Diagnostic Accuracy of D-Dimer in Periprosthetic Joint Infection: a diagnostic meta-analysis

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Abstract

Background: Periprosthetic joint infection (PJI) is one of the most devastating complications after total joint replacement. Up to now, the diagnosis of PJI is still in a dilemma. As a novel biomarker, whether D-Dimer is valuable in the diagnosis of PJI remains controversial. This meta-analysis attempts to determine the diagnostic accuracy of D-Dimer in PJI.

Methods: Relevant literature was retrieved from PubMed, Embase, Web of Science, and Cochrane Library (from database establishment to April 2020). Literature quality was evaluated using Revman (Version 5.3). The random effect model was used in Stata version 14.0 software to combine sensitivity, specificity, likelihood ratio (LR), diagnostic odds ratio (DOR), summary receiver operating characteristic (SROC) curve and area under SROC (AUC) to evaluate the diagnostic value of overall D-Dimer for PJI. Meta regression and subgroup analysis were performed according to the threshold, the study design, the sample size, the diagnostic gold standard, the country of study, and the type of sample.

Results:A total of 9 studies were included in this study, including 1592 patients. The pooled sensitivity and specificity of D-Dimer for PJI diagnosis are 0.82(95%CI, 0.72~0.89) and 0.73(95%CI, 0.58~0.83), respectively. The pooled positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were 2.99 (95%CI, 1.84~4.88) and 0.25 (95%CI, 0.15~0.41), respectively. The pooled AUC and diagnostic odds ratios were 0.85 (95%CI, 0.82~0.88) and 12.20 (95% CI, 4.98~29.86), respectively.

Conclusion: D-Dimer is a promising biomarker for the diagnosis of PJI, which should be used in conjunction with other biomarkers or as an adjunct to other diagnostic methods to enhance diagnostic performance.

Introduction

Periprosthetic Joint Infection (PJI) is regarded as a destructive complication after total joint replacement(TJA)[1], accounting for approximately 15% and 25% of the failure factors of total hip and knee arthroplasty, respectively[2, 3]. With the extension of the average life span of human beings, there are an increasing number of TJA operations, and the resulting number of PJI patients has also been increasing year by year[4]. The existence of PJI seriously reduces the quality of life of patients, exacerbates the difficulty of treatment for orthopedic surgeons, and aggravates the financial burden of the national health system[5-7]. Moreover, it is extremely difficult to accurately diagnose PJI, due to the atypical symptoms of many PJI patients[8]. Many scholars jointly established the American Academy of Orthopedic Surgeon (AAOS)' s guidelines, Musculoskeletal Infection Society (MSIS) and, International Consensus Meeting (ICM) diagnostic criteria in 2010, 2011 and 2013 respectively, which have been widely used[9-11]. However, currently, there is still no diagnostic standard or indicators that can achieve 100% diagnostic accuracy, and some standards including synovial fluid detection are invasive, expensive, and inconvenient to obtain[12]. Given this situation, there is an urgent demand for joint surgeons to look for diagnostic markers with efficiency, cheapness, and convenience [13]. D-dimer is a fibrin degradation product formed by fibrinolysis of fibrin clots, which reflects the state of blood coagulation and increases in systemic or local infections, thrombosis, and neoplastic diseases[14-16]. Based on this principle, Shahi et al. And Li et al. speculated that d-dimer in PJI patients might serve as a neoteric diagnostic biomarker[17, 18]. Nevertheless, their findings are contradictory. There is also no agreement on the conclusions of the other similar studies. Therefore, we conducted a systematic review and meta-analysis of these literatures to study the diagnostic value of D-dime in PJI. By consulting the relevant database, it is confirmed that this study is the first meta-analysis to evaluate the accuracy of D-dimer in the diagnosis of PJI.

Methods

Our study is carried out strictly in accordance with the criterion of the preferred report items of systematic review and meta-analysis report. The research scheme is determined by all the authors, and the steps of literature retrieval, literature quality evaluation, data statistics, result merging, and report writing are completed in turn.

Retrieval strategy

Under the guidance of the Cochrane Review method, two authors (Haitao Zhang and Xingyang Zhu) search online databases such as PubMed, Embase, Web of Science, and Cochrane Library. The search subject words and Mesh words are as follows: "periprosthetic joint infection" or "prosthesis-related infections" stands for disease, "D-dimer" or "D-dimer fibrin" or "D-dimer fragments" or "fibrin fragment D1 dimer" or "fibrin fragment DD" or "fibrin fragment D-dimer" represents target index. The range of retrieval dates is from the

establishment of the database to April 2020. When searching, we only include English literature. After database screening, we manually searched some of the references included in the literature to obtain the valuable literature for this study.

Study selection

The title, abstract or full text of all search results are reviewed by two censors (Haitao Zhang and Xiaobo Sun) in detail. When there is still a disagreement between the two examiners after reading the full text, it will be left to Professor (Yirong Zeng) to make the final decision. The inclusion criteria of the literature are as follows:(1) Using D-Dimer as an index for the diagnosis of PJI;(2) Have integrated data (including true positive, false negative, false positive, and true negative) to construct a 2×2 table;(3) There is a definite gold standard such as Musculoskeletal Infection Society (MSIS) or International consensus on infection□ICM) to compare the diagnostic accuracy with D-dimer.

Data extraction and quality assessment

The following data extraction and literature quality evaluation are completed by (Pengfei Xin and Ke Jie), two researchers who are familiar with the knowledge of statistics, back to back, and the extracted data are input into a table in Excel. The data include: the author of the study, the year, the country or region in which the article was published, the design type of the study, the number of cases, sex ratio, patient's age and BIM index, the gold standard used in the study, the detection method and the cut-off value of D-dimer. In addition, the diagnostic accuracy of D-dimer (AUC) and the true positive, false positive, true negative, and false negative data used to construct 2 × 2 table were also recorded in detail.

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) in Revman (Version5.3) software was used to evaluate the quality of all the literature included in the study. QUADAS-2 is an updated version of the original QUADAS, including four aspects of patient selection, index test, reference standard, and flow and timing, which has a more accurate bias level and applicability to the original research than the original QUADAS.

Statistical analysis

All data analysis and picture production are carried out by using the commands in the Stata14.0 software. The bivariate random effect model was selected to analyze the tp, fp, fn, tn values of 2 × 2 table extracted in the study and to test the heterogeneity. The sensitivity, specificity, positive likelihood ratio (PLR), Negative likelihood ratio (NLR), diagnostic score, and diagnostic odds ratio (DOR) were obtained after integration. Among them, the higher the value of DOR, the higher the diagnostic value.

