Biomarkers in Diagnosis of Sepsis and Systemic Infection in Adult Patients: A Systematic Review and Bayesian Network Meta-Analysis

Hao-Min Lan  
CGU: Chang Gung University

Chin-Chieh Wu  
CGU: Chang Gung University

Su-Hsun Liu  
Far Eastern Memorial Hospital

Chih-Huang Li  
CGMH: Chang Gung Memorial Hospital

Yu-Kang Tu  
NTU: National Taiwan University

Kuan-Fu Chen (drkfchen@gmail.com)  
Chang Gung Memorial Hospital Keelung Branch  
https://orcid.org/0000-0001-7287-9497

Research

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Abstract

Background

Sepsis is estimated to affect over 30 million people worldwide and to result in six million deaths every year. The definition of sepsis has been heavily revised in recent years, resulting in the need for a comprehensive comparison for clinicians to choose among the current biomarkers for sepsis.

Purpose

We conducted a systematic review and synthesized both direct and indirect evidence by using network meta-analyses with bivariate hierarchical random-effects arm-based model in a Bayesian framework. We applied the Quality Assessment of Diagnostic Accuracy Studies-2 criteria to assess the risk of bias, investigated heterogeneity using Bayesian network meta-regression models, and estimated optimal adjusted cutoff values for each included biomarker.

Data sources

PubMed, EMBASE, and Scopus from their inception to May 2019

Study Selection, Data Extraction

Studies assessing the diagnostic performance of biomarkers in adult patients with suspected infection were included. We excluded studies not detecting systemic infection or sepsis, only including burns patients, or with non-systemic inflammatory response syndrome patients as the reference group.

Data Synthesis

We identified 336 unique studies and included 134 studies representing 20,564 patients for evidence synthesis. Among the seven most-studied biomarkers, presepsin displayed the significantly better pooled sensitivities than procalcitonin to detect systemic infection and sepsis (0.85 and 0.83; 95% credible interval [CrI]: 0.79-0.89 and 0.77-0.88; relative sensitivity 1.13 and 1.10, 95% CrI: 1.04-1.20 and 1.01-1.18). However, CD64 showed the significantly better pooled specificities than presepsin in detecting systemic infection and sepsis (0.87 and 0.99; 95% CrI: 0.81-0.92 and 0.92-1.00, relative specificity 1.19 and 1.49, 95% CrI: 1.07-1.34 and 1.31-1.70). After adjusting for study quality, study populations, types of specimens, year of the study conducted and sponsorship, CD64 showed the best-pooled sensitivities and specificities. However, owing to the lack of a unifiable measuring unit, we cannot provide optimal cutoffs for CD64.

Conclusions

CD64 performed the best in detecting both systemic infection and sepsis in adult patients. Further investigations will be needed to assess the potential risks of biases and the use of post-hoc cutoffs.
Registration

PROSPERO number: CRD42018086545

Introduction

Sepsis is estimated to affect over 30 million people worldwide and result in six million deaths annually. Despite being a substantial public health burden worldwide, sepsis lacks a reliable gold standard for diagnosis.[1, 2] Accordingly, there have been a total of three historical revisions made in the definition of sepsis in the recent decades.[3–5] The contemporary 3.0 version sepsis (Sepsis-3) utilizes the change of Sequential Organ Failure Assessment (SOFA) score to obtain an operational diagnosis as an infection-induced life-threatening organ dysfunction associated with high mortality risk. The revision of sepsis also results in the need for a comprehensive comparison of biomarkers.

On the other hand, few studies exist to compare several biomarkers simultaneously for sepsis, which prevent an objective ranking of the performance of these biomarkers. Furthermore, conflicting results and insufficient evidence comparing performance biomarkers exist.[6–9] With the advantages of the Bayesian network meta-analysis, we can rank the biomarkers and obtain more precision by incorporating indirect evidence with well-quantified relative accuracies and credible intervals between biomarkers.[10, 11]

In this systematic review and Bayesian network meta-analysis, we compared the performance of well-studied biomarkers in the detection of systemic infection and sepsis among adult patients with suspected infection. We aimed to provide an up-to-date insight into the diagnostic value of biomarkers under different definitions of sepsis in adult patients.

