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Head-to-head comparison of procalcitonin and presepsin for the diagnosis of sepsis in critically ill adult patients: a protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction: Early diagnosis and immediate therapeutic intervention, including appropriate antibiotic therapy and goal-directed resuscitation, are necessary to reduce mortality in patients with sepsis. However, a single clinical or biological marker indicative of sepsis has not been adopted unanimously. Although procalcitonin and presepsin are promising biomarkers that can effectively differentiate between sepsis/infection and systemic inflammatory response syndrome of non-infectious origin, little is known about which marker is superior.

Methods and analysis: We will conduct a systematic review and meta-analysis of procalcitonin and presepsin for the diagnosis of sepsis/infection in critically ill adult patients. The primary objective is to evaluate the diagnostic accuracy of these 2 biomarkers to a reference standard of sepsis/infection and to compare the diagnostic accuracy with each other. We will search electronic bibliographic databases such as MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials for retrospective and prospective diagnostic test studies. We will assign 2 reviewers to review all collected titles and associated abstracts, review full articles, and extract study data. We will use the Quality of Diagnostic Accuracy Studies-II tool to report study characteristics and to evaluate methodological quality. If pooling is possible, we will use bivariate random effects and hierarchical summary receiver operating characteristic (ROC) models to calculate parameter estimates to output summary ROCs, pooled sensitivity and specificity data, and 95% CIs around the summary operating point. We will also assess heterogeneity via clinical and methodological subgroup and sensitivity analyses.

Ethics and dissemination: This systematic review will provide guidance on the triage of these tests, help to determine whether existing tests should be revised or replaced, and may also identify knowledge gaps in sepsis diagnosis that could direct further research in the field. Research ethics is not required for this review. The findings will be reported at conferences and in peer-reviewed publications.

Strengths and limitations of this study

- We will conduct a systemic review of procalcitonin and presepsin for the diagnosis of sepsis or bacterial infection using appropriate methodologies and quality assessment tools that may feed into an evidence-based clinical practice.
- This will be the first systematic review to directly compare the diagnostic accuracy of these two biomarkers to a reference standard of sepsis/infection with each other.
- The results from this systematic review will be highly dependent on the quality of the underlying primary studies, which will be mainly cohort or case–control studies.
- The other limitation is that the included studies may be various with significant clinical and statistical heterogeneity, and may not be generalisable to other settings.

Trial registration number: CRD42016035784.

INTRODUCTION

Sepsis is one of the most common causes of death worldwide. A systematic review of studies addressing global sepsis epidemiology revealed yearly incidences of 22–240 per 100 000 inhabitants for sepsis and 13–300 per 100 000 inhabitants for severe sepsis, with fatality rates as high as 30% for sepsis and 50% for severe sepsis.[1] Sepsis is originally a systemic inflammatory response syndrome (SIRS) triggered by infection and can in some conditions lead to organ failure or dysfunction.[2] Innate and adaptive immune responses are fundamental in the defence of the host against infectious microorganisms.

However, these responses also help to intensify proinflammatory mechanisms, endothelial dysfunction and imbalances in coagulation that exacerbate organ injury.[3] Although recent advances and breakthroughs in the management of bundled care for patients with sepsis have significantly decreased mortality, the fatality rate of these patients remains high.[1]

In critical care settings, the diagnosis of patients who present with signs of infection can be difficult. In particular, bacterial infection, viral infection, non-infectious disorders, trauma and perioperative surgical care can all lead to fever with SIRS, so a serial laboratory and imaging work-up should be necessary to diagnose sepsis or infection correctly. Presently, clinical findings, biological markers and microorganism isolation comprise the basis for diagnosing sepsis. However, a single clinical or biological marker indicative of sepsis has not been adopted unanimously.[4] Meanwhile, evidence for early antimicrobial therapy has been reported in patients with sepsis,[5 6] and the time to administration of antibiotic drugs is recognised as a key performance indicator in the management of sepsis.[7 8] Clinical practice guidelines emphasise early diagnosis to enable the timely start of appropriate antimicrobial therapy to improve outcomes in sepsis,[9] so the early diagnosis of sepsis or infection is necessary to reduce the morbidity and mortality from these conditions.

