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Original Article

Meta-analysis of the accuracy of CD64, HBP, and PCT in differential diagnosis of sepsis patients

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Abstract

Introduction: The aim of this study was to systematically evaluate the accuracy of the cluster of differentiation 64 (CD64) molecule, heparin binding protein (HBP), and procalcitonin (PCT) in the differential diagnosis of sepsis patients.

Methodology: Literature in multiple Chinese and English databases were searched to screen for CD64, PCT, and HBP related studies that focused on the differential diagnosis of sepsis. The literature was reviewed to extract the true positive, false positive, true negative, and false negative data; and STATA 17.0 software was used to combine the sensitivity, specificity, and area under the sensitivity receiver operating characteristic curve (SROC) of CD64, PCT, and HBP.

Results: This study included 17 articles. The combined sensitivity of CD64, HBP, and PCT were 0.87 [0.73~0.94], 0.85 [0.71~0.93], and 0.86 [0.64~0.96], respectively. The combined specificity of CD64, HBP, and PCT were 0.87 [0.78~0.93], 0.80 [0.06~1.00], and 0.63 [0.23~0.91], respectively; and all showed significant heterogeneity. There was a significant change in diagnostic odds ratio (DOR) values after excluding individual studies. The DOR value was overestimated when the sample size was small. The specificity of research in China was relatively low.

Conclusions: CD64, HBP, and PCT are all useful in the diagnosis of sepsis; and further optimization of diagnostic thresholds is needed before clinical application to improve the quality of testing. A prospective study with larger sample size is needed to improve the reliability of meta-analysis results.

Key words: CD64; HBP; PCT; sepsis; diagnosis.

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Introduction

Sepsis is a serious infectious disease associated with high mortality rates [1]. In China, the incidence rate of intensive care unit (ICU) sepsis was 20.6%, the case fatality rate was 35.5%, and the case fatality rate of severe sepsis was > 50% in 2022 [2]. Sepsis has a hidden onset, rapid progression, and difficult diagnosis. The clinical manifestations of sepsis are diverse and often not specific, resulting in frequent misdiagnosis with other systemic inflammatory response syndromes (SIRS) [3]. At present, there is no gold standard for the diagnosis of sepsis, and clinical judgment needs to be based on the patient's infection history, physical signs, laboratory tests, and imaging examinations [4]. Early identification and timely treatment of sepsis are key to reducing mortality and improving prognosis. Multiple serological indicators are often used for auxiliary diagnosis in clinical practice due to the complex pathogenesis of sepsis. Therefore, early diagnosis of sepsis requires examination of various serological factors.

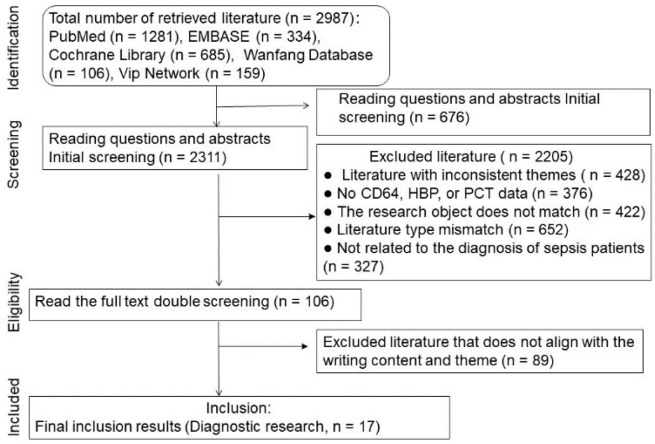
The expression level of neutrophil cluster of differentiation 64 (CD64) as a lysozyme receptor can indicate infection and inflammatory response [5], and procalcitonin (PCT) is a prostaglandin induced by inflammatory mediators in response to bacterial infection [6]. Researchers have determined that the expression of CD64 is superior to PCT and C-reactive protein (CRP) in diagnosing sepsis in the ICU [7]. Gu *et al*. reported that PCT levels can effectively distinguish sepsis infections in leukemia patients [8]. Rothe *et al.* proposed that the use of PCT and hematuria culture can improve the diagnostic rate of urinary sepsis in hospital patients [9]. Kapoor *et al.* reported that PCT is helpful in distinguishing the septic course and drug hypersensitivity response of discitis [10]. Spoto *et al*. suggested that the combined application of PCT and mid-regional pro-adrenomedullin (MR proADM) can improve the etiological diagnosis and prognosis prediction of sepsis and septic shock [11]. Song *et al.* have shown that interleukin 6 (IL-6), pronucleus 3 (PN3), and PCT can assist in distinguishing sepsis from septic shock [12]. This indicates that PCT is suitable for distinguishing sepsis and septic shock. Heparin binding protein (HBP) is present in Gram-negative bacteria and binds to lipopolysaccharides [13]. Thus, all three

(CD64, PCT, and HBP) can serve as markers of infection and inflammation.

