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

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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 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., ≥ 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, Cochran-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). [24–140] 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 [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; 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% CrI: 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 need 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

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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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References

1. Liu V, Escobar GJ, Greene JD, Soule J, Whippy A, Angus DC, Iwashyna TJ: **Hospital deaths in patients with sepsis from 2 independent cohorts.** *JAMA* 2014, **312**(1):90-92.
2. Rhee C, Dantes R, Epstein L, Murphy DJ, Seymour CW, Iwashyna TJ, Kadri SS, Angus DC, Danner RL, Fiore AE *et al*: **Incidence and Trends of Sepsis in US Hospitals Using Clinical vs Claims Data, 2009-2014.** *JAMA* 2017, **318**(13):1241-1249.
3. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ: **Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine.** *Chest* 1992, **101**(6):1644-1655.
4. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G *et al*: **2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference.** *Intensive Care Med* 2003, **29**(4):530-538.
5. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM *et al*: **The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).** *JAMA* 2016, **315**(8):801-810.
6. Kondo Y, Umemura Y, Hayashida K, Hara Y, Aihara M, Yamakawa K: **Diagnostic value of procalcitonin and presepsin for sepsis in critically ill adult patients: a systematic review and meta-analysis.** *J Intensive Care* 2019, **7**:22.
7. Wu CC, Lan HM, Han ST, Chaou CH, Yeh CF, Liu SH, Li CH, Blaney GN, 3rd, Liu ZY, Chen KF: **Comparison of diagnostic accuracy in sepsis between presepsin, procalcitonin, and C-reactive protein: a systematic review and meta-analysis.** *Ann Intensive Care* 2017, **7**(1):91.
8. Tang BM, Eslick GD, Craig JC, McLean AS: **Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis.** *Lancet Infect Dis* 2007, **7**(3):210-217.
9. Wacker C, Prkno A, Brunkhorst FM, Schlattmann P: **Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis.** *Lancet Infect Dis* 2013, **13**(5):426-435.
10. Tonin FS, Rotta I, Mendes AM, Pontarolo R: **Network meta-analysis: a technique to gather evidence from direct and indirect comparisons.** *Pharm Pract (Granada)* 2017, **15**(1):943.
11. Nyaga VN, Aerts M, Arbyn M: **ANOVA model for network meta-analysis of diagnostic test accuracy data.** *Stat Methods Med Res* 2018, **27**(6):1766-1784.
12. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thorlund K, Jansen JP *et al*: **The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations.** *Ann Intern Med* 2015, **162**(11):777-784.
13. Lan HM, Chen KF: **Comparing among the diagnostic performance of procalcitonin (PCT) and other septic biomarkers: a systematic review and network meta-analysis.** *PROSPERO* 2018(ID:

CRD42018086545. Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018086545).

14. Greenhalgh DG: **Sepsis in the burn patient: a different problem than sepsis in the general population.** *Burns Trauma* 2017, **5**:23.
15. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM, Group Q-: **QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies.** *Ann Intern Med* 2011, **155**(8):529-536.
16. Whiting P, Rutjes A, Westwood M, Mallett S, Deeks J, Reitsma J, Leeflang M, Sterne J, Bossuyt P: **QUADAS-2: an updated quality assessment tool for diagnostic accuracy studies.** In: *19th Cochrane Colloquium Abstracts*. Madrid, Spain; 2011.
17. Landis JR, Koch GG: **The measurement of observer agreement for categorical data.** *Biometrics* 1977, **33**(1):159-174.
18. Deeks JJ, Macaskill P, Irwig L: **The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed.** *J Clin Epidemiol* 2005, **58**(9):882-893.
19. van Enst WA, Ochodo E, Scholten RJ, Hooft L, Leeflang MM: **Investigation of publication bias in meta-analyses of diagnostic test accuracy: a meta-epidemiological study.** *BMC Med Res Methodol* 2014, **14**:70.
20. Zhang J, Carlin BP, Neaton JD, Soon GG, Nie L, Kane R, Virnig BA, Chu H: **Network meta-analysis of randomized clinical trials: reporting the proper summaries.** *Clin Trials* 2014, **11**(2):246-262.
21. Hong H, Chu H, Zhang J, Carlin BP: **A Bayesian missing data framework for generalized multiple outcome mixed treatment comparisons.** *Res Synth Methods* 2016, **7**(1):6-22.
22. Veroniki AA, Vasiliadis HS, Higgins JP, Salanti G: **Evaluation of inconsistency in networks of interventions.** *Int J Epidemiol* 2013, **42**(1):332-345.
23. Lan HM, Wu CC, Chen CW, Hsu KH, Chen KF: **Diagnostic network meta-analysis and network meta-regression for Biomarkers of Sepsis.** *Mendeley Data* 2019.
24. Abidi K, Khoudri I, Belayachi J, Madani N, Zekraoui A, Zeggwagh AA, Abouqal R: **Eosinopenia is a reliable marker of sepsis on admission to medical intensive care units.** *Crit Care* 2008, **12**(2):R59.
25. Aikawa N, Fujishima S, Endo S, Sekine I, Kogawa K, Yamamoto Y, Kushimoto S, Yukioka H, Kato N, Totsuka K *et al*: **Multicenter prospective study of procalcitonin as an indicator of sepsis.** *J Infect Chemother* 2005, **11**(3):152-159.
26. Aksaray S, Alagoz P, Inan A, Cevan S, Ozgultekin A: **Diagnostic value of sTREM-1 and procalcitonin levels in the early diagnosis of sepsis.** *North Clin Istanbul* 2016, **3**(3):175-182.
27. Ali FT, Ali MA, Elnakeeb MM, Bendary HN: **Presepsin is an early monitoring biomarker for predicting clinical outcome in patients with sepsis.** *Clin Chim Acta* 2016, **460**:93-101.
28. Al-Nawas B, Krammer I, Shah PM: **Procalcitonin in diagnosis of severe infections.** *Eur J Med Res* 1996, **1**(7):331-333.

