Diagnostic value of neutrophil CD64, procalcitonin, and interleukin-6 in sepsis: A meta-analysis

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Abstract

The aim of the study was to conduct a meta-analysis to evaluate the accuracy of neutrophil CD64, procalcitonin (PCT), and interleukin-6 (IL-6) for the diagnosis of sepsis. The sample articles were searched in various databases to collect published studies on the diagnosis of sepsis by neutrophil CD64, PCT, and IL-6. By using the Stata SE 15.0 software, forest plots and the area under the summary receiver operating characteristic curves were drawn. The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, and area under the curve (AUC) were calculated. 54 articles were included in the study. The number of studies that evaluated the diagnostic value of neutrophil CD64, PCT, and interleukin-6 were 20, 39, and 15, respectively. The pooled sensitivity, specificity, and AUC of neutrophil CD64 for the diagnosis of sepsis were 0.88 [95% confidence interval (CI), 0.81–0.92], 0.88 (95% CI, 0.83–0.91), and 0.94 (95% CI, 0.91–0.96), respectively. The pooled sensitivity, specificity, and AUC of PCT for the diagnosis of sepsis were 0.82 (95% CI, 0.78–0.85), 0.78 (95% CI, 0.74–0.82), and 0.87 (95% CI, 0.83–0.89), respectively. Subgroup analysis showed that the AUC for PCT diagnosis of intensive care unit (ICU) sepsis was 0.86 (95% CI, 0.83–0.89) and the AUC for PCT diagnosis of non-ICU sepsis was 0.82 (95% CI, 0.78–0.85). The pooled sensitivity, specificity, and AUC of IL-6 for the diagnosis of sepsis were 0.72 (95% CI, 0.65–0.78), 0.70 (95% CI, 0.62–0.76), and 0.77 (95% CI, 0.73–0.80), respectively. Of the three biomarkers studied, neutrophil CD64 showed the highest diagnostic value for sepsis, followed by PCT, and IL-6. On the other hand, PCT showed a better diagnostic value for the diagnosis of sepsis in patients with severe conditions compared with that in patients with non-severe conditions.

Background

In recent years, the incidence and mortality of sepsis have increased significantly due to the increase of drug-resistant bacteria, the widespread use of antibiotics, and the aging of the population. The latest epidemiological study, including septicemia cases in 195 countries around the world, showed that in 2017 there were 48.9 million sepsis patients and 11 million deaths from sepsis worldwide, which was equivalent to 19.7% of total deaths throughout the year [1]. The definition of sepsis has been updated three times. In 1991, the American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM) first defined sepsis as the systemic inflammatory response syndrome (SIRS) caused by infection, named Sepsis 1.0 [2]. However, when applying it to clinical practice, it was found that the definition included a wide range of contents, which made many non-specific diseases included in sepsis, and its defect was low specificity, which might cause excessive diagnosis of sepsis. At the 2001 Washington Conference, the Sepsis 2.0 definition was jointly launched by the SCCM, the European Society of Intensive Care Medicine (ESICM), the ACCP, the American Thoracic Society (ATS), and the Surgical Infection Society (SIS). The definition was based on Sepsis 1.0, and the PIRO system for sepsis was developed using the TNM tumor staging method. It mainly includes the following four aspects: predisposition (P), insult infection (I), response (R), and organ dysfunction (O) [3]. Nevertheless, its diagnosis is too complicated, clinical application is poor, and it has a lack of sufficient research foundation and scientific research evidence support. In 2016, the SCCM and ESICM jointly issued the definition of Sepsis 3.0 with the body’s dysregulation by the infection and organ dysfunction as the core, defining sepsis as the life-threatening organ dysfunction caused by dysregulation of the host’s response to infection [4]. At the same time, the diagnostic criteria for sepsis were proposed. For patients with ICU infection or suspected infection, sepsis is diagnosed when the sequential organ failure assessment (SOFA) score is ≥ 2 [5]. However, considering the limitations of the diagnostic criteria and the lack of clinically relevant data in many patients, a simplified method was proposed, named “quick SOFA”, (also known as “qSOFA”), that includes a systolic blood pressure ≤ 100 mmHg, a respiratory frequency ≥ 22 times/min, or change of consciousness. When there are two or more score exceptions, this can be considered a high-risk sepsis population [6]. However, Williams et al. [7] found that although qSOFA score was highly specific, its sensitivity was poor, which might not be suitable for early diagnosis of sepsis. Although blood culture is an important tool for sepsis diagnosis that identifies pathogenic bacteria and allows antibiotic susceptibility testing, it is a time-consuming protocol and has a high false-negative rate, especially after antibiotic use [8]. Therefore, the blood culture alone is not enough to assist clinicians to make accurate early diagnosis in patients with sepsis. According to statistics, if sepsis patients can be correctly diagnosed and treated within 1 hour of infection, their survival rate will reach more than 80%, whereas if patients are diagnosed and treated after 6 hours of infection, their survival rate drops to 30% [9]. Therefore, it is crucial to find a biomarker for the early diagnosis of sepsis.

