0.852, 0.810 and 0.808, respectively). D-dimer only exhibited better performance than white blood cells (0.590). Compared with D-dimer, the diagnostic level of plasma fibrinogen was closer to that of the traditional inflammatory markers ESR and CRP. Moreover, the author also analysed the diagnostic accuracy of D-dimer and fibrinogen with coagulation-related comorbidities (malignancy, autoimmune disease, cardiovascular disease and cerebrovascular disease). The diagnostic accuracy of D-dimer ranged from 50–57.7%. For plasma fibrinogen, the diagnostic accuracy ranged from 52.4 to 92.3%. Plasma fibrinogen had a better diagnostic accuracy than D-dimer, especially in patients with malignancy. The diagnostic value of plasma D-dimer and fibrinogen before reimplantation in two-stage exchange arthroplasty for periprosthetic hip infection was assessed by Chi Xu et al [32], and the plasma D-dimer had lower sensitivity and specificity than fibrinogen (83.3% and 41.9% vs. 87.5% and 62.8%, respectively). However, the plasma D-dimer was inferior to fibrinogen. Nevertheless, compared with the previous studies of serum CRP and ESR reported before reimplantation, plasma D-dimer seems to be a better diagnostic indicator [33, 34]. The first serum D-dimer study by Shahi et al also found that the two failure cases of second stage replacement caused by reinfection had increased D-dimer levels before reimplantation surgery, while the serum CRP and ESR levels were normal [13].

Compared with previous meta-analyses of PJI diagnoses [35, 36], all included papers in this study used similar gold standards. Nonetheless, there were still several limitations in the current meta-analysis. First, of the 7 total included studies, 6 studies came from China. Whether there are any differences in D-dimer values for the diagnosis of PJI in different countries or races is unclear. However, one study on American community-dwelling elderly persons indicated that black individuals had significantly higher D-dimer levels than white individuals [37]. Further research on the D-dimer level, whether influenced by racial differences in normal or PJI patients, is needed. Second, among these 7 research papers, we only found two studies describing the situation of antibiotic use [13, 23]. In addition, all of these publications used different exclusion criteria, which might impact the diagnostic results. Third, from the meta-analysis results, we found that serum D-dimer had a better sensitivity and specificity than plasma D-dimer (86% and 84% vs. 67% and 60%, respectively). However, due to the limited data, only three studies utilized plasma D-dimer in PJI. Therefore, more PJI studies are needed to compare the diagnostic value of serum D-dimer and plasma D-dimer in the future.

Conclusion

The current study had some limitations: the measurement of D-dimer might be affected by the different exclusion criteria, cut-offs, races of the populations, etc. The overall meta-analysis result of D-dimer (serum and plasma) had low sensitivity and specificity. However, based on the present literature and our subgroup analysis results, we found that serum D-dimer had better diagnostic value than plasma D-dimer for the diagnosis of PJI.

Abbreviations

AAOS
American Academy of Orthopedic Surgeons
AUC
Area under the curve
BMI
Body mass index
CI

Confidence interval
CRP
C-reactive protein
DOR
Diagnostic odds ratio
EBJIS
European Bone and Joint Infection Society
ESR
Erythrocyte sedimentation rate
FN
False negative
FP
False positive
FDP
Fibrin degradation product
IDSA
Infectious Diseases Society of America
ICM
International Consensus Meeting
IL-6
Interleukin-6
MeSH
Medical subject headings
MSIS
Musculoskeletal Infection Society
NLR
Negative likelihood ratio
PJI
Periprosthetic joint infection
PLR
Positive likelihood ratio
SROC
Summary receiver operating characteristic
SE
Standard error
Sen
Sensitivity
Spe
Specificity
TN
True negative
TP
True positive

Declarations

Ethics approval and consent to participate

Not applicable.

Consent to publish

Not applicable.

Availability of data and materials

Data was extracted from references [13–17,23,24].