Methods

We reported our study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for network meta-analysis (PRISMA-NMA).[12] This study has been registered on the International Prospective Register 61 of Systematic Reviews (PROSPERO) database (number: CRD42018086545).[13]

Data sources and Search strategy

A comprehensive systematic search including published literature from their inception to May 2019 was conducted in the following databases: (1) PubMed, (2) EMBASE, and (3) Scopus. We used sets of keywords consisting of the names of biomarkers, as well as the keywords “diagnosis”, “sepsis”, and “adult” to search in these databases (Appendix pp. 3–4). The references of the eligible papers were also screened to identify additional studies.

Study selection and data extraction
Two authors (CCW and HML) independently scrutinised and evaluated the studies according to the pre-
identified selection criteria. Studies that met the following criteria were included: (1) original articles; (2) 
adult patients (i.e., \( \geq 18 \) years old); (3) patients with suspected infection; (4) studies containing 
diagnostic accuracy assessments of sepsis. We did not apply any language restriction, however, studies 
were excluded if any of the following conditions occurred: (1) not detecting systemic infection or sepsis; 
(2) non-diagnostic studies; (3) non-original articles; (4) duplicated search results; (5) lack of necessary 
parameters for diagnostic accuracy assessments (Appendix pp. 3–4); (6) only including burns patients; 
[14] (7) using only non-systemic inflammatory response syndrome (SIRS) patients as the reference group 
(extreme-control); (8) biomarkers with sufficient numbers (more than three) of original studies to allow for 
meta-analyses. Finally, the included studies were classified into two groups according to the two 
reference standards for clinical diagnosis of sepsis: (1) the Sepsis-3 (sepsis) group to study the 
diagnostic performance of biomarkers for Sepsis-3,[5] including the former severe sepsis and septic 
shock,[3, 4] (2) the Sepsis-1 (systemic infection) group to study how biomarkers performed in 
differentiating infectious from non-infectious SIRS.[3, 4]

We further extracted information from either the full texts or the published abstracts of each study, 
including the year of publication, country, clinical settings, criteria of sepsis, study design, sample sizes, 
targeted biomarkers, types of specimen, methods of measurement, sponsorships, cut-off values, 
proportions of patients with sepsis, sensitivities, and specificities. All disagreements between authors 
were resolved by consensus meetings with the third clinical expert (KFC).

**Quality assessment**

For each included study, two authors (CCW and HML) independently assessed the quality of the study 
according to our modification to the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) 
criteria (Appendix pp. 4–5).[15, 16] Only the studies that satisfied all the signaling questions were marked 
as “low risk”. The degree of agreement between the two authors was measured using Cohen's Kappa 
statistic.[17] Any disagreement was resolved through consensus meetings. Additionally, the publication 
bias was tested by using Deek's funnel plot.[18, 19]

**Data synthesis**

For Bayesian network meta-analyses, we applied the bivariate hierarchical random-effects arm-based 
model.[11, 20, 21] Unlike conventional methods, which only allow for pairwise comparison between two 
biomarkers, this model compares multiple biomarkers simultaneously. In brief, we incorporate direct 
evidence with indirect evidence through a third biomarker between the other two biomarkers (Fig. 1). We 
applied the preferred Bayesian framework for network meta-analysis with potential multiple comparison 
issues, using Hamiltonian Monte Carlo random sampling methods in Stan language with the rstan 
package (Version 2.18.2) and the NO-U-Turn sampler within in R (version 3.5.3). We reproduced the 
simulations for 50,000 iterations in four chains with 25,000 burn-in iterations until convergence, which 
was evaluated by timeseries plots of the parameters. The results of data synthesis were presented as a
point estimate with a 95% credible interval (CrI). In order to test the validity of indirect comparison, we also calculated the inconsistency factor with the node-splitting model.[22]

**Heterogeneity and Bayesian network meta-regression**

In diagnostic studies, between-study heterogeneity can be caused by two effects, threshold and non-threshold. For the potential threshold effect, we calculated the Spearman correlation coefficients between logit-transformed sensitivities and false-positive rates; for the potential non-threshold effect, we calculated the Chi-square statistics, Cochrane-Q test, and the $I^2$ metric. We further performed univariable Bayesian network meta-regression analysis to explore possible sources of variability by considering (1) regions of the study (Asian/Europe); (2) patient sources (ICU/ED); (3) patient characteristics (medical/surgical); (4) specimen types (plasma/serum/whole blood); (5) using non-infectious SIRS patients as the reference group; (6) sponsorship; (7) case-control study design; (8) risks of bias and applicability of study based on QUADAS-2; and (9) accessibility to the full text content. To adjust the diagnostic accuracies based on the variables accounting for significant heterogeneity from the univariable Bayesian network meta-regression, we performed the multivariable Bayesian network meta-regression. In order to analyse the potential effect of the data obtained from non-full text and the outliers, as well as year of the study conducted, we performed sensitivity analyses with data removing these studies separately.

