

Diagnostic Value of Presepsin for Sepsis

A Systematic Review and Meta-Analysis

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Abstract: Several individual studies have reported the diagnostic accuracy of presepsin (sCD14-ST) for sepsis, but the results are inconsistent.

The present systematic review and meta-analysis pooled data to better ascertain the value of circulatory presepsin as a biomarker for sepsis.

Studies published in English before November 7, 2014 and assessing the diagnostic accuracy of presepsin for sepsis were retrieved from medical databases.

The quality of eligible studies was assessed using a revised Quality Assessment for Studies of Diagnostic Accuracy (QUADAS-2). The overall diagnostic accuracy of presepsin for sepsis was pooled according to a bivariate model. Publication bias was assessed using Deek funnel plot asymmetry test.

Eleven studies satisfied the inclusion criteria. The overall diagnostic sensitivity of presepsin for sepsis was 0.83 (95% CI: 0.77–0.88), and specificity was 0.78 (95% CI: 0.72–0.83). The area under the summary receiver operating characteristic curve was 0.88 (95% CI: 0.84–0.90). The pretest probability of sepsis was 0.56 among all subjects. When presepsin was introduced as the diagnostic test for sepsis, the posttest probabilities were 0.81 for a positive result and 0.19 for a negative. The major design deficits of the included studies were lack of prespecified thresholds and patient selection bias. The publication bias was negative.

Presepsin is an effective adjunct biomarker for the diagnosis of sepsis, but is insufficient to detect or rule out sepsis when used alone.

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Abbreviations: ABA = American Burn Association, ACCP = American College of Chest Physicians, AUC = area under curve, ELISA = enzyme-linked immunosorbent assay, ICU = intensive care unit, IPSCG = International Pediatric Sepsis Consensus Guidelines, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, QUADAS = Quality Assessment for Studies of Diagnostic Accuracy, ROC = receiver operating characteristic, SCCM = Society of Critical Care Medicine, SIRS

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= systemic inflammatory response syndrome, SSIDCM = Spanish Society of Infectious Diseases and Clinical Microbiology.

INTRODUCTION

Sepsis is a major challenge in emergency departments and intensive care units (ICUs), causing high mortality and morbidity.^{1,2} Early diagnosis and timely intervention are essential to improve the prognosis of septic patients.³ Bacterial culture is generally regarded as the gold standard for the diagnosis of sepsis, but it is time-consuming, frequently yields false-negative results, and microbial contamination can greatly affect its diagnostic value.⁴ Thus, the treatment of sepsis is often based on the clinician's experience, which risks an increase in antibiotic resistance and the cost of medical care. It is therefore necessary and urgent to develop a rapid and accurate method for the diagnosis of sepsis.

Various biomarkers have been reported useful in sepsis diagnosis, such as procalcitonin and C-reactive protein.^{5,6} However, these biomarkers may also be elevated in nonseptic conditions such as trauma, burn, and postoperative settings, and some are slow to rise after the onset of sepsis.^{5,6} It thus remains necessary to find reliable biomarkers to replace or improve those that are currently available.

Cluster of differentiation 14 (CD14) is a coreceptor working with toll-like receptor 4 (TLR4) on the surface of phagocytes such as monocytes, macrophages, and granulocytes.⁷ Once activated by lipopolysaccharide, CD14 with lipopolysaccharide binding protein (LBP) can induce the production of various proinflammatory cytokines.^{8,9} By shedding CD14 from the cell membrane (known as soluble CD14, or sCD14), the lipopolysaccharide–LBP–CD14 complex is released into the blood.¹⁰ In addition to phagocytes, hepatocytes have been reported able to secrete CD14.^{11,12} In blood, sCD14 can be cleaved by proteases, generating a truncated form of 64 amino acid residues known as sCD14 subtype (sCD14-ST), or presepsin.^{13,14} Therefore, the levels of presepsin in free circulation may reflect systemic inflammation, and therefore have diagnostic value in sepsis. Numerous studies have assessed the diagnostic value of presepsin for sepsis, with conflicting results.

To summarize the results of available studies and better guide future studies, we performed a systematic review and meta-analysis to ascertain the diagnostic value of presepsin for sepsis.

