

Presepsin as a diagnostic marker for sepsis: evidence from a bivariate meta-analysis

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Background: The diagnosis of sepsis remains a clinical challenge. Many studies suggest that presepsin plays a role in diagnosing sepsis, but the results remain controversial. This study aimed to identify the overall diagnostic accuracy of presepsin for sepsis through meta-analysis.

Methods: A systematic literature search was performed in PubMed and EMBASE to identify studies evaluating the diagnostic accuracy of presepsin in sepsis patients. Data were retrieved and the pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio (DOR) were calculated. A summary receiver operating characteristic curve and area under curve (AUC) were used to evaluate the overall diagnostic performance. The statistical analysis was performed using Stata 12.0 and Meta-DiSc 1.4 software.

Results: Eleven publications with 3,106 subjects were included in the meta-analysis. The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and DOR were 0.83 (95% confidence interval [CI] 0.77–0.88), 0.81 (95% CI 0.74–0.87), 4.43 (95% CI 3.05–6.43), 0.21 (95% CI 0.14–0.30), and 21.56 (95% CI 10.59–43.88), respectively. The area under the curve was 0.89 (95% CI 0.86–0.92). Estimated positive and negative post-probability values for a sepsis prevalence of 20% were 53% and 5%, respectively. No publication bias was identified.

Conclusion: Based on currently available evidence, presepsin may have a valuable role in the diagnosis of sepsis, and its results should be interpreted carefully in the context of clinical condition and traditional markers.

Keywords: sepsis, presepsin, diagnosis, meta-analysis

Introduction

Sepsis is defined as a potentially fatal systemic inflammatory response syndrome (SIRS) caused by severe infection.^{1,2} Sepsis affects millions of patients worldwide each year, and in the USA is the cause of almost 750,000 hospital visits, 570,000 emergency department admissions, 200,000 deaths, and 16.7 billion dollars in medical expenditure every year.^{2,3} Based on report of the promoting global research excellence in severe sepsis, in developing countries, the mortality rate for sepsis tends to be worse, at 56% in Brazil and 45% in other developing countries, as compared with 30% in developed countries.⁴ According to the latest published literature, during the first decade of the 21st century, the nationwide average mortality was nearly one per 100,000 persons in mainland China.⁵ Further, the occurrence of sepsis continues to increase.¹

Current guidelines recommend that antibacterial therapy should be initiated as soon as possible to optimize clinical outcomes in patients with sepsis.⁶ However, due to the coexistence of non-infectious SIRS in many critical patients without specific symptoms, how to identify and differentiate sepsis from SIRS at an early stage remains a clinical challenge. Many biomarkers can be used in the diagnosis of sepsis, but none has sufficient specificity or sensitivity to be routinely employed in clinical practice.

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Procalcitonin and C-reactive protein have been widely used, but have a limited ability to distinguish sepsis from other inflammatory conditions or to predict outcome.⁷ Therefore, the search for a novel and reliable biomarker which is helpful for early diagnosis of sepsis is ongoing.

In 2005, presepsin, a new sCD14-subtype biomarker, was identified.⁸ Presepsin is a soluble N-terminal fragment of the cluster of differentiation (CD) marker protein CD14.⁸ Presepsin is released into the circulation during activation of monocytes upon recognition of lipopolysaccharide from infectious agents, so has a role in the diagnosis of sepsis.^{8,9} In recent years, a number of studies have investigated the potential of presepsin in the diagnosis of sepsis, and have reached conflicting conclusions about whether presepsin can provide adequate differentiating power.¹⁰ To reach a more reliable conclusion, we performed a meta-analysis of the literature reporting on the use of presepsin to diagnose sepsis.

Materials and methods

This meta-analysis was performed using the guidelines of the Preferred Reporting Items for Systematic Reviews, as well as the meta-analysis statement and methods recommended by the Cochrane Diagnostic Test Accuracy Working Group.^{11,12} Institutional review board approval was not required for this retrospective meta-analysis, and no ethics statement was needed.

