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Role of interleukin-6 to differentiate sepsis from non-infectious systemic inflammatory response syndrome

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ABSTRACT

Differentiating between sepsis and non-infectious systemic inflammatory response syndrome (SIRS) poses a great challenge. Several potential bloodstream biomarkers including Interleukin 6 (IL-6) have been investigated for their ability to diagnose sepsis. We conducted the present meta-analysis to evaluate the diagnostic quality of IL-6 in differentiating sepsis from non-infectious SIRS in adults. We also compared its accuracy with procalcitonin (PCT) and C-reactive protein (CRP). PubMed and EMBASE were systematically searched for studies published up to January 18, 2016. Twenty articles containing 22 studies and 2680 critically ill patients were included, of which, 21 studies also involved PCT and 14 involved CRP. Quantitative synthesis of studies showed that the pooled sensitivity/specificity of IL-6 and PCT were 0.68/0.73 and 0.78/0.67. The area under the curve (AUC) of IL-6, PCT and CPR for diagnosis of sepsis was 0.80, 0.83, and 0.71, respectively. This meta-analysis provides evidence that the IL-6 test has moderate diagnostic performance in differentiating sepsis from non-infectious SIRS in adults. IL-6 and PCT test has similar diagnostic value but higher than CRP. Considering its relatively high specificity, we recommend the use of IL-6 as a diagnostic aid to confirm infection rather than exclude infection in patients with SIRS.

1. Introduction

Sepsis is recognized as a systemic inflammatory response syndrome (SIRS) with a confirmed infectious disease [1,2]. Despite an increased acknowledge of the pathophysiology of sepsis and great advance in critical care management and preventative strategies, sepsis is still an important clinical problem with significantly high morbidity and mortality, especially among young, elderly, critically ill and immunocompromised patients [3]. Based on data in North America and Europe, 28.3–41.1% of septic patients did not survive and multi-organ failure was the main cause of death [4]. According to the update of the Surviving Sepsis Campaign, emergency physicians are now required to rapidly and accurately diagnose sepsis, evaluate its severity, and provide appropriate therapy for septic patients [5,6]. However, the differentiation between sepsis and other non-infectious SIRS conditions such as surgery and major trauma is rather complicated in clinical practice. Although microbiological culture is considered as the criterion standard for the diagnosis of infection, blood culture results are generally not available for 48–72 h and may sometimes be false negative. Diagnostic delay and uncertainty may interfere with the initiation of lifesaving standard therapies, whereas indiscriminate use of antibiotics is associated with adverse effects, development of antimicrobial resistance and super-infection with multidrug-resistant organisms [7].

Infection induces host response, humoral elements (complement, acute-phase proteins and cytokines) and cellular elements (monocytes, macrophages, and anti-inflammatory mediators) were activated. Several potential bloodstream biomarkers have been considered for sepsis diagnosis. Of which, interleukin 6

Abbreviations: AUC, area under the curve; CI, confidence intervals; CRP, C-reactive protein; DOR, diagnostic odds ratio; FN, false negative; FP, false positive; I^2, inconsistency index; IL-6, interleukin 6; NLR, negative likelihood ratio; PCT, procalcitonin; PLR, positive likelihood ratio; QUADAS-2, Quality Assessment Tool for Diagnostic Accuracy Studies version 2; SEN, sensitivity; SIRS, systemic inflammatory response syndrome; SPE, specificity; SROC, summary receiver-operating characteristic curve; TN, true negative; TP, true positive.

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(IL-6), procalcitonin (PCT), and C-reactive protein (CRP) are most widely used in clinical routine. Normally, PCT is produced by C-cells in the thyroid gland. In case of systemic bacterial infection, production of PCT also occurs in many non-thyroidal cells, the levels of PCT dramatically increase within a few hours. In a recent systemic review and meta-analysis, PCT is confirmed to be a helpful biomarker for early diagnosis of sepsis from non-infectious SIRS patients [8]. Synthesis of CRP is induced by IL-6 and other pro-inflammatory cytokines in response to inflammation or infections. However, it is reported that CRP is not specific enough for diagnosis of sepsis [9]. IL-6 is an important cytokine during the acute phase reaction in response to inflammation and sepsis [10]. The normal serum concentration of IL-6 is less than 5 pg/mL. Serum levels of IL-6 have been shown to rise within 1 h and rapidly peaked within 2 h after the infectious stimulus [11]. In patients with sepsis, IL-6 values were found elevated persistently, usually >500 pg/mL [9,12]. The level of IL-6 usually increases earlier than that of PCT [13,14], CRP and fever [15]. Several studies have discussed the diagnostic value of IL-6 in septic patients, but the findings have been disputed. Moreover, a previous meta-analysis has shown that IL-6 is a valid marker for predicting neonatal sepsis [16]. The present meta-analysis was performed to evaluate the role of IL-6 to differentiate sepsis from non-infectious SIRS in adult and pediatric (non-neonate) population. In addition, we also compared its accuracy with PCT and CRP.