MATERIALS AND METHODS

Search Strategy and Study Selection

This meta-analysis was performed and reported in accordance with the guidelines of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).¹⁵ Two investigators independently retrieved eligible studies published before November 7, 2014. The electronic databases used for the literature search were Medline (using the PubMed search

engine) and EMBASE. Search terms for PubMed were (“pre-sepsin” or “sCD14” or “soluble CD14”) and “sepsis.” Similar terms were used for EMBASE. A manual search was also conducted using the references of the primary research and review articles retrieved.

The systematic review included studies concerned with the diagnostic value of presepsin for sepsis; and studies that provided diagnostic characteristics, that is, the area under the receiver operating characteristic (ROC) curve (AUC), or sensitivity and specificity. Excluded were animal studies, duplicate studies, non-English publications, studies with a sepsis or control sample size <10 (since studies with small sample sizes yield great bias), and conference abstracts (for lack of sufficient details for analysis). The titles and abstracts of the retrieved papers were reviewed to identify the eligible studies. Any disagreement on study selection was resolved by full text review or discussion between the investigators.

Because all analyses were based on previous published studies, therefore, we did not obtain ethical approval or patient consent.

Data Extraction and Quality Assessment

The following information was extracted from the eligible studies: publication year, country of origin, inclusion criteria, control groups, test methods, reference standard, and diagnostic performances (AUC, threshold, sensitivity, and specificity).

Two investigators independently assessed the quality of eligible studies using the revised Quality Assessment for Studies of Diagnostic Accuracy tool (QUADAS-2).¹⁶ Studies that enrolled healthy individuals as a component of the controls were regarded as cross-sectional, if the data regarding the healthy individuals were not included in the final analysis; otherwise, they were considered to be case-control studies, and the risk of bias of the QUADAS-2 patient selection domain was labeled *high*. Any disagreement in data extraction and quality assessment was resolved by discussion.

Statistical Analyses

The overall diagnostic power of presepsin was pooled using the bivariate model.¹⁷ This model uses paired specificity