Competing interests

The author(s) declare(s) that they have no competing interests.

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Authors' Contributions

LC and DM searched the database, performed the meta-analysis and drafted the manuscript. COT and CP proposed the idea of the study and contributed to the editing of the study. AT, COT and DM edited and reviewed the manuscript. All authors have seen and approved the final version of the paper before submission.

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References

1. Li C, Renz N, Trampuz A. Management of Periprosthetic Joint Infection. Hip Pelvis. 2018;30:138–146.
2. Berbari E, Mabry T, Tsaras G, Spangehl M, Erwin PJ, Murad MH, et al. Inflammatory blood laboratory levels as markers of prosthetic joint infection: a systematic review and meta-analysis. J Bone Joint Surg Am. 2010;92:2102–2109.
3. Lee YS, Koo K-H, Kim HJ, Tian S, Kim T-Y, Maltenfort MG, et al. Synovial Fluid Biomarkers for the Diagnosis of Periprosthetic Joint Infection: A Systematic Review and Meta-Analysis. J Bone Joint Surg Am. 2017;99:2077–2084.
4. Nelson GN, Paxton ES, Narzikul A, Williams G, Lazarus MD, Abboud JA. Leukocyte esterase in the diagnosis of shoulder periprosthetic joint infection. J Shoulder Elbow Surg. 2015;24:1421–1426.
5. Wiler JL, Costantino TG, Filippone L, Satz W. Comparison of ultrasound-guided and standard landmark techniques for knee arthrocentesis. J Emerg Med. 2010;39:76–82.
6. Sendi P, Müller AM, Berbari E. Are All Joints Equal? Synovial Fluid Analysis in Periprosthetic Joint Infection. J Bone Jt Infect. 2018;3:258–259.
7. Li C, Renz N, Trampuz A, Ojeda-Thies C. Twenty common errors in the diagnosis and treatment of periprosthetic joint infection. Int Orthop. 2020;44(1):3–14; Available from: http://dx.doi.org/10.1007/s00264-019-04426-7
8. Parvizi J, Zmistowski B, Berbari EF, Bauer TW, Springer BD, Della Valle CJ, et al. New definition for periprosthetic joint infection: from the Workgroup of the Musculoskeletal Infection Society. Clin Orthop Relat Res. 2011;469:2992–2994.
9. Johnson AJ, Zywiel MG, Stroh A, Marker DR, Mont MA. Serological markers can lead to false negative diagnoses of periprosthetic infections following total knee arthroplasty. Int Orthop. 2011;35:1621–1626.
10. Pérez-Prieto D, Portillo ME, Puig-Verdié L, Alier A, Martínez S, Sorlí L, et al. C-reactive protein may misdiagnose prosthetic joint infections, particularly chronic and low-grade infections. Int Orthop. 2017;41:1315–1319.
11. Yoo M-C, Cho Y-J, Ghanem E, Ramteke A, Kim K-I. Deep vein thrombosis after total hip arthroplasty in Korean patients and D-dimer as a screening tool. Arch Orthop Trauma Surg. 2009;129:887–894.
12. Jiang Y, Li J, Liu Y, Li Y-C, Zhang W-G. Risk factors for deep vein thrombosis after orthopedic surgery and the diagnostic value of D-dimer. Ann Vasc Surg. 2015;29:675–681.
13. 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;99:1419–1427.
14. Huang J, Zhang Y, Wang Z, Dong Y, Zhao Y, Zheng J, 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;14:407.
15. 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;35:229–234.
16. 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;34:1197–1200.
17. 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;14:240.
18. Parvizi J, Gehrke T, International Consensus Group on Periprosthetic Joint Infection. Definition of periprosthetic joint infection. J Arthroplasty. 2014;29:1331.
19. Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2013;56:e1–25.
20. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. N Engl J Med. 2004;351:1645–1654.
21. Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155:529–536.
22. Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. BMC Med Res Methodol. 2006;6:31.
23. 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;34:2454–2460.