29. Anand D, Das S, Bhargava S, Srivastava LM, Garg A, Tyagi N, Taneja S, Ray S: **Procalcitonin as a rapid diagnostic biomarker to differentiate between culture-negative bacterial sepsis and systemic inflammatory response syndrome: a prospective, observational, cohort study.** *J Crit Care* 2015, **30**(1):218 e217-212.
30. Balç IC, Sungurtekin H, Gurses E, Sungurtekin U, Kaptanoglu B: **Usefulness of procalcitonin for diagnosis of sepsis in the intensive care unit.** *Crit Care* 2003, **7**(1):85-90.
31. Barati M, Bashar FR, Shahrami R, Zadeh MH, Taher MT, Nojomi M: **Soluble triggering receptor expressed on myeloid cells 1 and the diagnosis of sepsis.** *J Crit Care* 2010, **25**(2):362 e361-366.
32. Battista S, Audisio U, Galluzzo C, Maggiorotto M, Masoero M, Forno D, Pizzolato E, Ulla M, Lucchiari M, Vitale A *et al*: **Assessment of Diagnostic and Prognostic Role of Copeptin in the Clinical Setting of Sepsis.** *Biomed Res Int* 2016, **2016**:3624730.
33. Behnes M, Bertsch T, Lepiorz D, Lang S, Trinkmann F, Brueckmann M, Borggrefe M, Hoffmann U: **Diagnostic and prognostic utility of soluble CD 14 subtype (presepsin) for severe sepsis and septic shock during the first week of intensive care treatment.** *Crit Care* 2014, **18**(5):507.
34. Beqja-Lika A, Bulo-Kasneji A, Refatllari E, Heta-Alliu N, Rucaj-Barbullushi A, Mone I, Mitre A: **Serum procalcitonine levels as an early diagnostic indicator of sepsis.** *Mater Sociomed* 2013, **25**(1):23-25.
35. Brenner T, Fleming T, Uhle F, Silaff S, Schmitt F, Salgado E, Ulrich A, Zimmermann S, Bruckner T, Martin E *et al*: **Methylglyoxal as a new biomarker in patients with septic shock: an observational clinical study.** *Crit Care* 2014, **18**(6):683.
36. Brunkhorst FM, Wegscheider K, Forycki ZF, Brunkhorst R: **Procalcitonin for early diagnosis and differentiation of SIRS, sepsis, severe sepsis, and septic shock.** *Intensive Care Med* 2000, **26** Suppl 2:S148-152.
37. Cardelli P, Ferraironi M, Amodeo R, Tabacco F, De Blasi RA, Nicoletti M, Sessa R, Petrucca A, Costante A, Cipriani P: **Evaluation of neutrophil CD64 expression and procalcitonin as useful markers in early diagnosis of sepsis.** *Int J Immunopathol Pharmacol* 2008, **21**(1):43-49.
38. Carpio R, Zapata J, Spanuth E, Hess G: **Utility of presepsin (sCD14-ST) as a diagnostic and prognostic marker of sepsis in the emergency department.** *Clin Chim Acta* 2015, **450**:169-175.
39. Castelli GP, Pognani C, Meisner M, Stuardi A, Bellomi D, Sgarbi L: **Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction.** *Crit Care* 2004, **8**(4):R234-242.
40. Chan YL, Tseng CP, Tsay PK, Chang SS, Chiu TF, Chen JC: **Procalcitonin as a marker of bacterial infection in the emergency department: an observational study.** *Crit Care* 2004, **8**(1):R12-20.
41. Dimoula A, Pradier O, Kassenger Z, Dalcomune D, Turkan H, Vincent JL: **Serial determinations of neutrophil CD64 expression for the diagnosis and monitoring of sepsis in critically ill patients.** *Clin Infect Dis* 2014, **58**(6):820-829.
42. Dorizzi RM, Polati E, Sette P, Ferrari A, Rizzotti P, Luzzani A: **Procalcitonin in the diagnosis of inflammation in intensive care units.** *Clin Biochem* 2006, **39**(12):1138-1143.

