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Original Contribution

Interleukin-6 as a diagnostic marker for infection in critically ill patients: A systematic review and meta-analysis

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ABSTRACT

Background: The ability of blood levels of interleukin (IL)-6 to differentiate between infection and non-infection in critically ill patients with suspected infection is unclear. We assessed the diagnostic accuracy of serum IL-6 levels for the diagnosis of infection in critically ill patients.

Methods: We systematically searched the PubMed, MEDLINE, Cochrane Resister of Controlled Trials, Cochrane Database of Systematic Reviews, CINAHL, and Igaku Chuo Zasshi databases for studies published from 1986 to August 2016 that evaluated the accuracy of IL-6 levels for the diagnosis of infection. We constructed 2 × 2 tables and calculated summary estimates of sensitivity and specificity using a bivariate random-effects model.

Results: The literature search identified 775 articles, six of which with a total of 527 patients were included according to the predefined criteria. The pooled sensitivity, specificity, and diagnostic odds ratio were 0.73 (95% confidence interval [CI], 0.61–0.82), 0.76 (95% CI, 0.61–0.87), and 2.31 (95% CI, 1.20–3.48), respectively. The area under the curve (AUC) of the summary receiver operator characteristic (SROC) curve was 0.81 (95% CI, 0.78–0.85). In the secondary analysis of two studies with a total of 263 adult critically ill patients with organ dysfunction, the pooled sensitivity, specificity, and diagnostic odds ratio were 0.81 (95% CI, 0.75–0.86), 0.77 (95% CI, 0.67–0.84), and 2.87 (95% CI 2.15–3.60), respectively.

Conclusions: Blood levels of IL-6 have a moderate diagnostic value and a potential clinical utility to differentiate infection in critically ill patients with suspected infection.

1. Introduction

Sepsis is a life-threatening condition caused by dysregulated host response to infection [1]. In the pathogenesis of sepsis, excessive humoral mediators including interleukin-6 (IL-6) produced by innate immune cells via recognition of microbial pathogens play a key role in the dysregulated response and subsequent organ dysfunction. Sepsis remains a leading cause of death in intensive care units (ICU); recent clinical practice guidelines emphasize that early recognition and initiating treatment for sepsis are key to improving clinical outcomes [2]. Clinical and laboratory/imaging approaches are essential to detect infection. However, rapid diagnosis of infection is not always easy, especially in cases with atypical clinical findings [3,4]. In addition, rapid microbiological identification methods are yet to be put into practice and standard culture-based microbial testing requires time to obtain clear results. Thus, there remain unmet needs for early and reliable diagnostic biomarkers for infection in critically ill patients with suspected infection.

A number of potential biomarkers for diagnosing infection have been investigated [3,5]; some promising biomarkers can be routinely measured in clinical laboratories [6-9]. A recent study comparing the diagnostic values of four clinically measurable biomarkers including procalcitonin (PCT), presepsin, IL-6, and C-reactive protein (CRP) in critically ill patients with organ dysfunction and suspected infection revealed that serum levels of IL-6 had the highest diagnostic value for infection [10]. Several meta-analyses of PCT or presepsin for diagnosing infection in critically ill patients [6,8,9,11-13] have reported its utility; however, to our knowledge, there has been no systematic review and meta-analysis of IL-6 for the differential diagnosis of infection in critically ill patients.

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Thus, we conducted a systematic review and meta-analysis to evaluate the ability of IL-6 levels to differentiate between infection and non-infection in critically ill patients with suspected infection. First, we investigated the diagnostic accuracy of blood IL-6 levels for infection in critically ill patients with suspected infection. Second, we investigated the diagnostic accuracy of blood IL-6 levels for infection in adult critically ill patients with both organ dysfunction and suspected infection, because organ dysfunction become one of the diagnostic criteria of the novel definition of sepsis (Sepsis-3).