24. Li R, Shao H-Y, Hao L-B, Yu B-Z, Qu P-F, Zhou Y-X, 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;101:613–619.
25. Kwon Y-M, Antoci V Jr, Leone WA, Tsai T-Y, Dimitriou D, Liow MHL. Utility of Serum Inflammatory and Synovial Fluid Counts in the Diagnosis of Infection in Taper Corrosion of Dual Taper Modular Stems. J Arthroplasty. 2016;31:1997–2003.
26. Shahi A, Deirmengian C, Higuera C, Chen A, Restrepo C, Zmistowski B, et al. Premature Therapeutic Antimicrobial Treatments Can Compromise the Diagnosis of Late Periprosthetic Joint Infection. Clin Orthop Relat Res. 2015;473:2244–2249.
27. 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:1482–1486.
28. Saleh A, George J, Faour M, Klika AK, Higuera CA. Serum biomarkers in periprosthetic joint infections. Bone Joint Res. 2018;7:85–93.
29. Ribera T, Monreal L, Armengou L, Ríos J, Prades M. Synovial fluid D-dimer concentration in foals with septic joint disease. J Vet Intern Med. 2011;25:1113–1117.
30. Lee YS, Lee Y-K, Han SB, Nam CH, Parvizi J, Koo K-H. Natural progress of D-dimer following total joint arthroplasty: a baseline for the diagnosis of the early postoperative infection. J Orthop Surg Res. 2018;13:36.
31. Shohat N, Bauer T, Buttaro M, Budhiparama N, Cashman J, Della Valle CJ, et al. Hip and Knee Section, What is the Definition of a Periprosthetic Joint Infection (PJI) of the Knee and the Hip? Can the Same Criteria be Used for Both Joints?: Proceedings of International Consensus on Orthopedic Infections. J Arthroplasty. 2019;34:S325–327.
32. Xu C, Qu P-F, Chai W, Li R, Chen J-Y. Plasma fibrinogen may predict persistent infection before reimplantation in two-stage exchange arthroplasty for periprosthetic hip infection. J Orthop Surg Res. 2019;14:133.
33. Ghanem E, Azzam K, Seeley M, Joshi A, Parvizi J. Staged revision for knee arthroplasty infection: what is the role of serologic tests before reimplantation? Clin Orthop Relat Res. 2009;467:1699–1705.
34. Lindsay CP, Olcott CW, Del Gaizo DJ. ESR and CRP are useful between stages of 2-stage revision for periprosthetic joint infection. Arthroplast Today. 2017;3:183–186.
35. Li C, Ojeda-Thies C, Trampuz A. Culture of periprosthetic tissue in blood culture bottles for diagnosing periprosthetic joint infection. BMC Musculoskelet Disord. 2019;20:299.
36. Li C, Renz N, Thies CO, Trampuz A. Meta-analysis of sonicate fluid in blood culture bottles for diagnosing periprosthetic joint infection. J Bone Jt Infect. 2018;3:273–279.
37. Pieper CF, Rao KM, Currie MS, Harris TB, Cohen HJ. Age, functional status, and racial differences in plasma D-dimer levels in community-dwelling elderly persons. J Gerontol A Biol Sci Med Sci. 2000;55:M649–657.