43. Endo S, Suzuki Y, Takahashi G, Shozushima T, Ishikura H, Murai A, Nishida T, Irie Y, Miura M, Iguchi H *et al*: **Usefulness of presepsin in the diagnosis of sepsis in a multicenter prospective study.** *J Infect Chemother* 2012, **18**(6):891-897.
44. Enguix-Armada A, Escobar-Conesa R, Garcia-De La Torre A, De La Torre-Prados MV: **Usefulness of several biomarkers in the management of septic patients: C-reactive protein, procalcitonin, presepsin and mid-regional pro-adrenomedullin.** *Clin Chem Lab Med* 2016, **54**(1):163-168.
45. Feng L, Zhou X, Su LX, Feng D, Jia YH, Xie LX: **Clinical significance of soluble hemoglobin scavenger receptor CD163 (sCD163) in sepsis, a prospective study.** *PLoS One* 2012, **7**(7):e38400.
46. Festic E, Siegel J, Stritt M, Freeman WD: **The utility of serum procalcitonin in distinguishing systemic inflammatory response syndrome from infection after aneurysmal subarachnoid hemorrhage.** *Neurocrit Care* 2014, **20**(3):375-381.
47. Gaini S, Koldkjaer OG, Pedersen C, Pedersen SS: **Procalcitonin, lipopolysaccharide-binding protein, interleukin-6 and C-reactive protein in community-acquired infections and sepsis: a prospective study.** *Crit Care* 2006, **10**(2):R53.
48. Gamez-Diaz LY, Enriquez LE, Matute JD, Velasquez S, Gomez ID, Toro F, Ospina S, Bedoya V, Arango CM, Valencia ML *et al*: **Diagnostic accuracy of HMGB-1, sTREM-1, and CD64 as markers of sepsis in patients recently admitted to the emergency department.** *Acad Emerg Med* 2011, **18**(8):807-815.
49. Garnacho-Montero J, Huici-Moreno MJ, Gutierrez-Pizarra A, Lopez I, Marquez-Vacaro JA, Macher H, Guerrero JM, Puppo-Moreno A: **Prognostic and diagnostic value of eosinopenia, C-reactive protein, procalcitonin, and circulating cell-free DNA in critically ill patients admitted with suspicion of sepsis.** *Crit Care* 2014, **18**(3):R116.
50. Gerrits JH, McLaughlin PM, Nienhuis BN, Smit JW, Loeff B: **Polymorphic mononuclear neutrophils CD64 index for diagnosis of sepsis in postoperative surgical patients and critically ill patients.** *Clin Chem Lab Med* 2013, **51**(4):897-905.
51. Giamarellos-Bourboulis EJ, Mega A, Grecka P, Scarpa N, Koratzanis G, Thomopoulos G, Giamarellou H: **Procalcitonin: a marker to clearly differentiate systemic inflammatory response syndrome and sepsis in the critically ill patient?** *Intensive Care Med* 2002, **28**(9):1351-1356.
52. Giamarellos-Bourboulis EJ, Mouktaroudi M, Tsaganos T, Koutoukas P, Spyridaki E, Pelekanou A, Kotzampassi K: **Evidence for the participation of soluble triggering receptor expressed on myeloid cells-1 in the systemic inflammatory response syndrome after multiple trauma.** *J Trauma* 2008, **65**(6):1385-1390.
53. Gibot S, Bene MC, Noel R, Massin F, Guy J, Cravoisy A, Barraud D, De Carvalho Bittencourt M, Quenot JP, Bollaert PE *et al*: **Combination biomarkers to diagnose sepsis in the critically ill patient.** *Am J Respir Crit Care Med* 2012, **186**(1):65-71.
54. Gibot S, Kolopp-Sarda MN, Bene MC, Cravoisy A, Levy B, Faure GC, Bollaert PE: **Plasma level of a triggering receptor expressed on myeloid cells-1: its diagnostic accuracy in patients with suspected sepsis.** *Ann Intern Med* 2004, **141**(1):9-15.