2. Material and methods

2.1. Studies

We included studies that evaluated the diagnostic accuracy of IL-6 for detecting infection in critically ill patients with suspected infection.

2.2. Search strategy and selection criteria

We systematically searched the PubMed, MEDLINE (via EBSCOhost), Cochrane Resister of Controlled Trials (via EBSCOhost), Cochrane Database of Systematic Reviews (via EBSCOhost), CINAHL (via EBSCOhost), and Igaku Chuo Zasshi (the Japana Centra Revuo Medicina) databases for studies that evaluated the accuracy of blood IL-6 levels for the diagnosis of infection. All databases were searched from 1986 (when IL-6 was identified) to August 2016. The search query we used was as follows: ("critically ill patients" OR "critical illness" OR "critical care" OR "intensive care units" OR "organ dysfunction" OR "organ failure") AND ("suspected sepsis" OR infection OR sepsis OR "septic shock") AND (Interleukin-6) AND (diagnosis OR sensitivity OR specificity). We did not use search filters or apply any restrictions such as publication type and language.

The eligible studies were required to have a well-defined reference standard for infection, which included the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) criteria [14], the International Sepsis Forum (ISF) Consensus Conference on Definitions of Infection [15], or the Centers for Disease Control and Prevention/National Healthcare Safety Network (CDC/NHSN) Surveillance Definition of Healthcare-Associated Infection and Criteria for Specific Types of Infections in the Acute Care Setting [16]. In accordance with these definitions, the presence of infection had to be microbiologically confirmed or at least clinically suspected according to laboratory and radiographic data.

We included studies with sufficient information to construct the 2×2 table.

2.3. Procedures

Two investigators (SI and TN) independently identified potentially eligible studies based on titles and abstracts. We excluded studies that did not investigate the diagnostic accuracy of blood IL-6 levels as a marker for infection. Animal experiments, case reports, commentaries and letters, meta-analyses, reviews, editorials, meeting abstracts, poster presentations, and correspondence were also excluded. We then retrieved the full-text copy of each potentially eligible study and conducted a full-text review [17] (Table S1). The methodological quality of the studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [18].

2.4. Statistical analysis

We primarily analyzed "critically ill patients with suspected infection" as patient (P) and infection as outcome (O). We secondarily analyzed "adult critically ill patients with organ dysfunction with suspected infection" as patient (P) and infection as outcome (O). True positives (TP), false positives (FP), false negatives (FN), true negatives (TN), sensitivities and specificities, and 95% confidence intervals (CIs) were calculated. Combined plots of sensitivities and specificities were created using the R package *metafor*. Forest plots of sensitivities and specificities were also created. Summary receiver operating characteristic (SROC) curves were used to summarize the study results. For meta-analyses, a bivariate random-effects model was used to calculate the summary estimates of sensitivity and specificity and to fit a hierarchical summary receiver operating characteristic (HSROC) curve using STATA 13 (Stata Corporation, College Station, TX) and the R package *mada* [19]. This model considers potential threshold effects and the correlation between sensitivity and specificity. It also allows addition of covariates for investigation of potential sources of heterogeneity. The analyses were performed using R (version 3.3.3; www.R-project.org) and STATA.

3. Results

The literature search of the databases identified 775 articles. Of these, 700 articles were excluded after reviewing the titles and abstracts (Fig. 1). We performed a full-text review of 75 articles and excluded 69 studies for the following reasons: reference group or control did not correspond to our definitions ($n = 34$), well-defined reference standard according to guidelines were not described ($n = 17$), and unable to construct a 2×2 contingency table ($n = 18$). Thus, six studies [10,20-24] were included in the primary analysis.