A study with low sample size determined that CD64 can be used for determining the diagnostic stage of sepsis, and even for differentiating from bacterial infections. PCT can be used for early diagnosis of patients with alcoholic hepatitis and sepsis [14,15]. Some scholars also believe that changes in HBP and PCT within 72 hours of admission can help predict the severity of septic shock patients in the ICU [16]. Researchers have used HBP as a tool for early diagnosis of sepsis and risk of early death in the emergency room [17,18]. Thus, CD64, PCT, and HBP are evaluation indicators for early diagnosis of sepsis. However, the diagnostic value of CD64, PCT, and HBP in the clinical differential diagnosis of sepsis varies depending on the research findings, and the independent differential efficacy of the three markers is controversial.

Although existing research suggests that CD64, PCT, and HBP may be helpful in the diagnosis of sepsis, there are some methodological limitations, including small sample sizes, inconsistent testing methods, lack of quality evaluation, and publication bias; which may reduce the reliability of the results. Therefore, this study aimed to conduct a systematic evaluation and meta-analysis of diagnostic tests based on strict screening of selected studies, in order to provide more reliable evidence support. This study evaluated the sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and other indicators of CD64, PCT, and HBP; and compared differences in their efficacy using a summary of subject work characteristic curves. The study assumed that CD64, HBP, and PCT can be used for the differential diagnosis of sepsis; but their efficacy varies to some extent. All selected studies underwent quality evaluation to reduce the impact of bias on the meta-analysis results. The study evaluated and compared the application value of CD64, HBP, and PCT in the differential diagnosis of sepsis, and provided evidence-based conclusions for the standardized diagnosis and treatment of sepsis. The results of this study provide a more reliable reference for sepsis diagnosis and treatment decisions.

Figure 1. Schematic diagram of the screening process.



CD64: cluster of differentiation 64; HBP: heparin binding protein; PCT: procalcitonin

Methodology

Search strategy

An advanced search of literature databases was conducted using the search terms: "sepsis", "CD64", "PCT", "HBP", their synonyms, and theme words. The search was conducted in Chinese and English databases such as PubMed, EMBASE, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Database, and Weibo. At the same time, manual reference screening was conducted to obtain all existing literature that evaluated the effectiveness of CD64, PCT, and HBP in the differential diagnosis of sepsis. Unpublished research was not considered. The language was limited to Chinese and English.

The inclusion criteria were: (1) The study subjects were adult sepsis patients. (2) All prospective or retrospective studies using CD64, PCT, or HBP for the differential diagnosis of sepsis. (3) The number of true positive, false positive, true negative, and false negative cases were provided in the study; or sensitivity and specificity could be calculated from the raw data.

The exclusion criteria were: (1) Studies with fewer than 30 cases. (2) Studies where true positive, false positive, true negative, and false negative cases could not be extracted from the data provided in the article. (3) Repeatedly published research. (4) Studies for which the original literature could not be obtained, such as conference summaries. A rigorous literature screening process was used to obtain authentic and reliable high-quality research, to have a reliable basis for performance evaluation in this meta-analysis.

Literature screening

After obtaining potentially relevant literature through database retrieval, the title and abstract were reviewed for preliminary screening, and literature that clearly did not meet the standards were excluded. Next, the articles were downloaded and the full text was reviewed to determine the suitability of each literature according to the predetermined inclusion and exclusion criteria. Two evaluators independently conducted literature screening and cross checked before deciding

Table 1. Chi-square test criteria.

Chi -square test	Result	Performance	Research method
I^2	$I^2 < 50\%$	Low heterogeneity	Fixed effects model
	$I^2 > 50\%$	Significant heterogeneity	Random effect model

whether the articles would be included in the study. The reasons for exclusion were documented throughout the entire process. If the results of two reviewers are inconsistent, a third reviewer decided whether to include the literature.

Data extraction

Two evaluators independently read the included articles and extracted the following information according to a predetermined table: study characteristics (study design, sample size, etc.); and true positive, false positive, true negative, and false negative cases. Questionable research studies identified during the extraction were resolved through discussion or contact with the original author.

