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Presepsin as an important diagnostic biomarker that differentiates sepsis from non-infectious SIRS in critical ill adult patients: A system review and meta-analysis

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Abstract: **Introduction:** Identifying sepsis from non-infectious SIRS is difficult, especially in patients with severe diseases, such as multiple trauma, pancreatitis, peritonitis, ongoing surgery and severe burns. There is no standard biomarker for sepsis, not even procalcitonin (PCT). Presepsin was reported as a promising marker for diagnosis of bacterial infections. In this study, we conducted a meta-analysis to investigate the accuracy and clinical value of presepsin in diagnosing sepsis from SIRS of non-infectious origin in adult patients with critical illness. **Methods:** Systematical literature search was performed on Medline, Embase and the Cochrane Library. Only studies with presepsin for septic patient diagnosis were included. Outcomes of each study were independently examined by two reviewers. MetaDiSc 1.4 software was used for pooling estimates, and sensitivity and specificity analysis. I2 and meta-regression were adopted to evaluate and explore the source of heterogeneity. **Results:** 5 of 314 reports met the inclusion criteria. Those 5 studies included 468 patients. The pooled diagnosis sensitivity and specificity were 0·86 (95% CI 0.82–0.89) and 0.69 (95% CI 0.63–0.75) respectively. The summery receiver operating characteristic curve was 0.8799. Only studies with the blood sample collected on admission were analyzed, with the mean estimates of sensitivity and specificity at 0.85(95% CI: 0.79–0.90) and 0.72 (95% CI: 0.64–0.79) respectively. The area under the curve was 0.9256. The studies had substantial heterogeneity. None of the subgroups investigated could account for the heterogeneity. **Conclusion:** Presepsin is a significant marker for sepsis diagnosis in critically ill patients. Presepsin detection on patient admission can improve the diagnostic capability in differentiating sepsis from non-infectious SIRS.

Keywords: presepsin; sepsis; systemic inflammatory response syndrome

Sepsis is a systemic host response to invasive infection and can lead to severe sepsis or septic shock. Sepsis, severe sepsis and septic shock are common in the emergency department (ED) and ICU, even with modern antibiotic therapy in conjunction with cardiovascular and respiratory support. Mortality rate remains high [1-4]. Therefore, accurate and timely diagnosis can minimize morbidity, shorten the hospital stay, reduce costs, and improve patients' life quality.

Sepsis is diagnosed based on evidence of infection along with the presence of systemic inflammatory response syndrome (SIRS) defined by the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) guidelines [5]. Diagnosis of sepsis is challenging, because early clinical symptoms of sepsis, such as fever, tachycardia, and leucocytosis, are not specific and may overlap with

symptoms of other SIRS with non-infectious causes, especially in patients who have severe diseases, such as multiple trauma, pancreatitis, peritonitis, ongoing surgery and severe burns. Standard microbiological cultures can be used to distinguish sepsis from non-infectious SIRS. However, this method doesn't have the required sensitivity and specificity, and it takes some time before positive results can be obtained. On the other hand, if plasma C-reactive protein (CRP) and procalcitonin (PCT) values are more than two standard deviations (SD) above the normal levels, those indicators, along with infection documented or only suspected, can be used to identify sepsis [6-7]. However, due to the increasing number of patients with non-septic conditions (for example, trauma, surgery, heatstroke), the specificity of this method is questionable[8].

In recent years, presepsin became a reliable marker in sepsis diagnosis. Cluster of differentiation 14 (CD14) is a glycoprotein expressed on the membrane surface of monocytes and macrophages and serves as a receptor for complexes of lipopolysaccharides (LPSs) and LPS-binding proteins (LPBs). It plays an important role in the innate immune system by activating a pro-inflammatory signaling cascade when contacted with microorganisms [9]. With the inflammatory stress, soluble CD14 (sCD14) fragments are cleaved. One of those fragments is sCD14 subtype (sCD14-ST), or presepsin, which normally presents at very low concentrations in the serum of healthy individuals and increases in response to bacterial infections. Presepsin level in plasma can be readily measured using the chem-luminescent enzyme immunoassay (PATHFAST).

In this study, we conducted a meta-analysis to investigate the feasibility of using presepsin in sepsis diagnosis among non-infection-related SIRS in adult patients with critical illness. The heterogeneity of patients and the affect of individual covariates were also discussed.