The six studies were published from 1993 to 2016. A total of 527 critically ill patients with suspected infection were included (Table 1). Of these, 303 patients (57%) had infection; the prevalence of infection among studies ranged between 0.16 and 0.77. All studies investigated adult patients in ICUs. Four studies (studies # 1, 2, 4 and 5) evaluated the diagnostic accuracy of IL-6 to distinguish infection from non-infectious systemic inflammatory response syndrome (SIRS). One study (study # 3) evaluated ventilator-associated pneumonia; another (study # 6) evaluated nosocomial infections. The cut-off IL-6 concentrations ranged from 35 to 620 pg/mL (median 176 pg/mL). Two studies (study # 1 and 3) investigated adult ICU patients with organ dysfunction, which were included in the secondary analysis.

The methodological quality of the six studies was evaluated using the QUADAS-2 tools (Fig. 2). One study (# 1) had a low risk of bias in all four domains of QUADAS-2. Five studies did not predefine the cut-off value, and Five studies did not predefine the cut-off value, and three studies (#2, 3, and 4) were at high risk in the "reference standard (risk of bias)". According to the results of the methodological assessment, all included studies had acceptable quality.

In the primary analysis of six studies using the bivariate diagnostic random-effects meta-analysis, the pooled sensitivity, specificity, and diagnostic odds ratio were 0.73 (95% CI, 0.61–0.82), 0.76 (95% CI, 0.61–0.87), and 2.31 (95% CI, 1.20–3.48), respectively (Fig. 3). The area under the SROC curve was 0.81 (95% CI, 0.78–0.85) (Fig. 4). In the secondary analysis of two studies (#1 and 3) containing a total of 263 adult critically ill patients with organ dysfunction, the pooled sensitivity, specificity, and diagnostic odds ratio were 0.81 (95% CI, 0.75–0.86), 0.77 (95% CI, 0.67–0.84), and 2.87 (95% CI 2.15–3.60), respectively (see Additional File 1: Fig. S1). The area under the SROC curve was 0.86 (95% CI, 0.82–0.90) (see Additional File 1: Fig. S2).

4. Discussion

The present study conducted a systematic review and meta-analysis of studies that evaluated the ability of blood IL-6 levels to differentiate between infection and non-infection in critically ill patients with suspected infection. The results of the meta-analysis indicated that blood IL-6 levels had good diagnostic value for infection in critically ill patients with suspected infection.

In the current international definitions, sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. The release of cytokines including IL-6 through the