Serum procalcitonin (PCT) is the inactive propeptide of the hormone calcitonin released by hepatocytes and peripheral monocytes and also by C cells of the thyroid gland[10] and is a biological marker of increasing interest for detecting bacterial infections including sepsis.[11 12] It has been widely investigated that an increase in serum PCT correlates closely with the inflammatory response to microbial infections.[10] Three previous meta-analyses conducted on this subject have yielded conflicting results.[12–14] The most recent analysis included 30 studies. The results of these studies showed quite high heterogeneity (I^2=96%); the optimal cut-off value for the detection of bacterial sepsis with PCT was 1.1 ng/mL (mean sensitivity, 77% (95% CI 72% to 81%); mean specificity, 79% (95% CI 74% to 84%)).[13]

Soluble CD14 subtype (sCD14-ST, presepsin (P-SEP)) is a new and also promising biomarker first found in 2004 that has been shown to increase in the response of a host to microbial infection.[15] When the proinflammatory signalling cascade against infectious agents is activated, soluble forms of CD14 are produced and released into circulation either by secretion following phagocytosis or through proteolytic cleavage on activated monocytes.[15 16] The P-SEP level specifically increases during sepsis and less intensively so during SIRS. An increasing number of studies have shown the ability of P-SEP to serve as a valuable marker in sepsis diagnosis.[17 18] So far, however, although P-SEP appears to be superior to other biomarkers (C reactive protein, interleukin-6, and PCT) for the diagnosis of sepsis,[15 19] no meta-analysis has been conducted to compare the prognostic performance between PCT and P-SEP.

The objective of this study is thus to determine and compare the diagnostic performance of PCT and P-SEP for the diagnosis of early-stage sepsis in critically ill patients. Identifying the potential role of these biomarkers and comparing the diagnostic values in the existing diagnostic pathways will be useful in the management of critically ill patients and in designing future studies to evaluate the accuracy of diagnostic tests. Ultimately, this study is expected to provide clinicians with novel quantitative evidence and aid in the establishment of evidence-based guidelines for diagnosing sepsis, resulting in improvement in the management of patients with sepsis as effective treatment of sepsis requires accurate diagnosis.

METHODS AND ANALYSIS

Protocol

This study will follow the recommendations on conducting and reporting systematic reviews and meta-analyses set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[20–22] the Meta-Analysis of Observational Studies in Epidemiology proposal,[23] and the Cochrane Diagnostic Test Accuracy Working Group.[24] The protocol has been registered in PROSPERO, an International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO/; Registration No. CRD42016035784).

Focused review questions

Primary objective: To determine the accuracy of PCT and P-SEP when used to diagnose bacterial infection in adult critically ill patients.

Secondary objective 1: To determine which marker is superior for the diagnosis of bacterial infection in critically ill adult patients.

Secondary objective 2: To determine the diagnostic accuracy of PCT and P-SEP for the diagnosis of bacterial sepsis with organ dysfunction in critically ill adult patients.

Types of studies

We will include all studies that compare PCT and P-SEP in adult critically ill patients with suspected bacterial infection or sepsis. Diagnostic accuracy studies are typically of a delayed cross-sectional design. However, we will also include randomised controlled trials, cohort studies and case–control studies. Included studies should have sufficient information to build a 2×2 contingency table (true and false, positive and negative). Case–control studies will be excluded when the control group entails healthy volunteers as they are not representative of the population in which PCT/P-SEP will be performed. Articles with experimental animals, narrative reviews, correspondence, case reports, expert opinions and editorials will be excluded.

Types of participants

We will include studies that evaluate critically ill patients 18 years of age or older and with suspected infection or

sepsis. Since 'critical illness' is somewhat poorly defined we will include critical illnesses whose definitions are generally accepted, such as acute respiratory distress syndrome, sepsis and SIRS, in this review. These will include participants from different clinical settings, such as emergency departments, hospital wards and intensive care units. We will exclude all studies investigating animals, those predominantly comprising neonates or postcardiac surgical, heart failure, or perioperative patients, and those comprising healthy participants as controls.

Studied tests

We will include studies with a description of the index test being the measurement of PCT or P-SEP in plasma or serum.

Reference standards

We will include studies that used one of the three reference gold standards for infection or sepsis:

1. Sepsis definitions established by the American College of Chest Physicians and Society of Critical Care Medicine Consensus Conference in 1991.[2]
2. Sepsis definitions established by the Society of Critical Care Medicine, European Society of Intensive Care Medicine, American College of Chest Physicians, American Thoracic Society and Surgical Infection Society in 2001.[9]
3. Recently updated sepsis definitions: the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) in 2016.[25]
4. Other well-defined, author-defined reference standards for sepsis. We are aware that clinical diagnostic criteria have changed over time and vary depending on the study country. Studies in which the clinical diagnosis is not complete based on the above criteria will be included in the review only if the authors can cite or provide an explanation for the clinical diagnostic criteria they used.