Figures

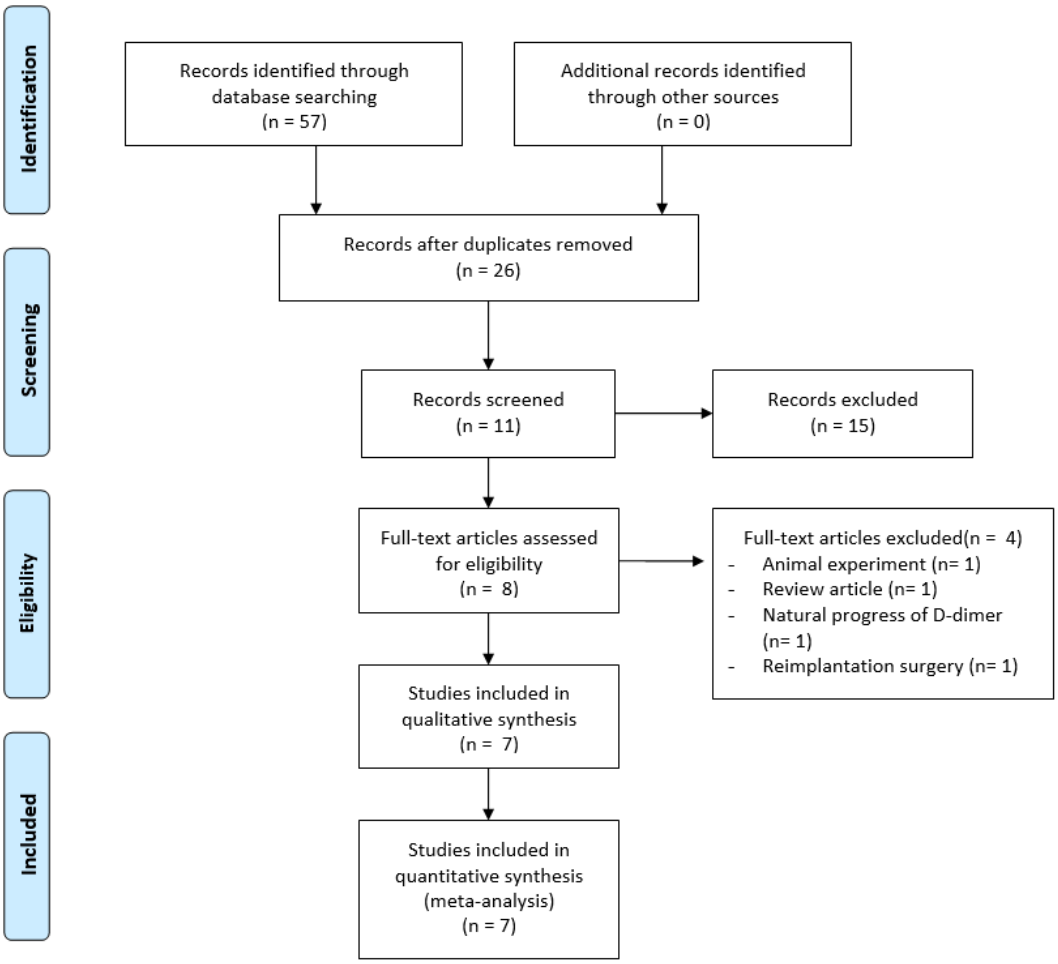

Figure 1

The flow diagram of the selection process for eligible studies

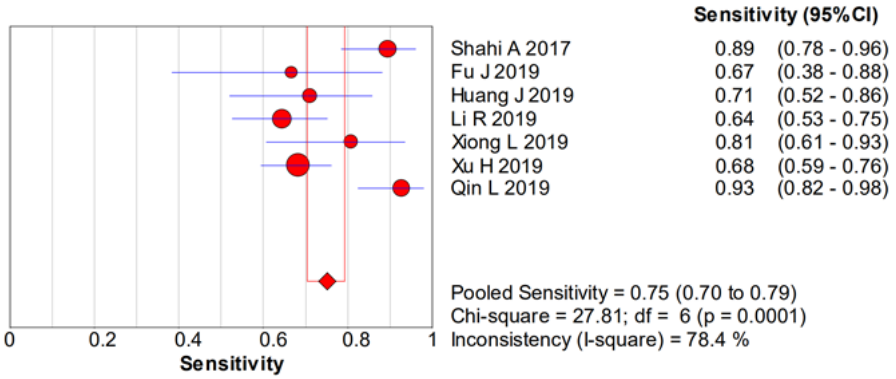

Figure 2

Forest plots of sensitivity of D-dimer for PJI diagnosis

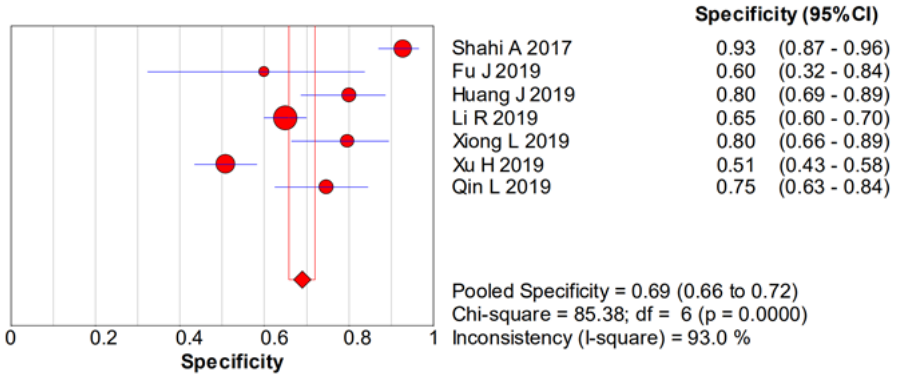