2. Materials and methods

2.1. Literature search strategy

We systematically searched PubMed and EMBASE databases to identify potentially relevant articles up to Jan 18, 2016 using the following keywords: (interleukin-6 OR IL-6) AND (sepsis OR "systemic inflammatory response syndrome" OR SIRS) AND diagnosis. We also hand-searched the reference lists of retrieved articles to identify any additional studies.

2.2. Inclusion and exclusion criteria

The inclusion criteria were: (1) clinical trials that evaluated IL-6 alone or compared with other biomarkers such as PCT or CRP to diagnose sepsis in patients with SIRS; (2) the studies had to provide sufficient information to construct 2-by-2 contingency tables from which the common diagnostic test parameters could be calculated, e.g. values of true positive (TP), false positive (FP), false negative (FN), true negative (TN), sensitivity (SEN), specificity (SPE), positive likelihood ratio (PLR) and negative likelihood ratio (NLR); (3) only studies including at least 10 patients were selected; (4) no overlapping data, or else only studies with the largest number of patients were included in the final analysis; (5) only literatures in English were included. Animal studies, abstracts, review articles, case reports, letters, editorials, comments and

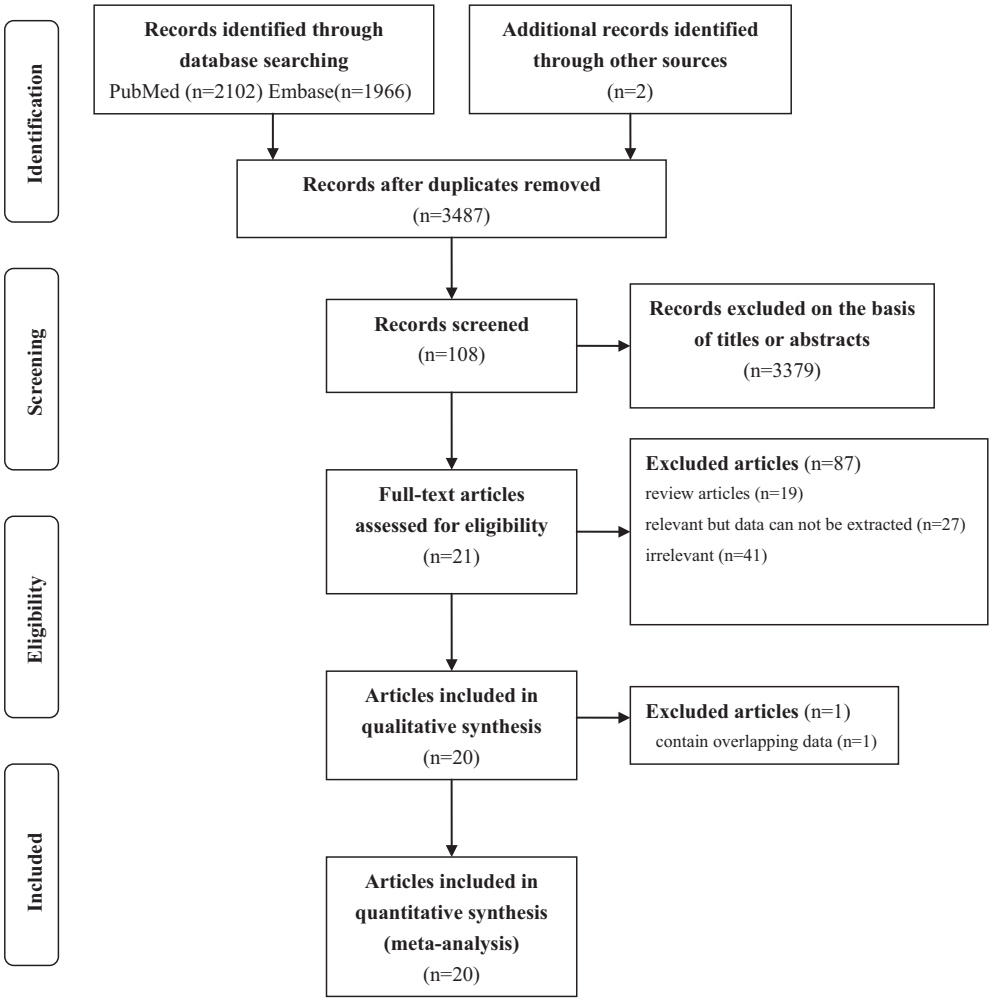

Fig. 1. Flow diagram of the study selection process.