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# Meta-analysis of the diagnostic value of serum procalcitonin for burn sepsis in adults

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**Abstract. – OBJECTIVE: Serum procalcitonin (PCT) reflects the infection status of the organism and the severity of the infection. The purpose of this study was to systematically evaluate the diagnostic value of serum PCT for burn sepsis in adults and to provide a factual basis for future clinical diagnosis and decision-making.**

**MATERIALS AND METHODS: On August 16, 2022, six databases were searched in this study and a total of 856 studies were found. The retrieved literature was comprehensively evaluated according to the inclusion and exclusion criteria, and the valid data were extracted and included for analysis. The number of true positives, false positives, true negatives and false negatives were used as indicators to evaluate the diagnostic value of serum PCT for burn sepsis in adults.**

**RESULTS: In total, 15 studies met the inclusion criteria. Meta-analysis showed a combined sensitivity of 0.78 (95% CI: 0.69-0.84), a combined specificity of 0.85 (95% CI: 0.77-0.91), a combined positive likelihood ratio of 5.17 (95% CI: 3.25-8.25), a combined negative likelihood ratio of 0.26 (95% CI: 0.19-0.37), and a combined diagnostic ratio of 19.63 (95% CI: 10.17-37.90). The AUC was 0.88 (95% CI: 0.85-0.90).**

**CONCLUSIONS: Serum PCT provides good early diagnostic benefits for burn sepsis in adults. More high-quality studies are required to clarify its specific early diagnostic value.**

*Key Words:*
Procalcitonin, Burn sepsis, Diagnosis, Meta-analysis.

## Introduction

Burns are common injuries in life, mainly manifested by physical or chemical damage to the skin, which leads to a reduction or even loss of the barrier function of the skin[1]. The skin is the first barrier of the body against infection by external pathogens and is one of the most important physical barriers. Severe burns will lead to a decrease in the defensive function of the skin and increase the risk of infection, the larger the burn area, the higher the risk of infection. The incidence of sepsis has been reported to be 3%-30% in patients with >20% of the body surface burn area[2]. Burn sepsis refers to secondary systemic organ failure caused by a dysregulated response to infection in burn patients[3]. Burn sepsis has an insidious onset, rapid progression, and poor prognosis, and is one of the leading causes of death in patients with severe burns[4]. Therefore, early detection of high-risk groups prone to burn sepsis is crucial to reduce patient mortality and improve patient prognosis.

Blood culture is the gold standard for the clinical diagnosis of burn sepsis. However, the lengthy duration and low positivity of blood cultures, as well as the prophylactic use of antibiotics in burn patients compromise the accuracy of blood cultures and may also increase bacterial resistance[5]. Besides, other blood tests, such as leukocytes, neutrophils, and liver and kidney function, are heavily influenced by other factors, resulting in low sensitivity and specificity for the diagnosis of burn sepsis[6]. Thus, there exists an urgent need for a serum marker with rapid detection and high sensitivity and specificity to facilitate the determination of the presence of sepsis in burn patients so as to reduce morbidity and mortality and improve prognosis.

Procalcitonin (PCT) is a precursor of calcitonin, a non-hormonally active glycoprotein consisting of 116 amino acids[7]. Under normal conditions, PCT is secreted by thyroid C cells and is involved in calcium metabolism by cleavage of specific protein hydrolases to obtain calcitonin. The plasma levels of PCT are extremely low under healthy conditions, but during systemic inflammatory reactions or severe bacterial infections, the expression of extrathyroidal non-neuroendocrine calcitonin genes is upregulated under the stimulation of inflammatory factors, causing the release of uncleaved PCT into the blood, which increases the plasma PCT concentration[8]. Serum PCT levels in patients with combined severe bacterial infections are closely related to



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the duration of infection: serum PCT often rises rapidly within 6-8 hours and peaks at 24 hours, which provides a factual basis for clinicians to infer the duration of infection and subsequent management of patients[9]. In recent years, various studies[10-12] have indicated an important role of serum PCT in the early diagnosis of burn sepsis. However, no definitive conclusion about the early diagnostic value of PCT for adult burn sepsis is available. To this end, this meta-analysis was performed to systematically evaluate the diagnostic value of serum PCT for burn sepsis in adults and to provide a factual basis for future clinical diagnosis and decision making.

## Materials and Methods

### PICO Principles

P (patient): patient with burn sepsis. I (intervention): detection of serum PCT. C (comparison): blood culture. O (outcome): assessment of the validity of serum PCT for early diagnosis of burn sepsis.

### Literature Search

The search strategy was developed according to the "PICOS principles" in the Cochrane Systematic Evaluation Manual, and the databases searched included PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure (CNKI), Wanfang Database, and Sinomed. The search time was limited from the inception of the database to August 16, 2022.

The search keywords were different for both English and Chinese databases. In the English databases, free words such as "Burns", "Burn sepsis", "Burn", "Procalcitonin", "PCT", "Calcitonin Precursor Polyprotein", "Calcitonin-1", "Calcitonin 1", "Diagnosis" were used in combination with subject terms, and the search strategy was determined after several pre-searches. The Chinese databases were searched by using "Burns", "Burn sepsis", "Calcitoninogen", "Calcitonin-1", "Calcitonin-1" "Calcitonin-related polypeptide alpha", "Diagnosis" in CNKI, Wanfang database, and Sinomed.

### Literature Inclusion and Exclusion Criteria

Inclusion criteria: (1) the included literature evaluated and explored the diagnostic value of PCT in burn sepsis patients over 18 years of age; (2) the included literature included burn sepsis patients who met the diagnostic criteria defined by the American Burn Association (ABA) conference[13]; (3) comparative data on clinical diagnosis and blood culture results are available; (4) outcome indicators included sensitivity, specificity, or the number of true positives (TP), false positives (FP), true negatives (TN) and false negatives (FN) are provided.

Exclusion criteria: (1) poor experimental design or implementation resulted in the inability to extract accurate data for the construction of 2×2 four-grid tables; and (2) the study population included children.

### Literature Quality Evaluation and Data Extraction

The literature was assessed separately by two trained investigators as per the inclusion and exclusion criteria. The initial screening was performed based on the title and abstract. After the initial screening, literature that met the inclusion criteria was retrieved and read in full, and the original authors were contacted if necessary to avoid data omission. In the event of inconsistent evaluation of the literature, a third party was engaged to address the issue and achieve a consensus. The methodological quality of the included studies was evaluated as per the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool, which includes case selection, experimental protocol design and implementation, gold standard, case flow, and progress status. The results of the methodological quality assessment were classified into 3 risk levels: low risk of bias, high risk of bias, and unknown risk. Each risk level has a specific entry corresponding to it in QUADAS-2[14]. QUADAS-2 scoring was done independently by two investigators, and a third party was invited to resolve discrepancies in the results. The extracted data items included article author, year of publication, country, experimental design protocol, sample size, PCT diagnostic threshold, number of true positives, number of true negatives, number of false positives, number of false negatives, and percentage of burned area. The meta-analysis followed PRISMA guidelines.