Methods

Search strategy and selection criteria

We systematically searched Medline (via PubMed), Embase and the Cochrane Library for studies that reported the accuracy of presepsin in sepsis diagnosis in adult patients without restrictions on regions, publication types, or languages. The search terms used (free terms) were "(presepsin OR soluble CD14 OR sCD14) AND (sepsis OR "bacterial infection" OR "systemic inflammatory response syndrome" OR SIRS)". We searched the data in each databases ranging between its inception and Oct 24, 2014. We also searched the reference lists of each identified primary study and review. Studies were included in our analysis if they assessed the accuracy of presepsin in differentiating sepsis from other non-infection diseases with a systemic inflammatory response syndrome.

To be eligible, studies must meet one or more SIRS criteria and a well-defined reference standard for sepsis, which included the use of definitions established by the American College of Chest Physicians/ Society of Critical Care Medicine Consensus Conference. Furthermore, the studies must provide sufficient information for the 2×2 contingency table—ie, false and true positives and negatives. Studies on patients without infections or patients younger than 18 years were excluded.

Procedures

Two investigators (DX, KPH) independently extracted the general information and exact data, and independently made the quality assessment on the retrieved studies. Discrepancies were resolved in a consensus meeting. The general information included the first author of the publication, publication year, country of origin, patients demographics, setting (emergency department, intensive care unit), admission category (surgical or medical), patient quantity, sample size, the time point of blood sample collection, severity of illness (sepsis, severe sepsis, or septic shock), diagnostic cut-off points, and disease prevalence. The exact data for extraction was true positive, false positive, false negative and true negative in patients with sepsis and systemic inflammatory response syndrome, stratified by studies. We used the numbers to calculate the pooled diagnosis sensitivity and specificity, and a corresponding CI.

Quality assessment

The methodological quality was assessed by the Newcastle-Ottawa quality assessment scale (NOS) [10], which was developed for cohort and case control studies. The NOS consists of three factors: selection, comparability and outcome (cohort studies) or exposure (case control studies). A score of 0 to 9 (allocated as stars) was assigned during the semi-quantitative assessment of each study, with five or higher numbers indicating high quality.

Statistical analysis

The standard methods recommended for the diagnostic accuracy of meta-analyses were used [11]. The following indexes of test accuracy were calculated for each study: sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR) and a corresponding CI. The diagnostic threshold identified for each study was used to plot the summary receiver operating characteristic (SROC) curve [12]. The Spearman model was applied to assess heterogeneity caused by different cut-off values. Heterogeneity among combined study results was assessed by the degree of inconsistency (I^2) [13]. I^2 greater than 50% indicated a substantial heterogeneity. If I^2 was greater than 50%, the random-effect model (DerSimonian–Laird method) was conducted for the meta-analysis to calculate the pooled sensitivity, specificity, PLR, NLR, DOR and SROC; otherwise, the fixed -effect model (Mantel–Haenszel method) was chosen. If heterogeneity among studies was recorded, meta-regression and subgroup analysis were performed to investigate the source of heterogeneity [14]. The potential factors evaluated by meta-regression analysis were admission category, blood sample, disease severity, disease prevalence, and the time point of sample collection. Since we analyzed the studies that only included the blood sample collected with patient admission, we also tested the potential presence of publication bias using Deeks' funnel plots, since the publication bias was relevant to meta-analyses of diagnostic studies [15]. Analyses were performed using MetaDiSc 1.4 software (http://www.hrc.es/investigacion/metadisc.html) and STATA (version 12.0). All statistical tests were two sided, and statistical significance was defined as P-value <0.05.

Results

Quality of reporting and study characteristics

A total of 314 reports were identified from Medline, EMBASE and the Cochrane Library (Figure 1). Search of the reference lists of those articles and related reviews did not identify more relevant publications. Only five reports [16-20] were included in this meta-analysis. Because in one study investigators reported diagnostic accuracy at two time points, each study was divided into two parts, and six datasets were analyzed. 468 patients and 665 blood samples were included in this analysis.

Among these 665 blood samples, 429 (65%) had sepsis and 236 (35%) had systemic inflammatory response syndrome from noninfectious origins. Neither of the five studies was randomized controlled trial study. The quality assessment was performed using NOS, while technical aspects of each study were not assessed. Two studies were assigned six stars, and the other three studies were assigned seven stars. These studies are summarized in Table 1.