Neutrophil CD64 is the Fc portion of a high-affinity receptor. Neutrophil CD64 is a member of the immunoglobulin superfamily and is mainly found in the antigen-presenting cells, such as monocytes, macrophages, and dendritic cells. The receptor is located on the cell surface and its expression is regulated by cytokines. When the body is infected, or a large number of bacterial endotoxins are present, neutrophils are exposed to lipopolysaccharides (LPS), complement system molecules, IL-8, IL-12, IFN-γ, TNF-α, granulocyte colony-stimulating factor, and other cytokines. Such molecules stimulate the expression of CD64 on neutrophils and they remain stable for a certain period of time [10]. Although neutrophil CD64 expression is low on resting neutrophils, the stimulating factor-activated CD64 increases rapidly, and its expression level can be rapidly increased 10-fold, reaching a peak within 4 to 6 hours. The basal expression is achieved 7 days after the stimulation disappears [11]. Neutrophil CD64 is relatively stable in blood samples studied in vitro and is easily detected by flow cytometry. The stable characteristics of neutrophil CD64 make it suitable as a diagnostic indicator.

Biomarkers procalcitonin (PCT) and interleukin-6 (IL-6) have been widely used in the diagnosis and identification of infections. Under normal physiological conditions, PCT is produced almost exclusively in thyroid C cells. Induced by the stimulation of glucocorticoids, calcitonin gene-related peptide, glucagon, gastrin, or β-adrenergic signaling, PCT is converted into calcitonin before entering the circulatory system. Healthy individuals usually show very low levels of serum PCT (< 0.02 ng/mL). PCT is a very stable protein in vitro and in vivo, with a half-life of about 20-24 h [12, 13]. Patients with infections can produce PCT through an alternative pathway in non-thyroid tissue. There are two main alternative pathways: the direct pathway, induced by LPS or other toxic microbial metabolites, and the indirect pathway, induced by several inflammatory mediators such as IL-6 and TNF-α [14]. Due to the lack of pathways to convert PCT to calcitonin, PCT enters the circulatory system and its levels can rapidly increase more than 400-fold (> 4.0 ng/mL) compared to basal levels [15].

IL-6 is an important pro-inflammatory factor in the initial stage of inflammation. It induces multiple cells to synthesize and secrete acute phase proteins; promotes the production and activation of neutrophils during infection; promotes the proliferation and differentiation of B cells; produces immunity globulins;
promotes T cell proliferation and differentiation\textsuperscript{[14]}. The levels of IL-6 in healthy people are extremely low, generally not exceeding 7 pg/mL, whereas the levels of IL-6 in the serum of sepsis patients increases rapidly in the early stage of infection, and can reach a peak within 2 hours\textsuperscript{[17]}. The aim of our study was to integrate the clinical studies to compare the diagnostic accuracy of neutrophil CD64, PCT, and IL-6 for sepsis by meta-analysis.

\section*{Materials And Methods}

\subsection*{Study Selection}

The articles were manually retrieved from PubMed, Web of Science, Medline, The Cochrane Library, Wan Fang, China Biology Medicine, China National Knowledge Infrastructure, and VIP databases, by searching all publications from the earliest entries to December 2018. Languages were English and Chinese. Firstly, the studies were chosen based on the following subject terms: sepsis, neutrophil CD64, procalcitonin, Interleukin-6, and diagnosis. Then, a relevant-free terms search was carried out, and finally, the two search strategies were combined. Additionally, the references cited in the retrieved articles were also manually retrieved as supplements. Endnote version X7.8 was used for reference management. Two researchers carried out the same search independently, and in case of disagreement, a third researcher was involved to discuss the results and reach an agreement.

\subsection*{Inclusion and exclusion criteria}

Inclusion Criteria: 1. Studies focused on the diagnostic value of neutrophil CD64, PCT and IL-6 for sepsis; 2. The observation group included adult sepsis patients, aged $\geq 18$ years old. The control group included patients or healthy people in the same period; 3. Diagnostic criteria: clinical diagnostic criteria (Sepsis 1.0, Sepsis 2.0, and Sepsis 3.0) or blood culture; 4. Prospective or retrospective studies; 5. True positive (TP), false positive (FP), true negative (TN) or false negative (FN) results for neutrophil CD64, PCT and IL-6 in the diagnosis of sepsis could be obtained directly or calculated from data.

Exclusion Criteria: 1. Abstracts, conference reports, summaries, and comments; 2. TP, FP, TN, and FN cannot be obtained according to the reported data. 3. Repeated research subjects.