**Optimal cutoff evaluation**

We further estimated optimal cutoffs based on adjusted diagnostic performance metrics using multivariable Bayesian network meta-regression models (Appendix pp. 7). The optimal cutoffs were determined using locally weighted scatterplot smoothing plot based on the meta-regression-adjusted sensitivities and specificities. We determined the optimal ranges of biomarkers by identifying cutoffs that result in the maximal differences between the adjusted sensitivities and false-positive rates ($1$-specificity).

**Data sharing**

With the publication of this article, the full dataset and codes will be freely available online in Mendeley Data, a secure online repository for research data (DOI: 10.17632/cdftd22xgs.1).[23]

**Role of the funding source**

The funder of this study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit this paper publication. The authors had full access to all the data, and the corresponding author was responsible for the decision to submit for publication.

**Patient and public involvement**

Our study contained no direct patient or public involvement; however, the research question was informed by front line health care providers who need accurate biomarkers to detect patients with systemic infection or sepsis.
Results

Search results and characteristics of included studies

After searching and screening the literature, 336 unique studies were identified; seven biomarkers with sufficient numbers (more than three) of original studies to allow for meta-analyses were included: procalcitonin, C-reactive protein (CRP), interleukin-6 (IL-6), presepsin (cluster of differentiation [CD] neutrophil marker 14 subtype), CD64, soluble triggering receptor expressed on myeloid cells 1 (sTREM-1), and lipopolysaccharide-binding protein (LBP). Among these, 134 studies comprising of 20,564 patients published from 1996 to 2019 met the inclusion criteria and were included (Fig. 2, Appendix pp. 73–95).

Overall, 33 studies were evaluated for the diagnostic performance of biomarkers for sepsis (using Sepsis-3 definition). An additional 115 studies for systemic infection (Sepsis-1 definition, Appendix pp. 73). Procalcitonin was found to be the most investigated biomarker in all studies (Fig. 1). The median number of patients per study was 101 (interquartile range [IQR]: 70–172), and the median proportion of patients with the outcome of interest was 52% for Sepsis-3 (IQR: 41%-64%) and 58% for Sepsis-1 (IQR: 44%-69%, Appendix pp. 74–84). The median cutoffs used for presepsin were 530 pg/mL (IQR: 462.1-603.8) for Sepsis-3 and 575 pg/mL (IQR: 426.2-634.2) for Sepsis-1 (Appendix pp. 85–95).

Risk of bias across studies

Quality assessments were performed with a satisfactory inter-observer agreement (Cohen's Kappa ranged from 0.86-1.00, Appendix pp. 96). The issues arising from the patient selection risk of bias included: case-control design[33, 35, 44, 75, 103, 131] and retrospective design.[74, 77, 90, 105, 137] Furthermore, several studies excluded specific patient populations, did not claim random or consecutive selection and included the non-SIRS patients in their reference groups. Most studies used post-hoc cutoffs to determine the performance of biomarkers (Fig. 4, Appendix pp. 97–101).

Quantitative results

Among the included seven biomarkers, presepsin displayed the significantly better pooled sensitivities than procalcitonin for the detection of both Sepsis-1 and Sepsis-3 (0.85 and 0.83, 95% credible interval [Crl]: 0.79–0.89 and 0.77–0.88; relative sensitivity 1.13 and 1.10, 95% Crl: 1.04–1.20 and 1.01–1.18; Fig. 3). However, CD64 showed the significantly better pooled specificities than presepsin in the detection of both Sepsis-1 and Sepsis-3 (0.87 and 0.99, 95% credible interval: 0.81–0.92 and 0.92-1.00; relative specificity 1.19 and 1.49, 95% Crl: 1.07–1.34 and 1.31–1.70)

Publication bias

Furthermore, we noticed significant publication biases in the studies using procalcitonin for Sepsis-1 (p < 0.01), and three outlier studies accounted for the majority of the bias.[75, 102, 135] Significant $I^2$ (> 75%) were found for all biomarkers under both definitions, except for LBP for Sepsis-1 and IL-6 for Sepsis-3 (Appendix pp. 102). We did not find any inconsistency of network between presepsin and procalcitonin.
for both Sepsis-3 (inconsistency factor (IF) for sensitivity: −0.17–0.23, IF for specificity: −0.1–0.44) and Sepsis-1 (IF for sensitivity: −0.13–0.12, IF for specificity: −0.12–0.19, Appendix pp. 102).