### Statistical Analysis

Data statistical analysis was performed using RevMan 5.4 software (Cochrane Collaboration, London, UK) and Stata 15 software (StataCorp LLC, Texas, USA) recommended by the Cochrane Collaboration Network. The receiver op-

erating characteristic (ROC) curve was used to evaluate the diagnostic threshold effect. A binary mixed-effects regression model with a 95% confidence interval (CI) was used to calculate sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and the combined diagnostic odds ratio (DOR), and the corresponding forest plots were drawn. Sensitivity analysis and meta-regression were used to explore the sources of study heterogeneity. The Deeks test was used to detect publication bias, and in the presence of publication bias, the cut-and-patch method was used to explore whether publication bias had an impact on the conclusions drawn from this study. $p<0.05$ indicates a statistically significant difference in results.

## Results

### Results of the Literature Search

A total of 856 papers were obtained from the literature search, including 431 from Chinese databases (92 from CNKI, 147 from Wanfang, and 192 from SinoMed) and 425 from English databases (52 from PubMed, 177 from Embase, and 196 from Web of Science). After the initial screening, 304 duplicates were excluded and 10 duplicates were ruled out for other reasons, resulting in 542 articles. After reading the titles and abstracts, 460 papers were excluded for the following reasons: (1) the papers were systematic reviews or meta-analyses (33 papers); (2) the topics did not match the purpose of the study (322 papers); and (3) the papers were non-diagnostic trials (105 papers). The above-mentioned literature after the initial screening was searched and 15 of them were excluded due to the unavailability of the corresponding article content. Finally, a final screening of the above-mentioned literature was performed, and 52 articles were excluded after reading the full text owing to the discrepancies between the outcome indicators in the excluded literature and the outcome indicators developed in this study. A total of 15 studies[15-29] were included in this research. The literature search process and results are shown in Figure 1.

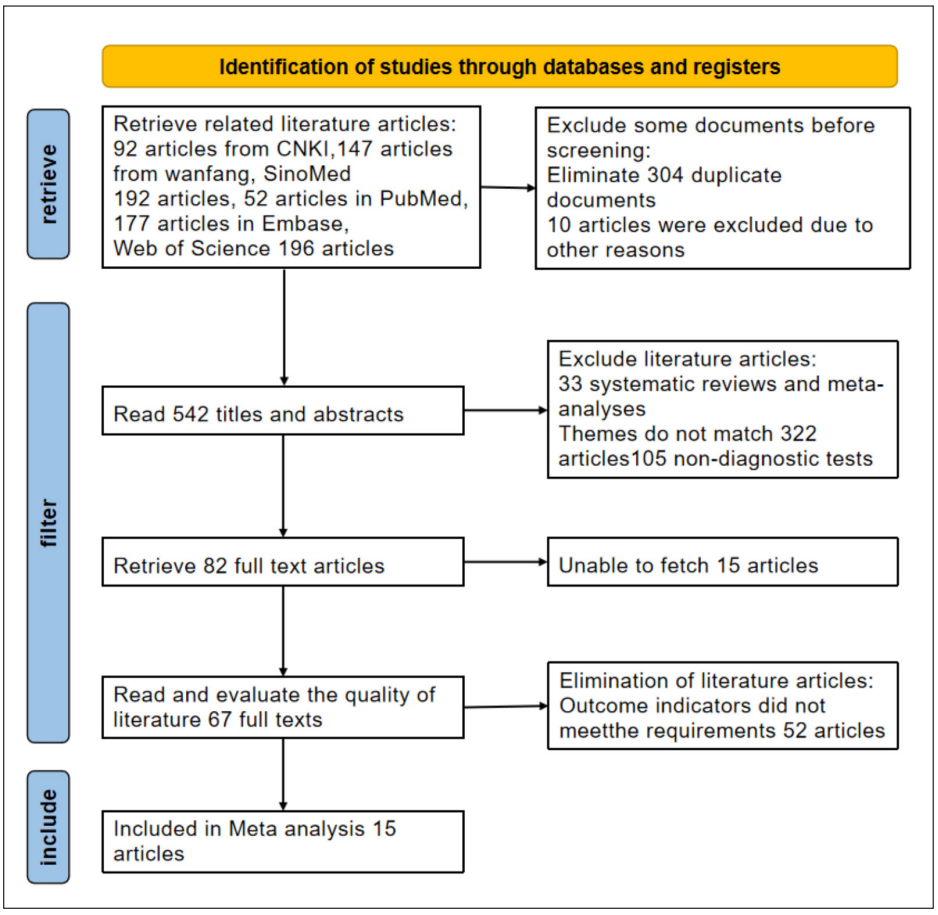


**Figure 1.** Flow chart for literature search based on PRISMA guidelines.

### Overall Characteristics of the Literature and Quality Assessment

The results of the 15 included studies were published between 2004 and 2020, with 997 patients and 6,629 timepoints. The studies were conducted in China, France, Greece, Turkey, Spain, and Australia, and 4 of the 15 studies[22,24,26,28] were retrospective and 11 were prospective[15-21,23,25,27,29]. Burn cases were divided into a burn sepsis group, a burn non-sepsis group, and an unburned control group. Blood cultures were used as the gold standard for this diagnostic study, and serum PCT concentrations were collected and measured at several specific time points to characterize the diagnostic value of serum PCT for burn sepsis. The sensitivity, specificity, positive predictive value, negative predictive value, and corresponding sample size of serum PCT for the diagnosis of burn sepsis were reported in each of the 15 studies. The number of true positives, false positives, true negatives and false negatives were calculated from the above data and organized into a table with the baseline characteristics of the patients, as shown in Table I. Fifteen studies were evaluated for quality according to QUADAS-2, and 12 studies[15-16,18-21,23,24-28] had a QUADAS score of over 10 (Figures 2 and 3).

### Statistical Data Analysis

The sensitivity and specificity of the above 15 studies were combined using Stata 15.0 software, and the results showed that the combined sensitivity was 0.78 (95% CI: 0.69-0.84) and the heterogeneity test result was $I^2$=94.52% (95% CI: 92.73%-96.31%), indicating that there was significant heterogeneity in the studies, so the random effects model was used. The combined specificity was 0.85 (95% CI: 0.77-0.91) and the test result of heterogeneity was $I^2$=98.92% (95% CI: 98.70%-99.31%), indicating a significant heterogeneity of the study, so the random effects model was used (Figure 4). Similarly, the combined positive likelihood ratio was 5.17 (95% CI: 3.25-8.25), $I^2$=98.33% (95% CI: 98.33%-98.91%), and the combined negative likelihood ratio was 0.26 (95% CI: 0.19-0.37), $I^2$=96.83% (95% CI: 95.95%-97.70%) (Figure 5). The combined diagnostic score was 2.98 (95% CI: 2.32-3.64), $I^2$=96.57% (95% CI: 95.60%-97.54%), and the combined diagnostic ratio was 19.63 (95% CI: 10.17-37.90), $I^2$=100% (Figure 6).

