RESEARCH ARTICLE

Synovial calprotectin for the diagnosis of periprosthetic joint infection: a diagnostic meta-analysis

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Abstract

Background: Periprosthetic joint infections (PJI) are a rare but severe complication of total joint arthroplasty (TJA). However, the diagnosis of PJI remains difficult. It is one of the research that focuses about diagnosis for PJI for majority researchers to discover a novel biomarker. This meta-analysis tried to evaluate diagnostic value of synovial calprotectin for PJI.

Methods: This meta-analysis search of the literature was conducted in PubMed, EMBASE, Web of Science, and the Cochrane Library. Literature quality was appraised using Quality Assessment of Diagnostic Accuracy Studies (QUA-DAS-2) based on RevMan (version 5.3). The diagnostic value of calprotectin for PJI was evaluated by calculating sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), diagnostic score and area under SROC (AUC) based on the Stata version 14.0 software. We conduct subgroup analysis according to the study design, cutoff values, the country of study, and gold standard.

Results: Seven studies were included in this meta-analysis. The pooled sensitivity of synovial calprotectin for the diagnosis of PJI was 0.94 (95% CI, 0.87–0.98), and the specificity was 0.93 (95% CI, 0.87–0.96). The pooled AUC, PLR, and NLR for synovial calprotectin were 0.98 (95% CI, 0.96–0.99), 13.65 (95% CI, 6.89–27.07), and 0.06 (95% CI, 0.02–0.15), respectively. The pooled diagnostic score and DOR were 5.4 (95% CI, 3.96–6.85) and 222.32 (95% CI, 52.52–941.12), respectively.

Conclusion: In summary, this meta-analysis indicates that synovial calprotectin is a promising biomarker of assistant diagnosis for PJI, as well as recommended test for excluding diagnostic tool.

Keywords: Periprosthetic joint infection, Calprotectin, Diagnosis, Meta-analysis

Introduction

With the development of social economy, the caseload of primary and revision hip and knee arthroplasty surgeons is gradually increasing [1]. Periprosthetic joint infections (PJI) are a rare but severe complication of total joint arthroplasty (TJA) [2], with a prevalence ranging between 0.7 and 2.4% [3]. PJI and concomitant revision arthroplasty exert enormous pressure on surgeons, healthcare institutions, and especially patients [4–6]. Accurate diagnosis of PJI is very difficult for surgeons on early stage, because the symptoms are atypical and identified difficultly. For a long time, a lack of standardized diagnostic criteria is the barrier to manage PJI for surgeons and researchers [7]. Several groups, such as the American Academy of Orthopedic Surgeons (AAOS),

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Peng *et al. Journal of Orthopaedic Surgery and Research*   (2022) 17:2

Page 2 of 12

Musculoskeletal Infection Society (MSIS), the European Bone and Joint Infection Society (EBJIS) and Infectious Diseases Society of America (IDSA), have been committed to make the diagnostic criteria of PJI perfect [8, 9]. Although the newest criteria after International Consensus Meeting (ICM) in 2018 have been published for PJI, the diagnosis of PJI is still challenging [10]. The 39th Annual Meeting of EBJIS will be held this year. The diagnosis of PJI is reliant upon laboratory examinations, and therefore a growing number of researchers lay emphasis on finding more valuable and effective biomarkers for detection of PJI [11, 12].

Calprotectin, a 36 kDa zinc and calcium binding protein, is mostly released by neutrophilic granulocytes and monocytes/macrophages, when receiving inflammatory stimulation [13, 14]. It is shown that calprotectin can promote inflammation reaction and is regarded as the detection of inflammatory markers for rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and spondyloarthritis [15–18]. Recent follow-up studies suggest that the synovial calprotectin was a useful biomarker for the diagnosis of PJI [19].

The aim of this study was to systematically review the literature regarding calprotectin concentrations in synovial fluid of joint with PJI and to investigate diagnostic value of calprotectin in PJI.

Materials and methods

Our research was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20].

Search strategy

This meta-analysis systematically searched all literature about calprotectin in the diagnosis of PJI in PubMed, EMBASE, Web of Science, and Cochrane Library (all up to June 2021), only including English literature. Combinations of the terms, "periprosthetic joint infection" or "prosthesis-related infections" and "calprotectin," were used. Moreover, we searched manually the references of the included research and related literature on calprotectin to gain the literature that we needed for this study (Additional file 1).

Inclusion and exclusion criteria

Two researchers reviewed independently the title and abstract of each assay to select those that were likely for further screening. When two researchers were in the face of disagreement, they were going to submit the problem to Professor Zhihui Pang and the final result depends on him. Inclusion/exclusion criteria were established before the literature search. The following inclusion criteria were applied: (1) using calprotectin as an index for the diagnosis of PJI. (2) Sufficient data can be extracted for the construction of a 2×2 contingency table. Exclusion criteria were: insufficient data to calculate sensitivity and specificity; case reports, commentaries, expert opinion, and narrative reviews; duplicates.

Data extraction and quality assessment

Two reviewers (Yingjie Ge, Miaoxin Cai) extracted information independently from each study, using a standardized data extraction form, which included general study characteristics and patients' clinical characteristics [author, year of publication, country, the design type of the study, number of patients and controls, age and body mass index (BMI) of patients and controls, the gold standard used in the study, the detection method, and the cutoff value of calprotectin]. It was very vital for them to extract information false/true positive, false/true negative from 2×2 table for diagnostic studies, sensitivity, and specificity.

We appraised the quality of all the literature included studies according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) in the RevMan (version5.3).