Exclusion criteria

We will exclude the following studies in which true-positive and false-positive and negative rates are lacking, cannot be calculated from the text or appendices, or are not provided by the authors; abstracts that provide inadequate information with which to assess methodological quality; and duplicates or subcohorts of already published cohorts.

Search strategy

We will search the following databases for relevant studies: MEDLINE (via PubMed), EMBASE and the Cochrane Central Register of Controlled Trials. We have developed a search strategy using a combination of keywords and Medical Subject Heading (MeSH)/EMTREE terms, which are "(procalcitonin OR PCT OR presepsin OR "soluble CD14 subtype" OR "sCD14-ST" OR P-SEP) AND (sepsis OR "bacterial infection" OR "systemic inflammatory response syndrome" OR SIRS)". The search will be limited to the years 1992 onwards because the first article on PCT was published in 1992[26] and that on P-SEP in 2004.[15] We will not use a diagnostic accuracy search filter because it can sometimes exclude relevant articles in systematic reviews of diagnostic accuracy studies. We will not apply any language restriction to the electronic searches. We will evaluate the reference lists of all relevant papers to determine if additional studies can be found. We will also contact the authors of ongoing or unpublished trials to obtain additional details and information on these trials. Our MEDLINE search strategy will be adapted for searches in the other two databases.

Citation management and screening

Citations will be stored and duplicates will be removed using EndNote software (Thomson Reuters, Toronto, Ontario, Canada). Initially, two authors (YK and YH) will independently screen the studies by title and abstract and will eliminate those that do not meet the screening criteria. These authors will resolve disagreements by discussion and the participation of a third author (KY) if necessary. Following the initial screening process, the same two authors (YK and YH) will independently review the full text of the remaining studies to determine inclusion or exclusion in the final study. As before, disagreements will be resolved by discussion and referral to a third author (KY) if necessary. We will use the PRISMA flow diagram to document the study selection process.

Data abstraction

The study characteristics of all included studies will be extracted by two authors (YK and YH). Extracted data will include that necessary to assess quality and to investigate heterogeneity. These authors will transfer the data into a study-specific format. If necessary, a third author (KY) will help to adjudicate any disagreements. We will use 2×2 tables to cross-tabulate the positive or negative numeric data from the index test results (positive or negative) against the target disorder and will display all results in various tables. In the case of missing data, we will contact the authors of the primary studies to provide said data.

Assessment of risk of bias

The quality of the included studies will be independently assessed by two authors (YK and YH) and verified by a third (KY) if necessary. Study quality of each article will be reported according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.[27] We will specifically assess the presence of spectrum, threshold, disease progression, and partial or differential verification bias. We will assign a judgement for each domain that categorises the risk of bias as high, low or unclear. If insufficient detail is reported to evaluate the risk of bias,

we will ask for clarification from the trial's corresponding author, if possible.

Data synthesis

To visually assess between-study variability, we will present the results in a forest plot and with receiver operating characteristic (ROC) curves after plotting estimates of the sensitivities and specificities (with 95% CIs). We will use Review Manager (RevMan V.5.3) software (Nordic Cochrane Centre, Cochrane Collaboration) to document the descriptive analyses.

We will pool studies only if they meet the following criteria: a common threshold is used in each study, the studies are performed in identical or comparable settings, and the studies show adequate clinical homogeneity. In this meta-analysis, we will use a bivariable random-effects model to fit a summary ROC curve and calculate various indices of accuracy such as sensitivity, specificity and likelihood ratios with the MIDAS module for STATA software, V.14.0 (Stata Corporation, College Station, Texas, USA). Also, we will estimate positive predictive value and negative predictive value, which are more useful clinically. We will plot the 95% confidence ellipse and prediction region around averaged accuracy estimates in the ROC space. We will generate a nomogram, which is a user-friendly graphical depiction of positive predictive value and negative predictive value by prevalence.