Additionally, the summary receiver operating characteristic (SROC) was drawn by the Midas command, and the area under the curve (AUC) was calculated. AUC represents the diagnostic accuracy of D-dimer.

The heterogeneity is expressed as the inconsistency index (I2) statistic, the smaller the I2, the smaller the heterogeneity. When I2 is 75%, 50% and 25% respectively, it corresponds to large, medium and small literature heterogeneity, respectively. If the heterogeneity is large, meta-regression and subgroup analysis are performed to identify the source of heterogeneity. We believe that the variables that may affect the heterogeneity are the type of study design, the threshold used in the study, the number of cases, the index of diagnostic gold, the sample type, and the country or region in which the literature is published.

In order to definitely judge the publication bias, the funnel chart (Deeks' funnel plot) was drawn. Besides, the change of the diagnostic value of D-dimer on the incidence of PJI can be clearly shown by drawing a Fagan plot diagram.

Results

Search results and study characteristics

The details of the literature screening process are shown in Figure 1. Through preliminary search, a total of 76 articles were identified in three online databases. Among them, 19 articles were obtained by Pubmed, 24 articles were obtained by Web of science, and 33 articles were obtained by Embase. After 32 repeated literatures are excluded, there are 44 remaining ones. Then 22 articles were excluded by reading titles and abstracts, including 12 inconsistent research contents, 9 reviews, and 1 conference literature. Of the remaining 22 articles, 13 were deleted after reading the full text, including 1 literature with unavailable data, 1 literature with inconsistent research objects, and 11 reviews. Finally, a total of 9 articles were included in this study for meta-analysis.

A total of 1,592 patients were enrolled in nine studies[19-27], including 1061 patients with non-PJI and 531 patients with confirmed PJI. All of these patients underwent knee or hip arthroplasty, but no other parts of total joint arthroplasty were performed. Five studies were retrospective and four were prospective. Seven of the studies were from China and two were performed in the United States. Seven studies regarded MSIS as the “gold standard” for the diagnosis of PJI, and only 2 studies adopted ICM as “the gold” standard for diagnosis. Table 1 shows the detailed characteristics of all the studies. Table 2 summarizes the data extraction results of each study (2 × 2 table).

Quality assessment and publication biases

The quality assessment results of 9 studies using the QUADAS - 2 scale are shown in Figure 2. The figure shows that there are two “high risks”, and the rest are “unclear” or “low risk”. Generally speaking, the quality of literature is in the upper-middle level. By drawing the Deeks' funnel plot diagram, we can clearly see that there is a slightly symmetrical trend on both sides, and the p=0.21, much greater than 0.05. Therefore, there is no conspicuous publication bias (Fig. 3).

Threshold and Diagnostic accuracy of D-dimer for PJI

Regarding the cutoff value, four studies adopted the common threshold (850 ng/ml), while different thresholds were adopted by the remaining 5 studies. The forest diagram shows that the pooled sensitivity and specificity of D-Dimer for PJI diagnosis are 0.82(95%CI, 0.72~0.89) and 0.73(95%CI, 0.58~0.83), respectively (Fig. 4a). The sensitivity and specificity of the corresponding I2 statistics were 86.10(95%CI, 78.25~93.94) and 94.57(95%CI, 92.23-96.90), respectively. Thus it can be seen that there is a great heterogeneity among the studies. The pooled diagnostic score and diagnostic odds ratio were 2.50 (95% CI, 1.61~3.40) and 12.20 (95% CI, 4.98~29.86), respectively (Fig. 4b). The area under SROC (AUC) is 0.85 (95%CI, 0.82~0.88) (Fig. 5).

Evaluation of the Clinical Utility

The pooled PLR and NLR of d-dimer for PJI diagnosis were 2.99 (95%CI, 1.84~4.88) and 0.25 (95%CI, 0.15~0.41), respectively (Fig. 6). According to previous studies, the incidence of PJI accounts for approximately 20% of revision arthroplasty. Hence, 0.2 pre-test probabilities was selected to calculate the post-test probability through the likelihood ratio and the pretest probability[28]. The post-test probability of PJI was 6%, indicating negative D-dimer results (Fig.7).

Meta-regression and subgroup analysis

As can be seen from the forest map, there is a great heterogeneity in this study. So we conduct the following meta-regression (Fig. 8) and subgroup analysis to explore the sources of heterogeneity according to whether the threshold is the same, the study design, whether the sample size is greater than 110, the diagnostic gold standard, the country of the source of the study, and the type of sample(Table 3). Meta-regression results showed that the type of sample (serum or plasma) maybe the primary factor leading to heterogeneity of sensitivity. The country of origin of the study may be the main source of heterogeneity of specificity. The subgroup analysis results showed that the pooled sensitivity and specificity of the 4 studies with 850ng/ml were 0.85 (95%CI, 0.69~0.93) and 0.69 (95%CI, 0.43~0.86), respectively, and the diagnostic accuracy was 0.85 (95%CI, 0.82~0.88).

Discussion

Due to the considerable cost of treating PJI, it has caused a growing number of orthopedists to pay attention to this daunting disease[29]. As a prerequisite for determining the therapeutic regimen, an accurate diagnosis of PJI is urgent and necessary for us. As a matter of fact, it is quite arduous to accurately distinguish between aseptic loose artificial joints and PJI joints. This is because a biofilm is often formed on the surface of the prosthesis in patients with PJI, and the culture of pathogens sometimes shows negative results. Furthermore, when PJI patients present with chronic deep infection, there is no significant difference in clinical characteristics compared with aseptic loosened joints[30, 31]. It is gratifying that in recent years, an increasing number of biomarkers for the diagnosis of PJI have been found, including synovial quantitative alpha-defensin, serological white blood cell count (WBC), erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) interleukin-6 (IL-6), procalcitonin and so on[32]. Among them, ESR and CRP have been recommended by the American Infectious Diseases Association (IDSA) to conduct routine screening among all suspected PJI patients[33].

Recently, D-Dimer has been proposed by a number of experts as a novel serum marker. D-Dimer is a fibrin degradation product of disseminated intravascular coagulation and has been widely used in the diagnosis of venous thromboembolism (VTE) and infection in patients[34, 35]. According to Ribera et al., the level of synovial D-dimer is higher than normal in foal infectious joint disease[34]. The results of the study done by Bytniewski et al show that the level of D-Dimer in patients with early postoperative TJA changes faster than that of ESR and CRP, and can rise rapidly and return to normal level in a short time[36]. Subsequently, the diagnostic value of D-dimer in patients with PJI began to be valued by joint surgeons. Shai et al. put forward the threshold of D-dimer (850ng/ml) for the first time and considered that serum D-dimer has high sensitivity (89%) and specificity (93%). It is a valuable biomarker for the diagnosis of PJI[18]. Qin et al. used D-Dimer in combination with ESR or CRP to diagnose PJI and found that combined use had higher diagnostic performance than a single test[24]. Since then, several scholars have published controversial research results.