### Statistical analysis and heterogeneity assessment

Stata 14.0 software was used to conduct the statistical analysis of the study. The combination of the sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), summary receiver operating characteristic (SROC) curve, and the area under the curve (AUC) was based on the bivariate model by the "Midas" command. The diagnostic accuracy of calprotectin was assessed by AUC. Additionally, the heterogeneity was estimated by calculating the inconsistency index (I^2) statistic.

The value of I^2 was a range from 0 to 100%; I^2 value of 75%, 50%, and 25% indicates high, moderate, and low inconsistency, respectively. When there was high heterogeneity, we identified the source of heterogeneity by subgroup analysis. If statistical heterogeneity was remarkable, we found the potential sources of bias from the variables, such as the type of study design, cutoff value, the number of cases, diagnostic standard, and the country or region. The publication bias was estimated by drawing the funnel chart (Deeks' funnel plot). Moreover, the Fagan plot diagram was used to reveal the change of the diagnostic value of calprotectin.

Results

Search results and study characteristics

The flowchart about the study selection process is shown in Fig. 1. The electronic database search yielded a total of 25 studies (11 in PubMed, 7 in EMBASE, 6 in Web of

Fig. 1 Study flowchart
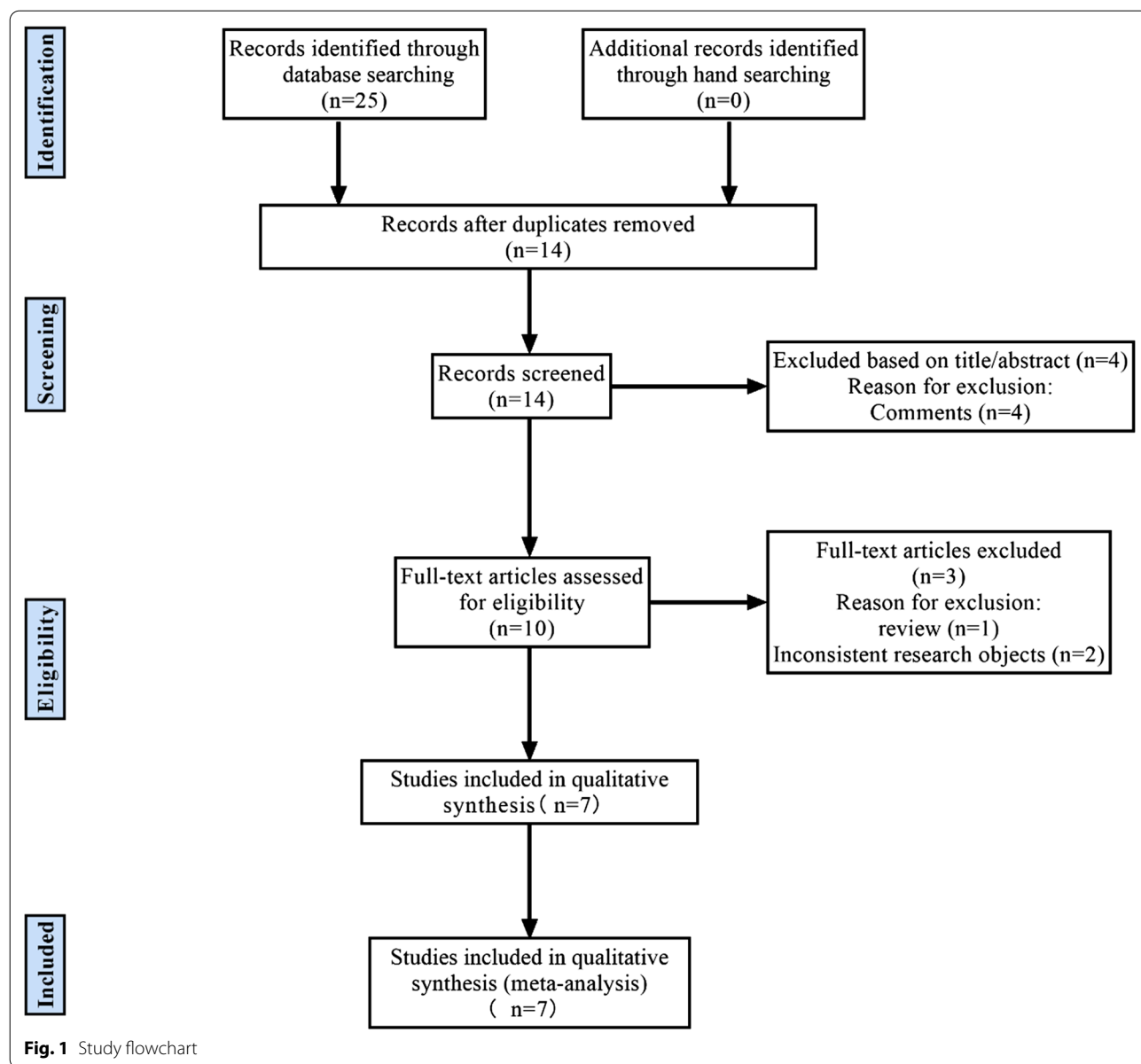
Science, and 1 in the Cochrane Library). After excluded 11 duplicates, 14 studies remained. Four studies were removed by scanning titles and abstracts. After reading the full text in detail, the meta-analysis included 7 studies finally [19, 21–26].