The diagnostic efficacy of PCT for adult burn sepsis was evaluated using the summary receiver operating characteristic curves (SROC) curve. The results suggested that the AUC=0.88 (95% CI: 0.85-0.90), indicating a good diagnostic efficacy of PCT (Figure 7). Fagan's column line plot shows that when the disease prevalence is 20%, the post hoc probability of a positive likelihood ratio is 56% and the post hoc probability of a negative likelihood ratio is 6% (Figure 8). Figure 9 shows the post hoc probability of positive likelihood ratio and negative likelihood ratio for PCT diagnosis of adult burn sepsis in relation to the *a priori* probability. As the *a priori* probability increased, the positive likelihood ratio and negative likelihood ratio post-test probability also increased. However, in the case of a low a priori probability, the former increased significantly more than the latter, while in the case of high *a priori* probability, the latter increased more than the former. The positive likelihood ratio of the diagnostic test >10 indicates a confirmatory value, and its negative likelihood ratio <0.1 indicates an exclusion value. To understand the diagnostic value of PCT for adult sepsis, a likelihood ratio quadrant distribution chart was created based on the positive likelihood ratio and negative likelihood ratio of PCT, and the results showed that PCT had a positive likelihood ratio <10 and a negative likelihood ratio >0.1 for the diagnosis of adult burn sepsis, indicating that PCT had neither a confirmatory nor an exclusionary value (Figure 10).

To explore the source of heterogeneity in this study, sensitivity analysis was performed on the diagnostic ratio (DOR) of PCT, and the results suggested that the DOR was within a reasonable interval with some stability after excluding each included literature one by one (Figure 11). To further explore whether the time of publication, country, and type of study of the included literature were sources of heterogeneity, a meta-regression analysis was performed on the above factors, and the results suggested that the time of publication and country of the literature had no significant effect on the sensitivity and specificity of this meta-analysis (Figure 12). Nonetheless, the type of study of the literature had implications for the sensitivity of the diagnosis, with the results suggesting that the sensitivity of retrospective studies (0.68, 95% CI: 0.51-0.85) was significantly lower than that of prospective studies (0.81, 95% CI: 0.73-0.89), $p$=0.02.

### Publication Bias

The 15 included studies were tested for publication bias using Stata 15.0. The results of the

**Table I.** Basic characteristics of the literature incorporating serum PCT for early diagnosis of burn sepsis features in adults ($\bar{x} \pm s$).

| Author | Year | Country | Design | PCT cut-off | Age | TBSA% burned | Time points | Sample size | TP | FP | FN | TN |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bargues et al[15] | 2007 | France | PS | 0.534 | 40 ± 14 | 40 ± 17 | 359 | 25 | 39 | 29 | 53 | 237 |
| Sun et al[16] | 2011 | China | PS | 2.2 | NA | NA | 14 | 14 | 13 | 3 | 1 | 47 |
| Lavrentieva et al[17] | 2007 | Greece | PS | 1.5 | 45.6 ± 20.1 | 41.4 ± 22 | 934 | 43 | 93 | 72 | 21 | 748 |
| Lv et al[18] | 2019 | China | PS | NA | 36.5 ± 19.2 | NA | 76 | 76 | 59 | 16 | 17 | 69 |
| Lavrentieva et al[19] | 2012 | Greece | PS | 1.5 | 48.2 ± 18.3 | 38.8 ± 18 | 145 | 145 | 54 | 5 | 9 | 67 |
| Huang et al[20] | 2004 | China | PS | 2.3 | NA | NA | 9 | 9 | 8 | 2 | 1 | 39 |
| Cakir et al[21] | 2013 | Turkey | PS | 0.759 | 40 ± 17 | 36.1 ± 23.4 | 611 | 37 | 181 | 79 | 59 | 292 |
| Seoame et al[22] | 2014 | Spain | RS | 1.7 | 52.5 ± 17.2 | 37.6 ± 22.9 | 34 | 34 | 4 | 0 | 12 | 18 |
| Paratz et al[23] | 2014 | Australia | PS | 1.4 | 40.16 (18-60) | 40.1 ± 16.0 | 344 | 53 | 38 | 190 | 10 | 106 |
| Zhang et al[24] | 2016 | China | RS | 4.63 | 37.91 ± 7.25 | 43.64 ± 5.13 | 40 | 40 | 29 | 4 | 11 | 28 |
| Mokline et al[25] | 2015 | Tunisia | PS | 0.69 | 37 ± 17 | 23 ± 17 | 121 | 121 | 39 | 12 | 5 | 65 |
| Cabral et al[26] | 2017 | Portugal | RS | 0.5 | 40.8 ± 79.0 | 16.0-38.8 | 3,419 | 150 | 463 | 1062 | 189 | 1705 |
| Zhou et al[27] | 2020 | China | PS | 4.05 | 30.93-54.31 | 40.6-53.7 | 68 | 68 | 14 | 7 | 4 | 43 |
| Liu et al[28] | 2019 | China | RS | 2 | 41.57 ± 12.03 | 80.88 ± 15.25 | 359 | 86 | 303 | 603 | 56 | 988 |
| Zhang et al[29] | 2015 | China | PS | 0.5 | 35.5 ± 10.1 | NA | 96 | 96 | 87 | 8 | 9 | 65 |

PS: prospective study; RS: retrospective study; PCT: procalcitonin; TBSA: total body surface area; TP: number of true positives; FP: number of false positives; FN: number of false negatives; TN: number of true negatives.