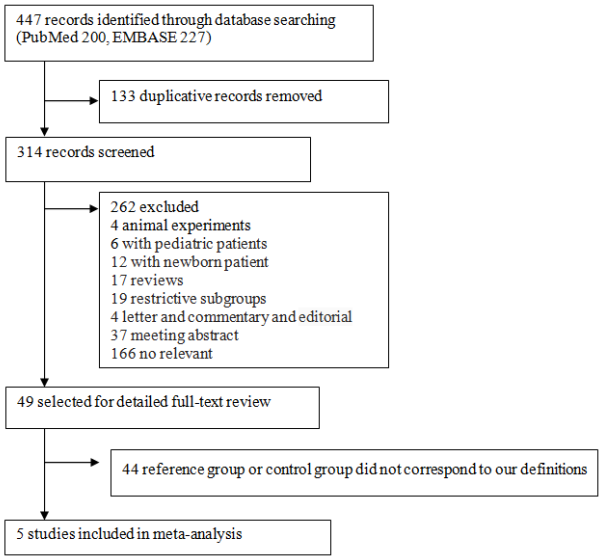

Figure 1: Process for identification of the included studies.

4.47) and 0.19(95% CI: 0.11–0.32), respectively. The pooled diagnostic odds ratio (DOR) was 17.79(95% CI: 7.41–42.68). The area under the receiver operating characteristic curve was 0.8779, and Q-value was 0.8083. (Figure 3)

Substantial heterogeneity existed among studies, but the Spearman value was only -0.143(p=0.787). Therefore, there was no evidence of a threshold effect. To explore the possible reasons for this heterogeneity, meta-regression analysis and subgroup analysis were performed. None of the potential covariates included in the meta-regression was found to be the significant source of heterogeneity (all $p > 0.05$, data not shown). Thus the heterogeneity could not be explained by meta-regression analysis. The analysis only included the blood sample collected on admission, with closely-test thresholds (600-647pg/ml). There was also high inconsistency among studies (I^2=86.6%), with mean estimates of sensitivity and specificity at 0.85 (95% CI: 0.79–0.90) and 0.72 (95% CI: 0.64–0.79) respectively. The overall PLR and NLR were 3.99 (95% CI: 1.64–9.68) and 0.12 (95% CI: 0.02–0.0.62), respectively. The pooled diagnostic odds ratio (DOR) was 37.64 (95% CI: 3.76–377.12). The area under the curve AUC was 0.9256, and Q value was 0.8599.

Publication bias evaluation

Publication bias was explored through Deeks' funnel plots. The shape of the funnel plot did not reveal any evidence of obvious asymmetry (Fig. 4). The Deeks' test also showed a statistically insignificant value (p = 0. 184), indicating that there was no potential publication bias.

Discussion

An accurate diagnosis of sepsis from other serious infections pre-

Study	Year	Admission category	Setting	Patients (n)	Blood sample(n)	The time of blood sample collection	Assay	Cutoff (pg/ml)	Severity	Prevalence (%)	Sensitivity (95%CI)	Specificity (95%CI)	NOS sore
Shozushima[14]	2011	Medical and surgical	ED and ICU	41	141	on admission, 12H,24H ,D3, D5, D7	PATHFAST	415	Sepsis and severe sepsis	71%	0.8 (0.64-0.81)	0.8 (0.65-0.91)	★★★★★★
Vodnik[15]	2013	Surgical	ED	60	60	on admission	PATHFAST	630	Sepsis, severe sepsis and septic shock	50%	1 (0.88-1.00)	0.93 (0.78-0.99)	★★★★★★
Ulla[16]	2013	Medical and surgical	ED	189	189	on admission	PATHFAST	600	Severe sepsis and septic shock	56%	0.78 (0.69-0.86)	0.6 (0.5-0.72)	★★★★★★★
Ishikura[17]	2014	Medical and surgical	ED and ICU	82	82	on admission	PATHFAST	647	Sepsis, severe sepsis and septic shock	52%	0.93 (0.81-0.99)	0.77 (0.61-0.89)	★★★★★★★
Behnes[18]	2014	Medical	ICU	96	96	D3	PATHFAST	530	Sepsis, severe sepsis and septic shock	84%	0.9 (0.81-0.96)	0.6 (0.32-0.84)	★★★★★★★
Behnes[18]	2014	Medical	ICU	96	96	D8	PATHFAST	530	Sepsis, severe sepsis and septic shock	50%	0.94 (0.83-0.99)	0.46 (0.28-0.66)	★★★★★★★

ED=emergency department , ICU=Intensive care unit , NOS = Newcastle-Ottawa quality assessment scale