The 7 studies consisted of 525 patients who had undergone hip, knee, shoulder, or elbow joint replacement, including 226 patients with PJI and 299 patients with non-PJI. Two studies used tests were dedicated to synovial fluid, one dedicated to plasma samples and dedicated 4 to fecal samples. Six studies were conducted prospectively and one retrospectively. Four studies applied the Musculoskeletal Infection Society

(MSIS) as the diagnosis standard, and 3 applied International Consensus on Infection (ICM). Detailed characteristics and the main results of each study are shown in Tables 1 and Table 2, respectively.

Quality and publication biases of the included studies

Through the QUADAS-2 scale, the quality of 7 included studies was assessed (Fig. 2). The publication bias for calprotectin was detected by evaluating funnel plot asymmetry according to the Deeks tests. The result of publication bias is shown in Fig. 3 and

Peng *et al. Journal of Orthopaedic Surgery and Research*   (2022) 17:2

Page 4 of 12

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

Study	Year	Country	Study design	Gender (M/F)	Mean age*	BMI*	Detection method	Cutoff values	Gold standard
Dariusz Grzelecki et al	2021	Poland	P	25/60	68.3 / 65.5	29.3/ 29.9	Immunoturbidi-metric Calprotec-tin Immunoassay (GCal, Gentian, Moss, Norway)	1.5 mg/L	ICM (2018)
Jared Warren et al	2021	USA	P	57/66	65.4 / 66.9	32.0/ 34.2	Lyfstone Cal-protectin Point of Care Test Kit (Lyfstone)	50 mg/L	MSIS (2013)
Alexander J Trot-ter et al	2020	TUK	R	37/32	NA	NA	The Lyfstone calprotectin test (Lyfstone AS, Tromsø, Norway)	14 mg/L	ICM (2018)
Marjan Wouthuyzen-Bakker et al	2017	Netherlan-ds	P	25/36	60/65	NA	The Rapid Calprotectin High Range Quantum Blue Assay (BÜHL-MANN laborato-ries AG)	50 mg/L	MSIS (2011)
Marjan Wouthuyzen-Bakker et al	2018	Netherlan-ds	P	NA	NA	NA	The Rapid Calprotectin High Range Quantum Blue Assay (BÜHL-MANN laborato-ries AG)	50 mg/L	MSIS (2011)
Paolo Salari et al	2019	Italy	P	36/40	NA	NA	Calprest NG (Eurospital, Trieste, Italy)	50 mg/L	ICM (2018)
Zeyu Zhang et al	2019	China	P	20/43	NA	NA	ELISA (Hycult Bio-tech, Uden, the Netherlands)	173 ug/ml	MSIS (2013)

*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
Dariusz Grzelecki et al	2021	43	2	2	38	85
Jared Warren et al	2021	52	3	1	67	123
AlexanderJ Trotter et al	2020	18	11	6	34	69
Marjan Wouthuyzen-Bakker et al	2017	17	4	2	38	61
Marjan Wouthuyzen-Bakker et al	2018	13	3	2	34	52
Paolo Salari et al	2019	28	2	0	42	72
Zeyu Zhang et al	2019	20	1	1	41	63

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

indicated no significant publication bias for calprotectin ($P = 0.18 > 0.1$).

Diagnostic value of calprotectin for PJI

The pooled sensitivity of 7 studies was 0.94 (95% CI, 0.87–0.98), and the pooled specificity was 0.93 (95% CI, 0.87–0.96). The corresponding I^2 statistics for sensitivity and specificity were 71.11 (95% CI, 48.63–93.58) and 76.90 (95% CI, 59.85–93.95), indicating that there

was substantial heterogeneity (Fig. 4). The pooled diagnostic score and DOR were 5.4(95% CI, 3.96–6.85) and 222.32(95% CI, 52.52–941.12), respectively (Fig. 5). The area under the SROC (AUC) was 0.98 (95% CI, 0.96–0.99) (Fig. 6).

Evaluation of clinical utility

We calculated the positive likelihood ratio (PLR) and negative likelihood ratio (NLR) of calprotectin for PJI

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

diagnosis by the forest diagram too. The pooled PLR was 13.65 (95% CI, 6.89–27.07), and the pooled NLR was 0.06 (95% CI, 0.02–0.15) (Fig. 7). When a pre-test probability was 0.2 (i.e., a 20% incidence of PJI in patients undergoing revision arthroplasty), a positive result of calprotectin for PJI diagnosis increased the probability of PJI from 20 to 77% and a negative result of calprotectin for PJI diagnosis decreased the probability of PJI to 2% presented in the Fagan plot (Fig. 8).

Subgroup analysis

As the I^2 statistics was > 50%, the result shows that there was heterogeneity between studies. We performed subgroup analysis to ascertain the potential source of heterogeneity necessarily. According to characteristics of the 7 studies, such as the study design, cutoff values, the country of study, and gold standard, we divided these studies into four subgroups based on same characteristics. In this MSIS subgroup, the overall pooled sensitivity and specificity were 0.94 (95% CI 0.86–0.98) and 0.94 (95% CI 0.89–0.97), respectively. The corresponding I^2 statistics for sensitivity