Although a recent meta-Analysis on circulating D-Dimer versus Fibrinogen in the Diagnosis of PJI has been published, we believe that one of their included literature is inconsistent with other subjects and should not be included in the meta-analysis. Because its research content is about D-Dimer predict persistent infection before reimplantation in two-stage exchange arthroplasty for PJI[37]. After excluding this study, they included only 5 studies that pooled the accuracy of d-dimer diagnosis. As a result, we suspect that their conclusion is unreliable . Compared with Zhang et al[38], our meta-analysis included more studies and patients (1592 patients in 9 studies) after rigorous screening and literature quality evaluation. The overall pooled AUC of d-dimer for diagnosis PJI was 0.85(95%CI, 0.82~0.88), which is higher than the AUC of D-Dimer calculated by Zhang et al (AUC=0.74). As a consequence, we deem that D-Dimer has good diagnostic value in PJI, which is inconsistent with the research conclusion of Zhang et al[38].In addition, the pooled sensitivity and specificity were calculated to be 0.82 and 0.73 respectively. From another point of view, this is equivalent to a higher false positive rate (27%) and a lower false negative rate (18%) in D-Dimer for PJI diagnosis. The LR and DOR usually indicate the effectiveness of diagnostic indicators in clinical practice[39]. A guideline defines that LR+>2, LR-<0.5, or DOR>4 is considered a viable predictor, and LR+>5, LR-<0.2, or DOR>10 is considered a good predictor[40]. Therefore, in terms of LR, D-Dimer is a predictable index for the diagnosis of PJI, and D-Dimer is a good predictive index when DOR is used as a reference parameter. Post-test probability is another parameter widely used by clinicians, including positive predictive value and negative predictive value. It reflects the probability of patients with PJI when the test results are negative or positive. The Fagan plot diagram shows that the ability of D-Dimer to distinguish between PJI is general.

There is great heterogeneity in the studies of Zhang et al, but they did not provide a reasonable explanation[38]. Another advantage of this study is that we performed reasonable meta regression and novel subgroup analysis to find the source of heterogeneity in this study. We originally considered the threshold as the main cause of heterogeneity, but the results were unexpected. In the subgroup analysis, the AUC of the same threshold group was completely consistent with the AUC of overall studies, and DOR was almost the same. We found that in the study design, the AUC and DOR of the retrospective group fluctuated downward, while the AUC and DOR of the prospective group were almost twice as high as those of all studies. Furthermore, the results of the serum group were similar with those of the prospective group. In meta-regression, the heterogeneity source of sensitivity is obviously reflected in the sample type (serum or plasma), while the specific heterogeneity source is mainly embodied in the country of study (China and USA). Therefore, we believe that the study design, sample type, and the country of study are the main factors that affect the Diagnostic accuracy of D-Dimer.

Admittedly, there are certain limitations in our research. First, a handful of studies have not excluded patients with inflammatory diseases, which, as mentioned above, affect D-Dimer levels. Second, there is still no gold standard for the detection of PJI, and the gold standard test used in the study is only approximate. Several positive patients still miss diagnosis because the gold standard cannot detect. Third, due to the incompleteness of the original data, it is impossible to calculate the optimal cutoff value of D-Dimer and conduct more detailed subgroup analysis such as the location of the joint.

Conclusions

This study shows that D-Dimer detection of PJI has good diagnostic accuracy, but unfortunately its specificity is not high. Consequently , We believe that D-Dimer is a promising biomarker for the diagnosis of PJI, which should be used in conjunction with other biomarkers or as an adjunct to other diagnostic methods to enhance diagnostic performance.

Abbreviations

PJI, Periprosthetic Joint Infection; AAOS, the American Academy of Orthopedic Surgeon; MSIS, Musculoskeletal Infection Society; ICM, International Consensus Meeting; LR, likelihood ratio; DOR, diagnostic odds ratio; SROC, summary receiver operating characteristic; AUC, area under the curve.

Declarations

Acknowledgments

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Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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Author Contributions

Conceptualization: Haitao Zhang and Yirong Zeng. Literature search: Haitao Zhang, Yan Lv and Xingyang Zhu. Data extraction and quality assessment: Pengfei Xin and Ke Jie. Software: Wenjun Feng, Yuqing Zeng and Jinlun Chen. Formal analysis: Haitao Zhang, Houran Cao, and Ke Jie. Validation: Jianchun Zeng, Jie Li and Yirong Zeng. Writing: Haitao Zhang, Xiaobo Sun. All authors read and approved the final manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are not publicly available due to feasibility but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Characteristics of the studies in meta-analysis for the diagnosis of PJI applying D-Dimer.

Study	Year	Country	Study design	Gender (M/F)	Median age*	BMI*	Detection method	Cut-off values	Gold standard
Pannu, T. S. et al. [23]	2020	USA	R	62/49	68 /70	30.5 /30.5	NA	850 ng/ml	ICM
Hu et al. [20]	2020	China	R	37/40	65.57/60.78	NA	Immunoturbidimetric assay	0.955ug/ml	MSIS
Xu et al. [27]	2019	China	R	NA	NA	NA	NA	1.02 mg/L FEU	MSIS
Xiong et al. [26]	2019	China	P	54/26	59.76/65.42	22.87/25.07	Immunoturbidimetric assay	756 ng/ml	MSIS
Qin et al. [24]	2019	China	P	53/69	64.66/ 65.89	23.84/22.12	NA	1170ng/ml	MSIS
Li et al. [22]	2019	China	R	470/95	61.3/ 63.7	25.15/25.01	STA-R Evolution analyzer	1.25 mg/mL	ICM
Shahi et al. [25]	2017	USA	P	101/94	NA	NA	NA	850 ng/ml	MSIS
Fu et al. [19]	2019	China	P	9/21	65.47/65.60	24.67/25.72	NA	850 ng/ml	MSIS
Huang et al. [21]	2019	China	R	NA	69.27 /64.94	NA	NA	850 ng/ml	MSIS

* The values were given as the number with Non-PJI / PJI, P prospective study, R retrospective study, NA not applicable.