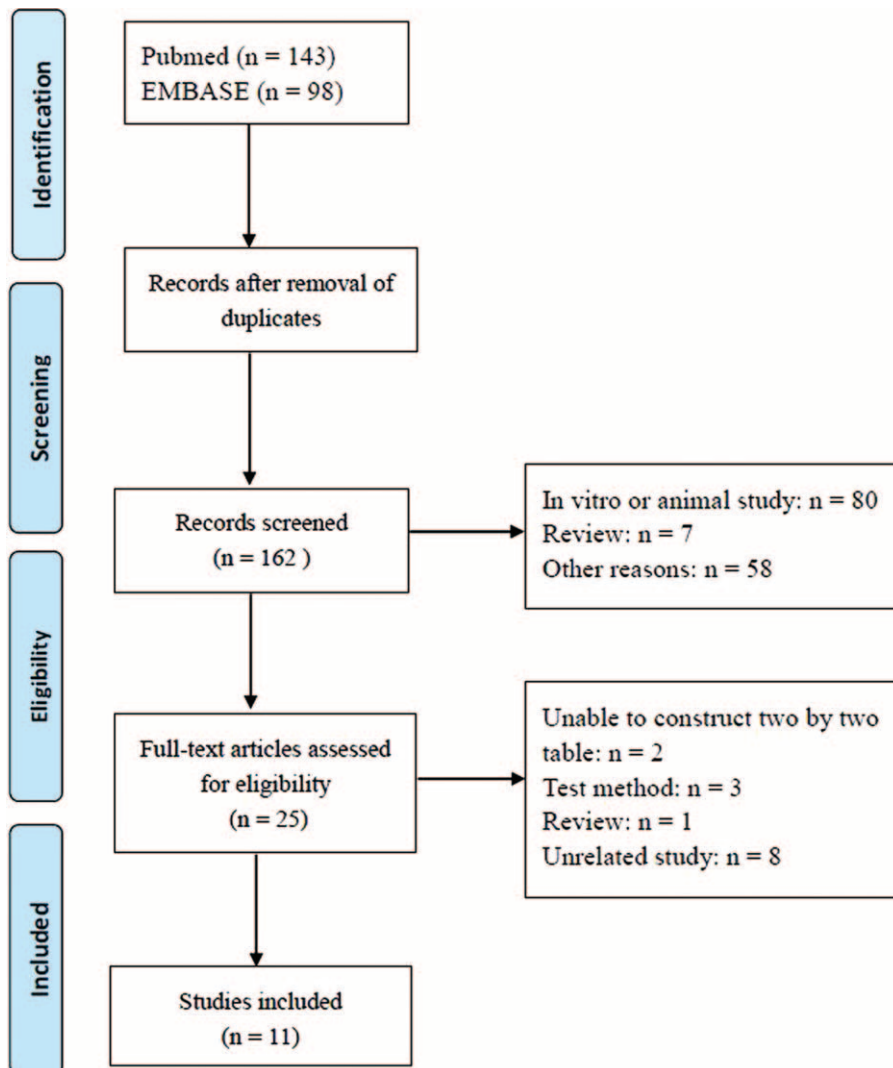


FIGURE 1. The systematic literature search and study selection process.

and sensitivity as the starting point of the analysis; therefore, the trade-off between sensitivity and specificity had been considered. The positive and negative likelihood ratio was estimated according to the overall sensitivity and specificity.

Publication bias was assessed using a funnel plot.¹⁸ The possible sources of heterogeneity across all eligible studies were explored through a meta-regression analysis. All analyses were performed in Stata 12.0 (Stata Corp LP, College Station, TX), and the *midas* command was used for all statistical analyses.¹⁹

RESULTS

Summary of the Eligible Studies

At the end of the systematic literature search and study selection process (Fig. 1), 11 studies^{14,20–29} were included (Table 1). The sample size of the eligible studies ranged from 60 to 959. The inclusion criteria for research subjects were heterogeneous: emergency department patients who met at least two^{20,23–25,27} or one²¹ of the criteria for systemic inflammatory response syndrome (SIRS); ICU patients^{28,29}; acute abdomen patients who met at least 2 criteria for SIRS²²; and burn patients.²⁶ One study did not report any inclusion or exclusion criteria.¹⁴

The characteristics of nonseptic controls were also heterogeneous, including those with SIRS,^{14,20,22–25,27,28} healthy individuals,^{14,20,24,27} and noninfected individuals.^{20,21}

The references used in these studies for determining a diagnosis of sepsis were: criteria established by the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM; the gold standard),³⁰ applied in 5 studies^{14,20–22,27,28}; the International Pediatric Sepsis Consensus Guidelines (IPSCG),³¹ used in 1 study³²; international guidelines^{33–35} used in 2 studies^{23,24}; criteria of the Spanish Society of Infectious Diseases and Clinical Microbiology (SSIDCM) applied in 1 study²⁵; and those of the American Burn Association (ABA)³⁶ applied in 1 study.²⁶

Ten studies^{20–29} employed a chemiluminescence enzyme immunoassay with a PATHFAST analyzer³⁷ (Mitsubishi

Chemical Medicine, Tokyo, Japan) to detect blood presepsin. One study was based on enzyme-linked immunosorbent assay (ELISA).¹⁴ Five studies used frozen samples for analysis.^{23–25,28,29}

Quality Assessment

The patient selection risk of bias domain in 4 studies was labeled as high risk because healthy controls were included in the final analysis.^{14,24,27,28} Three studies were labeled as unknown because the authors did not report whether the subjects were consecutively enrolled^{21,22} (Table 2). In addition, 3 studies^{20,26,28} collected more than one sample from the same patient, which may affect the disease spectrum significantly; the patient selection domain of these studies was labeled high risk.

The index test domain of some studies was labeled as high risk because they did not use a prespecified threshold,^{14,23,25,28,29} or it was labeled as unclear risk because the authors did not report whether the thresholds used were prespecified,^{20–22,27,29} or whether the performers were blinded to the clinical status of the subjects.^{20–22,27,29}

For applicability concerns, the patient selection domain of 4 studies was labeled as high risk because healthy individuals were enrolled.^{14,24,27,28}

Diagnostic Accuracy of Presepsin for Sepsis

All the studies in this meta-analysis found that blood presepsin was an effective biomarker for the diagnosis of sepsis (Table 3). The threshold ranged from 317 to 729 pg/mL, the AUC ranged from 0.70 to 1.00, the sensitivity ranged from 0.70 to 1.00, and the specificity ranged from 0.62 to 0.93.