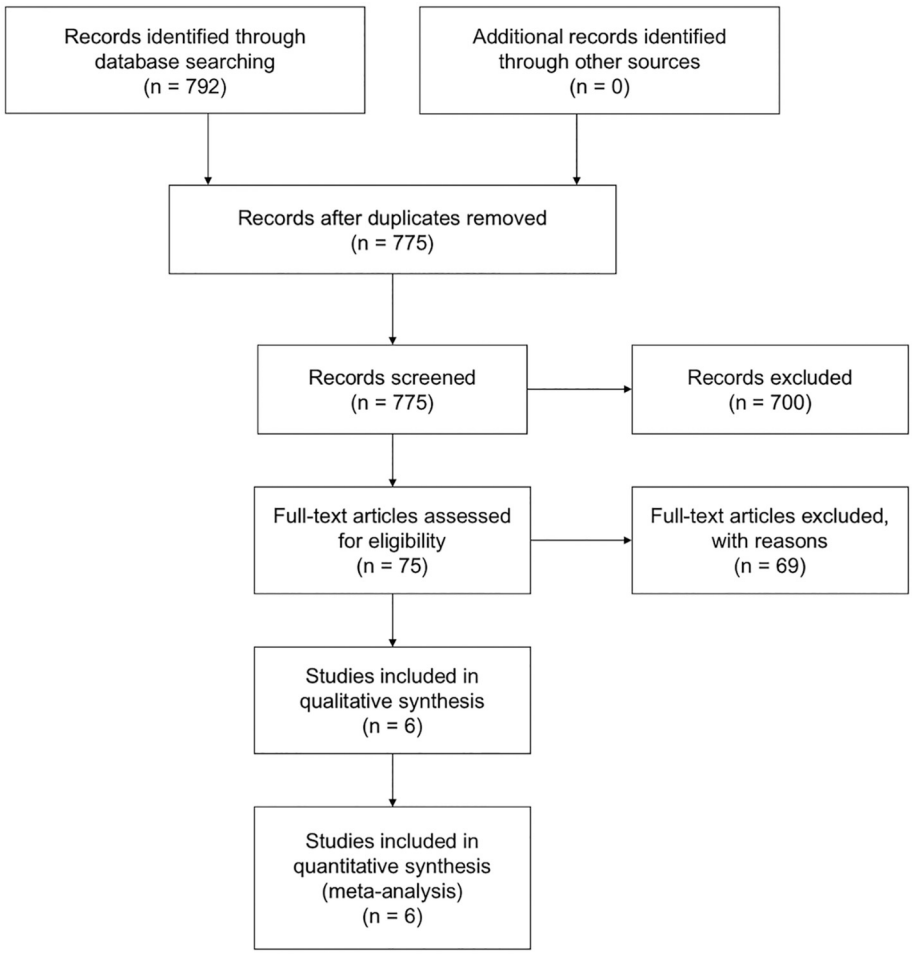

Fig. 1. Study selection flowchart.

innate immune recognition of pathogen-associated molecular patterns is a key process in the host response [4]. Therefore, blood levels of IL-6 are a potentially promising biomarker to differentiate sepsis from the viewpoint of sepsis pathophysiology. Recently, three systematic review and meta-analysis of IL-6 for infection were reported. Study subjects in these three were not limited to critically ill patient; the diagnostic value of IL-6 ranged from 0.79 to 0.87 [25-27]. These study results were in agreement with that of the present study showing good diagnostic value of blood IL-6 levels for infection. However, these three studies did not include analysis on critically ill patients. Thus, to our knowledge, the present study is the first systematic review and meta-analysis to evaluate the diagnostic value of IL-6 for infection in critically ill patients. Of six studies identified in the present study, there was no study identified in all the three systematic and metanalysis studies, which may highlight the importance of study subjects in systematic reviews. We evaluated the quality of six studies using QUADAS-2. Five studies (#2, 3, 4, 5, and 6) were at high risk in the "index test (risk of bias)", three studies (#2, 3, and 4) were at high risk in the "reference standard (risk of bias)", and four studies (#2, 3, 4, and 5) were at high risk in the "reference standard (applicability concerns)". Studies #2 and 4

Table 1
Study characteristics

	Author, (Country, year)	Setting	Cut-off, pg/mL	Patient, n (prevalence)	Severity	Reference standard	TP FN	FP TN	Sensitivity (95% CI)	Specificity (95% CI)
#1	Takahashi, (Japan, 2016)	Surgical/ Medical ICU	152	219 (0.74)	Organ dysfunction	ISF	132 11	31 45	0.81 (0.74–0.86)	0.80 (0.68–0.89)
#2	Li (China, 2013)	Surgical ICU	116.3	52 (0.73)	SIRS	ACCP/SCCM	19 7	19 7	0.50 (0.35–0.65)	0.50 (0.27–0.73)
#3	Ramirez (Spain, 2009)	Medical ICU	620	44 (0.20)	Ventilated	CDC	8 10	1 25	0.89 (0.57–0.98)	0.71 (0.55–0.84)
#4	Du (China, 2003)	ICU	290	51 (0.39)	SIRS	ACCP/SCCM	17 8	3 23	0.85 (0.64–0.95)	0.74 (0.57–0.86)
#5	Harbarth (Switzerland, 2001)	Surgical/ Medical ICU	200	7 (0.77)	SIRS	ACCP/SCCM	40 5	20 13	0.67 (0.54–0.77)	0.72 (0.49–0.88)
#6	Fassbender (Switzerland, 1993)	Surgical ICU	35	83 (0.16)	Nosocomial infection	CDC	9 2	4 68	0.69 (0.42–0.87)	0.97 (0.90–0.99)