Table 2. Data extracted for the construction of 2 × 2 table

Author	Year	TP	FP	FN	TN	Total
Pannu, T. S. et al.	2020	47	42	2	20	111
Hu et al.	2020	35	4	5	33	77
Xu et al.	2019	88	93	41	96	318
Xiong et al.	2019	21	11	5	43	80
Qin et al.	2019	51	17	4	50	122
Li et al.	2019	61	165	35	305	566
Shahi et al.	2017	51	10	6	128	195
Fu et al.	2019	10	6	5	9	30
Huang et al.	2019	22	14	9	56	101

TP True positive; FP False positive; FN False negative; TN True negative.

Table 3. Subgroup analysis of D-dimer for PJI diagnosis

Subgroup analyses	No. of studies	Sensitivity (95% CI)	Specificity (95% CI)	PLN (95% CI)	NLR (95% CI)	AUC (95% CI)	Diagnostic score (95% CI)	DOR (95% CI)
Overall studies	9	0.82（0.72-0.89）	0.73（0.58-0.83）	2.99(1.84-4.88)	0.25(0.15-0.41)	0.85 (0.82-0.88)	2.50(1.61-3.40)	12.20(4.98-29.86)
Study design								
Retrospective	5	0.80（0.63-0.90）	0.65（0.45-0.81）	2.27（1.35-3.84）	0.31（0.17-0.59）	0.80（0.76-0.83）	1.98(0.99-2.97)	7.24(2.68-19.53)
Prospective	4	0.86（0.75-0.92）	0.80（0.65-0.90）	4.34（2.22-8.49）	0.18（0.09-0.34）	0.90（0.87-0.93）	3.19(1.96-4.43)	24.39(7.12-83.52)
Cut-off value								
850ng/ml	4	0.85（0.69-0.93）	0.69（0.43-0.86）	2.71（1.40-5.27）	0.22（0.11-0.44）	0.85（0.82-0.88）	2.50(1.52-3.48)	12.14(4.56-32.31)
other	5	0.81（0.68-0.89）	0.76（0.60-0.87）	3.30（1.71-6.36）	0.25（0.13-0.51）	0.85（0.82-0.88）	2.57(1.25-3.88)	13.00(3.49-48.46)
Sample size								
＞110	5	0.85（0.70-0.94）	0.67（0.44-0.84）	2.57（1.33-4.98）	0.22（0.09-0.52）	0.85（0.81-0.88）	2.46(1.10-3.81)	11.65(3.00-45.26)
≤110	4	0.78（0.66-0.86）	0.80（0.71-0.87）	3.91（2.48-6.17）	0.28（0.17-0.45）	0.86（0.83-0.89）	2.65(1.76-3.53)	14.12(5.82-34.29)
Serum	6	0.87（0.78-0.92）	0.77（0.60-0.88）	3.72（2.09-6.62）	0.17（0.11-0.28）	0.90（0.87-0.92）	3.06(2.22-3.90)	21.37(9.21-49.63)
China	6	0.78（0.68-0.85）	0.72（0.62-0.81）	2.82（1.85-4.28）	0.31（0.19-0.49）	0.82（0.78-0.85）	2.22(1.35-3.08)	9.17(3.86-21.77)
MSIS	6	0.82（0.74-0.88）	0.78（0.65-0.87）	3.73（2.14-6.49）	0.23（0.14-0.36）	0.87（0.84-0.90）	2.78(1.77-3.80)	16.19(5.86-44.70)

AUC area under the curve of summary receiver-operating characteristic curves, CI confidence interval, PLR positive likelihood ratio, NLR negative likelihood ratio, DOR diagnostic odds ratio