We then performed a meta-analysis to estimate the diagnostic accuracy of presepsin for sepsis. The overall diagnostic sensitivity was 0.83 (95% CI: 0.77–0.88) and the specificity was 0.78 (95% CI: 0.72–0.83; Figure 2). In addition, the positive likelihood ratio was 3.9 (95% CI: 2.9–5.0), the negative likelihood ratio was 0.21 (95% CI: 0.15–0.30), and the diagnostic odds ratio was 18 (95% CI: 11–30).

TABLE 1. Summary of the Included Studies

	Country	Sepsis/ Controls	Inclusion Criteria	Controls	Reference	Tests	Design
Cakir Madenci et al ²⁶	Turkey	240/371	Admitted to burn center	NR	ABA	PATHFAST	Prospective
Endo et al ²¹	Japan	115/70	Presented to the ED with ≥1 criterion for SIRS	Noninfectious disease (n = 70)	ACCP/SCCM	PATHFAST	Prospective
Kweon et al ²⁷	Korea	73/45	Presented to the ED with ≥2 criteria for SIRS	SIRS (n = 20), HC (n = 25)	ACCP/SCCM	PATHFAST	Prospective
Liu et al ²⁴	China	680/279	Presented to the ED with ≥2 criteria for SIRS	SIRS (n = 179), HC (n = 100)	Int. guideline	PATHFAST	Prospective
Nakamura et al ²⁹	Japan	122/125	Admitted to ICU	NR	ACCP/SCCM	PATHFAST	Retrospective
Romualdo et al ²⁵	Spain	37/189	Presented to the ED with ≥2 criteria for SIRS	SIRS (n = 189)	SSIDCM	PATHFAST	Retrospective
Sargentini et al ²⁸	Italy	60/34	Admitted to ICU	SIRS (n = 14), HC (n = 30)	ACCP/SCCM	PATHFAST	Unknown
Shozushima et al ²⁰	Japan	101/41	Presented to the ED with ≥2 criteria for SIRS	SIRS (n = 41)	ACCP/SCCM	PATHFAST	Prospective
Ulla et al ²³	Italy	106/83	Presented to the ED with ≥2 criteria for SIRS	SIRS (n = 83)	Int. guideline	PATHFAST	Prospective
Vodnik et al ²²	Serbia	30/30	Acute abdomen with ≥2 criteria for SIRS	SIRS (n = 30)	ACCP/SCCM	PATHFAST	Prospective
Yaegashi et al ¹⁴	Japan	66/155	NR	SIRS (n = 80), HC (n = 75)	ACCP/SCCM	ELISA	Unknown

ABA = American Burn Association; ACCP = American College of Chest Physicians; ED = emergency department; HC = healthy controls; ICU = intensive care unit; Int. = international; IPSCG = International Pediatric Sepsis Consensus Guidelines; NR = not reported; SCCM = Society of Critical Care Medicine; SIRS = systemic inflammatory response syndrome; SSIDCM = Spanish Society of Infectious Diseases and Clinical Microbiology.

TABLE 2. Quality Assessment of the 11 Studies

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Cakir Madenci et al ²⁶	High	Unclear	Low	Low	High	Low	Low
Endo et al ²¹	Unclear	Unclear	Low	Low	Low	Low	Low
Kweon et al ²⁷	High	Unclear	Low	Low	High	Low	Low
Liu et al ²⁴	High	Low	Low	Low	High	Low	Low
Nakamura et al ²⁹	Low	High	Low	Low	Low	Low	Low
Romualdo et al ²⁵	Low	High	Low	Low	Low	Low	Low
Sargentini et al ²⁸	High	High	Low	Low	Low	Low	Low
Shozushima et al ²⁰	High	Unclear	Low	Low	Low	Low	Low
Ulla et al ²³	Low	High	Low	Low	Low	Low	Low
Vodnik et al ²²	Unclear	Unclear	Low	Low	Low	Low	Low
Yaegashi et al ¹⁴	High	High	Low	Low	High	Low	Low

The sROC AUC of presepsin for sepsis was 0.88 (95% CI: 0.84–0.90; Figure 3). According to the Fagan nomogram of the present meta-analysis (Fig. 4), the pretest probability of the presence of sepsis was 0.56 among all subjects (ie, a prevalence of 56%). When presepsin was introduced as a diagnostic test for sepsis, the posttest probabilities of sepsis was 0.81 for a positive result and 0.19 for a negative. Taken together, these results indicate that presepsin was a useful biomarker for sepsis diagnosis.