**Meta-regressions**

The Bayesian network meta-regressions model was used to adjust the effects of suboptimal quality, the study population, the types of serum specimen, and sponsorship. In the univariable Bayesian network meta-regression model for Sepsis-1, a significantly higher sensitivity was associated with Asian studies for CRP, whereas lower sensitivities were associated with sponsorship and applicability of patient selection in sTREM-1 (Appendix pp. 44–45). Meanwhile, significantly higher specificities were associated with medical patients for CRP and Asian studies for CD64, while lower specificities were associated with European studies for CD64, patients in ED for CRP, patients in ICU for CD64, serum specimens for procalcitonin and sponsorship for CRP. Furthermore, significantly higher specificities were associated with sponsorship and risk of bias in the index test for IL-6 in Sepsis-3 (Appendix pp. 46–47).

After selecting variables using univariable Bayesian network meta-regression to solve the heterogeneity issue, the types of serum specimen, European studies, ICU, medical patients, sponsorship, and the applicability of patient selection for Sepsis-1, sponsorship, and risk bias of index test for Sepsis-3 were selected in the multivariable Bayesian network meta-regression (Appendix pp. 44–47). The pooled sensitivities and specificities changed slightly after adjustment, after which CD64 showed the best pooled adjusted sensitivities and specificities (Appendix pp. 48–49). The sensitivity analyses demonstrated that that the studies from data obtained from non-full text abstract and the outliers only had a small effect (Appendix pp. 105). However, we found that studies performed later would demonstrate poorer performance for presepsin and sTREM-1 (Appendix pp. 108).

**Cutoffs recommendation**

The optimal cutoffs were further determined using adjusted values plotted in the locally-weighted scatterplot smoothing plots with 800–900 pg/mL and 600–700 pg/mL for presepsin for the detection of Sepsis-3 and Sepsis-1, respectively (Fig. 5, Appendix pp. 9–11). Similarly, we suggested a cutoff between 1.5-2.0 ng/mL and 1.0-1.5 ng/mL for the use of procalcitonin in the detection of Sepsis-3, and Sepsis-1, respectively (Fig. 5). Owing to the lack of a unifiable measuring unit, we cannot provide optimal cutoffs for CD64.

**Discussions**

The application of Bayesian network meta-analyses in our search resulted in a large number of included studies, allowing for a full recognition of the diagnostic performance between sepsis biomarkers. Overall, presepsin exhibited the best pooled sensitivities, whereas CD64 showed the best pooled specificity for both Sepsis-1 and Sepsis-3 detection. After adjusting for study quality, study populations, types of specimens, year of the study conducted and sponsorship, we found that CD64 showed the best-pooled sensitivities and specificities, and we provided suggested cutoffs for presepsin and procalcitonin.
This study has several strengths. First, it provides an up-to-date overview of the diagnostic performance of biomarkers in detecting either Sepsis-3 or Sepsis-1 by including a number of recent studies. In two of the previous systematic reviews and meta-analyses, presepsin was found to have a marginally superior sensitivity than procalcitonin in detecting Sepsis-1; however, the limited numbers of studies included in these meta-analyses prevent a conclusive comparison.[6, 7] Second, our work covered not only well-studied biomarkers, such as procalcitonin, but also some novel biomarkers such as CD64, thus contributing to the accumulating body of knowledge on their current utility. Third, the Bayesian network meta-analyses we applied allowed for the simultaneous pooling of sensitivities and specificities and provided well-quantified credible intervals for relative diagnostic performance, which strengthened the evidence, with a superior reliability than conventional methods (Appendix pp. 6–7). In previous meta-analyses that applied different methods to evaluate the performance, the pooled sensitivities and specificities were not stable and were sometimes contradictory (Appendix pp. 106–108). Fourth, we applied rigorous criteria to verify the quality of the studies, and thoroughly examined their influence on the diagnostic performance with Bayesian network meta-regressions. Therefore, we were able to evaluate the biomarkers more confidently. Lastly, an objective optimal cutoff was achieved after adjusting the heterogeneity with multivariable Bayesian network meta-regression. The optimal points were visualized as a locally weighted scatterplot smoothing plot.