TP, true positive; FN, false negative; FP, false positive; TN, true negative; CI, confidence interval; ICU, intensive care unit; ISF, International Sepsis Forum; ACCP/SCCM, American College of Chest Physicians/Society of Critical Care Medicine; CDC, Centers for Disease Control and Prevention.
IL-6 assay was Roche Diagnostics (#1), Boster Biological Technology (#2), Biosource (#3), Medgenics Diagnostics (#4), DPC Biermann (#5) and R&D System (#6).

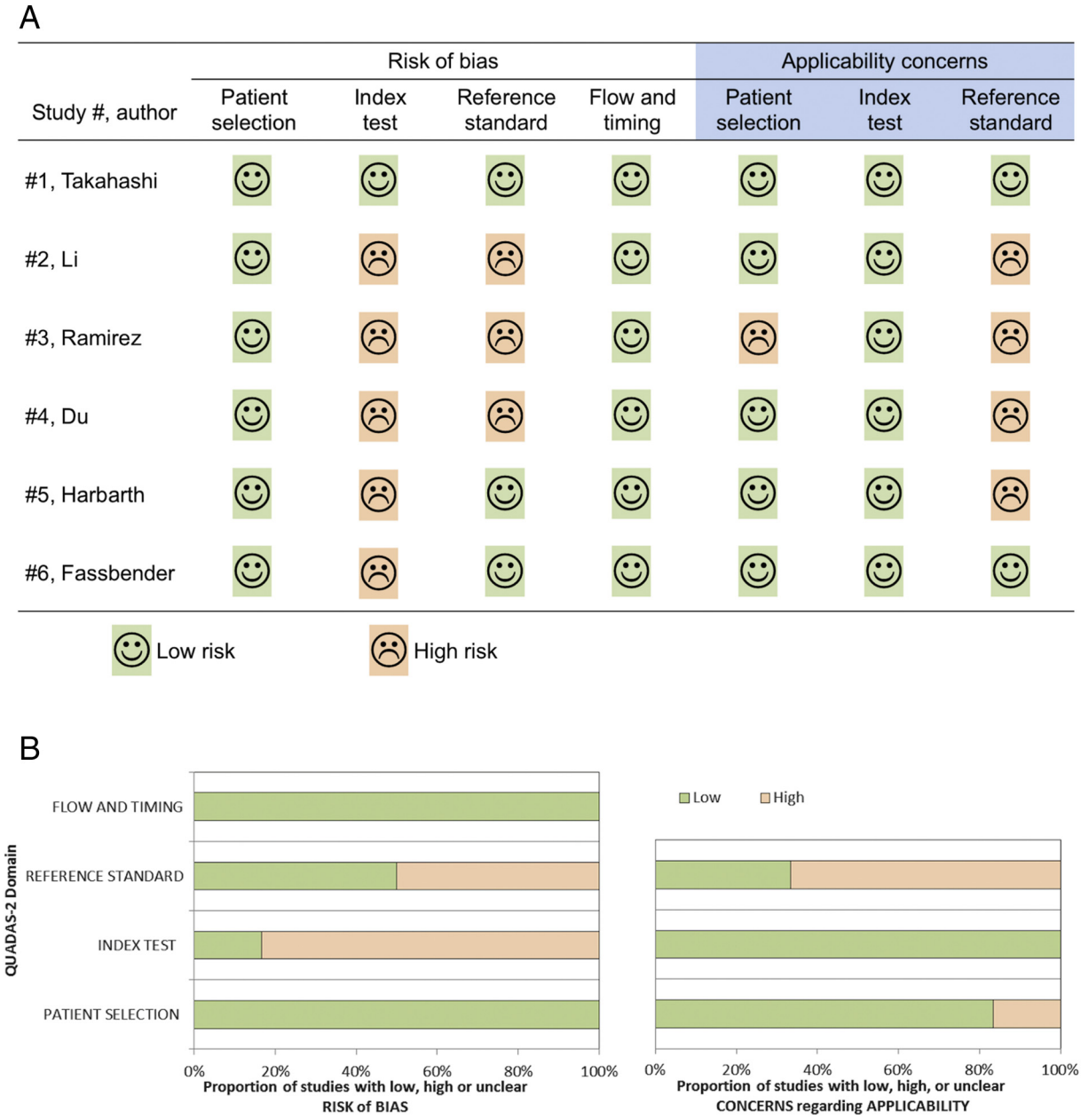

Fig. 2. Assessment of methodological quality using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.

used ACCP/SCCM criteria as their reference standards. In these studies, it was unclear that infection was defined as to be microbiologically confirmed or at least clinically suspected according to laboratory and radiographic data. ACCP/SCCM criteria are essentially the definition of SIRS. Therefore, the criteria are possibly not enough to diagnose infection and inferior to ISF or CDC definitions regarding diagnosis of infection. In study #3, it was unclear that the reference standard results interpreted without knowledge of the results of index test. Thus, the three studies (#2, 3, and 4) were assessed at high risk in "reference standard (risk of bias)". Although study #5 used ACCP/SCCM criteria, they clarified that they used microbiologic test or radiographic data for diagnosis of infection. As a result, study #5 was evaluated to be at a low risk in "reference standard". Overall, the included studies had acceptable quality.