Subgroup Analysis and Meta-Regression

The goal of a meta-analysis is not limited to pooling the results of available studies, but an exploration of the sources for heterogeneity is also important. In the present study, we found that the I^2 statistic for the present meta-analysis was 0.94 (95% CI: 0.90–0.99), indicating that great heterogeneity existed across all the studies. However, the proportion of heterogeneity that was likely due to the threshold effect was only 0.02, implying that nonthreshold effect factors accounted for the high heterogeneity. We hypothesized that the potential sources of heterogeneity were the study design or participant characteristics. Such factors might be the type of data collection (prospective or not), country of origin (Europe or not), sample size (> 200 or not), control group (whether healthy controls

were included), reference for criteria (ACCP/SCCM or not), or the site of subject enrollment (emergency department or not). Therefore, subgroup analyses and univariate meta-regression were performed to explore these potential sources of heterogeneity (Fig. 5).

Generally, the factors mentioned above could influence the sensitivity and specificity of presepsin as a diagnostic test. Knowing that the threshold effect was not taken into consideration in the subgroup analysis, we further explored the sources of heterogeneity via meta-regression. In the joint model, only the reference for criteria proved to be the source of heterogeneity across all studies ($P=0.03$). Thus, the source of heterogeneity was whether the ACCP/SCCM guideline was used as the criteria reference, and a study based on the ACCP/SCCM guideline had high diagnostic accuracy.

Publication Bias

Deek funnel plot test showed that publication bias was not statistically significant ($P=0.12$; Figure 6).

DISCUSSION

The present systematic review included 11 published studies that investigated the value of circulatory presepsin as

TABLE 3. Diagnostic Accuracy of the Eligible Studies

	Thresholds (pg/mL)	AUC	Sensitivity	Specificity	TP	FP	FN	TN
Cakir Madenci et al ²⁶	542	0.83	0.77	0.76	186	88	54	283
Endo et al ²¹	600	0.91	0.88	0.81	101	13	14	57
Kweon et al ²⁷	430	0.94	0.88	0.82	64	5	9	37
Liu et al ²⁴	317	0.82	0.71	0.86	481	40	199	239
Nakamura et al ²⁹	670	NR	0.70	0.81	86	23	36	102
Romualdo et al ²⁵	729	0.75	0.81	0.63	30	70	7	119
Sargentini et al ²⁸	600	0.89	0.86	0.72	52	12	8	32
Shozushima et al ²⁰	415	0.85	0.80	0.81	81	8	20	33
Ulla et al ²³	600	0.70	0.79	0.62	84	32	22	51
Vodnik et al ²²	630	1.00	1.00	0.93	30	2	0	28
Yaegashi et al ¹⁴	NR	0.82	0.92	0.75	61	39	5	116

AUC = area under sROC curve; FN = false negative; FP = false positive; NR = not reported; TN = true negative; TP = true positive.