Quality evaluation

The QUADAS-2 tool was used to evaluate the quality of the included studies [19]. The risk assessment covered four areas: patient selection, test gold standards, test indicators to be evaluated, and outflow/inflow status. The risks in each field are divided into three levels: high quality (☺), low quality (☹), and unclear (?). Two evaluators independently conducted quality evaluations and resolved differences through discussion. The evaluation followed strict screening, extraction, and quality evaluation protocols to obtain authentic and reliable raw data; and provide high-quality evidence support for the meta-analysis.

Statistical analysis

The meta-analysis was performed with the Stata 12.0 software. The efficacy of CD64, PCT, and HBP in the differential diagnosis of sepsis was evaluated using sensitivity, specificity, and 95% confidence interval (CI) as the response measures. First, the dataset from the selected literature was loaded into Stata, Then the dependent and independent variables were specified; the independent variables being CD64, PCT, and HBP; and the dependent variable was the patient's treatment outcome. The xtset in the software was used to specify the panel data structure, and the xtmixed and other commands were used to estimate the mixed model effect. Finally, the estat mtest command was used for meta-analysis. Chi square test was used to evaluate heterogeneity between studies. The standards for testing heterogeneity using Chi square test are shown in Table 1.

The study used Chi square test to analyze the sensitivity of biomarkers to heterogeneity changes, analyzing the main sources of heterogeneity by examining the sensitivity changes of the biomarkers under low and significant heterogeneity conditions. Stata was used to calculate the comprehensive sensitivity and specificity, diagnostic odds ratio (DOR),

Table 2. Basic characteristics of included literature.

Authors	Years	Region	Diagnosis criteria	Sample size	Biomarker
Dimoula *et al.* [35]	2014	Belgium	ISDC	468	CD64
Gerrits *et al.* [36]	2013	Netherlands	ISDC	44	CD64
Bauer *et al. [*37]	2016	America	Clinical	196	CD64
Bauer *et al.* [37]	2016	America	Clinical	216	PCT
Gamez-Diaz *et al.* [38]	2011	Colombia	Clinical	610	CD64
Gros *et al.* [39]	2012	France	clinical, culture+	293	CD64
Hsu *et al.* [40]	2011	China	clinical, culture+	66	CD64
Hsu *et al.* [40]	2011	China	clinical, culture+	66	PCT
Qian *et al*. [41]	2017	China	Sepsis3.0	108	HBP
Qian *et al.* [41]	2017	China	Sepsis3.0	108	PCT
Jämsä *et al.* [42]	2015	Finland	Clinical	42	CD64
Kahn *et al*. [43]	2019	Sweden, Switzerland, and Canada	Sepsis2.0	332	HBP
Kofoed *et al.* [44]	2007	Denmark	Clinical, culture+	151	PCT
Linder *et al.* [45]	2012	Sweden	Sepsis1.0	154	HBP
Linder *et al.* [45]	2015	Sweden, the United States, and Canada	Sepsis1.0	487	HBP
Llewelyn *et al.* [46]	2013	England	Sepsis2.0	162	HBP
Meynaar *et al.* [47]	2011	Netherlands	Clinical, culture+	76	PCT
Papadimitriou-Olivgeris *et al.* [48]	2015	Greece	Clinical, culture+	66	CD64
Selberg *et al.* [49]	2000	Germany	Clinical, culture+	33	PCT
Zhou *et al.* [50]	2019	China	Sepsis3.0	181	HBP
Zhou *et al.* [50]	2019	China	Sepsis3.0	181	PCT

CD64: cluster of differentiation 64; HBP: heparin binding protein; PCT: procalcitonin; ISDC: international standard diagnostic codes.

and area under the summarized subject operating characteristics (SROC) curve of the included studies. It is possible to intuitively understand which test is more effective in a specific context by comparing the SROC curve areas of different diagnostic tests. Sensitivity analysis was conducted on the included studies and changes were observed in the aggregated effect quantity after excluding a particular study to determine the robustness of the results. Subgroup analysis was conducted based on sample size and region, to evaluate the impact of the different features on diagnostic efficacy.

Results

Research screening

A total of 2,987 articles were screened, which included 1,281 articles from PubMed, 334 articles from Embase, 685 articles from Cochrane Library, 422 articles from China National Knowledge Infrastructure (CNKI), 106 articles from Wanfang Database, and 159 articles from Wikipedia. A total of 2,311 articles were retained after removing duplicate publications. 2,205 articles were preliminarily excluded after reading the abstracts and titles of the retained literature. Next, the articles were carefully read and 17 diagnostic studies were identified, including 8 related to CD64, 6 related to HBP, and 7 related to PCT (of which 5 were observed with 2 indicators). Figure 1 shows the schematic diagram of the screening process.

The basic characteristics of these 17 articles are summarized in Table 2. The quality of the literature was determined to be medium to high level (Table 3).