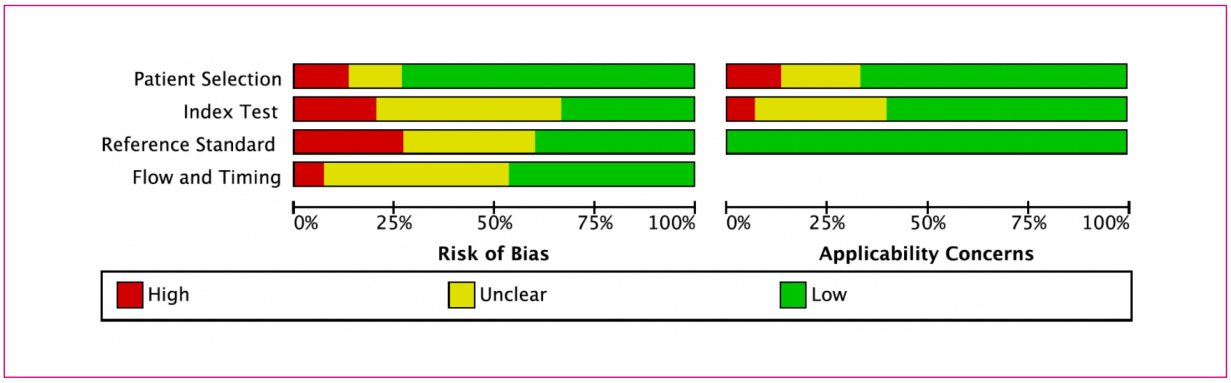


**Figure 2.** Risk of bias map for included studies.

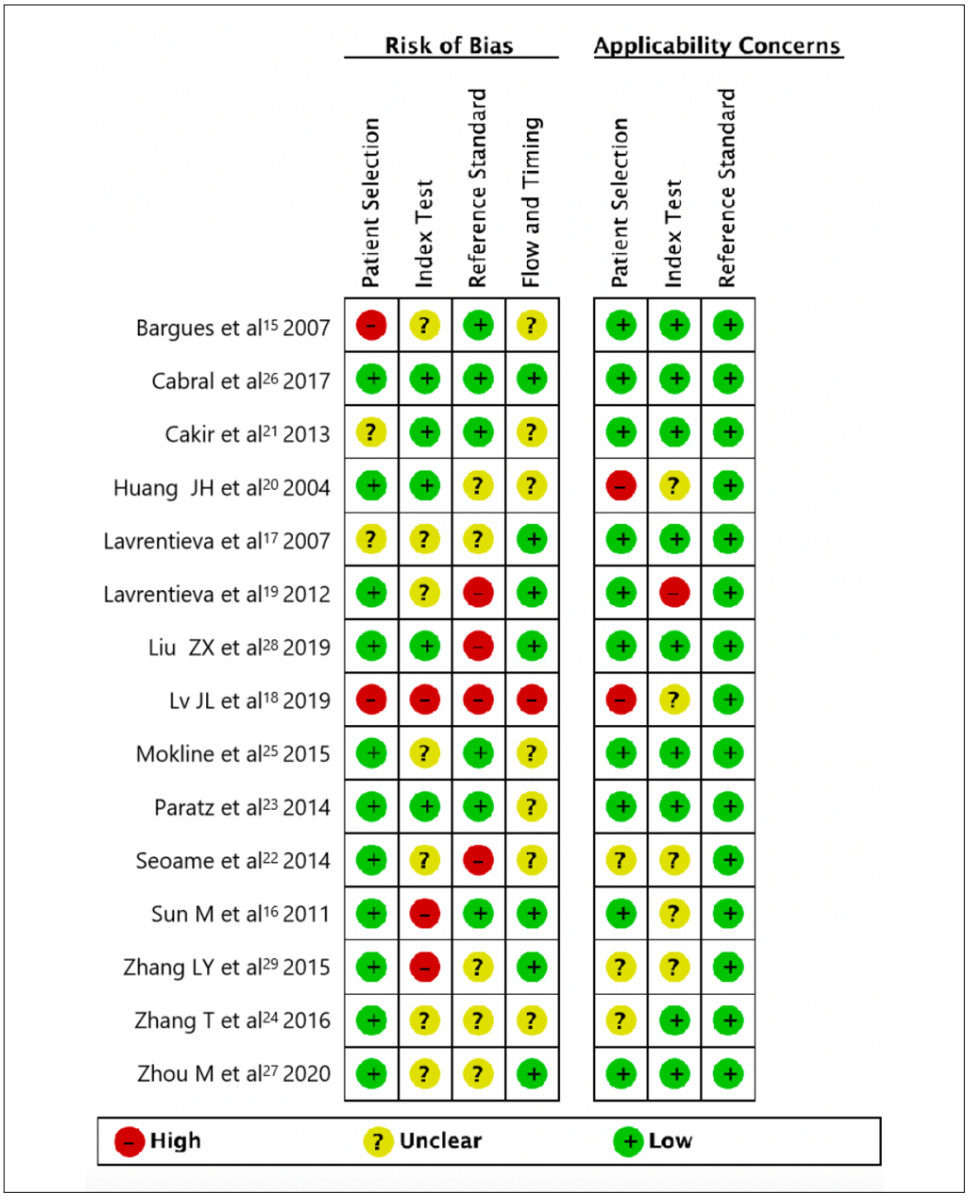


**Figure 3.** Pooled risk of bias for included studies.

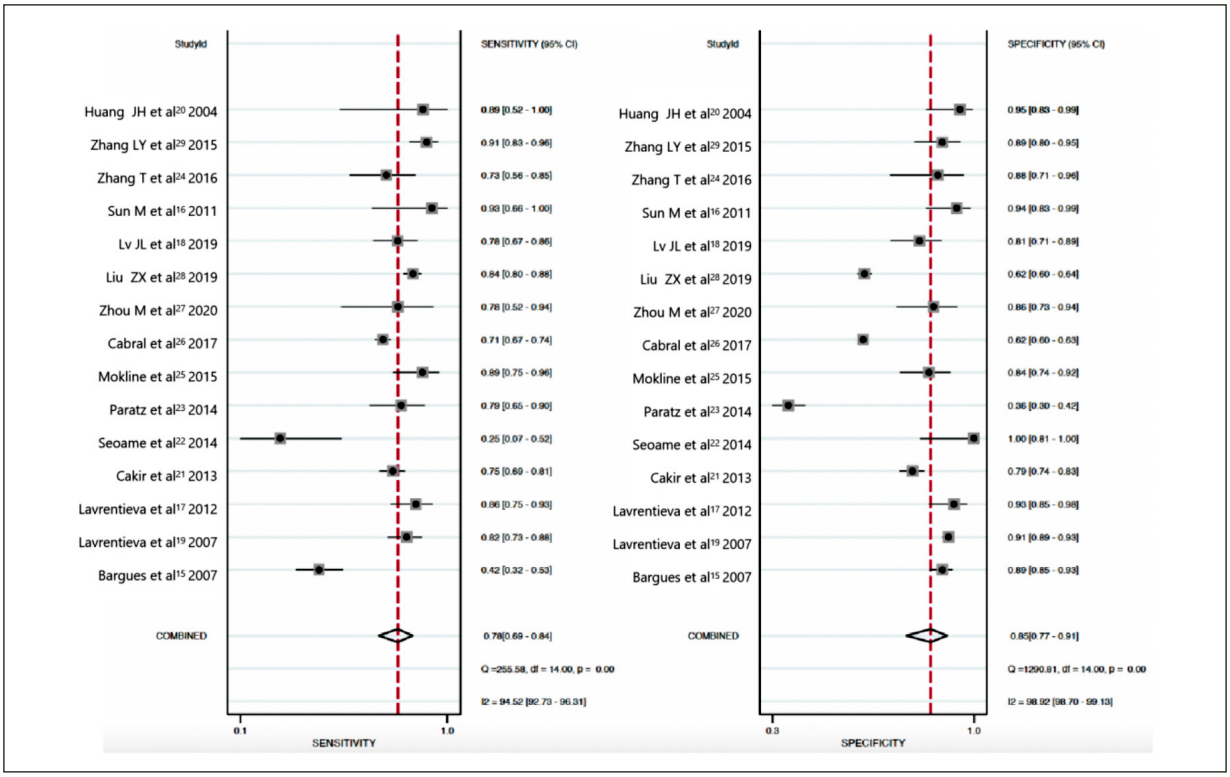


**Figure 4.** Forest plot of sensitivity and specificity of PCT for the diagnosis of burn sepsis in adults.

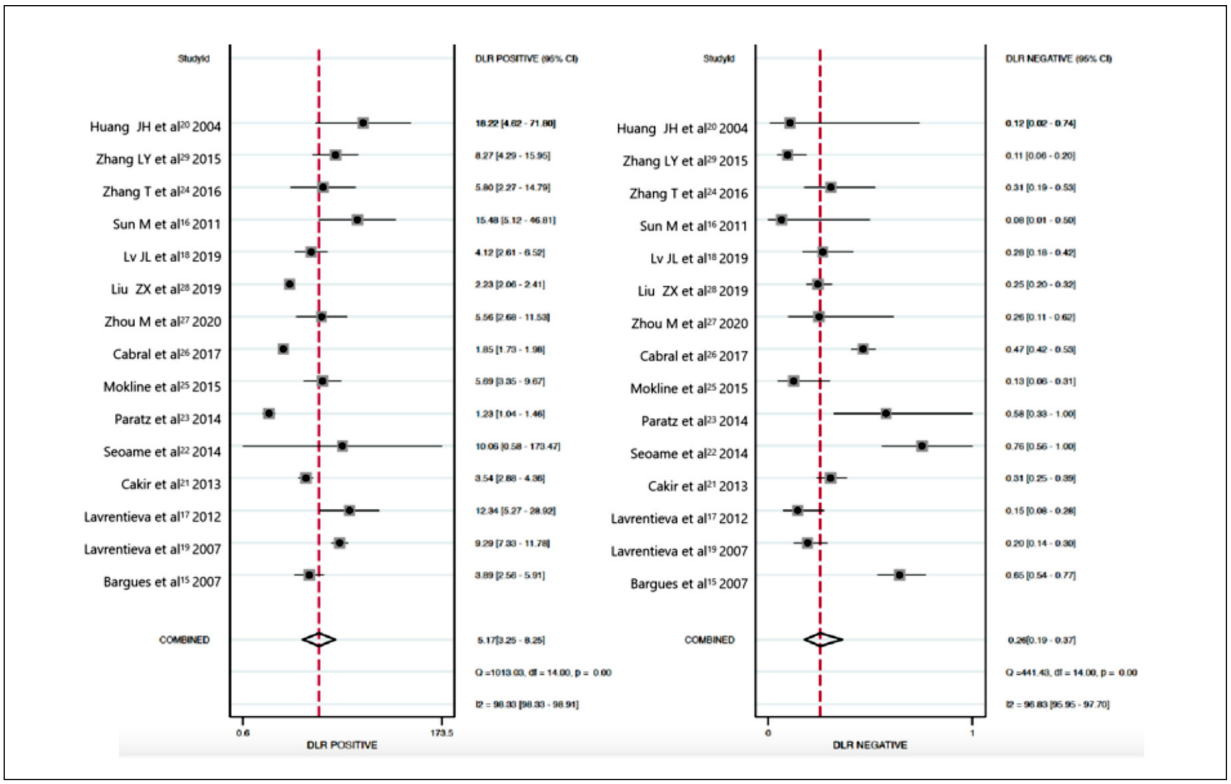


**Figure 5.** Forest plot of positive likelihood ratio and negative likelihood ratio of PCT for the diagnosis of burn sepsis in adults.

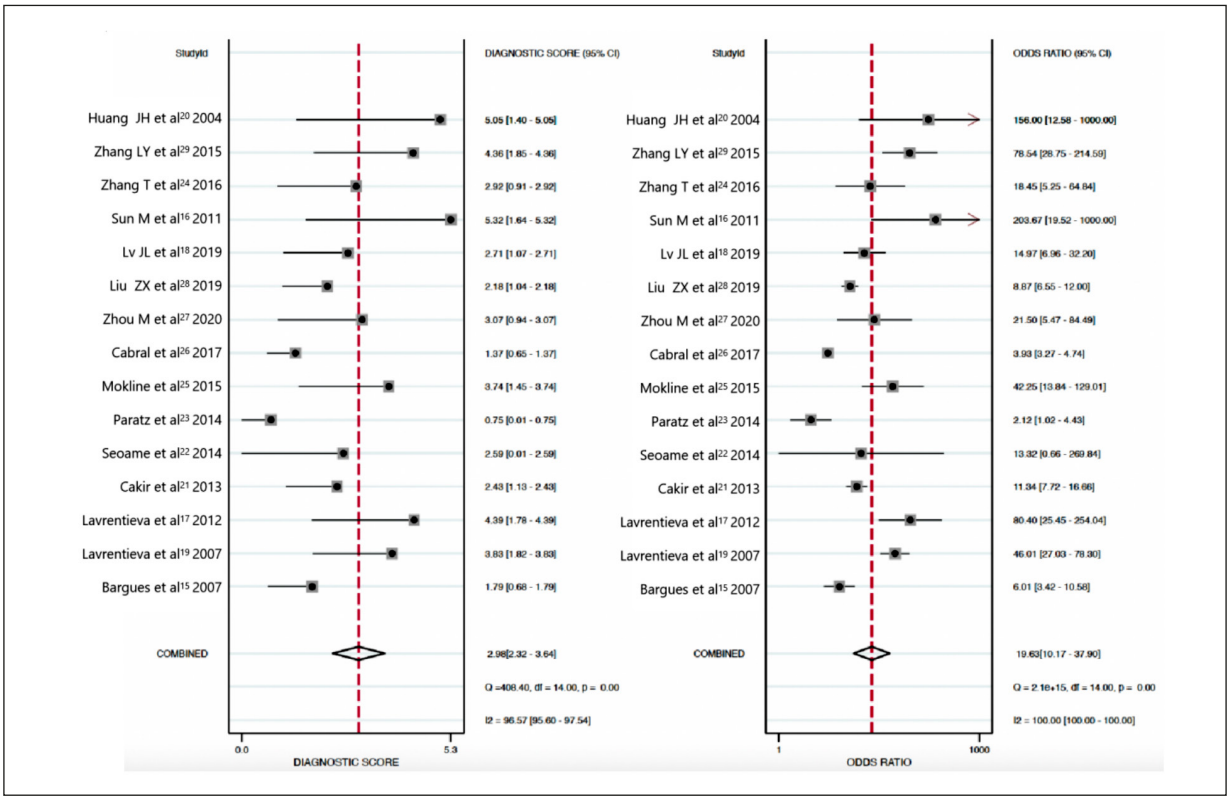


**Figure 6.** Forest plot of diagnostic score and diagnostic ratio of PCT for the diagnosis of burn sepsis in adults.

Deeks funnel plot suggested the presence of publication bias at $p$=0.01. Using the cut-and-patch method to explore the possible impact of this publication bias on the study results, the results showed that there was a statistically significant difference in the DOR before and after the cut-and-patch, indicating that the conclusions obtained herein were not heavily compromised by the publication bias of this meta-analysis (Figure 13 and 14).