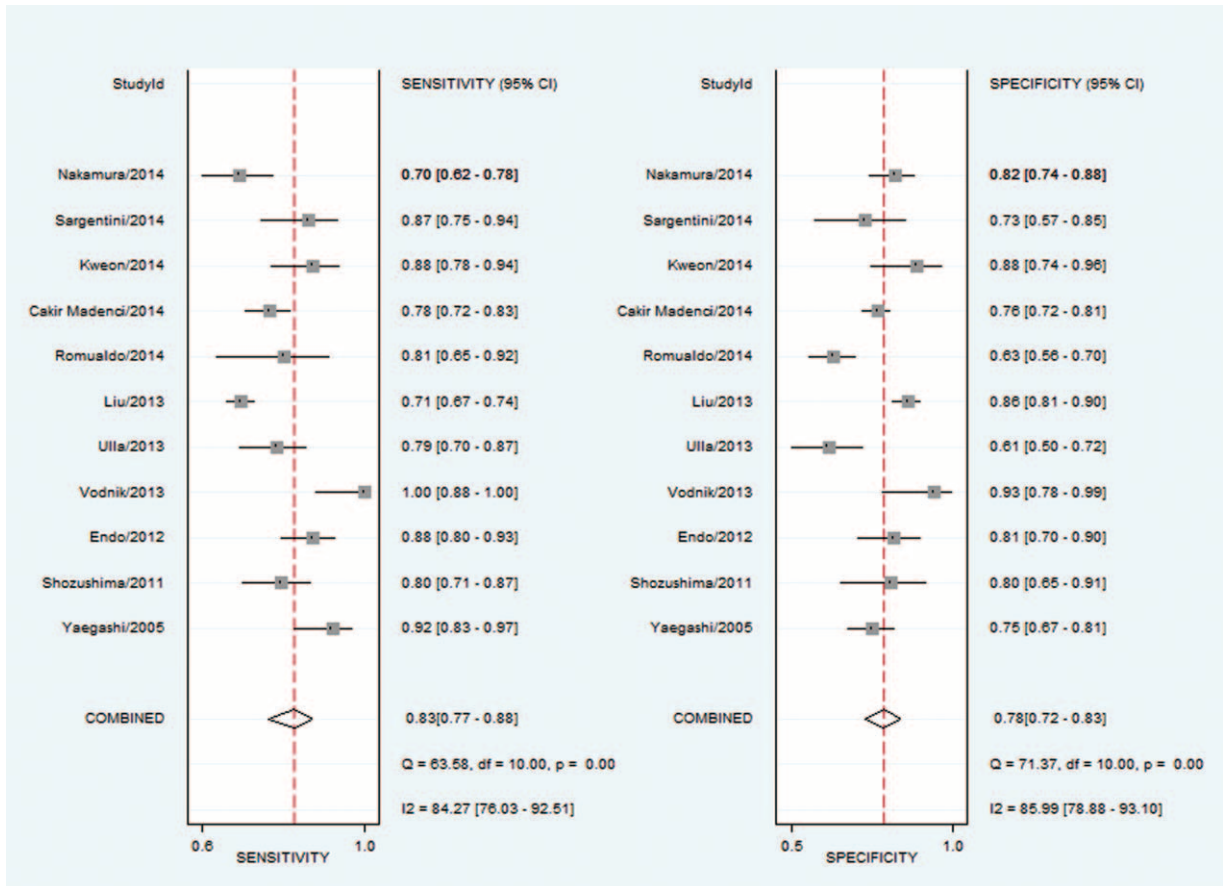


FIGURE 2. Sensitivity and specificity of presepsin for the diagnosis of sepsis assessed by Forest plots.

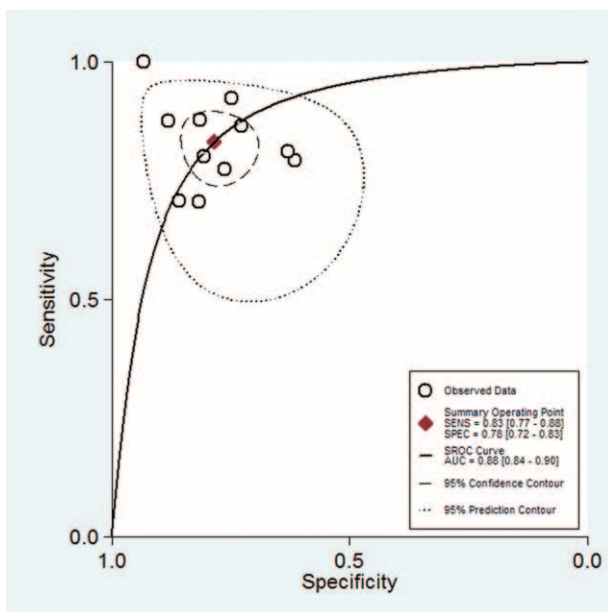


FIGURE 3. The AUC of presepsin for the diagnosis of sepsis. The overall diagnostic efficiency is summarized by the regression curve.

a biomarker for sepsis. The meta-analysis revealed that presepsin was an effective diagnostic marker for sepsis, with an overall sensitivity and specificity of 0.83 and 0.78, respectively. Some of the eligible studies had design defects, such as not enrolling subjects consecutively or not using a prespecified threshold. The publication bias across all the studies was negative.

Generally, there is a trade-off between sensitivity and specificity in a test of diagnostic accuracy. That is, an increase in sensitivity (the true positive rate) is usually accompanied by a reduction in specificity (the true negative rate). Therefore, sensitivity and specificity alone may not be the best estimation of diagnostic accuracy. Alternatively, the area under the sROC, or AUC, may be a better index. The AUC ranges between 0.50 and 1.00, and correlates with overall diagnostic accuracy. The present study found that the AUC for sROC was 0.88, indicating that presepsin was a useful diagnostic marker for sepsis.