Methodological results

The results of statistical analyses of the relevant data in the included study are summarized in Table 4. The combined sensitivity of CD64 was 0.87 [0.73~0.94], the combined specificity was 0.87 [0.78~0.93], the combined positive likelihood ratio was 6.9 [3.6~13.1], the combined negative likelihood ratio was 0.15 [0.07~0.34], and the combined DOR was 46 [12~177]. The combined sensitivity of HBP was 0.85 [0.71~0.93], the combined specificity was 0.80 [0.06~1.00], the combined positive likelihood ratio was 4.3 [0.1–132.4], the combined negative likelihood ratio was 0.19 [0.04~0.79], and the combined DOR was 23 [0–2868]. The combined sensitivity of PCT was 0.86 [0.64–0.96], the combined specificity was 0.63 [0.23–0.91], the combined positive likelihood ratio was 2.4 [0.7–7.6], the combined negative likelihood ratio was 0.21 [0.05–0.90], and the combined DOR was 11 [1–127]. The combined sensitivity of the three indicators was 0.87 [0.80~0.92], the combined specificity was 0.80 [0.69–0.88], the combined positive likelihood ratio was 4.4 [2.7–7.2], the combined negative likelihood ratio was 0.16 [0.10–0.25], and the combined DOR ratio was 28 [12–64].

Table 3. Results of quality evaluation of included literature.

Authors	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Dimoula *et al.* [35]	?	☺	☺	☺	☺	☺	☺
Gerrits *et al.* [36]	☺	☺	?	☺	☺	☺	☺
Bauer *et al.* [37]	☺	☺	?	☺	☺	☺	☺
Gamez-Diaz *et al.* [38]	☺	☺	☺	☺	☺	☺	☺
Gros *et al*. [39]	☺	☺	☺	☹	☺	☺	☺
Hsu *et al.* [40]	☺	?	☺	☹	☺	☺	☺
Qian *et al.* [41]	☺	☺	☺	☺	☺	☺	☺
Jämsä *et al*. [42]	☺	☺	☺	☺	☺	☺	☺
Kahn *et al.* [43]	☺	☺	☹	☺	☺	☺	☺
Kofoed *et al.* [44]	☺	☺	☺	☺	☺	☺	☺
Linder *et al.* [45]	☺	?	☺	☺	☺	☺	☺
Linder *et al.* [45]	☺	☺	☹	☺	☺	☺	☺
Llewelyn *et al.* [46]	☺	☺	☺	☺	☺	☺	☺
Meynaar *et al.* [47]	☺	☺	☺	☹	☺	☺	☺
Papadimitriou-Olivgeris *et al.* [48]	☺	☹	☺	☺	☺	☺	☺
Selberg *et al.* [49]	☺	☺	☺	☺	☺	☺	☺
Zhou *et al.* [50]	☺	☹	☺	☺	☺	☺	☺

☺ low risk; ☹ high risk; ? unclear risk.

Table 4. Relevant results of the included studies.

Authors	Years	TP	FP	FN	TN
Dimoula *et al.* [35]	2014	92	47	11	318
Gerrits *et al*. [36]	2013	25	1	0	18
Bauer *et al.* [37]	2016	84	20	26	66
Bauer *et al*. [37]	2016	88	25	32	71
Gamez-Diaz *et al.* [38]	2011	266	73	138	133
Gros *et al.* [39]	2012	93	16	55	129
Hsu *et al.* [40]	2011	49	1	6	10
Hsu *et al.* [40]	2011	31	0	24	11
Qian *et al.* [41]	2017	41	37	18	0
Qian *et al*. [41]	2017	33	37	26	0
Jämsä *et al.* [42]	2015	27	1	0	14
Kahn *et al.* [43]	2019	8	26	4	294
Kofoed *et al.* [44]	2007	77	23	19	32
Linder *et al.* [45]	2012	109	14	17	14
Linder *et al.* [45]	2015	110	82	31	264
Llewelyn *et al.* [46]	2013	68	48	19	27
Meynaar *et al.* [47]	2011	31	9	1	35
Papadimitriou-Olivgeris *et al.* [48]	2015	24	3	5	34
Selberg *et al.* [49]	2000	19	5	3	6
Zhou *et al.* [50]	2019	56	0	0	88
Zhou *et al.* [50]	2019	93	9	0	56

FN: false negative; FP: false positive; TN: true negative; TP: true positive.

Figure 2A. the overall forest map; **B.** forest map of CD64 related literature; **C.** forest map of HBP related literature; **D.** forest map of PCT related literature. The black boxes in the figure represent the OR values of each study, and the horizontal line represents 95% confidence interval.