In this study, we pooled together numerous studies evaluating the biomarkers for severe sepsis and Sepsis-3 to provide up-to-date evidence for clinicians to re-evaluate these biomarkers. The newly revised definition of Sepsis-3 reflects a paradigm shift from implicitly diagnosing a systemic infection to explicitly identifying a severe infection associated with mortality.[5] The biomarkers that were found to be associated with systemic infections, therefore, are not necessarily predictive of Sepsis-3. Therefore, the diagnostic performance of current biomarkers, especially procalcitonin, should be re-evaluated. To date, only a few studies have started to re-evaluate the biomarkers for Sepsis-3.[27, 132, 135]

Presepsin has been studied most extensively during the past decade with various degrees of investigation into biomarkers for the detection of sepsis.[106] By adding indirect comparisons, our Bayesian network meta-analysis indicates that presepsin has a significantly better sensitivity than procalcitonin for the detection of both Sepsis-1 and Sepsis-3. Furthermore, presepsin has similar specificities to procalcitonin in terms of the detection of both Sepsis-1 and Sepsis-3, which could also be used for the guidance of antimicrobial therapies.[141, 142] Presepsin also shows a greater sensitivity than the currently used screening tools, such as quick Sepsis-related Organ Failure Assessment (qSOFA) and the systemic inflammatory response syndrome (SIRS) criteria. In a systematic review and meta-analysis, the qSOFA score and SIRS criteria showed a pooled sensitivity of 0.51 and 0.29 for the detection of Sepsis-3, respectively.[143]

Due to its extensively varied performance across the studies, the diagnostic value of procalcitonin for Sepsis-1 was undetermined. The use of different study selection criteria has prevented a homogeneous conclusion being drawn in previous meta-analyses of procalcitonin (Appendix pp. 106–108). A univariable meta-analysis containing 2,097 patients in 2007 proclaimed the rather insufficient diagnostic
capacity of procalcitonin for Sepsis-1, targeting the general population but excluding non-adult patients, in addition to a limited spectrum of patients.[8] On the other hand, a more recent bivariate meta-analysis containing 3,487 patients in 2013 found that procalcitonin had an excellent diagnostic capacity, targeting a more general but heterogeneous population by including paediatric patients and patients with septic shock, as well as studies with only non-infectious SIRS as the reference group.[9] In our study, we define an adult population without burn patients and use the subgroups of Sepsis-1 and Sepsis-3 to perform a better comparison of the performance of the biomarkers.

The potential confounding results in terms of the performance evaluation of these biomarkers have been extensively evaluated in our study. Suboptimal quality, study populations, types of serum specimens, and sponsorships were found to significantly bias the results. After adjusting these biases, through the application of the multivariable Bayesian network meta-regression, surprisingly, CD64 became the biomarker that performed best in the detection of both Sepsis-1 and Sepsis-3.

Neutrophil CD64 is an Fcγ receptor commonly expressed on monocytes, as well as occasionally on polymorphonuclear leukocytes.[144] With a remarkably higher specificity for differentiating infectious from non-infectious SIRS, the potential superiority of neutrophil CD64 compared to procalcitonin was implied for use in antimicrobial therapies. However, the lack of a unifiable measuring unit for neutrophil CD64 means that the estimation of the optimal cutoff will needed to be determined in a future study.[145, 146]

The evaluation of the optimal cutoffs could assist clinicians in their decision making. In theory, a relevant diagnosis could be inferred during the synthesis of data from the cutoff parameters of the hierarchical summary receiver operating characteristic (HSROC) model,[147] or in other words, the back-transformed bivariate model. However, it was assumed that no covariates asymmetrically affected the overall diagnostic accuracies.[148] This assumption, in practice, could be violated by either including patients with different disease severities or non-SIRS controls. Another attempt was previously made from the previous meta-analysis, which suggested the use of 0.5-2.0 ng/mL as a cutoff range for procalcitonin detecting Sepsis-1 by finding the interquartile range (IQR) across studies.[9, 147] In this study, we provided suggested cutoffs by visualization of the optimal points, with the adjusted values plotted on a locally weighted scatterplot smoothing plot, thereby avoiding the need for an assumption or an adjustment for the confounders.

**Limitations**

A few methodological issues in this study were noted. First, a gold standard for the diagnosis of sepsis does not currently exist, although both Sepsis-3 and Sepsis-1 do provide operative definitions for the description of life-threatening organ failure status or systemic inflammatory response. However, with the current revised operational definition of Sepsis-3, clinicians would be able to treat their patients more accurately. Nonetheless, attempts to validate biomarkers for Sepsis-3 are still needed to draw more reliable conclusions.
Second, while the large number of the studies included in this review contributed to a better confidence, it also resulted in a higher heterogeneity. Our Bayesian network meta-regression suggested that those strictly implementing random selection processes were generally associated with a decreased sensitivity. It is also compulsory to investigate whether the exclusion of patients with other conditions, including malignancy, status post-operation, kidney diseases, and pregnancy, is associated with a significant influence on the diagnostic performance of biomarkers in the future.