Search strategy and literature selection

PubMed and EMBASE were used as the main search engines to identify suitable studies up to December 2014. The following key search terms were used: “sepsis OR severe sepsis OR septic shock” AND “sCD14-subtypes OR presepsin” AND “sensitivity OR specificity OR accuracy”. References of included articles were also searched manually to identify relevant publications. Included studies had to meet all of the following criteria: the study evaluated the diagnostic accuracy of presepsin for sepsis in humans; it had clear diagnostic criteria for sepsis; it could supply or calculate data for both sensitivity and specificity; and publication in English. Abstracts, letters, and reviews were excluded because of the limited information they provided; studies that did not report or could not calculate sensitivity or specificity and those with overlapping or repeating data were also excluded.

Data extraction and quality assessment

All included studies were assessed by two independent reviewers in order to reduce the risk of errors. In the event of disagreement, a third author assessed the articles and

made the final decision. A data extraction form was created and the data retrieved from the articles included first author, publication year, the country of origin, samples, presepsin assay methods, cutoff value, and true positive, false positive, true negative, and false negative numbers for each study. For studies containing several groups or different backgrounds, each one was treated as a single study. The quality of the selected studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) list, an evidence-based approach for quality assessment in systematic reviews of diagnostic accuracy studies, which includes 14 items assessing risk of bias, sources of variation (applicability), and reporting quality; each item is rated “yes”, “no”, or “unclear”. The maximum value for each study is 14.¹³

Meta-analysis

This study was performed according to the standard bivariate meta-analysis method.¹⁴ First, we calculated pooled estimates of sensitivity and specificity, with corresponding 95% confidence intervals (CIs). Based on the pooled estimates of sensitivity and specificity, we calculated positive likelihood ratios (PLRs), negative likelihood ratios (NLRs), and diagnostic odds ratios (DORs), which we used as overall indices of diagnostic accuracy. We also constructed a summary receiver operating characteristic (SROC) curve and calculated the area under the curve (AUC) to summarize the overall diagnostic performance of presepsin.

Heterogeneity was assessed using the I^2 inconsistency test. $I^2 > 50\%$ indicated substantial heterogeneity, which was then analyzed by meta-regression to identify potential covariates. Post-test probability was calculated using an overall prevalence of 20% with Fagan nomograms. A Deeks' funnel plot was used to detect publication bias.¹⁵ All analyses were performed using the Midas module in Stata 12.0 (Stata Corporation, College Station, TX, USA) and Meta-DiSc 1.4 for Windows (XI, Cochrane Colloquium, Barcelona, Spain). All statistical tests were two-sided, with P -values less than 0.05 taken as the threshold for statistical significance.

Results

Characteristics of included studies

A total of eleven publications including 12 studies published in 2011–2015 were included in this meta-analysis.^{16–26} The main reasons for excluding a study were: the study could not retrieve sensitivity and specificity data and reconstruct a 2×2 table or they were not diagnostic studies. The study selection process is shown in Figure 1.

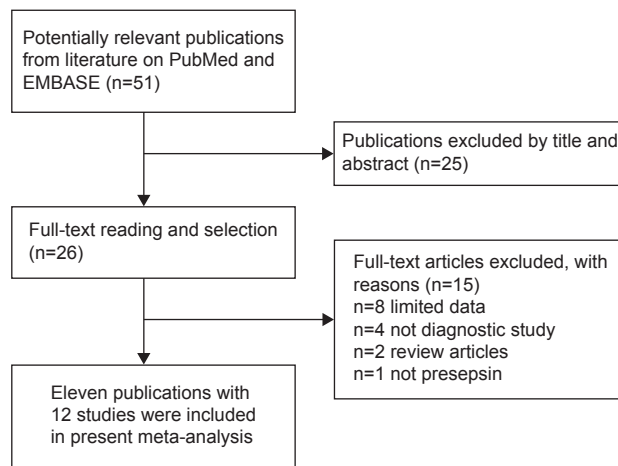


Figure 1 Flow of study identification, inclusion, and exclusion.