55. Gros A, Roussel M, Sauvadet E, Gacouin A, Marque S, Chimot L, Lavoue S, Camus C, Fest T, Le Tulzo Y: **The sensitivity of neutrophil CD64 expression as a biomarker of bacterial infection is low in critically ill patients.** *Intensive Care Med* 2012, **38**(3):445-452.
56. Guven H, Altintop L, Baydin A, Esen S, Aygun D, Hokelek M, Doganay Z, Bek Y: **Diagnostic value of procalcitonin levels as an early indicator of sepsis.** *Am J Emerg Med* 2002, **20**(3):202-206.
57. Han JH, Nachamkin I, Coffin SE, Gerber JS, Fuchs B, Garrigan C, Han X, Bilker WB, Wise J, Tolomeo P *et al*: **Use of a Combination Biomarker Algorithm To Identify Medical Intensive Care Unit Patients with Suspected Sepsis at Very Low Likelihood of Bacterial Infection.** *Antimicrob Agents Chemother* 2015, **59**(10):6494-6500.
58. Harbarth S, Holeckova K, Froidevaux C, Pittet D, Ricou B, Grau GE, Vadas L, Pugin J, Geneva Sepsis N: **Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis.** *Am J Respir Crit Care Med* 2001, **164**(3):396-402.
59. Hausfater P, Garric S, Ayed SB, Rosenheim M, Bernard M, Riou B: **Usefulness of procalcitonin as a marker of systemic infection in emergency department patients: a prospective study.** *Clin Infect Dis* 2002, **34**(7):895-901.
60. Hensler T, Sauerland S, Lefering R, Nagelschmidt M, Bouillon B, Andermahr J, Neugebauer EA: **The clinical value of procalcitonin and neopterin in predicting sepsis and organ failure after major trauma.** *Shock* 2003, **20**(5):420-426.
61. Hou YQ, Liang DY, Lou XL, Zhang M, Zhang ZH, Zhang LR: **Branched DNA-based Alu quantitative assay for cell-free plasma DNA levels in patients with sepsis or systemic inflammatory response syndrome.** *J Crit Care* 2016, **31**(1):90-95.
62. Hsu KH, Chan MC, Wang JM, Lin LY, Wu CL: **Comparison of Fcγ receptor expression on neutrophils with procalcitonin for the diagnosis of sepsis in critically ill patients.** *Respirology* 2011, **16**(1):152-160.
63. Ishikura H, Nishida T, Murai A, Nakamura Y, Irie Y, Tanaka J, Umemura T: **New diagnostic strategy for sepsis-induced disseminated intravascular coagulation: a prospective single-center observational study.** *Crit Care* 2014, **18**(1):R19.
64. Ivancevic N, Radenkovic D, Bumbasirevic V, Karamarkovic A, Jeremic V, Kalezic N, Vodnik T, Beleslin B, Milic N, Gregoric P *et al*: **Procalcitonin in preoperative diagnosis of abdominal sepsis.** *Langenbecks Arch Surg* 2008, **393**(3):397-403.
65. Jekarl DW, Lee SY, Lee J, Park YJ, Kim Y, Park JH, Wee JH, Choi SP: **Procalcitonin as a diagnostic marker and IL-6 as a prognostic marker for sepsis.** *Diagn Microbiol Infect Dis* 2013, **75**(4):342-347.
66. Jiang YN, Cai X, Zhou HM, Jin WD, Zhang M, Zhang Y, Du XX, Chen ZH: **Diagnostic and prognostic roles of soluble CD22 in patients with Gram-negative bacterial sepsis.** *Hepatobiliary Pancreat Dis Int* 2015, **14**(5):523-529.
67. Kece E, Yaka E, Yilmaz S, Dogan NO, Alyesil C, Pekdemir M: **Comparison of diagnostic and prognostic utility of lactate and procalcitonin for sepsis in adult cancer patients presenting to emergency department with systemic inflammatory response syndrome.** *Turk J Emerg Med* 2016, **16**(1):1-7.

68. Klouche K, Cristol JP, Devin J, Gilles V, Kuster N, Larcher R, Amigues L, Corne P, Jonquet O, Dupuy AM: **Diagnostic and prognostic value of soluble CD14 subtype (Presepsin) for sepsis and community-acquired pneumonia in ICU patients.** *Ann Intensive Care* 2016, **6**(1):59.
69. Kofoed K, Andersen O, Kronborg G, Tvede M, Petersen J, Eugen-Olsen J, Larsen K: **Use of plasma C-reactive protein, procalcitonin, neutrophils, macrophage migration inhibitory factor, soluble urokinase-type plasminogen activator receptor, and soluble triggering receptor expressed on myeloid cells-1 in combination to diagnose infections: a prospective study.** *Crit Care* 2007, **11**(2):R38.
70. Kweon OJ, Choi JH, Park SK, Park AJ: **Usefulness of presepsin (sCD14 subtype) measurements as a new marker for the diagnosis and prediction of disease severity of sepsis in the Korean population.** *J Crit Care* 2014, **29**(6):965-970.
71. Latour-Perez J, Alcala-Lopez A, Garcia-Garcia MA, Sanchez-Hernandez JF, Abad-Terrado C, Viedma-Contreras JA, Masia M, Gonzalez-Tejera M, Arizo-Leon D, Porcar MJ *et al*: **Diagnostic accuracy of sTREM-1 to identify infection in critically ill patients with systemic inflammatory response syndrome.** *Clin Biochem* 2010, **43**(9):720-724.
72. Lewis SM, Treacher DF, Edgeworth J, Mahalingam G, Brown CS, Mare TA, Stacey M, Beale R, Brown KA: **Expression of CD11c and EMR2 on neutrophils: potential diagnostic biomarkers for sepsis and systemic inflammation.** *Clin Exp Immunol* 2015, **182**(2):184-194.
73. Li L, Zhu Z, Chen J, Ouyang B, Chen M, Guan X: **Diagnostic value of soluble triggering receptor expressed on myeloid cells-1 in critically-ill, postoperative patients with suspected sepsis.** *Am J Med Sci* 2013, **345**(3):178-184.
74. Lin S, Huang Z, Wang M, Weng Z, Zeng D, Zhang Y, Zhu Y, Jiang J: **Interleukin-6 as an early diagnostic marker for bacterial sepsis in patients with liver cirrhosis.** *J Crit Care* 2015, **30**(4):732-738.
75. Liu B, Chen YX, Yin Q, Zhao YZ, Li CS: **Diagnostic value and prognostic evaluation of Presepsin for sepsis in an emergency department.** *Crit Care* 2013, **17**(5):R244.
76. Livaditi O, Kotanidou A, Psarra A, Dimopoulou I, Sotiropoulou C, Augustatou K, Papasteriades C, Armaganidis A, Roussos C, Orfanos SE *et al*: **Neutrophil CD64 expression and serum IL-8: sensitive early markers of severity and outcome in sepsis.** *Cytokine* 2006, **36**(5-6):283-290.
77. Loonen AJ, de Jager CP, Tosserams J, Kusters R, Hilbink M, Wever PC, van den Brule AJ: **Biomarkers and molecular analysis to improve bloodstream infection diagnostics in an emergency care unit.** *PLoS One* 2014, **9**(1):e87315.
78. Matera G, Puccio R, Giancotti A, Quirino A, Pulicari MC, Zicca E, Caroleo S, Renzulli A, Liberto MC, Foca A: **Impact of interleukin-10, soluble CD25 and interferon-gamma on the prognosis and early diagnosis of bacteremic systemic inflammatory response syndrome: a prospective observational study.** *Crit Care* 2013, **17**(2):R64.
79. Mat-Nor MB, Md Ralib A, Abdullah NZ, Pickering JW: **The diagnostic ability of procalcitonin and interleukin-6 to differentiate infectious from noninfectious systemic inflammatory response syndrome and to predict mortality.** *J Crit Care* 2016, **33**:245-251.