\subsection*{Quality Assessment}

We used the diagnostic test system evaluation tool Quality Assessment for Diagnostic Accuracy Studies-2 (QUADAS-2) from the Review Manager 5.3 software to assess the quality of all included articles. The QUADAS-2 scale includes four parts: case selection, trial to be evaluated, gold standard, and case process and progress.

\subsection*{Data Extraction}

The research data extraction was independently completed by two researchers. If the extraction results of the two were inconsistent, the third researcher and the first two jointly studied and decided. The data extraction information included the first author, publication time, country, study design, diagnostic criteria, clinical setting, sample size, average age, test method, TP FR FN, TN, sensitivity, and specificity.

\subsection*{Statistical Analysis}

This study was a diagnostic meta-analysis. The heterogeneity of the included articles was carried out to select the appropriate statistical model to help reduce the errors during data merging. The heterogeneity between the included studies was evaluated by calculating the chi-square test value and the $I^2$ statistics. If the $I^2 \leq 50 \%$, $P \geq 0.05$, the heterogeneity of the included studies was deemed small, and the fixed effect model was used to merge the statistical data. If the $I^2 > 50 \%$, $P < 0.05$, the heterogeneity was significant, and data were merged by the random effect model. The indexes included sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR). Additionally, a summary receiver operating characteristic (SROC) curve was drawn to calculate the area under the curve (AUC). The closer the AUC value was to 1, the higher the clinical diagnostic efficacy of this index was. The Deeks’ test was used to assess publication bias in the included articles. We used meta-regression, sensitivity analysis, and subgroup analysis to explore the sources of heterogeneity. We used Fagan’s nomogram to evaluate the post-test probabilities of the three studied biomarkers in sepsis. MetaDisc 1.4 software and STATA 12.0 were used for data analysis.

\section*{Results}

\subsection*{Literature Search}

In all, 10,026 articles in Chinese and English were retrieved through the preliminary screening of the databases. After reading the titles and abstracts, 300 articles were selected. Intensive reading was performed following strictly the inclusion and exclusion criteria. After the screening, a set of 54 articles were included in the study (Figure 1).

\section*{Study Characteristics}
In all, 9,842 participants were finally enrolled in this meta-analysis, with a sepsis prevalence of 54.8%. It included 20 studies related to neutrophil CD64, 39 studies related to PCT, and 15 studies related to IL-6. We found 37 articles that reported the average age of the study subjects, ranging from 42.0 to 92.6 years. Four papers focused on patients with specific sepsis, such as patients with acute abdominal sepsis, ventilator-associated pneumonia, and postoperative sepsis. Two articles addressed elderly patients with sepsis (aged > 65 and > 85 years), whereas another study included patients aged ≤ 65 and > 65 years. Two studies reported separately cases of positive and negative blood cultures. One paper included a study conducted in the medical ICU and surgical ICU patients. The detailed baseline characteristics of the included studies are summarized in Table 1.

Quality Assessment

We used the QUADAS-2 scale to evaluate the quality of the included articles. The results showed that all studies were of high quality and had clinical practicability (Figure 2).

Heterogeneity test

Spearman correlation coefficients of neutrophil CD64, PCT and IL-6 were -0.22 (P = 0.35), -0.054 (P = 0.729) and 0.326 (P = 0.217), respectively. The SROC curve of the three biomarkers did not show a significant shoulder-arm effect, suggesting that there was no threshold effect (Figure 3).

Pooled effect size result

Of all included articles, 20 of them reported the diagnostic value of neutrophil CD64 for sepsis. The results for these studies were: pooled sensitivity, 0.88 (95% CI, 0.81–0.92); pooled specificity, 0.88 (95% CI, 0.83–0.91) (Figure 4); pooled PLR, 7.2 (95% CI, 5.0–10.3); pooled NLR, 0.14 (95% CI, 0.09–0.22); pooled DOR, 51 (95% CI, 25–105); and the AUC was 0.94 (95% CI, 0.91–0.96) (Figure 3a). Thirty-nine studies reported the diagnostic value of PCT with the following results: pooled sensitivity, 0.82 (95% CI, 0.78–0.85); pooled specificity, 0.78 (95% CI, 0.74–0.82) (Figure 5); pooled PLR, 3.7 (95% CI, 3.1–4.50); pooled NLR, 0.23 (95% CI, 0.19–0.29); pooled DOR, 16 (95% CI, 11–23); and the AUC was 0.87 (95% CI, 0.83–0.89) (Figure 3b). We found 15 articles reporting the diagnostic value of IL-6 for sepsis. The results for this set of articles were: pooled sensitivity, 0.72 (95% CI, 0.65–0.78); pooled specificity, 0.70 (95% CI, 0.62–0.76) (Figure 6); pooled PLR, 2.4 (95% CI, 1.9–3.0); pooled NLR, 0.40 (95% CI, 0.32–0.51); pooled DOR, 6 (95% CI, 4.0–9.0); and the AUC was 0.77 (95% CI, 0.73–0.80) (Figure 3c).