The 12 studies included 1,725 sepsis patients and 1,381 control subjects. Eight studies were performed in Asia^{16–18,23–26} and four were done in Europe.^{19–22} Six studies used plasma as the assay sample,^{18–23} four used whole blood,^{16,17,24,26} and two used serum.²⁵ All the samples were analyzed by chemiluminescent enzyme immunoassay, and the cutoff values ranged from 317 to 864 pg/mL. For sepsis patients, all the studies supplied detailed diagnostic criteria, which are widely accepted for studies regarding sepsis. With the exception of one retrospective study,²⁵ all the studies were prospective. Except for one study with a QUADAS score <10,¹⁶ all studies had a QUADAS score ≥ 10 , indicating that our results were reliable. Table 1 summarizes the clinical characteristics and QUADAS scores for all the included studies.

Diagnostic accuracy

The following pooled parameters were calculated over all 12 studies examining presepsin for diagnosis of sepsis: sensitivity, 0.83 (95% CI 0.77–0.88); specificity, 0.81 (95% CI 0.74–0.87); PLR, 4.43 (95% CI 3.05–6.43); NLR, 0.21 (95% CI 0.14–0.30) (Figure 2); and DOR, 21.56 (95% CI 10.59–43.88). All five performance indices showed high I^2 values, ie, sensitivity 85.46%, specificity 82.65%, PLR 75.54%, NLR 84.38%, and DOR 100.00% (all $P < 0.05$), suggesting substantial heterogeneity among the included studies.

Figure 3 gives the SROC curve for the included studies, and shows a plot of the rate of true positives as a function of the rate of false positives for the individual studies. The AUC was 0.89 (95% CI 0.86–0.92), indicating a good discriminatory ability of presepsin measurement for sepsis. Fagan's nomogram for likelihood ratios indicates that using presepsin to diagnose sepsis increased the post-probability to 53% when the results were positive and reduced the

Table 1 Clinical summary of included studies

References	Year	Country	Sepsis	No sepsis	Samples	Method	Cutoff value	TP	FP	FN	TN	Design	QUADAS
Shozushima et al ¹⁶	2011	Japan	101	41	Whole blood	CLEIA	415 pg/mL	81	8	20	33	P	9
Endo et al ¹⁷	2012	Japan	115	70	Whole blood	CLEIA	600 pg/mL	101	13	14	57	P	10
Liu et al ¹⁸	2013	People's Republic of China	680	279	Plasma	CLEIA	317 pg/mL	481	40	199	239	P	10
Ulla et al ¹⁹	2013	Italy	106	83	Plasma	CLEIA	600 pg/mL	84	32	22	51	P	11
Vodnik et al ²⁰	2013	Serbia	30	100	Plasma	CLEIA	630 pg/mL	30	2	0	98	P	12
Behnes et al ²¹	2014	Germany	74	102	Plasma	CLEIA	700 pg/mL	67	24	7	78	P	11
Cakir Madenci et al ²²	2014	Turkey	26	11	Plasma	CLEIA	542 pg/mL	20	3	6	8	P	10
Ishikura et al ²³	2014	Japan	43	39	Plasma	CLEIA	647 pg/mL	40	9	3	30	P	10
Kweon et al ²⁴	2014	Korea	73	45	Whole blood	CLEIA	430 pg/mL	64	8	9	37	P	12
Nakamura et al ²⁵	2014	Japan	37	75	Serum	CLEIA	670 pg/mL	26	14	11	61	R	12
Nakamura et al ²⁵	2014	Japan	81	47	Serum	CLEIA	864 pg/mL	58	17	23	30	R	12
Takahashi et al ²⁶	2015	Japan	359	489	Whole blood	CLEIA	685 pg/mL	285	82	74	407	P	11

Abbreviations: CLEIA, chemiluminescent enzyme immunoassay; TP, true positive; FP, false positive; FN, false negative; TN, true negative; R, retrospective; QUADAS, Quality Assessment of Diagnostic Accuracy Studies.