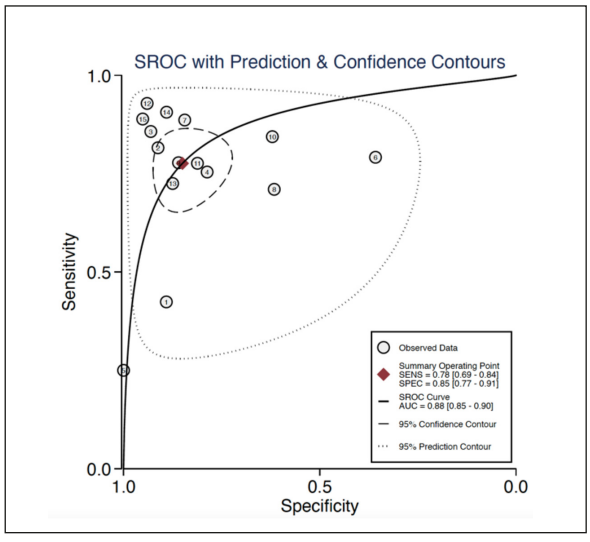


**Figure 7.** SROC curve for the accuracy of PCT in diagnosing burn sepsis in adults.

## Discussion

In this meta-analysis, a total of 15 studies were screened and included, and the QUADAS-2 scale was used to evaluate the quality of the above studies, among which 12 studies scored ≥10 points, indicating that the included studies in this institute were of good quality and could be continued for pooled analysis. The results showed that PCT for early diagnosis of burn sepsis in adults had a combined sensitivity of 0.78 (95% CI: 0.69-0.84), a combined specificity of 0.85 (95% CI: 0.77-0.91), a combined positive likelihood ratio of 5.17 (95% CI: 3.25-8.25), a combined negative likelihood ratio of 0.26 (95% CI: 0.19-0.37), a combined diagnostic ratio of 19.63 (95% CI: 10.17-37.90), and an AUC of 0.88

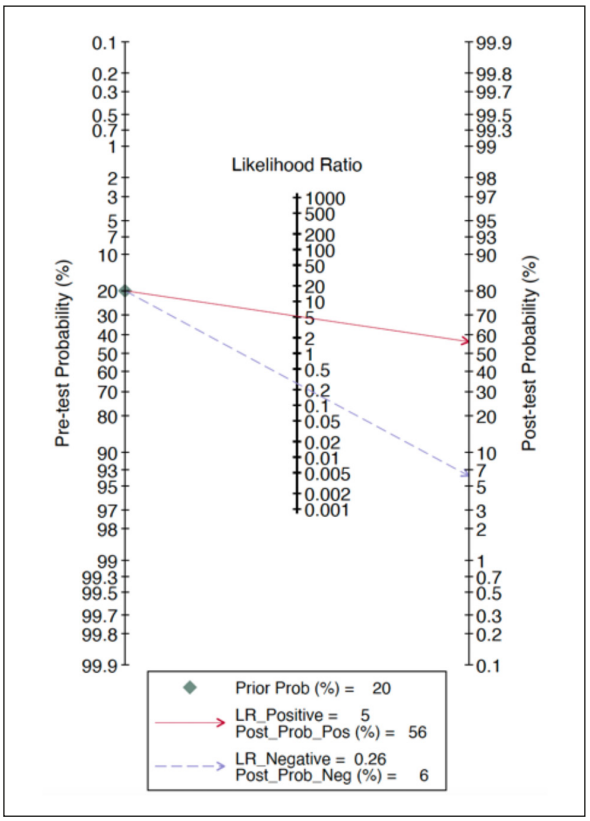


**Figure 8.** Fagan's plot for PCT diagnosis of burn sepsis in adults.

(95% CI: 0.85-0.90). The above results suggest that PCT offers a certain value for the early diagnosis of burn sepsis in adults, with the positive likelihood ratio in this study of 5.17 (<10) and the negative likelihood ratio of 0.26 (>0.1). Therefore, based on the literature included in the current analysis, evidence for the confirmatory and exclusionary value of PCT for burn sepsis in adults is still insufficient, which may be attributed to the low level of evidence in the included literature. Sensitivity analysis showed stable PCT diagnostic ratios, and exclusion of the included literature one by one resulted in no significant effect on the DOR. Meta-regression results suggest that study type may have implications for the sensitivity of early diagnosis of PCT, with the sensitivity of prospective studies being significantly higher than that of retrospective studies. Furthermore, publication bias was detected in the present study. The results of the cut-and-patch method showed that all DORs were statistically significantly different, indicating no major impact of publication bias on the conclusions drawn herein.

Cabral et al[30] found that PCT has a strong diagnostic ability to distinguish between septic and non-septic burn patients, with an overall pooled area under the curve of 0.83 and an estimated cut-off value of 1.47 ng/mL. Ren et al[31] conduct-