Figures

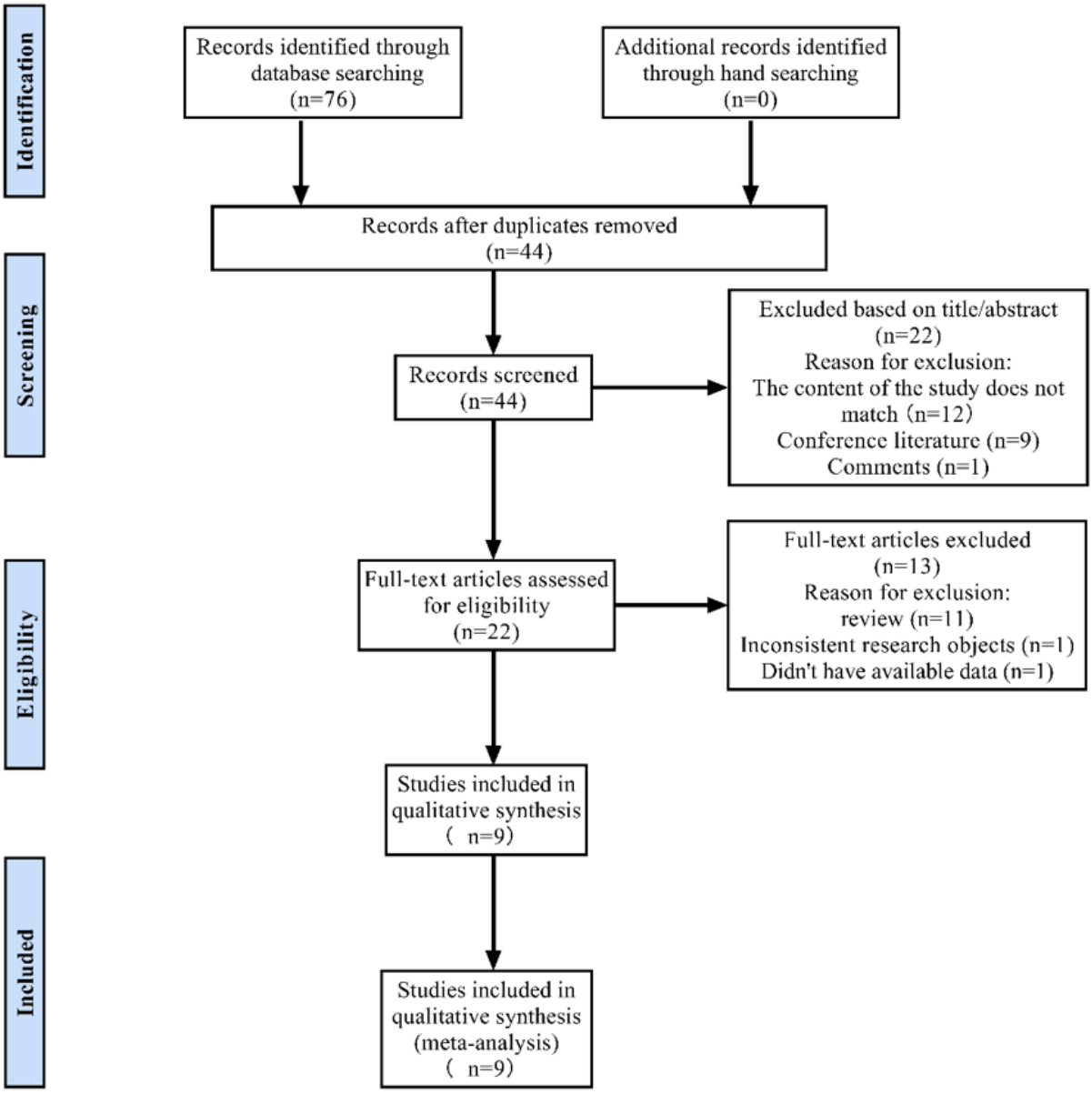


Figure 1

Flow diagram for study selection

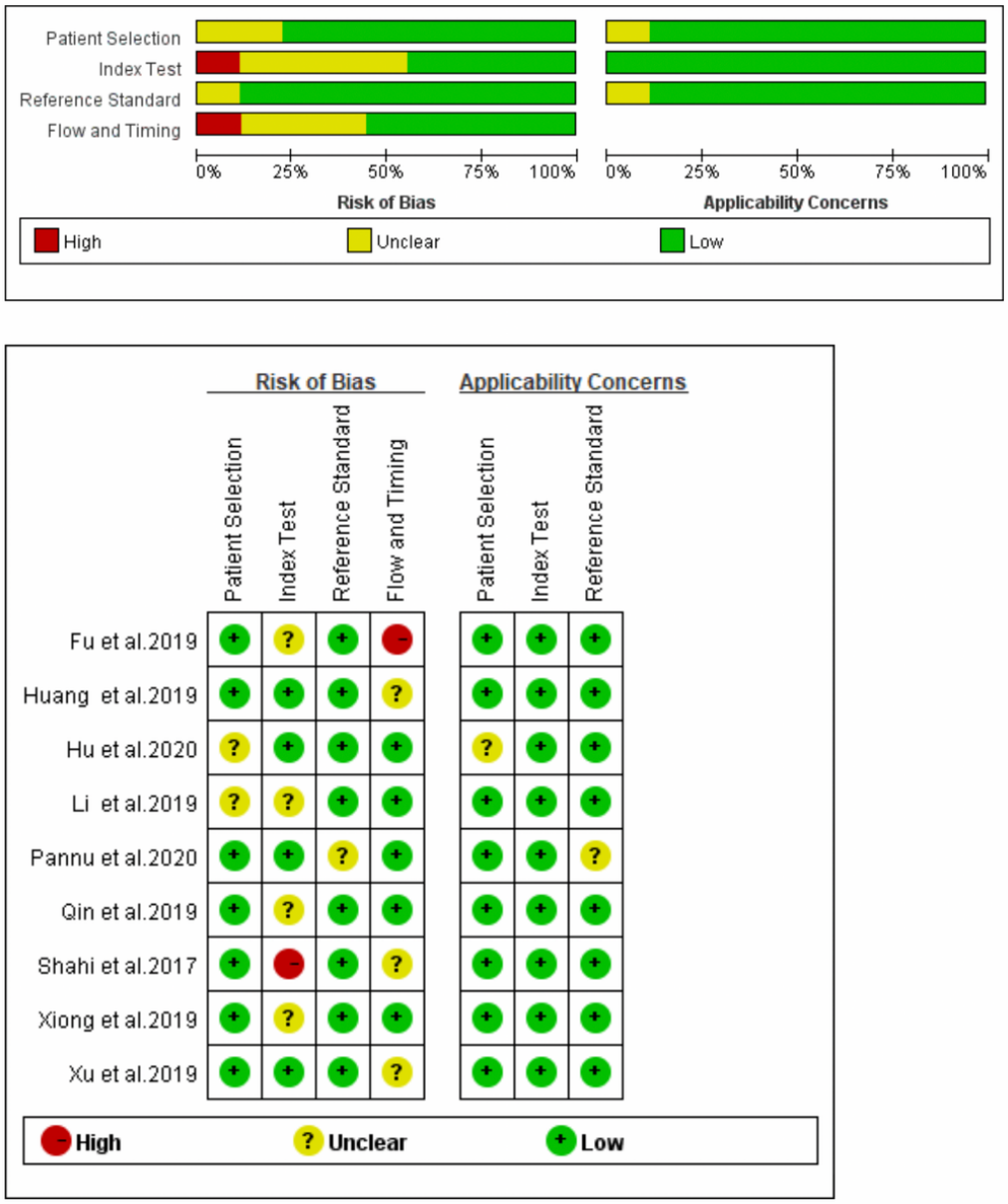


Figure 2

Quality assessment of included studies based on QUADAS-2 tool criteria

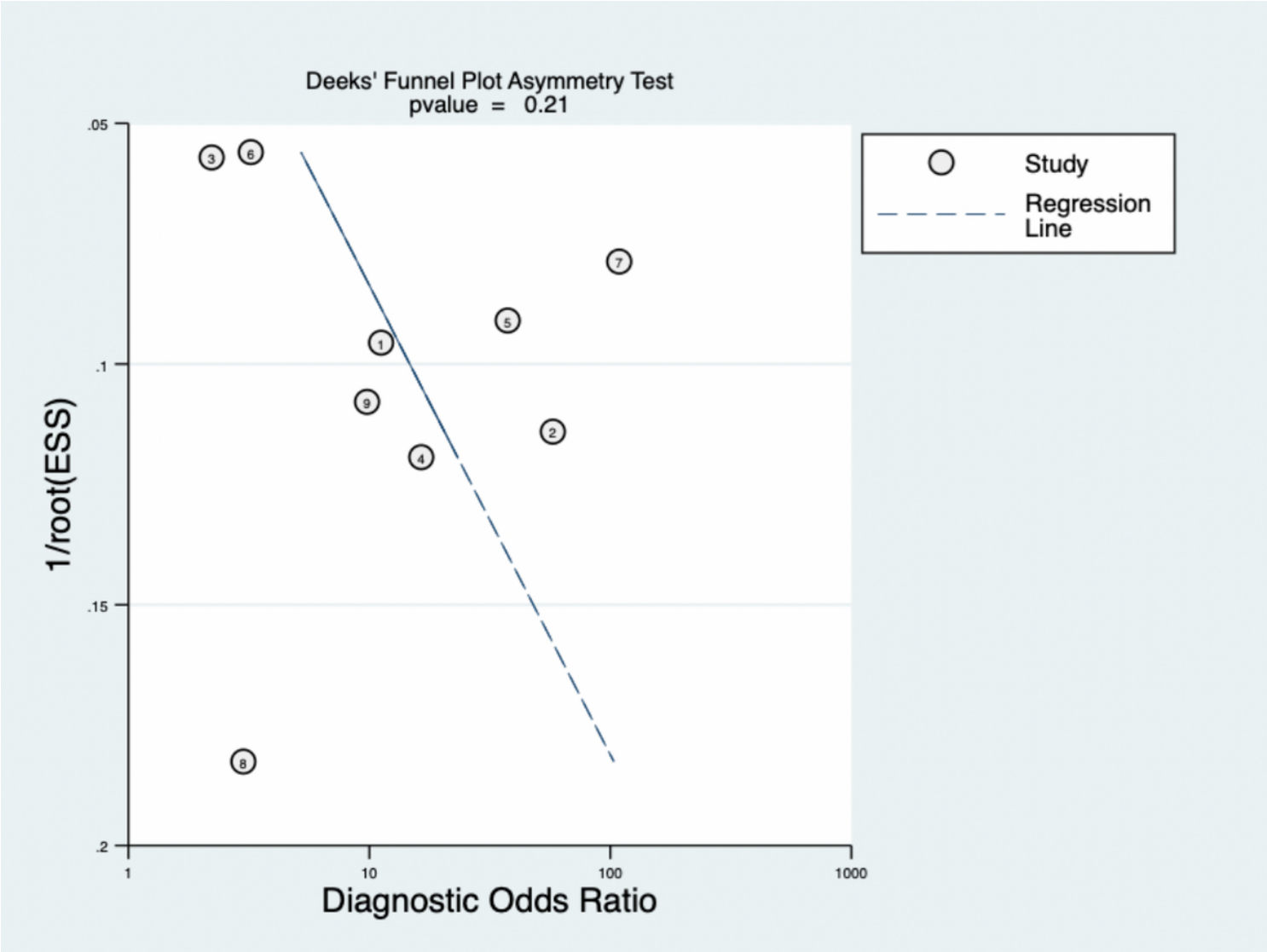