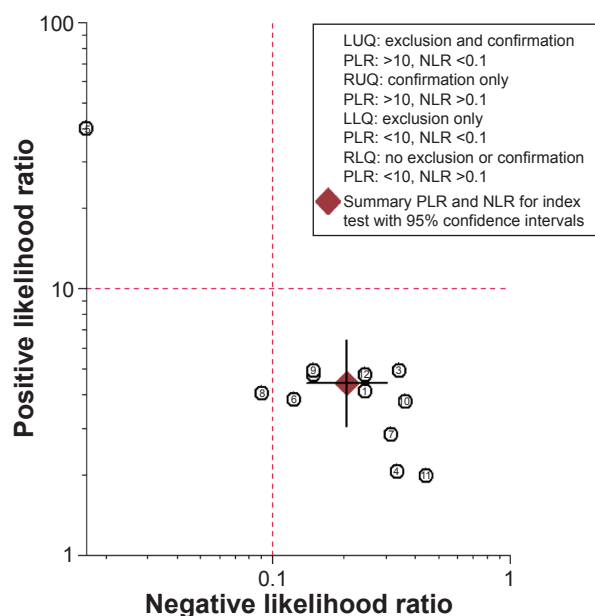


Figure 2 Scatterplot of the positive likelihood ratio and negative likelihood ratio when using presepsin to diagnose sepsis.

Abbreviations: LUQ, left upper quadrant; RUQ, right upper quadrant; LLQ, left lower quadrant; RLQ, right lower quadrant; PLR, positive likelihood ratio; NLR, negative likelihood ratio.

post-probability to 5% when the results were negative (Figure 4).

Meta-regression and publication bias

We identified significant heterogeneity among the included studies, so a meta-regression analysis was performed to explore the possible sources for this heterogeneity. We used

SROC with confidence and predictive ellipses

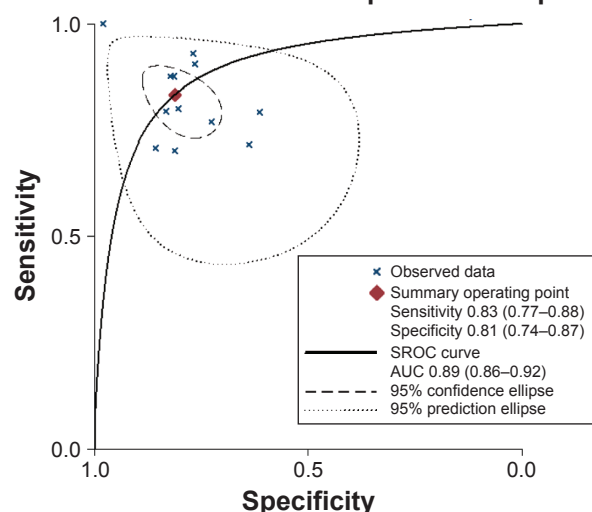


Figure 3 Summary receiver operating characteristic curve for presepsin measurements to diagnose sepsis.

Abbreviations: AUC, area under the curve; SROC, summary receiver operating characteristic.