80. Mearelli F, Fiotti N, Altamura N, Zanetti M, Fernandes G, Burekovic I, Occhipinti A, Orso D, Giansante C, Casarsa C *et al*: **Heterogeneous models for an early discrimination between sepsis and non-infective SIRS in medical ward patients: a pilot study.** *Intern Emerg Med* 2014, **9**(7):749-757.
81. Meynaar IA, Droog W, Batstra M, Vreede R, Herbrink P: **In Critically Ill Patients, Serum Procalcitonin Is More Useful in Differentiating between Sepsis and SIRS than CRP, IL-6, or LBP.** *Crit Care Res Pract* 2011, **2011**:594645.
82. Miglietta F, Faneschi ML, Lobreglio G, Palumbo C, Rizzo A, Cucurachi M, Portaccio G, Guerra F, Pizzolante M: **Procalcitonin, C-reactive protein and serum lactate dehydrogenase in the diagnosis of bacterial sepsis, SIRS and systemic candidiasis.** *Infez Med* 2015, **23**(3):230-237.
83. Miller PR, Munn DD, Meredith JW, Chang MC: **Systemic inflammatory response syndrome in the trauma intensive care unit: who is infected?** *J Trauma* 1999, **47**(6):1004-1008.
84. Mokart D, Merlin M, Sannini A, Brun JP, Delpero JR, Houvenaeghel G, Moutardier V, Blache JL: **Procalcitonin, interleukin 6 and systemic inflammatory response syndrome (SIRS): early markers of postoperative sepsis after major surgery.** *Br J Anaesth* 2005, **94**(6):767-773.
85. Muller B, Becker KL, Schachinger H, Rickenbacher PR, Huber PR, Zimmerli W, Ritz R: **Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit.** *Crit Care Med* 2000, **28**(4):977-983.
86. Muzlovic I, Ihan A, Stubljär D: **CD64 index on neutrophils can diagnose sepsis and predict 30-day survival in subjects after ventilator-associated pneumonia.** *J Infect Dev Ctries* 2016, **10**(3):260-268.
87. Nierhaus A, Klatte S, Linssen J, Eismann NM, Wichmann D, Hedke J, Braune SA, Kluge S: **Revisiting the white blood cell count: immature granulocytes count as a diagnostic marker to discriminate between SIRS and sepsis—a prospective, observational study.** *BMC Immunol* 2013, **14**:8.
88. Oberhoffer M, Russwurm S, Bredle D, Chatzinicolaou K, Reinhart K: **Discriminative power of inflammatory markers for prediction of tumor necrosis factor-alpha and interleukin-6 in ICU patients with systemic inflammatory response syndrome (SIRS) or sepsis at arbitrary time points.** *Intensive Care Med* 2000, **26 Suppl 2**:S170-174.
89. Oh JS, Kim SU, Oh YM, Choe SM, Choe GH, Choe SP, Kim YM, Hong TY, Park KN: **The usefulness of the semiquantitative procalcitonin test kit as a guideline for starting antibiotic administration.** *Am J Emerg Med* 2009, **27**(7):859-863.
90. Oshita H, Sakurai J, Kamitsuna M: **Semi-quantitative procalcitonin test for the diagnosis of bacterial infection: clinical use and experience in Japan.** *J Microbiol Immunol Infect* 2010, **43**(3):222-227.
91. Papadimitriou-Olivgeris M, Lekka K, Zisimopoulos K, Spiliopoulou I, Logothetis D, Theodorou G, Anastassiou ED, Fligou F, Karakantza M, Marangos M: **Role of CD64 expression on neutrophils in the diagnosis of sepsis and the prediction of mortality in adult critically ill patients.** *Diagn Microbiol Infect Dis* 2015, **82**(3):234-239.
92. Prucha M, Herold I, Zazula R, Dubska L, Dostal M, Hildebrand T, Hyanek J: **Significance of lipopolysaccharide-binding protein (an acute phase protein) in monitoring critically ill patients.** *Crit Care* 2003, **7**(6):R154-159.