Figure 3

Forest plots of specificity of D-dimer for PJI diagnosis

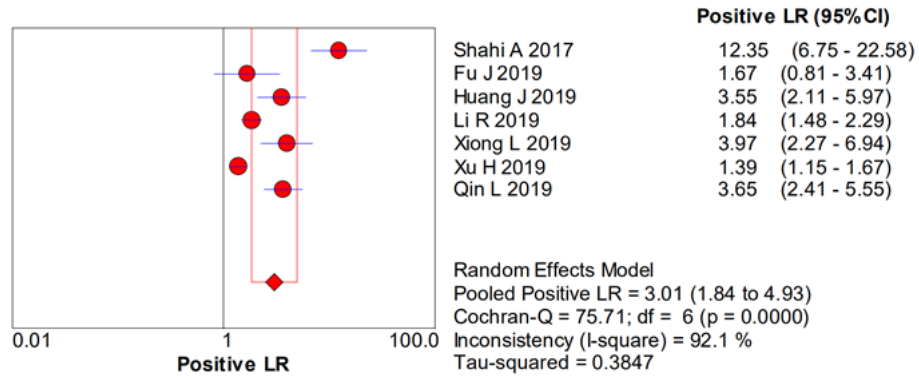

Figure 4

Forest plots of positive likelihood ratio of D-dimer for PJI diagnosis

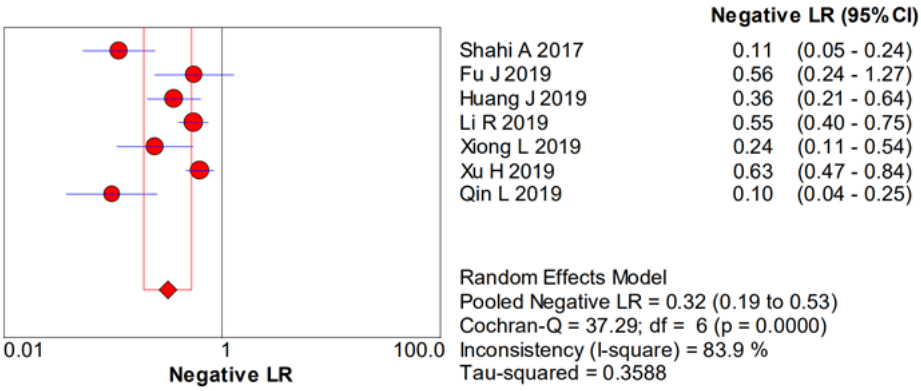

Figure 5