Publication bias analysis

Publication bias of studies regarding neutrophil CD64 showed that 20 articles were not evenly distributed on both sides of the regression line (t = 2.45, P = 0.025) (Figure 7a), suggesting a publication bias among the included studies. No significant bias was found for studies addressing PCT (t = 1.17, P = 0.249) (Figure 7b) or IL-6 (t = 0.53, P = 0.607) (Figure 7c).

Heterogeneity analysis

Meta-regression

Due to the heterogeneity caused by a non-threshold effect in the included studies, meta-regression was performed when the following criteria were met: a sample size of the study over 100; the patients were Chinese; the average age of patients was over 65 years old; the clinical setting was classified into ICU; and test methods. The meta-regression of neutrophil CD64 showed that the sample size had an influence on the heterogeneity of sensitivity and specificity, and regional difference was one of the factors that caused the heterogeneity of specificity (Figure 8a). The meta-regression of PCT showed that the above five factors are likely to be the sources of heterogeneity (Figure 8b). The meta-regression result of IL-6 indicated that the source of heterogeneity might be the sample size (Figure 8c).

Sensitivity analysis

Concerning the sensitivity analysis of neutrophil CD64, we found that when the article by Gámez-Díaz study was removed from the subset of studies, the overall heterogeneity of specificity of the 19 articles left decreased, suggesting that the Gámez-Díaz study was the cause for the heterogeneity of specificity (Figure 9a). When the other 19 studies were removed one by one, the sensitivity, specificity, and AUC showed no significant change. The sensitivity analysis of PCT and IL-6 showed that the sensitivity, specificity, and AUC did not change significantly when they were removed one by one (Figure 9b, 9c).

Subgroup analysis

Through a sensitivity analysis of neutrophil CD64, it was found that the Gámez-Díaz study had an influence on the heterogeneity of neutrophil CD64, so a subgroup analysis was conducted after excluding such study. The subgroup analysis of three biomarkers (Tables 2, 3, 4) indicated that the sample size might be the source of heterogeneity, since the heterogeneity decreased significantly in the group when a small sample size was analyzed, which might be due to the
large number of included cases, and a lack of consistency. The subgroup analysis of neutrophil CD64 indicated that regional differences were also a source of heterogeneity, which was consistent with the meta-regression results. Heterogeneity decreased significantly in the Chinese group but remained high in the non-Chinese group. The subgroup analysis showed that the sensitivity, specificity, and AUC of PCT in ICU patients were 0.82 (95% CI, 0.77–0.86), 0.78 (95% CI, 0.72–0.82), and 0.86 (95% CI, 0.83–0.89), respectively; and the SEN, SPE, and AUC of PCT in non-ICU patients were 0.77 (95% CI, 0.72–0.82), 0.74 (95% CI, 0.64–0.81), and 0.82 (95% CI, 0.78–0.85), respectively; suggesting that the diagnostic value of PCT in the ICU group was higher than that in the non-ICU group.

Clinical utility evaluation

We assumed a pre-test probability of 50%. The Fagan's nomogram of neutrophil CD64 (Figure 10a) showed a post-test probability of 88% positive and 12% negative. The Fagan's nomogram of PCT (Figure 10b) showed a post-test probability of 79% positive and of 19% negative, whereas the Fagan's nomogram of IL-6 (Figure 10c) showed a post-test probability of 70% positive and of 29% negative.

Discussion

Our results showed that neutrophil CD64 had the highest diagnostic value for sepsis with a pooled sensitivity of 0.88 (95% CI, 0.81–0.92); pooled specificity of 0.88 (95% CI, 0.83–0.91); and AUC of 0.94 (95% CI, 0.91–0.96), followed by PCT, with a pooled sensitivity of 0.82 (95% CI, 0.78–0.85); pooled specificity of 0.78 (95% CI, 0.74–0.82); and AUC of 0.87 (95% CI, 0.83–0.89). Of all three studied biomarkers, IL-6 showed the weakest diagnostic value for sepsis, with a pooled sensitivity of 0.72 (95% CI, 0.65–0.78), the pooled specificity of 0.70 (95% CI, 0.62–0.76), and AUC of 0.77 (95% CI, 0.73–0.80).