Although the AUC is a well-established index to estimate the overall diagnostic accuracy of an index test, it is not easy to interpret and use in clinical practice. By contrast, the positive and negative likelihood ratios are considered more clinically meaningful.³⁸ The present meta-analysis found that the positive and negative likelihood ratios of presepsin for revealing sepsis were 3.9 and 0.21, respectively. This indicates that the chance that a patient with sepsis has elevated presepsin is almost 4-fold that of a patient without sepsis, while a patient testing negative

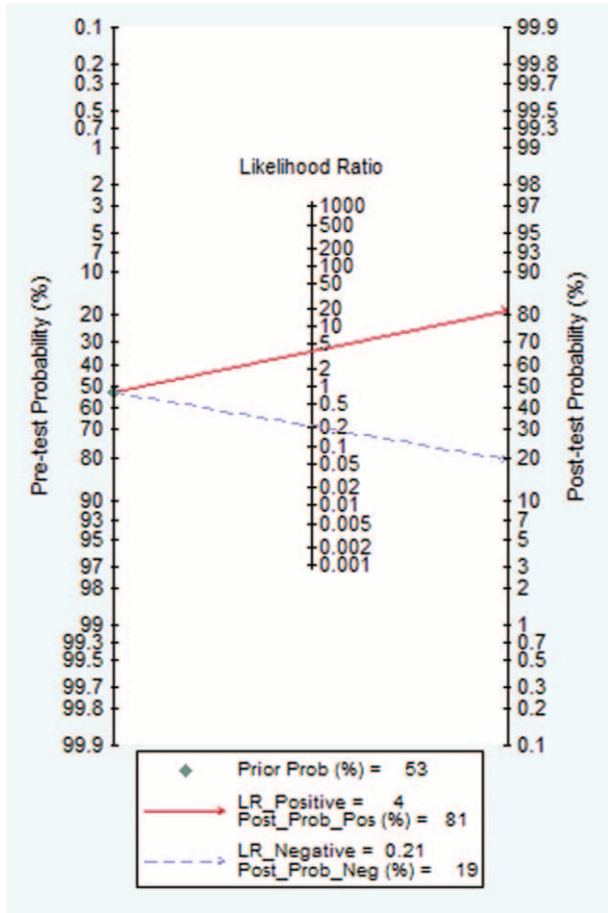


FIGURE 4. Fagan nomogram used to illustrate the posttest probabilities of presepsin.

for presepsin is only 21% likely to have sepsis. Generally, a positive likelihood ratio higher than 10 indicates that the test under consideration is sufficient to confirm the diagnosis, while a negative likelihood ratio less than 0.10 means that the negative index test is sufficient to rule out the target disease.³⁹ Therefore, we conclude that presepsin cannot be used to confirm or rule out sepsis when used alone, and its results should be interpreted within the clinical context. According to the Fagan nomogram, the posttest probability for presepsin indicating sepsis was 0.81 for a positive test result and 0.19 for a negative test result. This further confirmed our conclusion that presepsin, when used alone, is not sufficient to confirm or rule out sepsis.

We note that there was great heterogeneity across the 11 studies. A subgroup analysis revealed that the only verifiable source of heterogeneity was the reference that was used for diagnostic criteria. However, it should be noted that the possibility of other sources of heterogeneity should not be discounted, due to the small number of studies. In particular, characteristics of the enrolled subjects may be a potential source of heterogeneity, but because the inclusion and exclusion criteria of these studies varied and the number of studies in each subgroup was small, a subgroup analysis and meta-regression was not performed to resolve this question. This issue needs to be addressed in future studies.