Assessment of heterogeneity

Initially, to examine heterogeneity, we will visually inspect forest plots of each study's sensitivities and specificities as well as ROC curves related to the individual study results. Statistical heterogeneity will be evaluated informally from forest plots of the study estimates and more formally using the χ^2 test ($p<0.1$, significant heterogeneity) and I^2 statistic ($I^2>$ 50%=significant heterogeneity).

Assessment of publication biases

If a sufficient number of studies are identified, we will investigate publication biases by Deek's funnel plot. We will interpret publication bias with care because this test lacks statistical power, and adequate methods to detect publication bias in diagnostic test accuracy reviews have not been agreed on.

Sensitivity and subgroup analysis

We will conduct sensitivity analyses to determine the robustness of the meta-analyses and will exclude studies by using different components of the QUADAS-2 tool for assessing risk of bias. Our primary analysis will include all studies; sensitivity analysis will exclude studies with high risk of bias or if potential applicability is questionable.

If sufficient studies are available, we will undertake subgroup analyses to explore the sources of potential heterogeneity in sensitivity and specificity. Univariate meta-regression analysis and subgroup analysis will be performed using the following as covariates: year of publication, country, prevalence (<50% or ≥50%), sample size (<100 or ≥100), setting (emergency, intensive care units, hospital ward, mixed), admission category (surgical or medical), origin of infection, severity of illness (sepsis, severe sepsis or septic shock), comorbidities (whether the studies excluded patients who had comorbidities that were likely to influence P-SEP levels), clinical diagnostic criteria (the international consensus definition for sepsis in 1991, 2001 and 2016 (if applicable) and author-defined criteria for sepsis) and causal pathogens of sepsis (bacterial, fungal, viral or others). Also, because several diagnostic assays for PCT were developed using different technologies (ie, immunoluminometric, enzyme-linked immunofluorescent, chemiluminescent and electrochemiluminescent immunoassays), we will perform the subgroup analyses according to stratification based on the type of PCT assay used.

Interpretation and summary of findings

One primary goal of reviews of diagnostic test accuracy is to provide an estimation of a test's accuracy. However, knowing that a test has high sensitivity, for example, does not help us to determine the effect the test might have on the patient, nor can we know whether the use of this test in practice will benefit the patient or be cost-effective. A Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for diagnostic tests has now been developed, which provides guidance on how to translate accuracy data into a recommendation involving patient-important outcomes.[28] We will apply the GRADE approach to rate the quality of the evidence.

DISCUSSION

The wide variety of microbes and the poor specificity of symptoms often lead to inappropriate and overuse of antimicrobial agents. Clinical parameters and conventional laboratory markers, such as elevated white cell count and C reactive protein, cannot differentiate infectious from non-infectious inflammation. In addition, although isolation and culturing of pathogenic microorganisms from the bloodstream are considered the gold standard for the diagnosis of aetiology, this can be time-consuming, and the obtained blood cultures are positive in only 17% of patients with infection and 25% of patients with sepsis.[29] Therefore, developing strategies to improve the diagnosis of infection is still mandatory to guide physicians' decisions at the bedside. Recently, PCT and P-SEP have shown promise as biomarkers that can effectively differentiate between sepsis or infection and SIRS of non-infectious origin.

We will carry out a systemic review of diagnostic tests of biomarkers PCT and P-SEP for sepsis or bacterial infection using appropriate methodologies and quality assessment tools that may feed into an evidence-based

clinical practice. Greater scientific rigour is necessary when establishing a diagnostic strategy that represents current evidence accurately. Currently, few biological biomarkers have proved to be useful for diagnosing sepsis in the critical care setting, and available consensus-based guidelines lack the evidence to indicate triaging of these tests and whether they should be combined with existing tests or replace them. This systematic review can help address this gap and may also identify knowledge gaps in sepsis or infection diagnosis that could direct further research in the field.

ETHICS AND DISSEMINATION

Approval from an ethics committee is not required, since this systematic review will use publicly available data without directly involving human participants. Our findings will be presented at relevant scientific conferences and disseminated through publication in a peer-reviewed journal.

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Contributors KY contributed to the conception of the study. The manuscript protocol was drafted by KH and KY and was revised by MA. The search strategy was developed by all of the authors and will be performed by YH and YK, who will also independently screen the potential studies, extract data from the included studies, assess the risk of bias and complete the data synthesis. KY and KH will arbitrate in cases of disagreement and ensure the absence of errors. All authors approved the publication of this protocol.

Competing interests None declared.

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