The sensitivity, specificity, and AUC of the present study were 0.73, 0.76, and 0.81, respectively, which similar to those of PCT (sensitivity 0.77, specificity 0.79, AUC 0.85) [8] and presepsin (sensitivity 0.77, specificity 0.73, and AUC 0.86) in a recent meta-analysis [9]. Serum levels of PCT or presepsin are elevated in non-infectious patients with acute kidney injury (AKI), which may lead to inaccuracy in identifying infection in patients with AKI [28,29]. IL-6 had the highest diagnostic value among PCT, presepsin, and IL-6 in critically ill patients with organ dysfunction including AKI [10]. Thus, serum levels of IL-6 may be utilized as a diagnostic marker in patients with AKI.

Organ dysfunction is one of the diagnostic criteria of sepsis according to the current sepsis definition. Thus, the diagnostic value of IL-6 for infection in critically ill patients with organ dysfunction was secondarily analyzed. Even though the smaller subset analysis used only two studies ($n = 263$), the diagnostic value of infection remained high (sensitivity 0.81, specificity 0.77, diagnostic odds ratio 2.87), which indicates that blood level of IL-6 is a potentially accurate diagnostic marker of infection in the current sepsis definition.

In addition to the diagnostic value of blood IL-6 levels for infection, the high diagnostic value of IL-6 level in the cerebrospinal fluid for