93. Ratzinger F, Haslacher H, Perkmann T, Schmetterer KG, Poepl W, Mitteregger D, Dorffner G, Burgmann H: **Sepsis biomarkers in neutropaenic systemic inflammatory response syndrome patients on standard care wards.** *Eur J Clin Invest* 2015, **45**(8):815-823.
94. Ratzinger F, Schuardt M, Eichbichler K, Tsirkinidou I, Bauer M, Haslacher H, Mitteregger D, Binder M, Burgmann H: **Utility of sepsis biomarkers and the infection probability score to discriminate sepsis and systemic inflammatory response syndrome in standard care patients.** *PLoS One* 2013, **8**(12):e82946.
95. Reichsoellner M, Raggam RB, Wagner J, Krause R, Hoenigl M: **Clinical evaluation of multiple inflammation biomarkers for diagnosis and prognosis for patients with systemic inflammatory response syndrome.** *J Clin Microbiol* 2014, **52**(11):4063-4066.
96. Rivera-Chavez FA, Minei JP: **Soluble triggering receptor expressed on myeloid cells-1 is an early marker of infection in the surgical intensive care unit.** *Surg Infect (Larchmt)* 2009, **10**(5):435-439.
97. Rogina P, Stubljär D, Lejko-Zupanc T, Osredkar J, Skvarc M: **Expression of CD64 on neutrophils (CD64 index): diagnostic accuracy of CD64 index to predict sepsis in critically ill patients.** *Clin Chem Lab Med* 2015, **53**(4):e89-91.
98. Romualdo LG, Torrella PE, Gonzalez MV, Sanchez RJ, Holgado AH, Freire AO, Acebes SR, Oton MD: **Diagnostic accuracy of presepsin (soluble CD14 subtype) for prediction of bacteremia in patients with systemic inflammatory response syndrome in the Emergency Department.** *Clin Biochem* 2014, **47**(7-8):505-508.
99. Ruiz-Alvarez MJ, Garcia-Valdecasas S, De Pablo R, Sanchez Garcia M, Coca C, Groeneveld TW, Roos A, Daha MR, Arribas I: **Diagnostic efficacy and prognostic value of serum procalcitonin concentration in patients with suspected sepsis.** *J Intensive Care Med* 2009, **24**(1):63-71.
100. Rule JA, Hynan LS, Attar N, Sanders C, Korzun WJ, Lee WM, Acute Liver Failure Study G: **Procalcitonin Identifies Cell Injury, Not Bacterial Infection, in Acute Liver Failure.** *PLoS One* 2015, **10**(9):e0138566.
101. Ruokonen E, Ilkka L, Niskanen M, Takala J: **Procalcitonin and neopterin as indicators of infection in critically ill patients.** *Acta Anaesthesiol Scand* 2002, **46**(4):398-404.
102. Sakr Y, Burgett U, Nacul FE, Reinhart K, Brunkhorst F: **Lipopolysaccharide binding protein in a surgical intensive care unit: a marker of sepsis?** *Crit Care Med* 2008, **36**(7):2014-2022.
103. Sargentini V, Ceccarelli G, D'Alessandro M, Colleparado D, Morelli A, D'Egidio A, Mariotti S, Nicoletti AM, Evangelista B, D'Ettore G *et al.*: **Presepsin as a potential marker for bacterial infection relapse in critical care patients. A preliminary study.** *Clin Chem Lab Med* 2015, **53**(4):567-573.
104. Selberg O, Hecker H, Martin M, Klos A, Bautsch W, Kohl J: **Discrimination of sepsis and systemic inflammatory response syndrome by determination of circulating plasma concentrations of procalcitonin, protein complement 3a, and interleukin-6.** *Crit Care Med* 2000, **28**(8):2793-2798.
105. Seok Y, Choi JR, Kim J, Kim YK, Lee J, Song J, Kim SJ, Lee KA: **Delta neutrophil index: a promising diagnostic and prognostic marker for sepsis.** *Shock* 2012, **37**(3):242-246.