Table 1: Study characteristics and quality assessment

Diagnostic accuracy

The inter-study heterogeneity analysis revealed the I^2 values of sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and DOR were 77.8% , 78.7% , 75.5% , 64.3% , and 68.7% , respectively. Those results showed high levels of heterogeneity among the five studies [13]. Therefore, the random effect model was used in this meta-analysis to calculate pooled sensitivity, specificity, PLR, NLR and DOR. As a result, the pooled sensitivity and specificity were 0.86(95% CI: 0.82–0.89) and 0.69 (95% CI: 0.63–0.75), respectively (Figure 2). The overall PLR and NLR were 2.92(95% CI: 1.91–

sents challenges because clinical criteria for sepsis diagnosis overlap those for SIRS with noninfectious causes. The lack of a reliable gold standard for sepsis diagnosis is an ongoing challenging in clinical practice. The ideal biomarker should have high sensitivity, specificity, cost-effectiveness, and promptly availability. In recent years, Presepsin became as a promising new biomarker for adults with neonatal sepsis. However, no meta-analysis has been systematically carried out. In this study, we performed this meta-analysis to comprehensively investigate the diagnostic accuracy of presepsin for sepsis.

The present meta-analysis has shown that the pooled sensitivity of

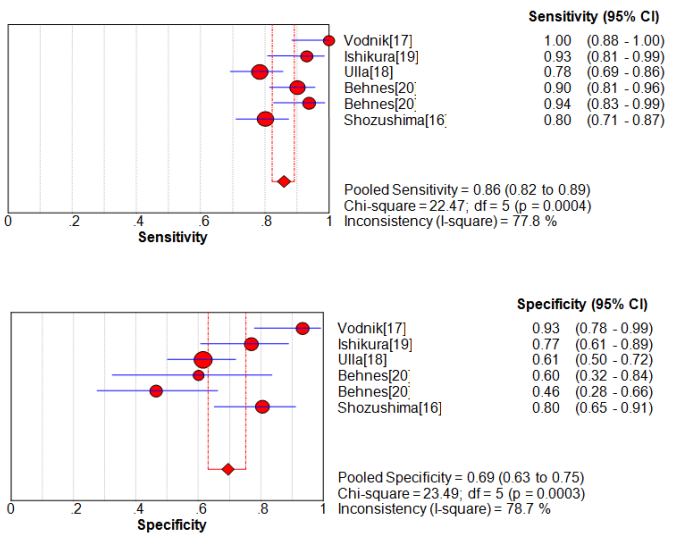

Figure 2: Forest plots of the sensitivity and specificity of presepsin in diagnosis of sepsis

presepsin was 0.86 while the pooled specificity was 0.69. The maximum joint sensitivity and specificity (Q value) was 0.8083, while the AUC was 0.8779, indicating a moderate capability of presepsin in sepsis diagnosis [21]. The DOR, the ratio of the odds of positivity among patients to the odds of positivity among normal individuals, is a single discriminative indicator of diagnostic test performance [22]. In this meta-analysis, the pooled DOR was 17.79, suggesting that presepsin could be used as a good indicator in sepsis diagnosis. However, the SROC curve and the DOR are not easy to interpret and use in clinical practice, while the likelihood ratio (PLR and NLR) is more meaningful for our clinical measures of diagnostic accuracy. A PLR value of 2.92 suggests that patients with sepsis would have 3-fold higher chance of being presepsin-positive compared to those with no-infectious SIRS, and this was not