In 2006, Davis et al. [24] reported for the first time the diagnostic potential of neutrophil CD64 in sepsis patients through a retrospective review of 100 blood samples and showed that the performance of neutrophil CD64 was better than white blood cell count, erythrocyte sedimentation, and C-reactive protein as a sepsis diagnostic marker. In the past 10 years, some prospective studies have shown the clinical value of CD64 in the diagnosis of sepsis. In previous studies, Hsu et al. [29] found that the accuracy of neutrophil CD64 was better than PCT in respiratory intensive care unit patients to distinguish systemic inflammatory response syndrome from severe sepsis and septic shock. Neutrophil CD64 was also found to be associated with mortality. However, some studies criticized the diagnostic value of neutrophil CD64 in sepsis. Gros et al. [32] showed that neutrophil CD64 has a low sensitivity in the diagnosis of sepsis in ICU or emergency department patients. However, due to its high specificity, when combined with other sensitive markers, it may contribute to the clinical diagnosis of sepsis. In 2016, Wang et al. [73] conducted a meta-analysis with 8 studies written in English, to assess the value of neutrophil CD64 for the diagnosis of sepsis. The results showed that the pooled sensitivity, specificity, and AUC were 0.76, 0.85, and 0.95 respectively, which suggested that neutrophil CD64 had a high specificity for sepsis. However, because of its low sensitivity, it couldn't be used alone in the diagnosis of sepsis. Our meta-analysis searched publications in more databases than other published meta-analysis, more comprehensive clinical research data was collected, and the results were more persuasive. In our study, 20 studies were included, showing that the neutrophil CD64 test has a high sensitivity and specificity in adult sepsis patients, and was superior to the traditional biomarkers PCT and IL-6. Li et al. [74] carried out a meta-analysis to evaluate the diagnostic value of CD64 in infectious diseases, including adults and newborns. The results showed that the pooled sensitivity, specificity, SROC curve, and AUC were 0.76, 0.85, and 0.92 respectively, which suggested that the neutrophil CD64 had a high specificity in sepsis. Due to the uniqueness of neonate sepsis in many aspects, our study only included studies on adult sepsis patients. We used meta-regression, subgroup analysis, and sensitivity analysis to explore the heterogeneity of data, and we found that the sample size and the country of study are contributing factors for heterogeneity. The sensitivity analysis should that the heterogeneity decreased significantly when Gámez-Díaz et al. [28] study was omitted. The sample size of this study was the largest among all included studies, and the study results were negative, which could lead to an increase in heterogeneity. Through the subgroup analysis of the articles, we found that PCT in the ICU group has a higher diagnostic efficacy for sepsis than that in the non-ICU group. The study of Yunus et al. [75] found that PCT was positively correlated with the severity of sepsis. Because the proportion of patients with severe sepsis and septic shock among ICU patients was large, the PCT in the ICU patients showed a better diagnostic efficiency. PCT had a better diagnostic value in critically ill patients than in non-severe patients. Future research on this subject should expand the scope, to overcome the existing publication bias.

Limitations:

Our research is limited by some factors. Firstly, the heterogeneity in the study is high. Although some sources of heterogeneity have been found through meta-regression, sensitivity analysis, and subgroup analysis, there are still other unidentified sources. Secondly, there is a publication bias in the analysis of the diagnosis accuracy of sepsis by neutrophils CD64. In the follow-up of this study, the scope should be expanded to overcome the publication bias. Thirdly, only Chinese and English language literature was included, which might exclude relevant data. Fourthly, due to the different test methods for the three biomarkers, the cut-off values varied between the included studies. Future studies are needed to determine the optimal cut-off value of biomarkers that confers the diagnostic value for sepsis.

Conclusions

Among the three biomarkers, neutrophil CD64 has the highest diagnostic value for sepsis, followed by PCT and IL-6. In the diagnosis of sepsis, the diagnostic value of PCT in severe patients is better than that in non-severe patients.

Abbreviations

AUC, area under the curve
Declarations

Ethics approval and consent to participate

Ethics approval was not applicable for this meta-analysis.

Availability of data and materials

All relevant data supporting the conclusion of this study are included within the paper.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SC and KW are the primary authors who are responsible for the entire project. TM and CT contributed to the systematic literature review and database search. XD and MZ performed the data collection and reference search. SC and TM analyzed the data and drafted the writing of the manuscript. KW drafted the first revision of the manuscript. All authors approved the interpretation of the results and took part in the final revision of the manuscript.