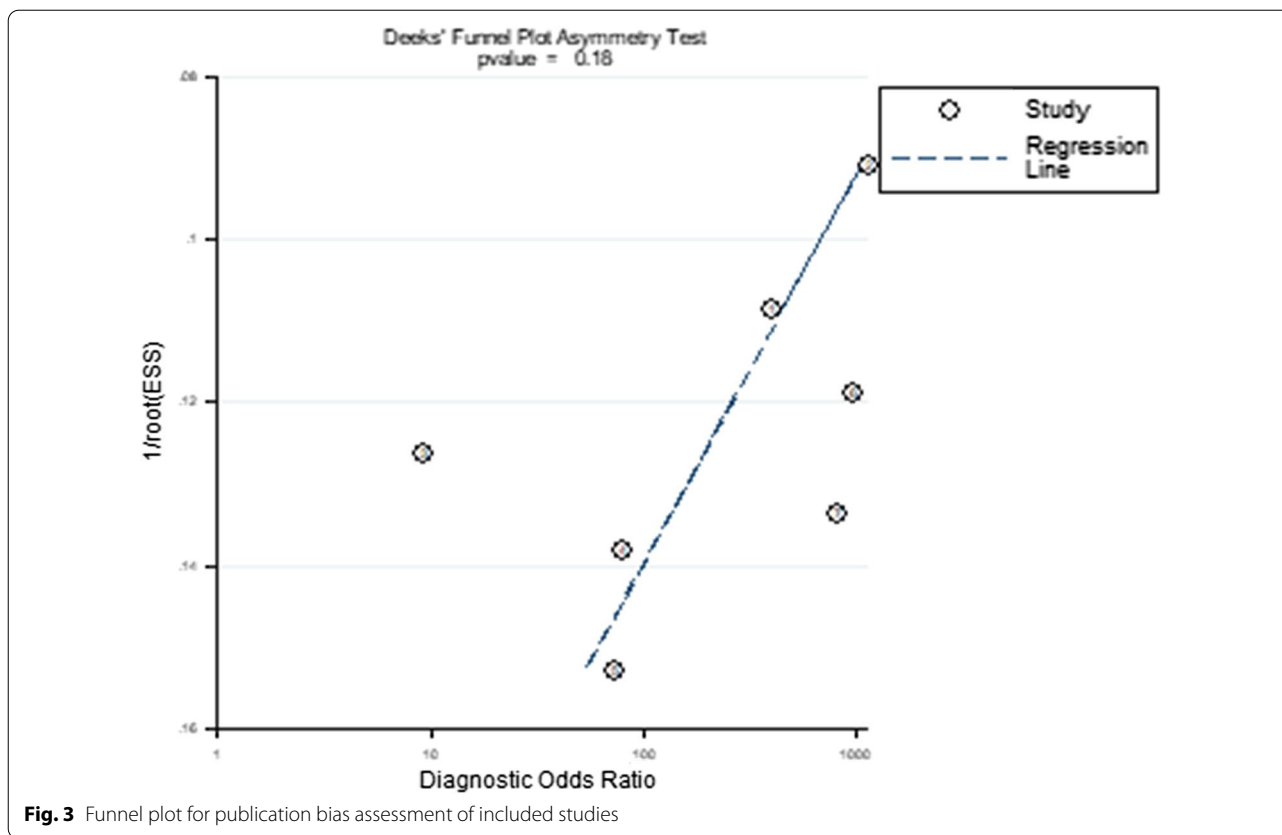Peng *et al. Journal of Orthopaedic Surgery and Research* (2022) 17:2

Page 6 of 12

Fig. 3 Funnel plot for publication bias assessment of included studies

and specificity were 23.46 and 0.00. The corresponding *P*-value for sensitivity and specificity was 0.27 and 0.45. Results of the subgroup analysis are presented in Table 3.

Discussion

Total joint arthroplasty (TJA) is the symbol of great progress for modern medical, because it can greatly relieve the pain of the patient, make restricted function to recover and improve the quality of life [27]. But PJI, a terrified complication after TJA, can be challenging and difficult to accurately diagnose and manage with effect for most surgeons [28, 29]. It is very vital for the management of PJI to distinguish between PJI and aseptic loosening in the face of the painful joint after arthroplasty [30, 31]. Orthopedic surgeons diagnose PJI according to the clinical manifestations, biomarkers from blood and synovial fluid, the microbiological results, molecular diagnosis, histopathology, and imaging results [32]. Biomarkers from blood and synovial fluid provide diagnose PJI with material evidence. For a host of researchers, much attention has been paid to discovering a novel and promising biomarker that has the potential to be a biomarker for diagnostic criteria compared with current ones [33]. Many researches show that synovial biomarkers are more

useful than those from blood at accuracy diagnosis of PJI, such as α-defensin, interleukin-6, interleukin-1β, leukocyte esterase, and interleukin-17 [11, 34].

Calprotectin from synovial fluid has been regarded as a promising test for diagnosis according to many studies [25, 35]. M. Wouthuyzen-Bakker et al. conducted a first study on diagnostic value of synovial calprotectin that a cutoff value of 50 mg/L has high sensitivity (89%) and specificity (90%), with a NPV of 97%. This study shows that calprotectin may become a promising test to exclude PJI [24]. D. Grzelecki et al. deemed that calprotectin was superior to CRP, ESR, interleukin-6 (IL-6), and leucocyte esterase (LE) on diagnostic value of chronic PJI [22]. However, there is not a meta-analysis on calprotectin in the diagnosis of PJI hitherto, and therefore it is very necessary for many researchers to analyze its diagnostic value.