Figure 3

Funnel plot for publication bias assessment of included studies.

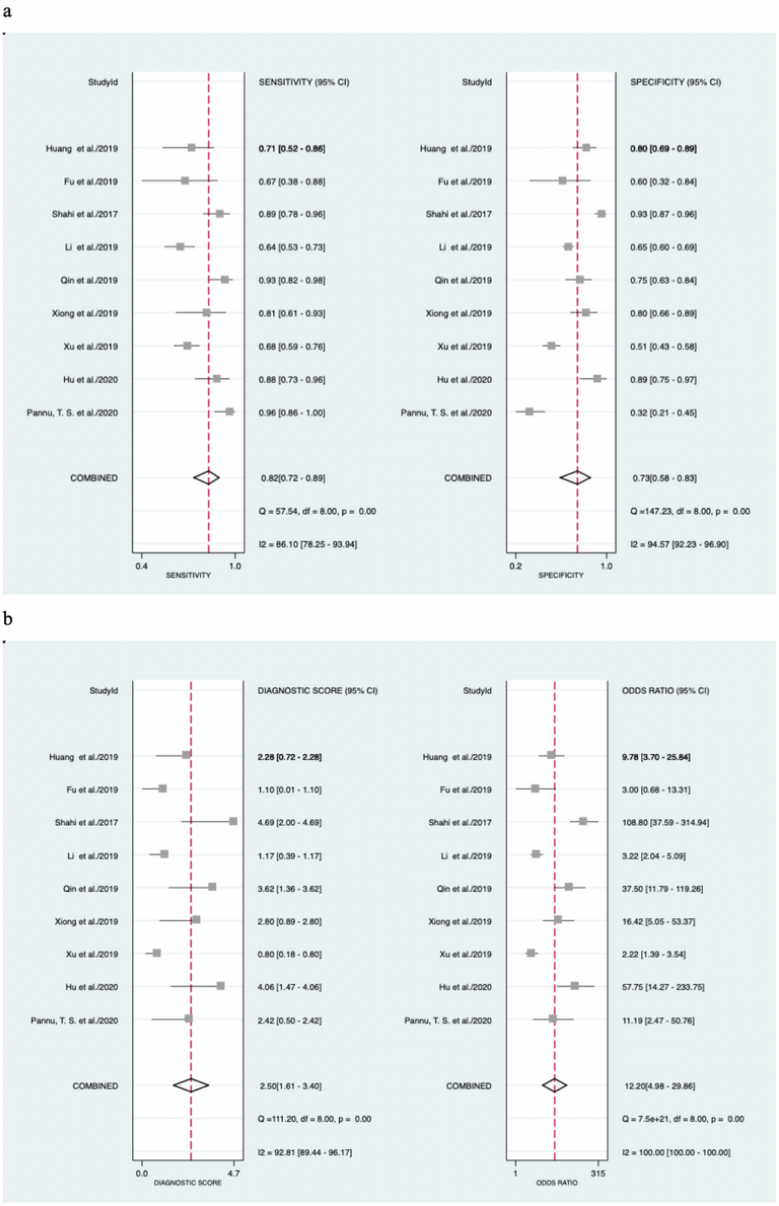


Figure 4

Forest plot of D-dimer for PJI. a Pooled sensitivity and specificity, b Pooled Diagnostic score and diagnostic odds ratio