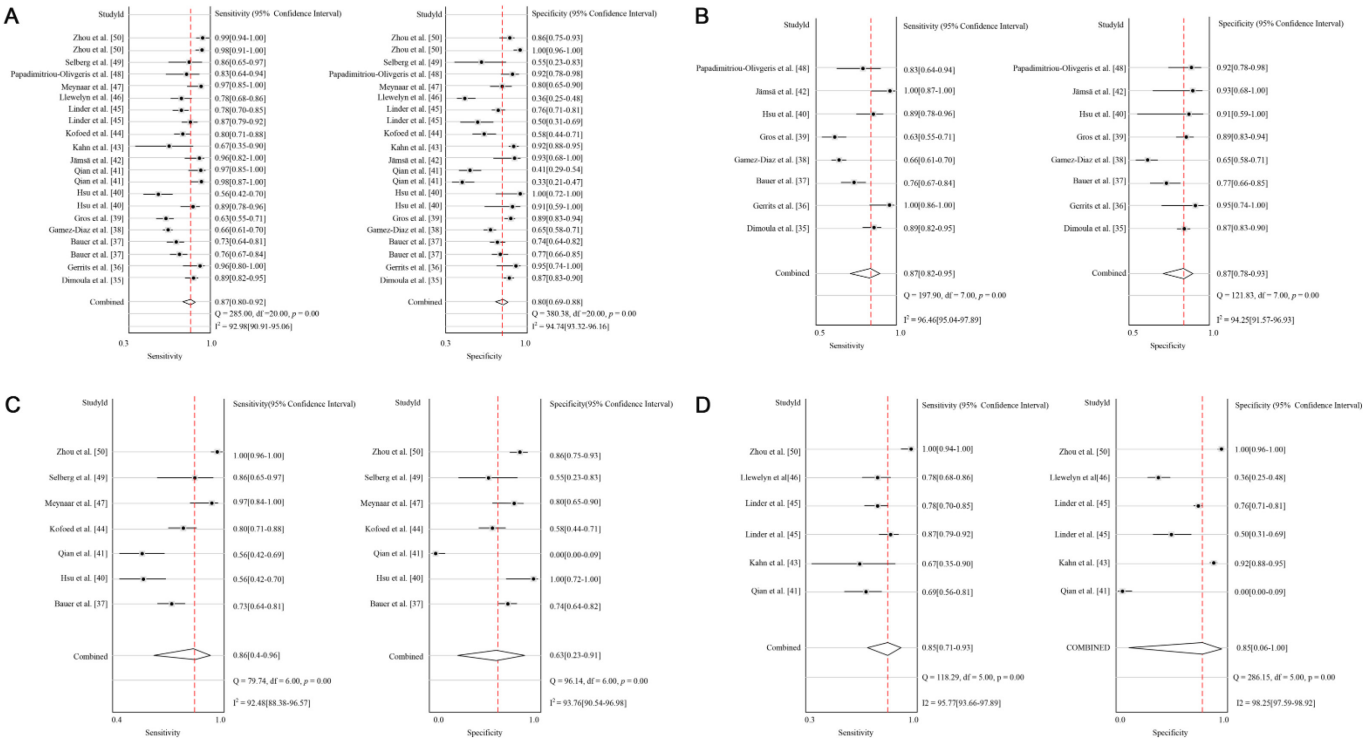
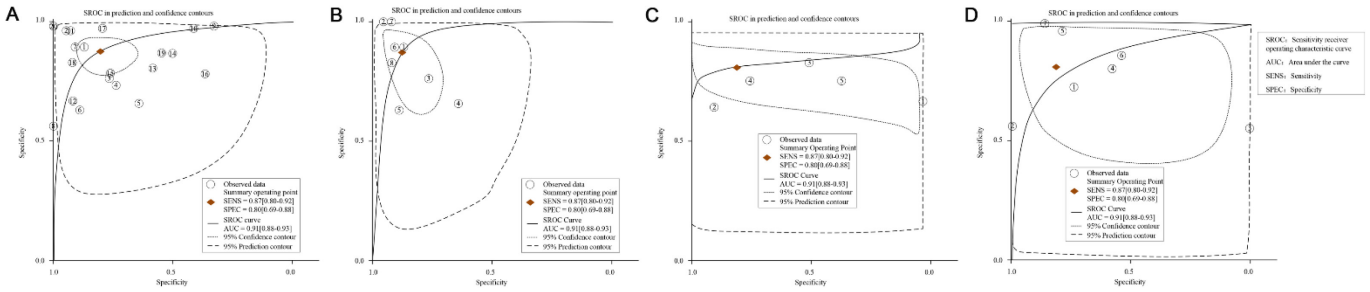


Figure 3A. the overall SROC diagram; **B.** the SROC diagram of CD64 related literature; **C.** SROC diagram of HBP related literature; **D.** SROC diagram of PCT related literature.