The meta-analysis including 7 studies shows that the calprotectin has excellent PJI diagnostic value, with high sensitivity (94%) and specificity (93%). But there was a great heterogeneity in this study, because the corresponding I^2 statistics for sensitivity and specificity was 71.11 and 76.9, respectively. The AUC for pooled data from the 7 studies was 0.98, demonstrating excellent diagnostic accuracy to identify PJI due to the AUC > 0.97
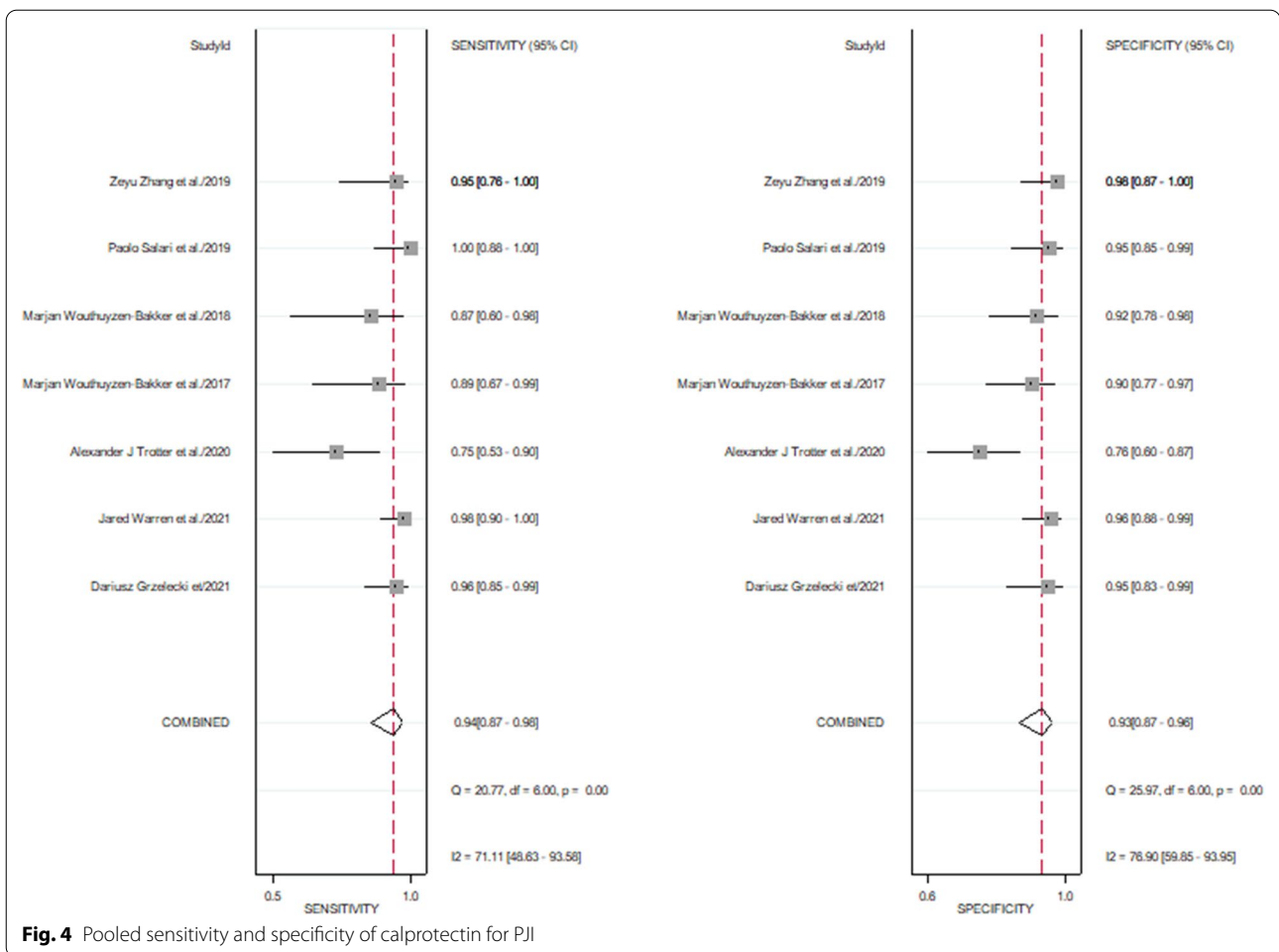
Fig. 4 Pooled sensitivity and specificity of calprotectin for PJI

[36]. The DOR of this meta-analysis was 222.32 (95% CI, 52.52–941.12) due to > 10, showing that calprotectin may serve as a good predictor for PJI. The PLR and the NLR of calprotectin were 13.65 (95% CI, 6.89–27.07) and 0.06 (95% CI, 0.02–0.15), respectively. It is indicated that calprotectin could be a biomarker of moderate diagnostic value in PJI, as the PLR was > 10 and the NLR was < 0.1. Besides, the Fagan plot diagram revealed that calprotectin was a promising and valuable biomarker for predicting and excluding PJI.

The C-reactive has been included in the diagnostic criteria in the 2018 ICM. Chi Wang et al. reported the pooled sensitivity and specificity for C-reactive were 0.92 (95% CI 0.86–0.96) and 0.90 (95% CI 0.87–0.93), respectively [37]. The pooled sensitivity and specificity of our meta-analysis are greater than the results done by Chi Wang et al. The American Academy of Orthopaedic Surgeons Clinical Practice Guideline "Diagnosis and Prevention of Periprosthetic Joint Infections" showed that α-defensin testing was good for the diagnosis of PJI [38]. The results of the study done by Giovanni Balato et al.

showed that the pooled sensitivity and specificity for α-defensin were 0.90 (95% CI 0.83–0.94) and 0.95 (95% CI 0.92–0.96), respectively [39]. The pooled sensitivity of our meta-analysis is greater than the results done by Giovanni Balato et al., but the pooled specificity is less than the results done by Giovanni Balato et al. So calprotectin was a valuable biomarker for diagnosis of PJI compared with α-defensin and C-reactive.