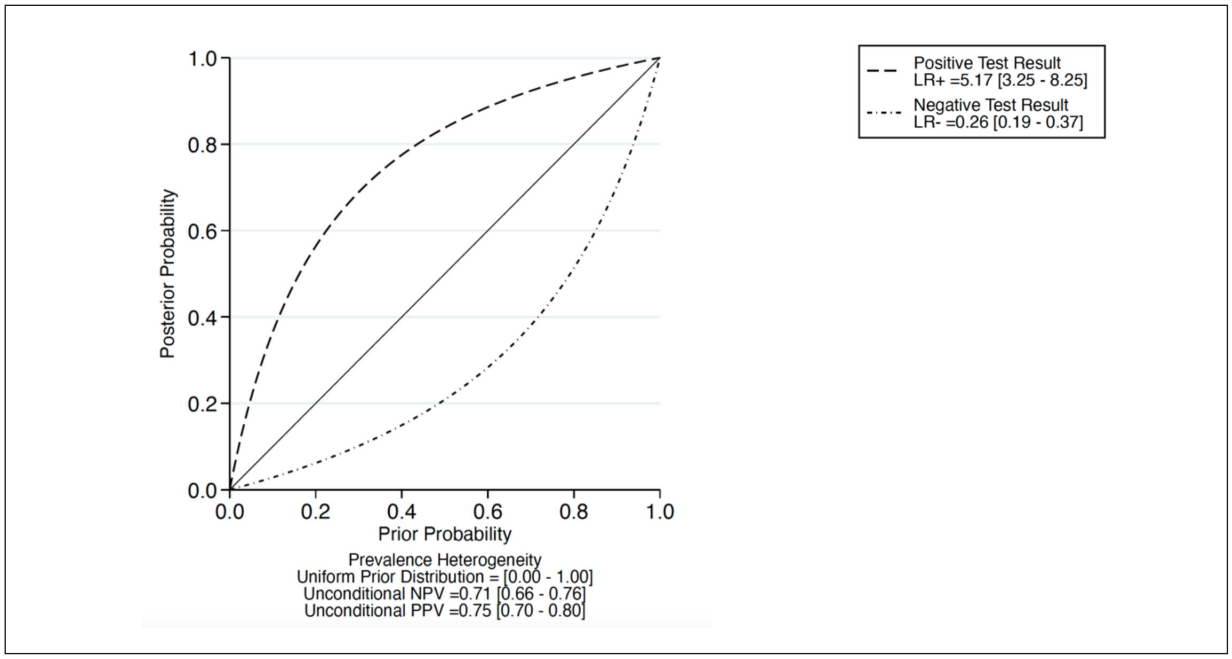


**Figure 9.** Line graph of the relationship between the post-test probability and the a priori probability of the positive likelihood ratio and the negative likelihood ratio for PCT diagnosis of burn sepsis in adults.

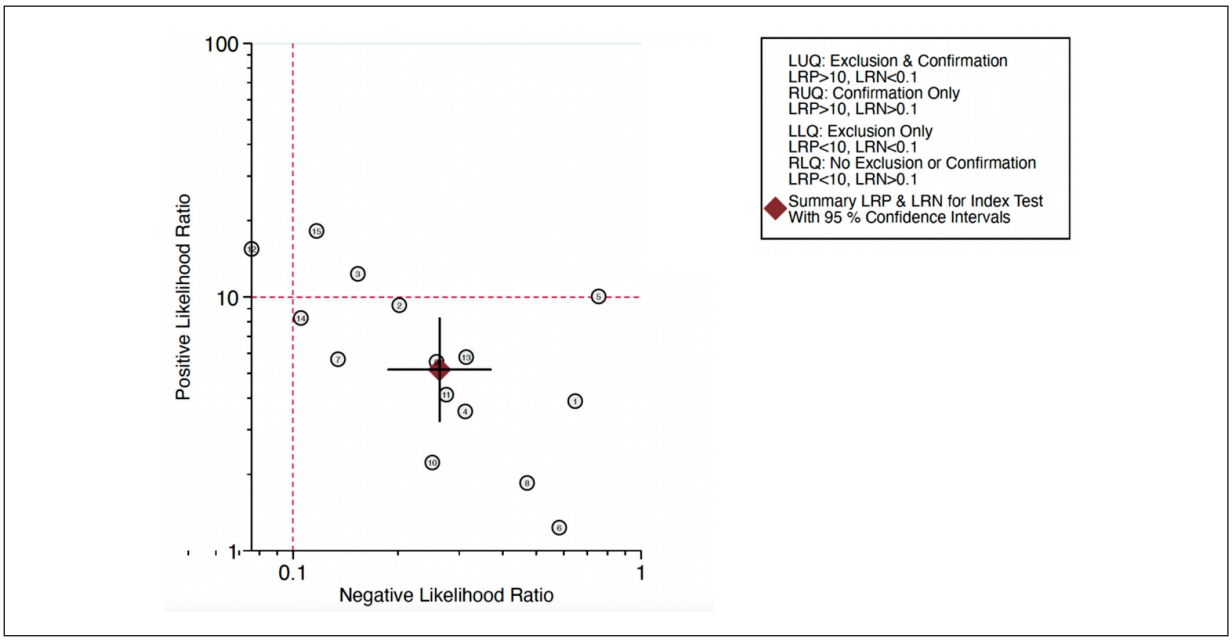


**Figure 10.** Quadrant distribution of positive likelihood ratio and negative likelihood ratio for PCT diagnosis.

ed a meta-analysis of clinical research results of 556 subjects in 9 studies and found that the AUC value of PCT in the diagnosis of burn sepsis was 0.92, indicating that PCT had good diagnostic value. Chen et al[32] found that the sensitivity, specificity, PLR, NLR and DOR of PCT in the diagnosis of burn sepsis were 0.67 (95% CI: 0.48-0.81), 0.87 (95% CI: 0.72-0.95), 5.20 (95% CI:

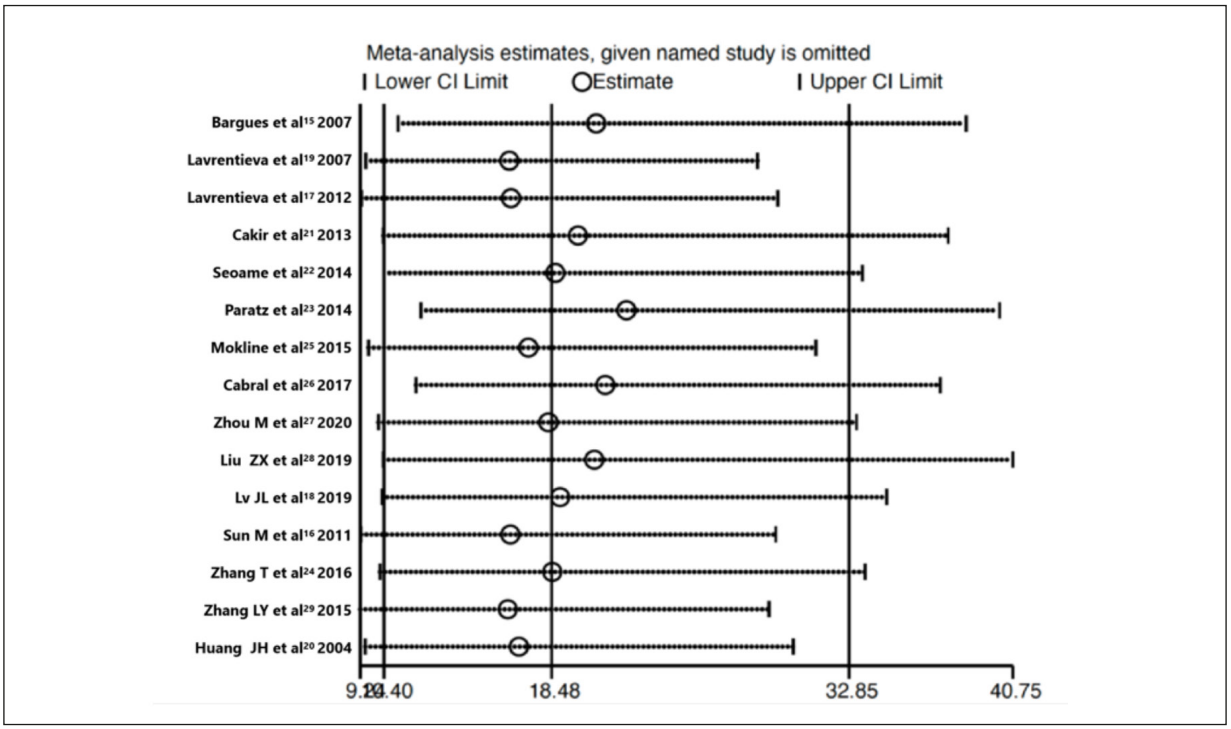


**Figure 11.** Sensitivity analysis of PCT diagnostic ratios.

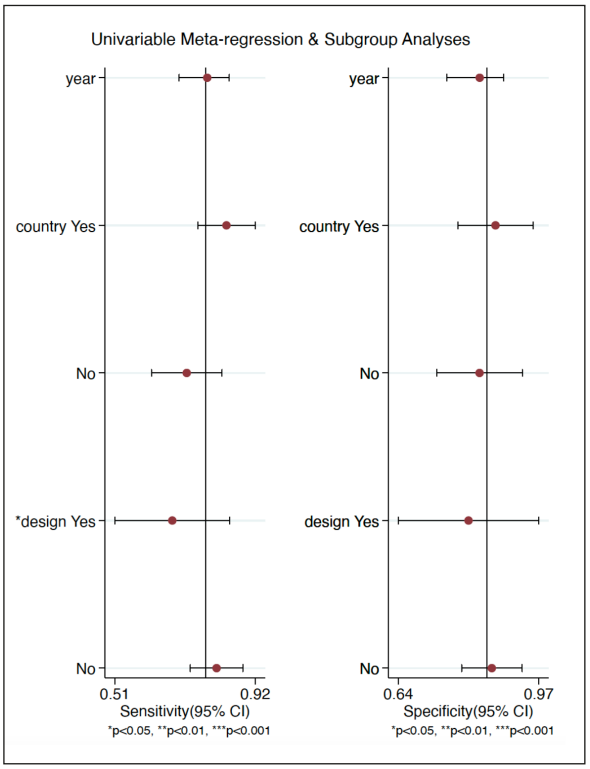


**Figure 12.** Meta-regression analysis.

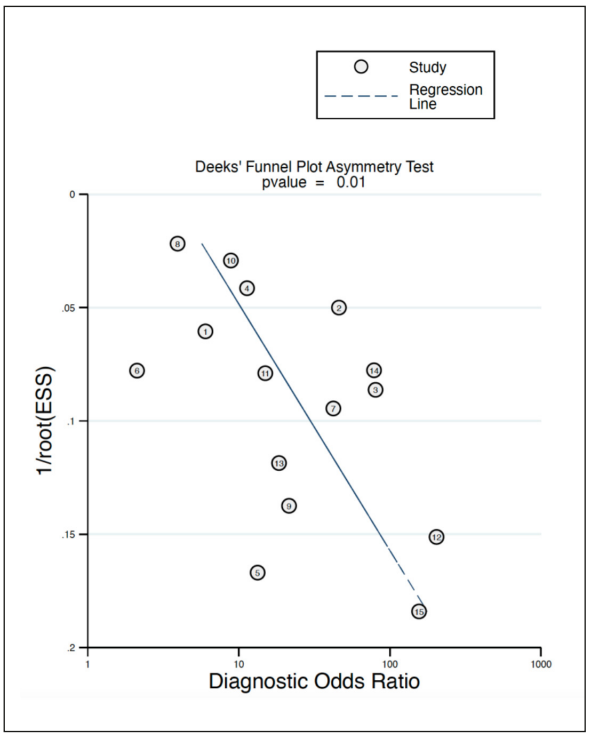


**Figure 13.** Publication bias.

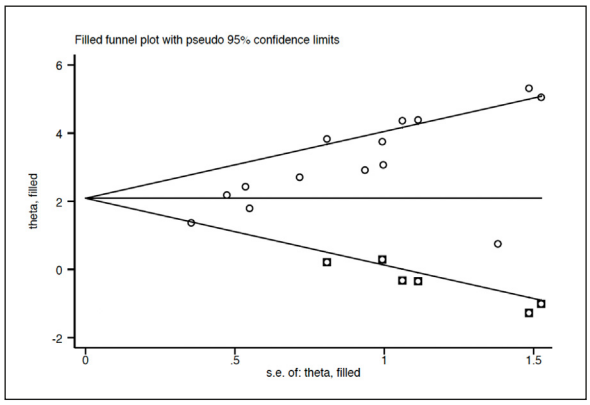


**Figure 14.** Cut-and-patch method.

2.49-10.84), 0.38 (95% CI: 0.24-0.61) and 13.70 (95% CI: 5.72-32.82), respectively, and the diagnostic AUC value was 0.85, indicating that PCT was of great significance in the early diagnosis of burn sepsis. In this study, we also reached a conclusion consistent with the above meta-analysis, namely, PCT has strong diagnostic value in the diagnosis of early burn sepsis, and can be used clinically in the future.

## Conclusions

Despite the high sensitivity, specificity, and AUC shown by PCT in the present meta-analysis, its positive likelihood ratio, and negative likelihood ratio failed to meet the requirements of diagnostic tests, which may be attributed to the insufficient level of evidence in the included literature. It has been suggested that PCT combined with interleukin-6 (IL-6) and C-reactive proteins (CRP) can improve the accuracy and reliability of early diagnosis of burn sepsis[32]. Therefore, clinical studies with higher levels of evidence and combining multiple indicators are expected to further enhance the diagnostic efficacy of burn sepsis.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

### PRISMA

The authors have read the PRISMA 2020 Checklist, and the manuscript was prepared and revised according to the PRISMA 2020 Checklist.

### Ethics Approval
Not applicable.

### Informed Consent
Not applicable.

### Availability of Data and Materials
All data generated or analysed during this study are included in this published article.

### Funding
None.

### Authors' Contribution
Conceptualization: YJZ, PD. Literature Search: YJZ, ZHG. Methodology: YJZ, ZHG, ZMH and PD. Data Extracted: YJZ, ZHG. Validation: YJZ, ZHG and ZGM. Formal analysis and investigation: YJZ, ZHG. Writing - original draft: YJZ, ZHG Writing - review and editing: ZMH, PD. Supervision: PD. All authors read and approved the final manuscript.

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