Forest plots of negative likelihood ratio of D-dimer for PJI diagnosis

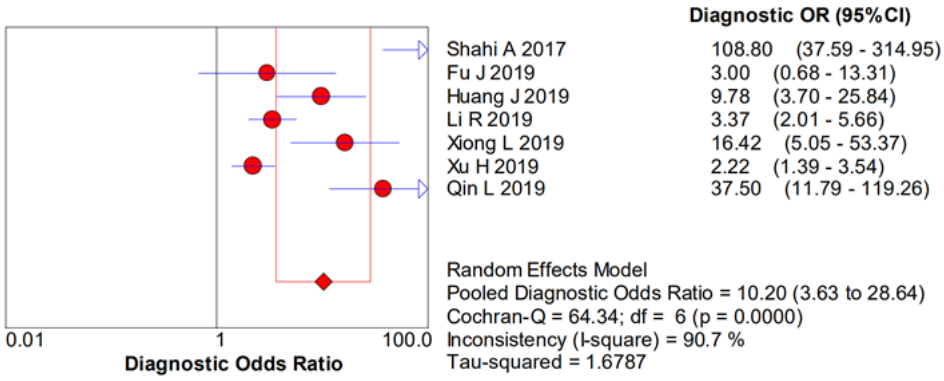

Figure 6

Forest plots of diagnostic odds ratio of D-dimer for PJI diagnosis

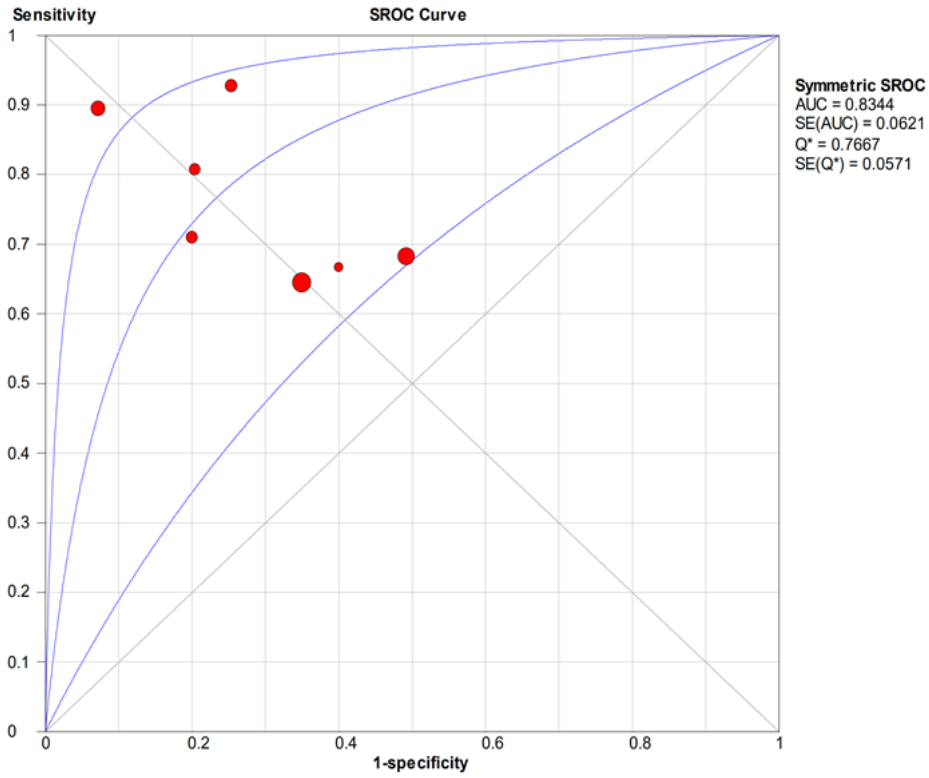

Figure 7

Summary of SROC of D-dimer for PJI diagnosis