Given remarkable heterogeneity from sensitivity and specificity, we must investigate the sources of heterogeneity in this study by subgroup analysis. One of the main sources of heterogeneity is the threshold effect for the diagnostic meta-analysis. Therefore, we divided four studies that regarded 50 mg/L as the diagnostic threshold of PJI as a subgroup. In this subgroup analysis, the AUC of 50 mg/L subgroup was 0.97 and less than the AUC (0.98) of overall studies. The corresponding I^2 statistics for sensitivity was 54.15 (> 50), indicating that there was still heterogeneity. Next, we explored other potential causes of heterogeneity such as diagnostic standard, study design, and the country of study by subgroup
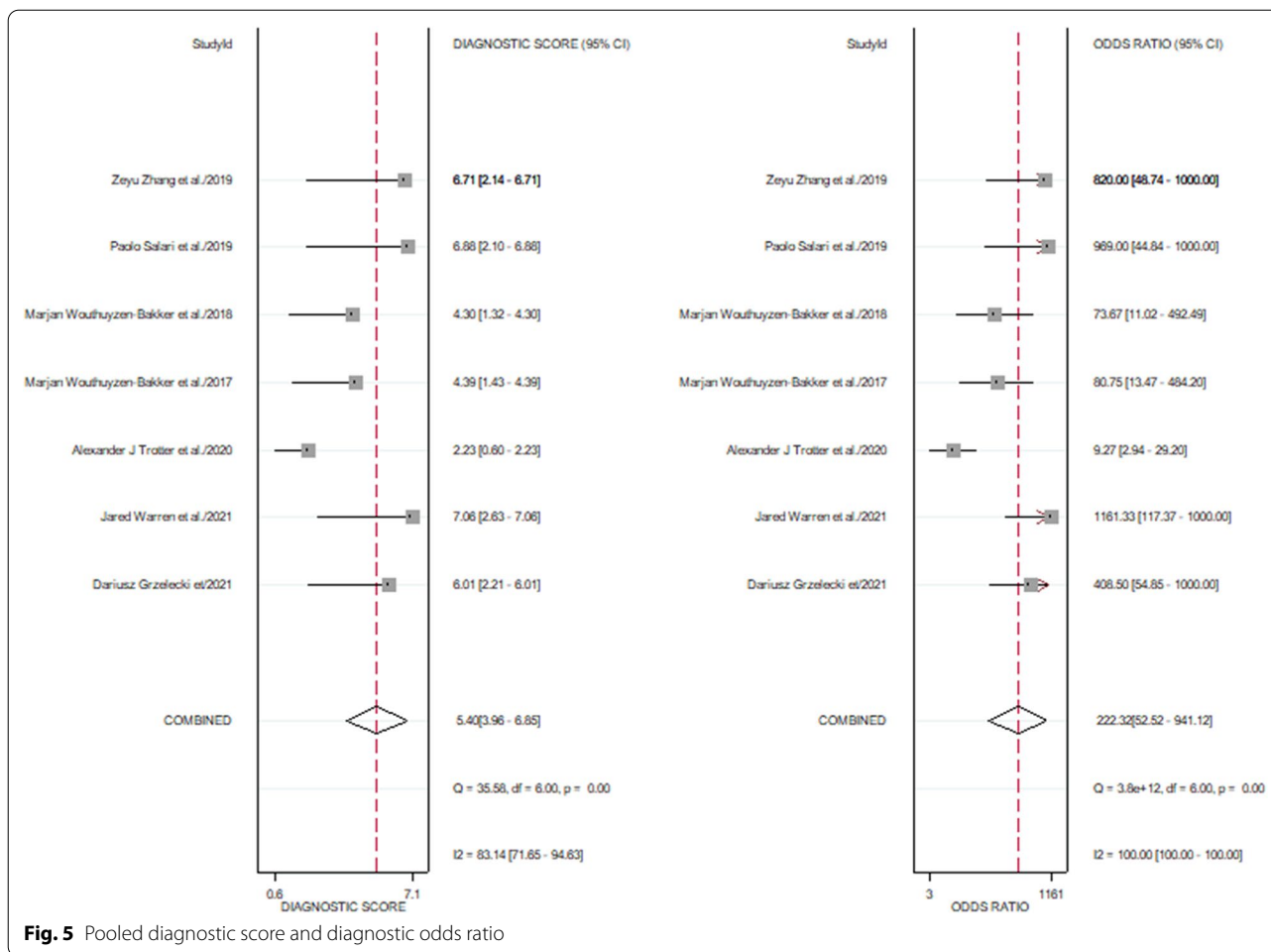
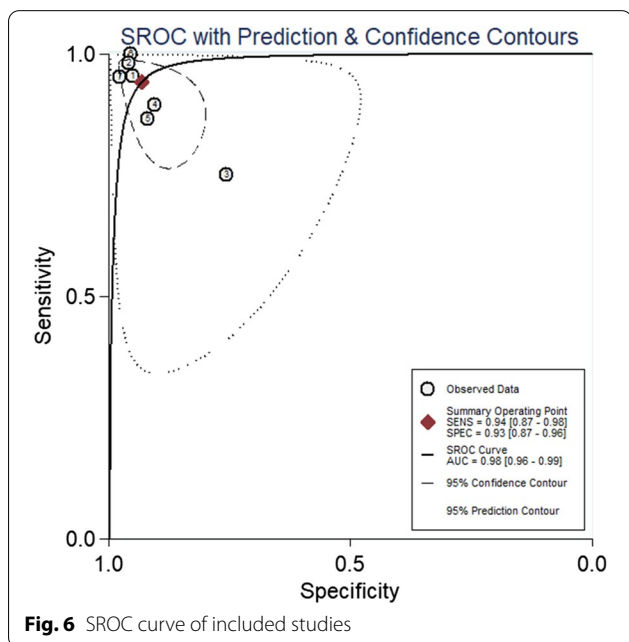**Fig. 5** Pooled diagnostic score and diagnostic odds ratio