**Conclusion**

In this study, we provided an accurate comparison and an up-to-date Bayesian network meta-analysis allowed for a more reliable comparison of biomarkers for diagnostic test accuracy studies for sepsis. Presepsin and CD64 were found to outperform procalcitonin and other biomarkers in their use for the detection of both systemic infection and sepsis. After adjusting for study quality, study populations, types of specimens, year of the study conducted and sponsorship, CD64 showed the best-pooled sensitivities and specificities. For presepsin and procalcitonin, 600–700 pg/mL and 1-1.5 ng/mL were suggested as the optimal cutoffs for detecting systemic infection, respectively. Nonetheless, owing to the lack of a unifiable measuring unit, we cannot provide optimal cutoffs for CD64. However, further investigation of these biomarkers will be needed to identify the potential biases caused by suboptimal quality, the study population, the type of specimen, sponsorship, and the use of post-hoc cutoffs.

**SUMMARY BOXES**

Section 1: What is already known on this topic

The definition of sepsis, a worldwide public health burden, has been heavily revised in recent years (Sepsis-3), resulting in the need for a comprehensive comparison for clinicians to choose among the current biomarkers for sepsis. Previous meta-analyses have mainly focused on the capacity of single biomarkers to detect the onset of systemic infection, previously defined as Sepsis-1.

Section 2: What this study adds

This systematic review and Bayesian network meta-analyses included the largest number of studies, allowing for the verification of the diagnostic performance of presepsin compared to other current biomarkers to provide different definitions of sepsis. In this analysis, the authors further adjusted the potential resources of heterogeneity and provided suggested cutoffs accordingly. CD64 and presepsin were found to outperform other biomarkers in detecting systemic infection and sepsis-3 without any significant inconsistency in the Bayesian network meta-analyses or meta-regression.

**Declarations**

**Authors’ contribution**
HML and KFC wrote the manuscript. HML and CCW performed the literature review. HML, CCW and KFC performed the statistical analysis. SHL, CHL, YKT and KFC revised the text. All authors read and approved the final manuscript.

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**Conflict of Interest Disclosure**

The authors declare that they have no conflicts of interest

**Acknowledgment**

Not applicable

**Declaration of interests**

The authors declare no conflicts of interest.

**Consent for publication**

Not applicable.

**Role of the funding source**

The funder of this study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit for publication. The authors had full access to all the data, and the corresponding author was responsible for the decision to submit for publication.

**Availability of supporting data**

With the publication of this article, the full dataset and codes will be freely available online in Mendeley Data, a secure online repository for research data (DOI: 10.17632/cdftd22xgs.1).

**Ethical statement**

This meta-analysis study is exempt from ethics approval, since the study authors were collecting and synthesising data from previous clinical studies in which informed consent has already been obtained by the investigators.

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Figures

**Figure 1**

Geometry of networks. Note: PCT: procalcitonin, CRP: C-reactive protein, IL-6: interleukin-6, CD64: neutrophil CD64, sTREM-1: soluble triggering receptor expressed on myeloid cells 1, LBP: lipopolysaccharide-binding protein.
Figure 2

Flow chart of the study selection process. Note: SIRS: systemic inflammatory response syndrome
**Figure 3**

Quality assessment, tests of heterogeneity, threshold effects and publication bias. Note: Degree of heterogeneity: ≥ 50%, > 75%; Threshold effect: ≥ 0.05, p<0.05; Publication bias: ≥ 0.05, p<0.05, ≥ p<0.01
Figure 4

Diagnostic performances of biomarkers compared to presepsin. Note: PCT: procalcitonin, CRP: C-reactive protein, IL-6: interleukin-6, CD64: neutrophil CD64, sTREM-1: soluble triggering receptor expressed on myeloid cells 1, LBP: lipopolysaccharide-binding protein.
Figure 5

Multivariable network meta-regressions and cutoff fitting with locally weighted scatterplot smoothing plot. Note: upper: coefficients of covariates (OR) used to adjust the cutoff using multivariable meta-regressions; lower: original logit-transformed diagnostic accuracies (points) and regression line based on the adjusted diagnostic accuracies (dash lines)

Supplementary Files

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