Fagan's nomogram

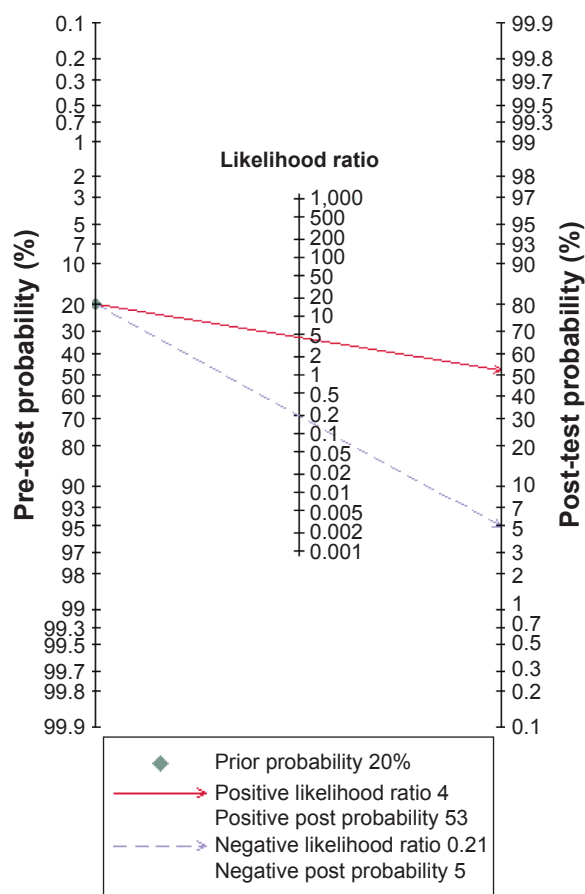


Figure 4 Fagan's nomogram for likelihood ratios and pre-test and post-test probabilities when using presepsin measurements to diagnose sepsis.

four covariates in the meta-regression: country of origin (Asia versus non-Asia); test samples (plasma versus serum or whole blood); cutoff value (≥ 600 versus < 600 pg/mL); and study design (prospective versus retrospective). The outcomes of the regression are shown in Table 2. In the present study, none of the above covariates were found to be significant sources of heterogeneity (all $P > 0.05$).

We used the Deeks' funnel plot asymmetry test to assess for the likelihood of publication bias. The slope coefficient for presepsin was associated with a P -value of 0.49, suggesting symmetry in the data and a low likelihood of publication bias (Figure 5).

Discussion

Making an early and accurate diagnosis is critical for improving the prognosis in patients with sepsis. Current methods or biomarkers used for the diagnosis of sepsis remain unsatisfactory,⁷ and more reliable diagnostic markers are needed. A growing number of studies suggest that presepsin

Table 2 Meta-regression of potential heterogeneity for the included studies

Covariates	Studies (n)	Coefficient	SE	RDOR (95% CI)	P-value
Country					
Asia	8	0.378	0.9665	1.46 (0.14–15.53)	0.7095
Non-Asia	4				
Sample					
Plasma	6	0.029	0.8383	1.03 (0.13–8.00)	0.9739
Non-plasma	6				
Cutoff value (pg/mL)					
≥ 600	8	0.483	0.7711	1.62 (0.25–10.69)	0.5543
< 600	4				
Design					
P	10	1.465	0.9315	4.33 (0.44–42.27)	0.1669
R	2				

Abbreviations: CI, confidence interval; P, prospective; R, retrospective; RDOR, relative diagnostic odds ratio; SE, standard error.

may play a role in identifying sepsis, and our present study summarizes the overall diagnostic performance of presepsin for sepsis based on the current available literature.

Our results reveal that the sensitivity and specificity of presepsin were 0.83 and 0.81, respectively, with a relatively high rate of missed diagnosis (17%) and misdiagnosis (19%). Likelihood ratios are indices that take into account the interaction between sensitivity and specificity in their calculation, and a PLR of 10 and NLR of 0.1 are considered to be convincing evidence to rule in or rule out a diagnosis, respectively.²⁷ In this study, the overall PLR was 4.43, suggesting that the likelihood of a positive presepsin assay result was about fourfold higher in sepsis patients than in patients without sepsis. The pooled NLR was 0.21, suggesting the subjects remains may be sepsis patients even the results of presepsin was negative. The DOR combines

the strengths of sensitivity and specificity and has the advantage of accuracy as a single indicator, with higher values indicating higher accuracy. In this meta-analysis, the mean DOR was 21.56, indicating a relatively high level of overall accuracy. The SROC curve was also used to summarize the overall diagnostic performance of the included studies, and the AUC was 0.89, indicating good diagnostic performance.