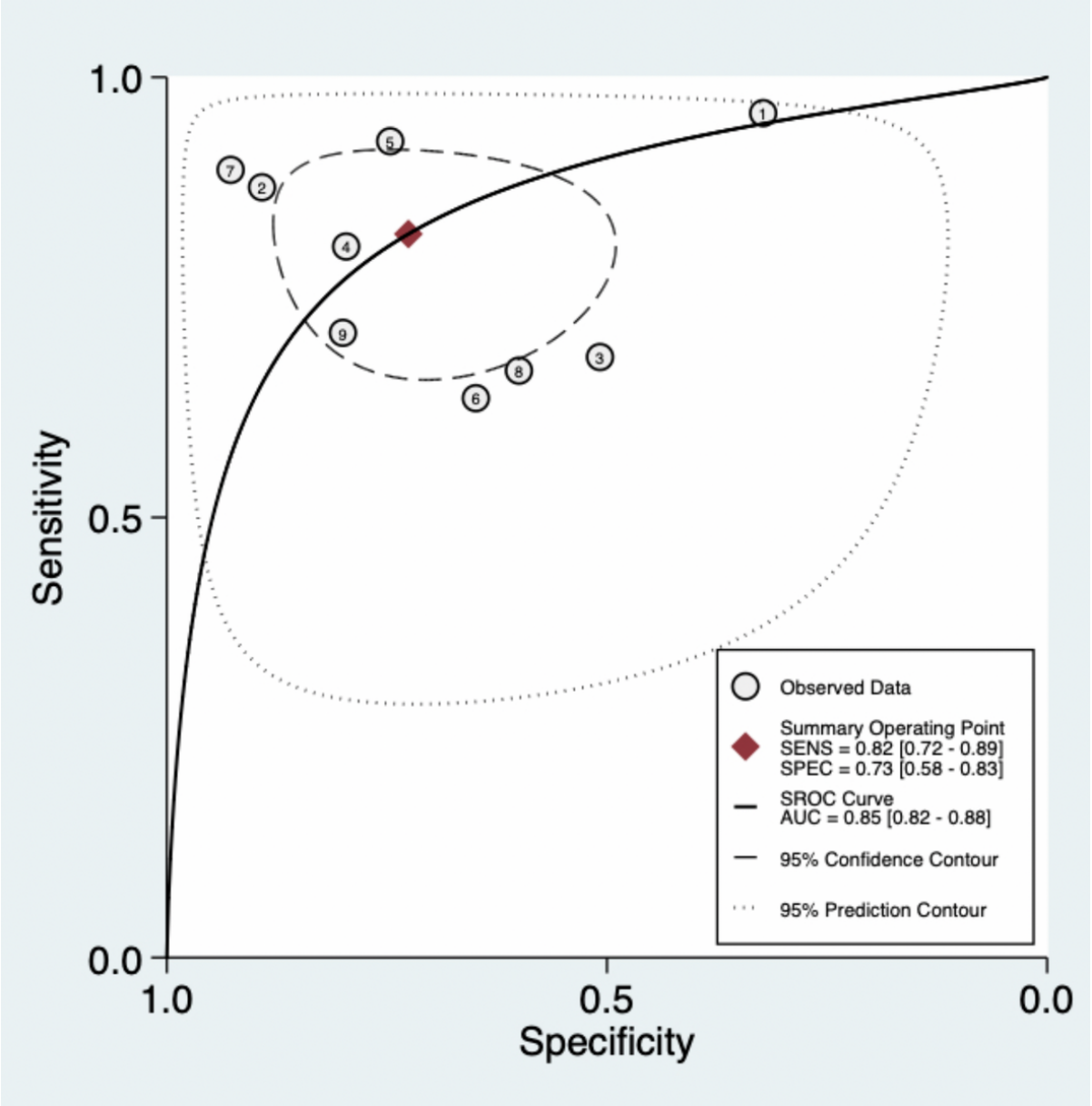
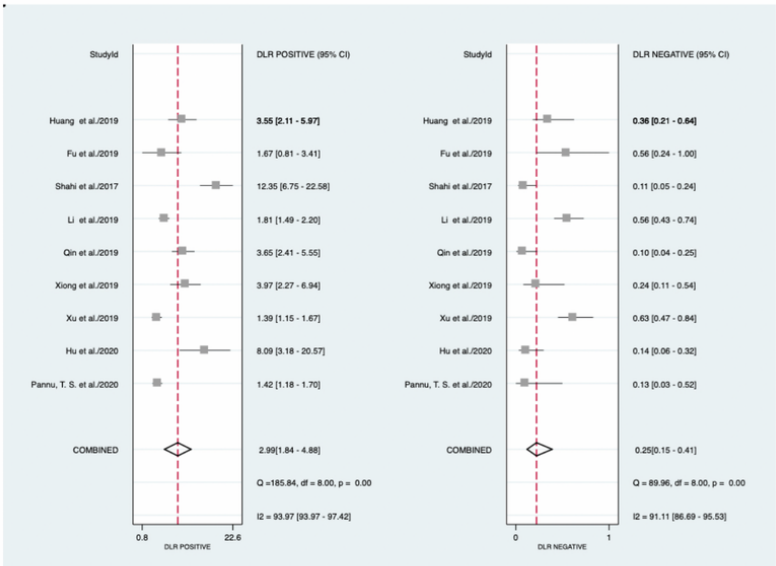


Figure 5

SROC curve of included studies.

a



b

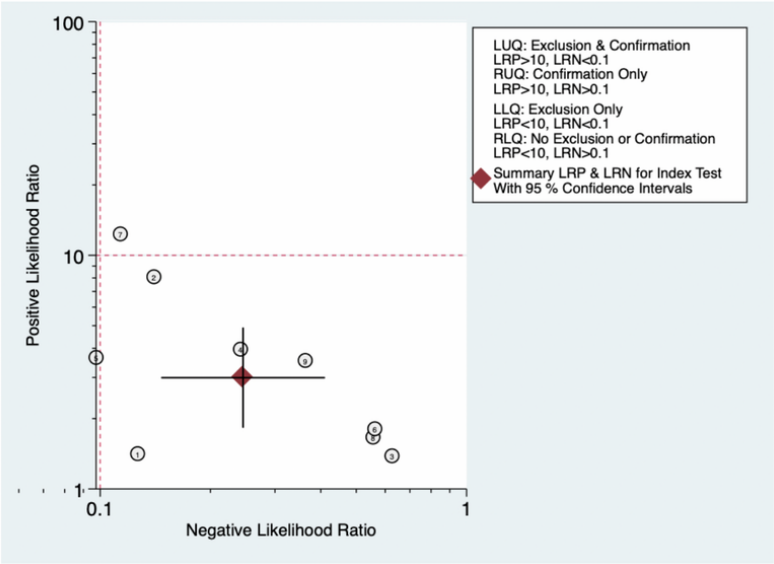


Figure 6

Forest plots of likelihood ratio (a) and Likelihood ratio scatter diagrams (b).