Fig. 6 SROC curve of included studies

analysis. Fortunately, we found finally that the sources of heterogeneity of the meta-analysis about calprotectin were originated from the diagnostic standard. The AUC and NLR of the MSIS subgroup were completely consistent with those of all studies. In addition, the corresponding I^2 statistics for sensitivity and specificity was 23.46 and 0.00, ($I^2 < 50$), respectively. The pooled sensitivity, specificity, PLR, diagnostic score, and DOR of the MSIS subgroup were greater than or equal to the overall studies.

The costs of synovial calprotectin test for PJI are relatively cheap compared with interleukin-6 and alpha-defensin measured with lateral flow immunoassays [40, 41]. It is available for majority hospitals to use calprotectin as biomarker of diagnosing PJI [42].

There are several limitations in the meta-analysis. First, this study includes the limited number of articles, and the included sample size is limited. So, it is very difficult for us to discover other potential heterogeneity by conducting further subgroup analyses. Second, there is no internationally recognized gold standard
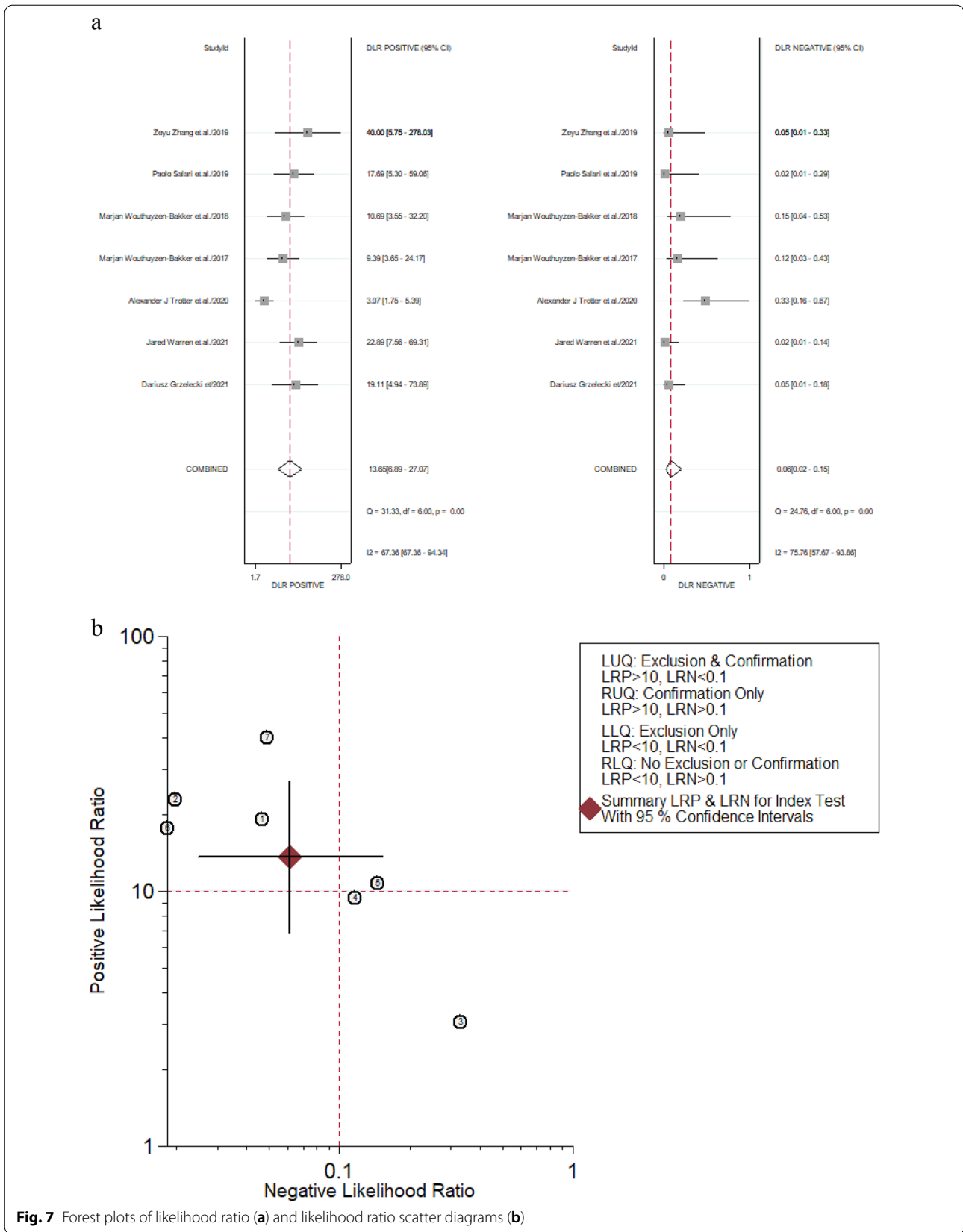
Fig. 7 Forest plots of likelihood ratio (**a**) and likelihood ratio scatter diagrams (**b**)