The x-axis in the figures represent the sensitivity of the diagnostic test; the y-axis in the figures represent the specificity of the diagnostic test, ○ represents a point contributed by each study, and the curve represents the sensitivity and specificity at different cut-off values. CD64: cluster of differentiation 64; HBP: heparin binding protein; PCT: procalcitonin; SROC: sensitivity receiver operating characteristic curve; AUC: area under the curve; SENS: sensitivity; SPEC: specificity.

The overall forest map (Figure 2A) showed sensitivity I^2 = 92.98 [90.91~95.06] and specificity I^2 = 94.74 [93.32~95.16]. The forest map of CD64 related literature (Figure 2B) showed sensitivity I^2 = 96.46 [95.04~97.89] and specificity I^2 = 94.25 [91.57~96.93]. HBP related literature forest map (Figure 2C) showed sensitivity I^2 = 95.77 [93.66~97.89] and specificity I^2 = 98.25 [97.59~98.92]. The forest map of PCT related literature (Figure 2D) showed that sensitivity I^2 = 92.48 [88.38~96.57] and specificity I^2 = 93.76 [90.54~96.98].

SROC plots of multiple diagnostic test results

Figure 3 shows that the combined total effect value area under the curve (AUC) of the overall SROC curve was 0.91 [0.88~0.93]. The combined total effect value AUC of the SROC curve of CD64 related literature was 0.93 [0.91~0.95]. The combined total effect value AUC of the SROC curve of HBP related literature was 0.87 [0.84~0.90]. The combined total effect value AUC of the SROC curve of PCT related literature was 0.85 [0.82~0.88].

Sensitivity analysis

After excluding the studies one by one, it was found that the DOR continued to decrease at 46 [12–177], and the meta-analysis results showed some sensitivity to individual studies. This was especially the case after excluding the research results of Gerrits *et al.* [36] when the DOR value decreased by about half from 17 [4–64]. This led to significant aggregation effects that may have existed in this study, and indicated that the meta-analysis results were not very robust.

Post biased reviews

The bias coefficient *p* values for publication bias of overall, HBP, and PCT were 0.104, 0.562, and 0.827, respectively (Table 5). The *p* values of the bias coefficients for publication bias of CD64 were all 0.034, indicating a significant bias coefficient. The funnel plot was skewed to the right, indicating a significant publication bias and an increased effect in small sample research reports (Figure 4). The publication bias in Figure 4B was the most obvious. Deeks' funnel plot asymmetry test value reached 0.03, showing a significant right side bias phenomenon, indicating the existence of publication bias driven by small sample studies, and its reliability was questionable.

Subgroup analysis

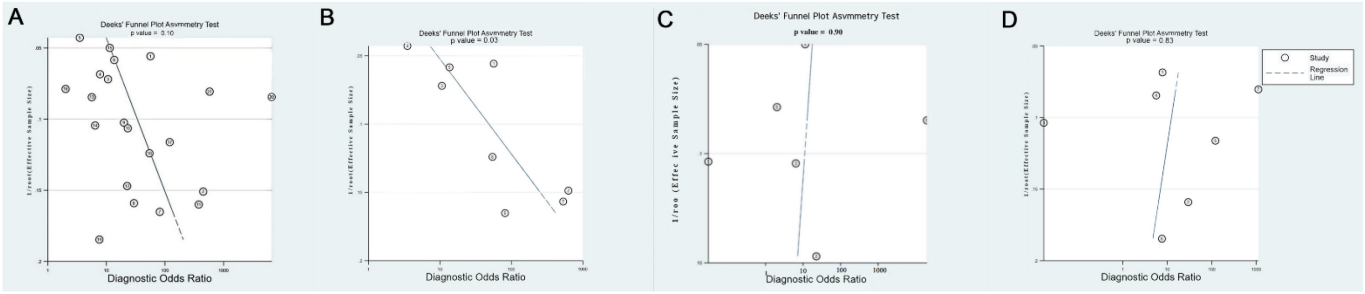
The sensitivity and specificity were relatively close between subgroups with sample sizes ≤ 100 and > 100, but there were certain differences in DOR (13 vs 23) (Table 6). As the sample size boundary was adjusted to

Table 5. Statistical analysis of meta-analysis publication bias.