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Tables

Table 1. Baseline characteristics of included studies in the meta analysis.
| first author | publication time | country | study design | diagnostic criteria | clinical setting | Biomarker | sample size | TP | FP | FN | TN | SEN (%) | S |
|--------------|------------------|---------|--------------|---------------------|------------------|-----------|-------------|-----|-----|----|-----|----------|---|
| Anand [18]a | 2015             | India   | PS           | culture+            | ICU              | PCT       | 118         | 68  | 6  | 4  | 40  | 94.4     | 8 |
| Anand [18]b | 2015             | India   | PS           | clinical,culture-  | ICU              | PCT       | 136         | 83  | 13 | 7  | 33  | 92.2     | 7 |
| Bauer [19]  | 2016             | America | PS           | clinical           | ICU              | PCT       | 216         | 88  | 25 | 32 | 71  | 73.1     | 7 |
| Cardelli [20]| 2008             | Italy   | PS           | clinical,culture+  | ICU              | CD64      | 196         | 84  | 20 | 26 | 66  | 76.4     | 7 |
| Castelli [21]| 2004             | Italy   | PS           | clinical,culture+  | ICU              | PCT       | 112         | 50  | 5  | 2  | 55  | 96.6     | 9 |
| Cheva [22]  | 2000             | France  | PS           | clinical           | ICU              | PCT       | 60          | 28  | 5  | 4  | 23  | 87.5     | 8 |
| Clec'h [23]a| 2006             | France  | PS           | clinical           | SICU             | PCT       | 67          | 28  | 9  | 3  | 27  | 91.7     | 7 |
| Clec'h [23]b| 2006             | France  | PS           | clinical           | MICU             | PCT       | 76          | 29  | 2  | 7  | 38  | 80.6     | 9 |
| Davis [24]  | 2006             | America | RS           | clinical,culture+  | ED               | CD64      | 100         | 33  | 18 | 5  | 44  | 86.8     | 7 |
| Dimoula [25]| 2014             | Belgium | PS           | clinical           | ICU              | CD64      | 468         | 92  | 47 | 11 | 318 | 89.3     | 8 |
| Du [26]     | 2003             | China   | PS           | clinical           | ICU              | PCT       | 51          | 16  | 8  | 4  | 23  | 80.0     | 7 |
| Fung [27]   | 2012             | China   | PS           | clinical           | ICU              | PCT       | 132         | 69  | 12 | 33 | 18  | 74.6     | 6 |
| Gaini [28]  | 2006             | Denmark | PS           | clinical           | GW               | PCT       | 93          | 56  | 9  | 18 | 10  | 75.7     | 5 |
| Gamez-Diaz  | 2011             | Colombia| PS           | clinical           | ED               | CD64      | 610         | 266 | 73 | 138| 133 | 65.8     | 6 |
| Gerrits [30]| 2013             | Nether- lands | PS     | clinical         | ICU              | CD64      | 44          | 25  | 1  | 0  | 18  | 100.0    | 9 |
| Gibot [31]  | 2012             | France  | PS           | clinical           | ICU              | CD64      | 300         | 130 | 7  | 24 | 139 | 84.4     | 9 |
| Gros [32]   | 2012             | France  | PS           | clinical,culture+ | MICU             | CD64      | 293         | 93  | 16 | 55 | 129 | 62.8     | 8 |
| Gupta [33]a | 2018             | India   | PS           | culture+           | ICU              | PCT       | 242         | 193 | 5  | 3  | 41  | 98.5     | 8 |
| Gupta [33]b | 2018             | India   | PS           | clinical,culture- | MICU             | PCT       | 109         | 55  | 10 | 8  | 36  | 87.3     | 7 |
| Harbarth [34]| 2001             | Switzerland | PS    | clinical           | ICU              | PCT       | 78          | 58  | 4  | 2  | 14  | 97.0     | 7 |
| Hausfater [35]| 2002            | France  | PS           | clinical           | ICU              | PCT       | 195         | 42  | 15 | 26 | 112 | 61.8     | 8 |
| Hsu [36]    | 2011             | China   | PS           | clinical,culture+ | RICU             | CD64      | 66          | 49  | 1  | 6  | 10  | 89.9     | 9 |
| Ivancevic [37]| 2008            | Serbia  | PS           | culture+           | ED               | PCT       | 98          | 42  | 15 | 26 | 127 | 72.4     | 6 |
| Jämsä [38] | 2015             | Finland | PS           | clinical           | ICU              | CD64      | 42          | 27  | 1  | 0  | 14  | 100.0    | 9 |
| Jekar [39]  | 2012             | Korea   | PS           | clinical           | ICU              | PCT       | 177         | 58  | 13 | 20 | 86  | 74.4     | 8 |
| Kofoed [40]| 2007             | Denmark | PS           | clinical,culture+ | ED/GW            | PCT       | 151         | 77  | 23 | 19 | 32  | 80.2     | 5 |
| Year | Country | Study Design | Setting | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 | Test 6 | Test 7 |
|------|---------|--------------|---------|--------|--------|--------|--------|--------|--------|--------|
| 2010 | Spain   | PS clinical  | ICU     | 114    | 53     | 5      | 19     | 37     | 73.6   | 8:     |
| 2015 | UK      | RS clinical+ | ICU     | 153    | 43     | 12     | 20     | 58     | 51.8   | 8:     |
| 2016 | Malaysia| PS clinical  | ICU     | 239    | 93     | 20     | 71     | 55     | 57     | 7:     |
| 2011 | Netherlands | PS clinical+ | ICU     | 76     | 31     | 9      | 1      | 35     | 97     | 8:     |
| 2014 | Italy   | PS clinical  | ICU     | 50     | 13     | 10     | 3      | 24     | 81     | 7:     |
| 2000 | Switzerland | PS clinical | MICU    | 101    | 53     | 3      | 6      | 39     | 89.8   | 9:     |
| 2016 | Slovenia | PS clinical+ | ICU     | 32     | 25     | 1      | 0      | 6      | 100    | 8:     |
| 2015 | Greece  | PS clinical+ | ICU     | 66     | 24     | 3      | 5      | 34     | 83     | 9:     |
| 2014 | Italy   | PS clinical+ | ICU     | 93     | 55     | 1      | 6      | 31     | 90.1   | 9:     |
| 2002 | Switzerland | PS clinical+ | ICU     | 208    | 110    | 24     | 52     | 22     | 67.9   | 4:     |
| 2000 | Germany | PS clinical+ | ICU     | 33     | 19     | 5      | 3      | 6      | 86     | 5:     |
| 2017 | Iran    | PS culture+  | ICU     | 192    | 76     | 18     | 16     | 82     | 82.6   | 8:     |
| 2017 | Iran    | PS culture+  | ICU     | 184    | 58     | 30     | 26     | 70     | 69.1   | 7:     |
| 2018 | Italy   | PS clinical+ | ICU/GW  | 159    | 60     | 1      | 49     | 49     | 55     | 9:     |
| 2000 | France  | PS clinical+ | ICU     | 95     | 49     | 6      | 26     | 14     | 65.3   | 7:     |
| 2014 | Iran    | PS clinical  | ED      | 100    | 44     | 14     | 6      | 36     | 88.8   | 7:     |
| 2016 | Malaysia| PS clinical+ | ED      | 51     | 34     | 1      | 8      | 8      | 80.9   | 8:     |
| 2002 | Netherlands | PS culture+ | ED      | 342    | 49     | 120    | 6      | 167    | 89.1   | 5:     |
| 2012 | America | PS clinical+ | ED      | 336    | 168    | 33     | 79     | 56     | 68     | 6:     |
| 2013 | China   | RS culture+  | ICU     | 586    | 100    | 162    | 20     | 304    | 83.3   | 6:     |
| 2017 | China   | PS clinical  | ICU     | 70     | 36     | 6      | 14     | 14     | 72     | 7:     |
| 2012 | China   | PS clinical  | ICU     | 72     | 40     | 3      | 9      | 20     | 82.3   | 8:     |
| 2016 | China   | PS clinical  | ICU     | 420    | 111    | 35     | 19     | 255    | 85.1   | 8:     |
| 2014 | China   | PS clinical  | ICU/RD  | 87     | 63     | 4      | 6      | 14     | 91.3   | 7:     |
| 2017 | China   | PS clinical  | ICU     | 221    | 74     | 24     | 15     | 108    | 83.2   | 8:     |
| 2016 | China   | PS clinical  | ICU     | 221    | 67     | 77     | 22     | 55     | 75.3   | 4:     |
| 2013 | China   | PS clinical  | ICU     | 149    | 84     | 6      | 8      | 51     | 91.3   | 8:     |
| 2009 | China   | PS clinical  | ICU/HD  | 68     | 57     | 1      | 1      | 9      | 98.3   | 9:     |
| 2012 | China   | PS clinical  | ICU     | 55     | 30     | 5      | 5      | 15     | 85.7   | 7:     |
Table 2. Subgroup analysis of CD64 in the diagnosis of sepsis