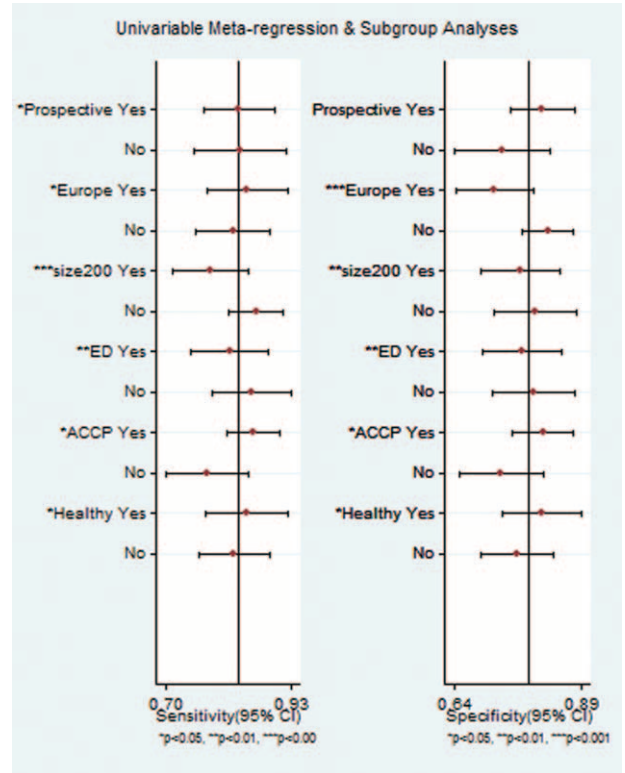


FIGURE 5. Subgroup analysis of presepsin for sepsis diagnosis.

Procalcitonin is an acknowledged biomarker for sepsis.⁴⁰ It would be valuable to address whether the combined use of procalcitonin and presepsin could improve the diagnostic accuracy of sepsis in a cost-effective manner. However, none of the eligible studies discussed this issue. Further studies are needed to settle this, using rigorous statistical methods such as a logistic regression model, net reclassification, and integrated discrimination.^{41–44}

Flaws in the design of these studies should be considered when interpreting the results of the present systematic review. Some studies included healthy individuals in the control group, which may lead to a great overestimation of the diagnostic value

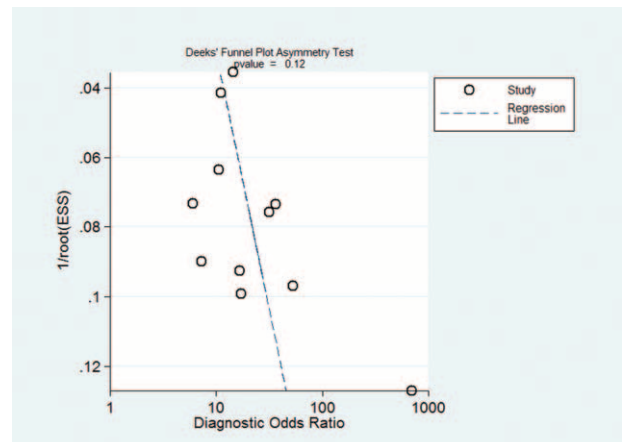


FIGURE 6. Funnel plot for the assessment of publication bias.

of presepsin.⁴⁵ Some of the studies were not in accordance with the Standards for Reporting of Diagnostic Accuracy.⁴⁶ For example, it is sometimes not clear how the investigators selected the subjects (consecutively, randomly, or neither).^{16,47} If the subjects were not recruited either consecutively or randomly, this may introduce selection bias. The thresholds used in the studies were not always prespecified, which may also introduce bias.⁴⁸ In addition, the stability of presepsin in storage should be accounted for. According to the package insert of the PATHFAST Presepsin kit, plasma samples are stable for only 3 days at 2 to 8°C and 9 months at -20°C or lower. Four^{23–25,32} of the studies used frozen samples for analysis, but they did not report the period between sample collection and analysis. If the sample storage period was more than 9 months, the test result may not be reliable and a bias may be introduced.

Some of the studies reviewed here also reported that presepsin correlated with procalcitonin,^{14,22,24} C-reactive protein,¹⁴ or scores for Sequential Organ Failure Assessment,¹⁴ Mortality in Emergency Department Sepsis,²⁴ and Acute Physiology and Chronic Health Evaluation II.^{20,22,24} Since all these indices are well-established prognostic factors in sepsis, it could be concluded that presepsin is also a potential prognostic biomarker. Indeed, 2 studies reported that presepsin was a useful predictor of 28-day²⁴ or 60-day²³ mortality. These results warrant further investigation into the prognostic value of presepsin for the diagnosis of sepsis.

CONCLUSIONS

The present systematic review indicates that presepsin is an effective biomarker for the diagnosis of sepsis, and may prove comparable to procalcitonin. However, when used as the only diagnostic test, presepsin is insufficient to rule out or confirm sepsis, and its diagnostic value should be interpreted with consideration given to the clinical context.

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