106. Shozushima T, Takahashi G, Matsumoto N, Kojika M, Okamura Y, Endo S: **Usefulness of presepsin (sCD14-ST) measurements as a marker for the diagnosis and severity of sepsis that satisfied diagnostic criteria of systemic inflammatory response syndrome.** *J Infect Chemother* 2011, **17**(6):764-769.
107. Sierra R, Rello J, Bailen MA, Benitez E, Gordillo A, Leon C, Pedraza S: **C-reactive protein used as an early indicator of infection in patients with systemic inflammatory response syndrome.** *Intensive Care Med* 2004, **30**(11):2038-2045.
108. Su L, Feng L, Song Q, Kang H, Zhang X, Liang Z, Jia Y, Feng D, Liu C, Xie L: **Diagnostic value of dynamics serum sCD163, sTREM-1, PCT, and CRP in differentiating sepsis, severity assessment, and prognostic prediction.** *Mediators Inflamm* 2013, **2013**:969875.
109. Su L, Han B, Liu C, Liang L, Jiang Z, Deng J, Yan P, Jia Y, Feng D, Xie L: **Value of soluble TREM-1, procalcitonin, and C-reactive protein serum levels as biomarkers for detecting bacteremia among sepsis patients with new fever in intensive care units: a prospective cohort study.** *BMC Infect Dis* 2012, **12**:157.
110. Sungurtekin H, Sungurtekin U, Balci C: **Circulating complement (C3 and C4) for differentiation of SIRS from sepsis.** *Adv Ther* 2006, **23**(6):893-901.
111. Suprin E, Camus C, Gacouin A, Le Tulzo Y, Lavoue S, Feuillu A, Thomas R: **Procalcitonin: a valuable indicator of infection in a medical ICU?** *Intensive Care Med* 2000, **26**(9):1232-1238.
112. Takahashi G, Shibata S, Ishikura H, Miura M, Fukui Y, Inoue Y, Endo S: **Presepsin in the prognosis of infectious diseases and diagnosis of infectious disseminated intravascular coagulation: a prospective, multicentre, observational study.** *Eur J Anaesthesiol* 2015, **32**(3):199-206.
113. Talebi-Taher M, Babazadeh S, Barati M, Latifnia M: **Serum inflammatory markers in the elderly: are they useful in differentiating sepsis from SIRS?** *Acta Med Iran* 2014, **52**(6):438-442.
114. Tan TL, Ahmad NS, Nasuruddin DN, Ithnin A, Tajul Arifin K, Zaini IZ, Wan Ngah WZ: **CD64 and Group II Secretory Phospholipase A2 (sPLA2-IIA) as Biomarkers for Distinguishing Adult Sepsis and Bacterial Infections in the Emergency Department.** *PLoS One* 2016, **11**(3):e0152065.
115. Tavladaki T, Spanaki AM, Dimitriou H, Kondili E, Choulaki C, Georgopoulos D, Briassoulis G: **Similar Metabolic, Innate Immunity, and Adipokine Profiles in Adult and Pediatric Sepsis Versus Systemic Inflammatory Response Syndrome-A Pilot Study.** *Pediatr Crit Care Med* 2017, **18**(11):e494-e505.
116. Tian G, Pan SY, Ma G, Liao W, Su QG, Gu BC, Qin K: **Serum levels of procalcitonin as a biomarker for differentiating between sepsis and systemic inflammatory response syndrome in the neurological intensive care unit.** *J Clin Neurosci* 2014, **21**(7):1153-1158.
117. Tromp M, Lansdorp B, Bleeker-Rovers CP, Gunnewiek JM, Kullberg BJ, Pickkers P: **Serial and panel analyses of biomarkers do not improve the prediction of bacteremia compared to one procalcitonin measurement.** *J Infect* 2012, **65**(4):292-301.
118. Tsalik EL, Jaggars LB, Glickman SW, Langley RJ, van Velkinburgh JC, Park LP, Fowler VG, Cairns CB, Kingsmore SF, Woods CW: **Discriminative value of inflammatory biomarkers for suspected sepsis.** *J Emerg Med* 2012, **43**(1):97-106.

119. Tsangaris I, Plachouras D, Kavatha D, Gourgoulis GM, Tsantes A, Kopterides P, Tsaknis G, Dimopoulou I, Orfanos S, Giamarellos-Bourboulis E *et al*: **Diagnostic and prognostic value of procalcitonin among febrile critically ill patients with prolonged ICU stay.** *BMC Infect Dis* 2009, **9**:213.
120. Ulla M, Pizzolato E, Lucchiari M, Loiacono M, Soardo F, Forno D, Morello F, Lupia E, Moiraghi C, Mengozzi G *et al*: **Diagnostic and prognostic value of presepsin in the management of sepsis in the emergency department: a multicenter prospective study.** *Crit Care* 2013, **17**(4):R168.
121. Vodnik T, Kaljevic G, Tadic T, Majkic-Singh N: **Presepsin (sCD14-ST) in preoperative diagnosis of abdominal sepsis.** *Clin Chem Lab Med* 2013, **51**(10):2053-2062.
122. Wang HX, Chen B: **Diagnostic role of soluble triggering receptor expressed on myeloid cell-1 in patients with sepsis.** *World J Emerg Med* 2011, **2**(3):190-194.
123. Wanner GA, Keel M, Steckholzer U, Beier W, Stocker R, Ertel W: **Relationship between procalcitonin plasma levels and severity of injury, sepsis, organ failure, and mortality in injured patients.** *Crit Care Med* 2000, **28**(4):950-957.
124. Xiao K, Su L, Yan P, Han B, Li J, Wang H, Jia Y, Li X, Xie L: **alpha-1-Acid glycoprotein as a biomarker for the early diagnosis and monitoring the prognosis of sepsis.** *J Crit Care* 2015, **30**(4):744-751.
125. Zeng M, Chang M, Zheng H, Li B, Chen Y, He W, Huang C: **Clinical value of soluble urokinase-type plasminogen activator receptor in the diagnosis, prognosis, and therapeutic guidance of sepsis.** *Am J Emerg Med* 2016, **34**(3):375-380.
126. Ahmadinejad ZD, B.; Jalili, M.; Soudbakhsh, A.; Rasolinejad, M.: **Evaluation of serum procalcitonin in patients with systemic inflammatory response syndrome with and without infection.** *Acta Medica Iranica* 2009, **47**(5):383-388.
127. Aziz SA, Nelwan EJ, Sukrisman L, Suhendro S: **Higher cut-off serum procalcitonin level for sepsis diagnosis in metastatic solid tumor patients.** *BMC Res Notes* 2018, **11**(1):84.
128. Halim B, Ozlem T, Melek C, Munip Hakan Y, Cevval U, Gonul DH, Cigdem Banu C: **Diagnostic and prognostic value of procalcitonin and sTREM-1 levels in sepsis.** *Turk J Med Sci* 2015, **45**(3):578-586.
129. Bell K, Wattie M, Byth K, Silvestrini R, Clark P, Stachowski E, Benson EM: **Procalcitonin: a marker of bacteraemia in SIRS.** *Anaesth Intensive Care* 2003, **31**(6):629-636.
130. Cheval C, Timsit JF, Garrouste-Orgeas M, Assicot M, De Jonghe B, Misset B, Bohuon C, Carlet J: **Procalcitonin (PCT) is useful in predicting the bacterial origin of an acute circulatory failure in critically ill patients.** *Intensive Care Med* 2000, **26 Suppl 2**:S153-158.
131. Dalal E, Soud; Olfat, Al, Amin; Amal, Al, Amin: **New era "soluble triggering receptor expressed on myeloid cells-I" as a marker for early detection of infection in trauma patients.** *Egyptian Journal of Anaesthesia* 2011, **27**(4):267-272.
132. Gao L, Yang B, Zhang H, Ou Q, Lin Y, Zhang M, Zhang Z, Kim S, Wu B, Wang Z *et al*: **DcR3, a new biomarker for sepsis, correlates with infection severity and procalcitonin.** *Oncotarget* 2018, **9**(13):10934-10944.
133. Godnic M, Stubljarić D, Skvarc M, Jukić T: **Diagnostic and prognostic value of sCD14-ST–presepsin for patients admitted to hospital intensive care unit (ICU).** *Wien Klin Wochenschr* 2015, **127**(13-14):521-