| category | studies | SEN (95% CI) | SPE (95% CI) | DOR (95% CI) | AUC (95% CI) | SEN-τ² (%) | SPE-τ² (%) |
|----------|---------|--------------|--------------|--------------|--------------|-------------|-------------|
| overall  | 19      | 0.89 [0.82, 0.93] | 0.88 [0.84, 0.92] | 59 [30, 115] | 0.94 [0.91, 0.96] | 90.39       | 76.03       |
| subgroup analysis based on sample size | | | | | | | |
| size≥100 | 8       | 0.82 [0.71, 0.89] | 0.87 [0.81, 0.91] | 29 [13, 64] | 0.91 [0.88, 0.93] | 91.53       | 78.72       |
| size<100 | 11      | 0.92 [0.86, 0.96] | 0.90 [0.84, 0.94] | 105 [44, 252] | 0.95 [0.93, 0.97] | 62.09       | 13.49       |
| subgroup analysis based on country | | | | | | | |
| China    | 6       | 0.89 [0.84, 0.93] | 0.86 [0.80, 0.91] | 53 [30, 92] | 0.92 [0.89, 0.94] | 49.79       | 0.00        |
| non-China| 13      | 0.88 [0.79, 0.94] | 0.89 [0.84, 0.93] | 64 [24, 168] | 0.94 [0.92, 0.96] | 92.42       | 83.07       |
| subgroup analysis based on patient source | | | | | | | |
| ICU      | 13      | 0.89 [0.80, 0.94] | 0.90 [0.86, 0.93] | 73 [29, 183] | 0.94 [0.92, 0.96] | 93.18       | 78.96       |
| non-ICU  | 4       | -             | -             | -            | -            | -           | -           |
| subgroup analysis based on assay method | | | | | | | |
| FMC      | 16      | 0.87 [0.82, 0.91] | 0.88 [0.83, 0.91] | 50 [27, 96] | 0.94 [0.91, 0.96] | 86.71       | 71.13       |
| Leuko64 kit | 3 | -             | -             | -            | -            | -           | -           |