Index	yb	Coefficient	Standard error	t	p	95% CI
Whole	Bias	21.35693	12.52329	1.71	0.104	– 4.854616~47.56847
	Intercept	1.382945	1.012698	1.37	0.188	–.7366558~3.502547
CD64	Bias	33.10049	12.11305	2.73	0.034	3.460937~62.74005
	Intercept	0.5702784	0.8728415	0.65	0.538	– 1.565488~2.706045
HBP	Bias	– 9.252044	65.83008	– 0.14	0.895	– 192.0256~173.5216
	Intercept	3.333038	5.282585	0.63	0.562	– 11.33377~17.99984
PCT	Bias	– 11.33583	49.20954	– 0.23	0.827	– 137.8330~115.1613
	Intercept	3.650547	4.772166	0.76	0.479	– 8.616696~15.91779

CD64: cluster of differentiation 64; HBP: heparin binding protein; PCT: procalcitonin; CI: confidence interval.

Figure 4A. the overall funnel diagram; **B.** funnel diagram of CD64 related literature; **C.** funnel diagram of HBP related literature; **D.** funnel diagram of PCT related literature.



Each point in the graph represents a separate study, with the horizontal axis representing the magnitude of the effect and the vertical axis representing the standard error or reciprocal of the sample size. The straight line represents the position of the aggregated effect quantity, usually centered on the aggregated effect quantity calculated by meta-analysis. CD64: cluster of differentiation 64; HBP: heparin binding protein; PCT: procalcitonin; ESS: effect size standardization.

200, the DOR of the ≤ 200 group was smaller (13 vs 21) and had higher specificity. The Chinese studies had a slightly higher sensitivity but lower specificity (0.46) and lower DOR (6 vs 16). The non-Chinese studies had a higher specificity (0.78) and a higher DOR (16).

When the sample size in the subgroup analysis of CD64 was > 100, the DOR was 13 [5–33], and when the sample size was ≤ 100, the DOR was 277 [29–2621]. As the sample size decreased, the DOR of CD64 increased.

Discussion

From a pathological perspective, increased vascular permeability may lead to the accumulation of tissue fluid, insufficient intravascular fluid, and ultimately lead to septic shock and multiple organ dysfunction syndrome [20]. The results of this study showed that the combined sensitivity of CD64 was 0.87 [0.73~0.94], and the combined specificity was 0.87 [0.78~0.93]. The combined sensitivity of HBP was 0.85 [0.71~0.93], and the combined specificity was 0.80 [0.06~1.00]. Compared to the results of Dou *et al*., the results of this study showed that the AUC (0.82) of HBP changed at 48 hours and had a higher predictive accuracy for mortality within 30 days [21]. The reason for this result may be that this study used meta-analysis to determine the diagnostic ability of HBP for severe sepsis, which improved the accuracy of prediction. In addition, the combined sensitivity of PCT was 0.86 [0.64~0.96], and the combined specificity was 0.63 [0.23~0.91]. The sensitivity and specificity of the three biomarkers were greater than 0.80, indicating that CD64, HBP, and PCT had good ability to differentiate between sepsis patients and non-sepsis patients. When these three biomarkers were positive, patients had a higher probability of developing sepsis. When the markers were negative, the probability of developing sepsis was lower. This result is similar to that of Wu *et al*., but the difference between the present study and that of Wu *et al.* is that in this study, the specificities of CD64 and HBP were high (both > 0.80), indicating a lower false positive rate and a lower possibility of misdiagnosis. The specificity of PCT was low (0.63) and there were certain false positive results [22].

To address the above issues, a combined detection kit for these three biomarkers, as proposed by the Torres *et al*., can be used to reduce false positive results [23]. Different biomarkers target different aspects of sepsis diagnosis. For example, CD64 is more suitable for early infection diagnosis [24], PCT monitors Gram negative and positive bacterial infections [25], and HBP is a monitoring indicator of the severity of sepsis related cardiovascular organ dysfunction [26]. Cabral *et al*. found that PCT had good discriminatory value in burn

Table 6. Sample size and regional subgroup analysis results.

Subgroup classification	Number of groups	Combined sensitivity	Combined specificity	Combined DOR
Sample size				
≤ 100	9	0.86 [0.78~ 0.92]	0.68 [0.38~ 0.88]	13 [3~64]
> 100	12	0.85 [0.73~ 0.92]	0.80 [0.66~ 0.89]	23 [6~ 86]
≤ 200	15	0.74 [0.65~ 0.82]	0.82 [0.73~ 0.89]	13 [6~28]
> 200	6	0.89 [0.79~ 0.94]	0.73 [0.39~ 0.92]	21 [3~151]
Area				
China	6	0.87 [0.63~0.96]	0.46 [0.01~0.98]	6 [0~779]
Non-China	15	0.82 [0.76~ 0.87]	0.78 [0.68~0.86]	16 [8~33]

DOR: diagnostic odds ratio.

sepsis patients [27]. Reasonable selection and combination of different biomarkers can improve the accuracy of diagnosis. These three biomarkers can also be combined with clinical manifestations and other diagnostic test results to establish a more robust prediction system using multivariate models.