Although presepsin has an important role in diagnosing sepsis, we suggest that measurement of presepsin be combined with other traditional markers, such as procalcitonin, C-reactive protein, and white blood cells. From a recent published meta-analysis, the sensitivity and specificity of procalcitonin in diagnosing sepsis were 0.77 and 0.79, respectively;²⁸ however, procalcitonin is still a valuable diagnostic marker for sepsis in clinical practice.²⁹ Further, sepsis patients may benefit from procalcitonin-guided therapy with a shorter duration of antibiotic treatment when compared with standard care.³⁰ In this study, we also noticed a relatively high rate of missed diagnosis and misdiagnosis using presepsin, so this indicator may not be reliable enough on its own but should instead be used in conjunction with more conventional tests, such as procalcitonin, rather than replace procalcitonin. Thus, it would be better to set up a diagnostic model or a decision tree when using these markers.^{31,32} With improvements in presepsin assay methods, presepsin may become a point-of-care tool for bedside diagnosis of sepsis in the future.

The clinical interpretation of presepsin results should take into account the clinical context of the patient. For example, the AUC was 0.784 in a non-acute kidney injury group and 0.698 in an acute kidney injury group when presepsin was used to diagnose sepsis.²⁵ In our meta-analysis, we also included patients with abdominal sepsis or burn sepsis, and

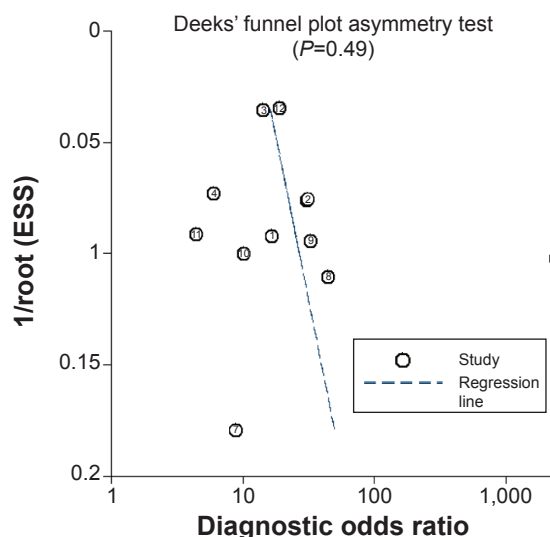


Figure 5 Deeks' funnel plot assessing the likelihood of publication bias.
Abbreviation: ESS, effective sample size.

the diagnostic performance of presepsin in these two kinds of sepsis were also different.^{20,22} Presepsin concentrations increase with age and kidney dysfunction, so interpretation of presepsin concentrations might be different in the elderly or in patients with impaired renal function.²⁵ Adapted thresholds are needed for specific populations in clinical practice.³³ We suggest that the results of a presepsin assay must be interpreted carefully in the context of medical history, physical examination, and microbiological assessment of patients.

Measurement of presepsin concentrations is not only useful for diagnosis of sepsis and evaluating its severity, but also for predicting the prognosis of patients with sepsis. Masson et al reported that early presepsin was higher in patients with severe sepsis or septic shock who died than in those who survived, and suggested that presepsin measurements may be of clinical importance for early risk stratification and provide useful prognostic information in these patients.³⁴ Further, Endo et al reported that continuous measurement of presepsin has a role in monitoring the clinical response to therapeutic interventions in patients with sepsis.³⁵ The results of these two results suggest that monitoring of presepsin is more clinically meaningful except for sepsis diagnosis.

Our study also has several limitations that should be discussed. First, we included only eleven publications because of our strict inclusion criteria, so our study may have lacked enough statistical power to draw a definite conclusion, and more clinical diagnostic studies are needed to be able to reach a final conclusion. Second, we identified significant heterogeneity among the included studies; although we performed a meta-regression to determine possible covariates, we did not find meaningful covariates. Thus, the heterogeneity could not be explained by meta-regression analysis. Further studies should pay attention to this problem. Finally, we only included studies published in English, which may have resulted in language bias, and the inclusion of other language publications or studies with null results may have yielded different results.

Conclusion

Taken together, our results suggest that presepsin plays a valuable role in the diagnosis of sepsis. Clinical interpretation of presepsin results should consider other traditional markers and the clinical context of the individual patient. Further studies should be performed to validate our findings.

Disclosure

The authors report no conflicts of interest in this work.

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