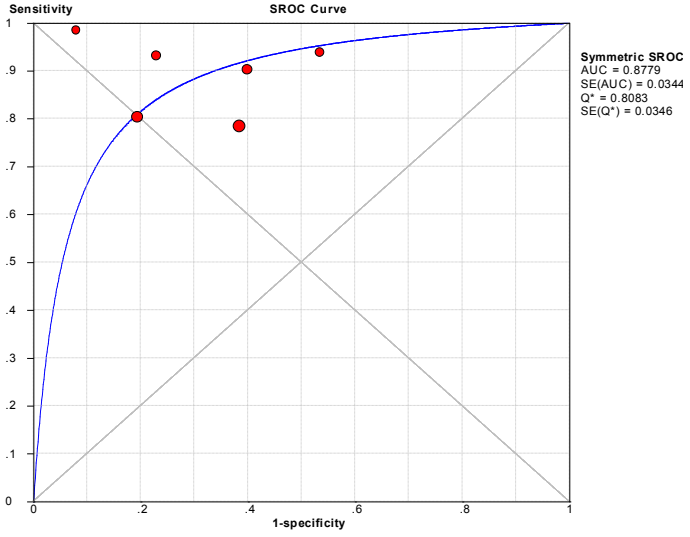

Figure 3: Summary receiver operating characteristic curve

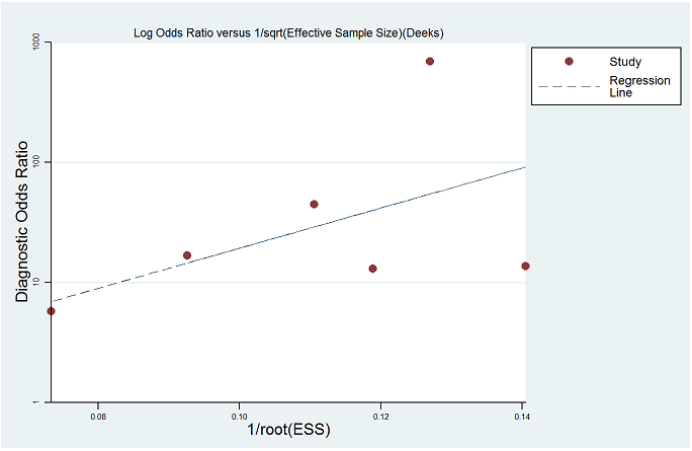

Figure 4: Funnel plot for the assessment of potential publication bias

high enough for clinical practice. On the other hand, the NLR was 0.19, which meant that the probability of sepsis in presepsin-negative patients was 19%, not a good rule-out test.

We did the sensitivity analysis with only the blood samples collected on admission. The specificity, PLR, SROC, Q-value and DOR all improved accordingly, while NLR decreased appreciably. The pooled DOR was 37.64, meanwhile the AUC was 0.9256 and Q value was 0.8599. These data suggested that presepsin detection on admission could improve the diagnosis accuracy of sepsis.

Heterogeneity is a major problem in interpreting the results of a meta-analysis. The threshold effect must be considered as the first factor in examining the analysis accuracy. Spearman value was -0.143(p = 0.787), implying that the heterogeneity was not caused by the threshold effect. We further measured the substantial heterogeneity between studies by meta-regression analysis, but none of the study characteristics was responsible for this heterogeneity. Thus, further unrecorded difference among those studies probably contributed to the heterogeneity. So, a random-effect model was used to eliminate some heterogeneity. In addition, there are other limitations in this meta-analysis. Some data, such as conference abstracts [23-25] and unpublished data were excluded. We also excluded the control group including healthy individuals and the control group with non-sepsis patients. Therefore, there were only five eligible studies included in this meta-analysis (six datasets were extracted). This sample number was too small for further subgroup analysis. However, no potential publication bias was found using Deeks' funnel plots in current meta-analysis.

Conclusion

In conclusion, presepsin is an important marker for sepsis diagnosis in critically ill patients. Presepsin detection on patient admission can increase the diagnostic capability of distinguishing sepsis from non-infection related SISR. However, no single marker can be used alone to diagnose all sepsis cases. It must be interpreted in context with information from medical history, physical examination, and clinical, radiological, and microbiological assessments. It should be used in combination with other biomarkers and clinical diagnostic scoring systems to enhance the overall diagnostic accuracy. Moreover, constant re-evaluation during

the course of disease is advised.

Abbreviations

SIRS**:** systemic inflammatory response syndrome; ED: emergency department; ICU: Intensive care unit; NOS: Newcastle-Ottawa quality assessment scale; CRP: C-reactive protein ; PCT: procalcitonin; SD: standard deviations; CD14: Cluster of differentiation 14; sCD14: soluble CD14; sCD14-ST : sCD14 subtype; LPSs: lipopolysaccharides; LPBs: LPS-binding proteins; RCT: randomized controlled trial; PLR: positive likelihood ratio; NLR: negative likelihood ratio; DOR: diagnostic odds ratio; SROC: summary receiver operating characteristic; AUC: area under the curve.

Authors contributions

DX and KPH participated in design of the study, database search, study selection and quality assessment, data extraction, and the statistical analysis. They also drafted the manuscript. The two authors contributed equally in this study. PRL,YX, YW and XGB participated in the design of the study, performed the statistical analysis and helped to draft the manuscript. KXZ conceived of the study, participated in its design, drafted the manuscript and critically revised the final manuscript, supervised the study. All authors read and approved the final manuscript.

Conflicts of interest

We declare that we have no conflicts of interest.

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