However, the I^2 values of the heterogeneity tests for the three biomarkers were relatively high, at 96.46%, 95.77%, and 92.48%, respectively, indicating significant heterogeneity in the results between the different studies. This result is similar to that of Menon *et al*., and the possible reasons for this result may be differences in patient population, testing methods, and other aspects [28]. Therefore, although the sensitivity and specificity of the three biomarkers were relatively good, the results still need to be explained carefully and cannot be blindly extrapolated to all populations.

There was a significant publication bias in the case of CD64 detection in this study. The publication bias analysis showed that the bias coefficient of CD64 was 33.10049, with a p value of $0.034 < 0.05$, indicating a statistically significant publication bias. Unlike other indicators, the funnel plot of CD64 appeared skewed on the right, possibly because small sample size studies tended to report larger effects. This indicated that small sample studies may have overestimated the diagnostic efficacy of CD64, increased the variability of the merge effect, and reduced the reliability of the results. This result coincides with the findings of Llitjos *et al*., but the publication bias in their research results was not significant [29]. The reason may be that the research sample in Llitjos *et al.*'s study had a high representativeness which could reflect the overall situation well, and they used randomized controlled trials to increase the credibility of the study. Additionally, the literature search in Llitjos *et al*.'s study was comprehensive, ensuring the comprehensiveness of the meta-analysis [29].

This study further conducted subgroup analysis of sample size and found that when the sample size was > 100, the DOR was 23. When the sample size was ≤ 100, the DOR significantly increased to 277. This indicated that the small sample size group overestimated the DOR value of CD64. The results of subgroup analysis of sample size partially explained the publication bias in CD64 related studies, while small sample studies drove overestimation of CD64 efficacy. This provided an important reference for correctly interpreting and measuring the diagnostic efficacy of CD64. However, it should still be noted that this study included a limited number of CD64 small sample studies, and subgroup analysis could fully correct for publication bias. However, publication bias may have potential adverse effects on the formulation of medical policies, the exploration of medical methods, and the cultivation of medical talents. The rank correlation method used in Celik *et al*. study, the safety factor method used by Schlapbach *et al*., study and the clipping method used by Póvoa *et al*. can be used to correct for publication bias in CD64 detection [30–32]. Further large-scale studies are needed to obtain more robust and reliable results for CD64 diagnosis.

Unlike the study conducted by Manabe *et al* [33], this study compared differences in data between native Chinese patients and foreign patients and analyzed the differences in geography, race, and underlying diseases using the same or similar cutoff values which may have led to a decrease in specificity [33]. This decrease may also be due to the lack of consideration for ethnic issues in the diagnostic threshold settings of research in China. Some studies have adopted too low cutoff values in pursuit of high sensitivity, resulting in a decrease in specificity. In addition, compared with the study by Arora *et al.*, this study may have some data bias due to the relatively small number of Chinese studies included, and some of those studies may not have standardized process quality control, resulting in more false positive results [34]. Future meta-analyses are needed to further examine whether there are any issues in this regard.

Conclusions

CD64, HBP, and PCT are all helpful in the diagnosis of sepsis, but the results should be interpreted with caution. It is necessary to further optimize the diagnostic threshold and improve the quality of testing, before clinical application. Prospective studies with larger sample sizes can help improve the reliability of meta-analysis results. More high-quality prospective research is needed in the future. Expanding the sample size can reduce random errors and provide more reliable quantitative effects. It is necessary to conduct confirmatory studies in multiple centers and regions to evaluate the accuracy of the three biomarkers in different populations. This will also be helpful for exploring sources of heterogeneity. Economic evaluation should be conducted to evaluate the cost-effectiveness of the three biomarkers in different situations, providing decision-making support for their implementation, and application, in low and middle-income countries; and their optimization diagnosis cutoff value.

This study redefined the appropriate threshold based on the local Chinese population. It standardized the diagnostic process, strictly controlled quality, and

reduced operational errors. Its validation with multicenter, large sample studies made the results more robust. In addition, this study attempted the use of new statistical methods to reduce the impact of method bias. Some new biomarkers such as circulating tumor DNA, microRNA, etc. have shown potential diagnostic value and can be used for comparative studies to determine optimal diagnostic strategies.

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Conflict of interests

No conflict of interests is declared.

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