Table.3 Subgroup analysis of calprotectin for PJI diagnosis

Subgroup analyses	No. of studies	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	AUC (95% CI)	Diagnostic score (95% CI)	DOR (95% CI)	I^2(Sen) (95% CI)	P-value (Sen)	I^2(Spe) (95% CI)	P-value (Spe)
Overall studies	7	0.94 (0.87–0.98)	0.93 (0.87–0.96)	13.7 (6.9–27.1)	0.06 (0.02–0.15)	0.98 (0.96–0.99)	5.4 (3.96–6.85)	222 (53–941)	71.11	0.00	76.90	0.00
Prospective	6	0.96 (0.91–0.98)	0.95 (0.91–0.97)	17.6 (10.5–29.4)	0.05 (0.02–0.10)	0.98 (0.96–0.99)	5.94 (4.95–6.93)	378 (141–1018)	31.00	0.20	87.49	0.00
50 mg/L	4	0.96 (0.87–0.99)	0.94 (0.89–0.97)	15.4 (8.3–28.5)	0.04 (0.01–0.15)	0.97 (0.95–0.98)	5.85 (4.29–7.40)	346 (73–1638)	54.15	0.09	0.00	0.64
Western countries	6	0.94 (0.85–0.98)	0.92 (0.85–0.96)	11.9 (5.9–24.01)	0.07 (0.02–0.18)	0.97 (0.96–0.98)	5.21 (3.65–6.77)	183 (39–871)	73.90	0.00	75.90	0.00
MSIS	4	0.94 (0.86–0.98)	0.94 (0.89–0.97)	16.3 (8.7–30.8)	0.06 (0.02–0.15)	0.98 (0.96–0.99)	5.60 (4.34–6.86)	271 (77–958)	23.46	0.27	0.00	0.45

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; Sen = sensitivity; Spe = specificity

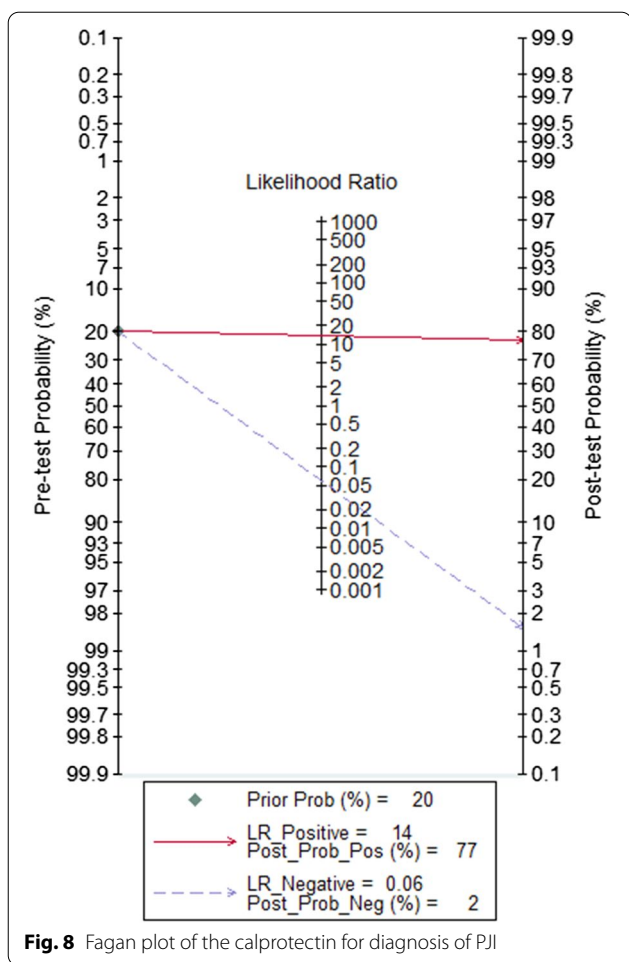**Fig. 8** Fagan plot of the calprotectin for diagnosis of PJI

for diagnosis of PJI, and this meta-analysis was used in multiple reference standards. Third, the studies included in this meta-analysis used tests dedicated to different samples (fecal, synovial fluid, plasma). This issue may influence on the received results and cutoff values. Finally, this meta-analysis lacks more studies about different calprotectin cutoff values. However, our subgroup analysis shows that there is no remarkable threshold effect.

Conclusion

We first evaluate diagnostic value about synovial calprotectin by meta-analysis. Our results reveal that synovial calprotectin for PJI has good diagnostic accuracy due to the high sensitivity and specificity. Besides, synovial calprotectin can serve as a significant tool to exclude PJI based on its low NLR (0.06) of overall pooled data. In spite of requiring more researches about calprotectin, we still deem that synovial calprotectin will serve as a promising biomarker for diagnosis

of PJI because of its advantages, such as high diagnostic accurate and convenience.

Abbreviations
PJI: Periprosthetic joint infection; AAOS: The American Academy of Orthopedic Surgeon; MSIS: Musculoskeletal Infection Society; ICM: International Consensus Meeting; IDSA: Infectious Diseases Society of America; LR: Likelihood ratio; DOR: Diagnostic odds ratio; SROC: Summary receiver operating characteristic; AUC: Area under the curve; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s13018-021-02746-2.

Additional file 1. Search strategy.

Authors' Contributions
XP and ZP conceptualized the study. XP, HZ, GB, and PX helped in literature search. YG and MC extracted the data and assessed the quality. RW and YG developed the software. XP and YF helped in formal analysis. ZP and YF validated the study. XP wrote the manuscript. 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.

Declarations

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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