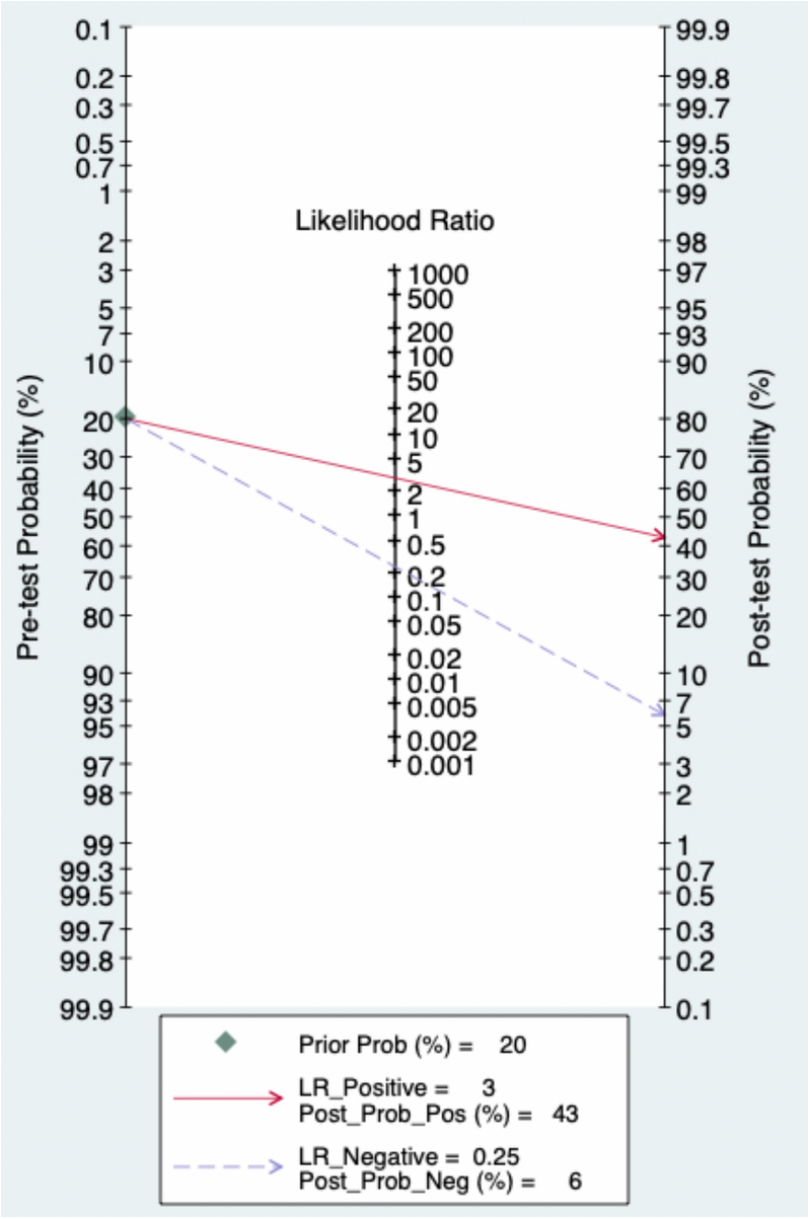


Figure 7

Fagan's nomogram of the D-dimer for diagnosis of PJI.

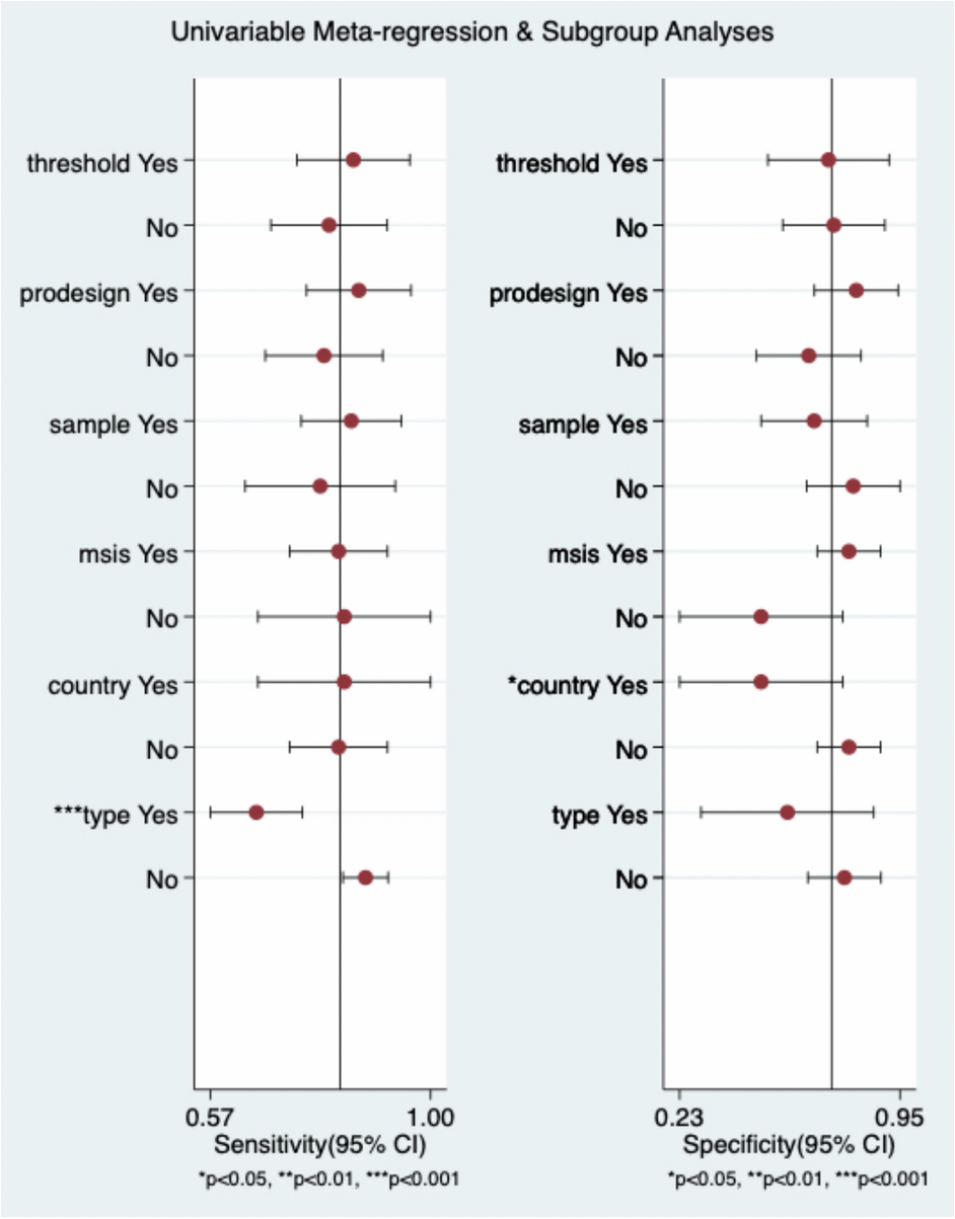


Figure 8

Meta-regression analysis for D-dimer with several variables

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Appendix1SearchStrategy.docx