Table 3. Subgroup analysis of PCT in the diagnosis of sepsis
## Table 4. Subgroup analysis of IL-6 in the diagnosis of sepsis

| category                | studies | SEN (95% CI) | SPE(95%CI) | DOR(95% CI) | AUC(95% CI) | SEN-²(%) | SPE-²(%) |
|-------------------------|---------|--------------|------------|-------------|-------------|----------|----------|
| overall                 | 16      | 0.72[0.65, 0.78] | 0.70[0.62,0.76] | 6[4, 9] | 0.77[0.73,0.80] | 89.27  | 85.07    |
| subgroup analysis based on sample size |         |              |            |             |             |          |          |
| size≥100                | 10      | 0.66[0.58,0.3] | 0.73[0.64,0.80] | 5[3,8] | 0.75[0.71,0.78] | 92.34  | 88.99    |
| size<100                | 6       | 0.83[0.73,0.83] | 0.64[0.51,0.75] | 8[5,14] | 0.81[0.77,0.84] | 52.42  | 62.91    |
| subgroup analysis based on country |         |              |            |             |             |          |          |
| China                   | 4       | -            | -          | -           | -           | -        | -        |
| non-China               | 12      | 0.69[0.59,0.77] | 0.70[0.63,0.77] | 5[3, 8] | 0.75[0.71,0.79] | 80.86  | 74.47    |
| subgroup analysis based on mean age |         |              |            |             |             |          |          |
| age≥65 y                | 8       | 0.79[0.72,0.8] | 0.84[0.75,0.90] | 20[12,34] | 0.88[0.85,0.91] | 86.45  | 74.39    |
| age<65 y                | 20      | 0.80[0.73,0.86] | 0.81[0.76,0.85] | 17[10,29] | 0.87[0.84,0.90] | 84.01  | 73.73    |
| subgroup analysis based on patient source |         |              |            |             |             |          |          |
| ICU                     | 27      | 0.82[0.77,0.86] | 0.78[0.72,0.82] | 16[10,24] | 0.86[0.83,0.89] | 86.20  | 76.10    |
| non-ICU                 | 10      | 0.77[0.72,0.82] | 0.74[0.64,0.81] | 9[6,15] | 0.82[0.78,0.85] | 74.39  | 90.16    |
| subgroup analysis based on assay method |         |              |            |             |             |          |          |
| EIA                     | 8       | 0.75[0.64,0.83] | 0.70[0.63,0.76] | 7[4,12] | 0.77[0.73,0.81] | 91.31  | 67.89    |
| ECLI                    | 8       | 0.69[0.59,0.77] | 0.69[0.56,0.80] | 5[3,9] | 0.75[0.71,0.78] | 83.28  | 90.73    |
Figure 1

PRISMA flow diagram of the search strategy and study selection process
Figure 2

a. risk of bias. b. clinical applicability

Figure 3

Summary receiver operator characteristic (SROC) of CD64 (a) across 20 studies, PCT (b) across 43 studies, and IL-6 (c) across 16 studies.
Figure 4

Forest plots of the sensitivity and specificity for CD64 with a 95% confidence interval on the 20 included studies.
Figure 5

Forest plots of the sensitivity and specificity for PCT with a 95% confidence interval on the 43 included studies.
Figure 6

Forest plots of the sensitivity and specificity for IL-6 with a 95% confidence interval on the 16 included studies.

Figure 7

Deeks’ funnel figure for the assessment of potential publication bias for neutrophil CD64 (a), PCT (b), and IL-6 (c) expression in the diagnosis of sepsis.
Figure 8
Meta-regression for neutrophil CD64 (a), PCT (b), and IL-6 (c) expression in the diagnosis of sepsis. Meta-regression was performed according to whether the sample size of the study was over 100, study subjects were Chinese, the average age of the study population was over 65, and the clinical setting was classified into ICU and measuring methods.

Figure 9
Sensitivity analysis for neutrophil CD64 (a), PCT (b), and IL-6 (c) expression in the diagnosis of sepsis.
Figure 10

Fagan's nomogram for neutrophil CD64 (a), PCT (b), and IL-6 (c) expression in the diagnosis of sepsis.