134. Karon BS, Tolan NV, Wockenfus AM, Block DR, Baumann NA, Bryant SC, Clements CM: **Evaluation of lactate, white blood cell count, neutrophil count, procalcitonin and immature granulocyte count as biomarkers for sepsis in emergency department patients.** *Clin Biochem* 2017, **50**(16-17):956-958.
135. Ljungstrom L, Pernestig AK, Jacobsson G, Andersson R, Usener B, Tilevik D: **Diagnostic accuracy of procalcitonin, neutrophil-lymphocyte count ratio, C-reactive protein, and lactate in patients with suspected bacterial sepsis.** *PLoS One* 2017, **12**(7):e0181704.
136. Lu B, Zhang Y, Li C, Liu C, Yao Y, Su M, Shou S: **The utility of presepsin in diagnosis and risk stratification for the emergency patients with sepsis.** *Am J Emerg Med* 2018, **36**(8):1341-1345.
137. Nakamura Y, Ishikura H, Nishida T, Kawano Y, Yuge R, Ichiki R, Murai A: **Usefulness of presepsin in the diagnosis of sepsis in patients with or without acute kidney injury.** *BMC Anesthesiol* 2014, **14**:88.
138. Righi SS, L.; Monsagrati, A.; Saliu, M.; Locati, L.; Radrizzani, D.: **Clinical Evaluation of Neutrophil CD64 as a Diagnostic Marker of Infection in a Polyvalent Intensive Care Unit.** *Infect Dis Clin Pract* 2014, **22**:32-37.
139. Whang KT, Steinwald PM, White JC, Nylen ES, Snider RH, Simon GL, Goldberg RL, Becker KL: **Serum calcitonin precursors in sepsis and systemic inflammation.** *J Clin Endocrinol Metab* 1998, **83**(9):3296-3301.
140. Zhang X, Liu D, Liu YN, Wang R, Xie LX: **The accuracy of presepsin (sCD14-ST) for the diagnosis of sepsis in adults: a meta-analysis.** *Crit Care* 2015, **19**:323.
141. de Jong E, van Oers JA, Beishuizen A, Vos P, Vermeijden WJ, Haas LE, Loeff BG, Dormans T, van Melsen GC, Kluiters YC *et al*: **Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial.** *Lancet Infect Dis* 2016, **16**(7):819-827.
142. Vijayan AL, Vanimaya, Ravindran S, Saikant R, Lakshmi S, Kartik R, G M: **Procalcitonin: a promising diagnostic marker for sepsis and antibiotic therapy.** *J Intensive Care* 2017, **5**:51.
143. Song JU, Sin CK, Park HK, Shim SR, Lee J: **Performance of the quick Sequential (sepsis-related) Organ Failure Assessment score as a prognostic tool in infected patients outside the intensive care unit: a systematic review and meta-analysis.** *Crit Care* 2018, **22**(1):28.
144. Qureshi SS, Lewis SM, Gant VA, Treacher D, Davis BH, Brown KA: **Increased distribution and expression of CD64 on blood polymorphonuclear cells from patients with the systemic inflammatory response syndrome (SIRS).** *Clin Exp Immunol* 2001, **125**(2):258-265.
145. Icardi M, Erickson Y, Kilborn S, Stewart B, Grief B, Scharnweber G: **CD64 index provides simple and predictive testing for detection and monitoring of sepsis and bacterial infection in hospital patients.** *J Clin Microbiol* 2009, **47**(12):3914-3919.
146. Lynema S, Marmer D, Hall ES, Meinen-Derr J, Kingma PS: **Neutrophil CD64 as a diagnostic marker of sepsis: impact on neonatal care.** *Am J Perinatol* 2015, **32**(4):331-336.
147. Rutter CM, Gatsonis CA: **A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations.** *Stat Med* 2001, **20**(19):2865-2884.

148. Harbord RM, Deeks JJ, Egger M, Whiting P, Sterne JA: **A unification of models for meta-analysis of diagnostic accuracy studies.** *Biostatistics* 2007, **8**(2):239-251.

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.

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Figure 2

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

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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

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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.

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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)

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)

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