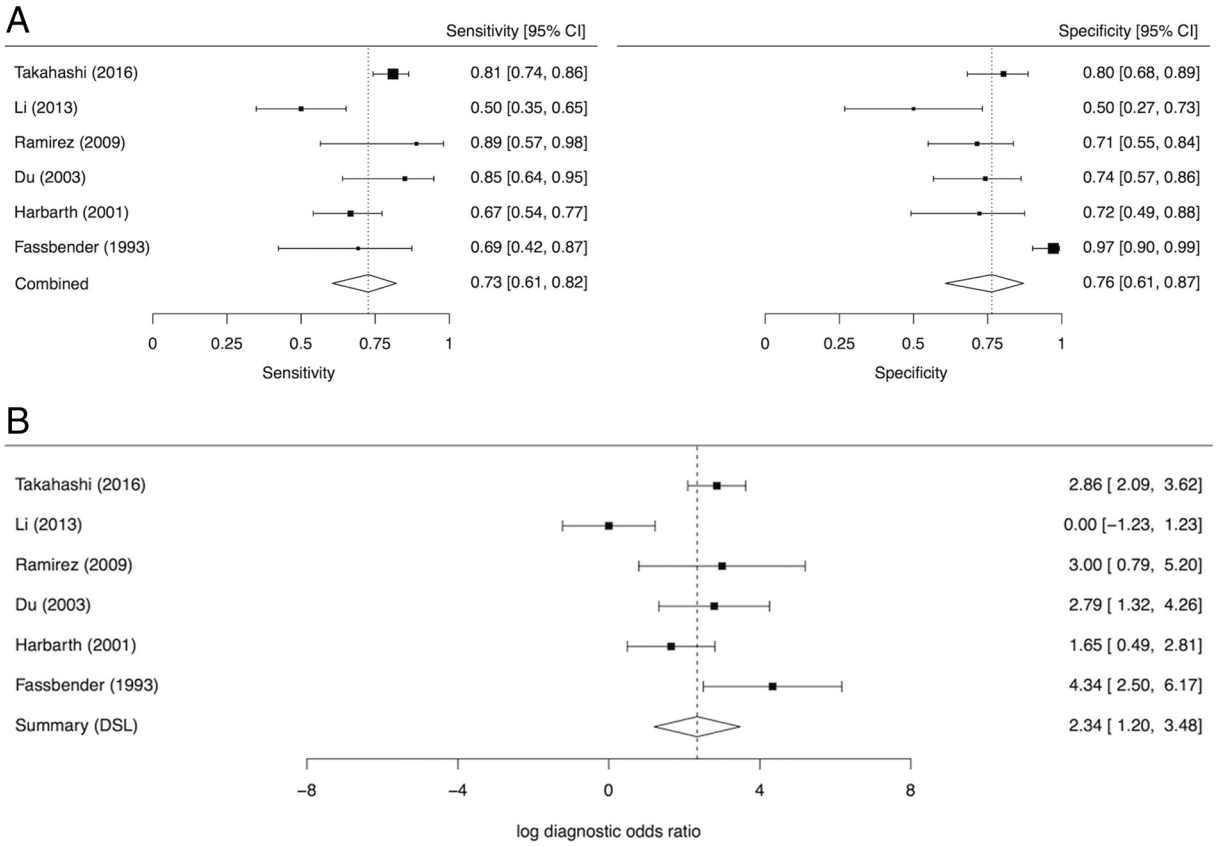

Fig. 3. Sensitivity, specificity, and diagnostic odds ratio of blood interleukin-6 levels for the diagnosis of infection. Panel A. Sensitivity, specificity; Panel B. Odds ratio. The pooled sensitivity, specificity, and diagnostic odds ratio were 0.73 (95% CI, 0.61–0.82), 0.76 (95% CI, 0.61–0.87), and 2.31 (95% CI, 1.20–3.48), respectively.

bacterial meningitis in critically ill patients with suspected meningitis (AUC 0.962) has also been reported [30]. Furthermore, blood levels of IL-6 were associated with the severity or prognosis of critically ill patients [7,10,31]. Blood levels of IL-6 were positively correlated with sequential organ failure assessment (SOFA) score in patients with SIRS [7]. Serum levels of IL-6 had the highest AUC value for predicting 28-day mortality in critically ill patients with suspected infection among IL-6, PCT, presepsin, and CRP [10]. Furthermore, in a study on the prognostic value of seven parameters including human leukocyte antigen-antigen D-related (HLA-DR), CD4 T-cell, CD8 T-cell, tumor necrosis factor (TNF), IL-6, IL-1beta, and IL-10 in critically ill patients with severe sepsis, only sustained levels of IL-6 were associated with increased 28-day mortality in a multivariate analysis [31]. Thus, serum levels of IL-6 can be utilized beyond the differential diagnosis of infection in critically ill patients.

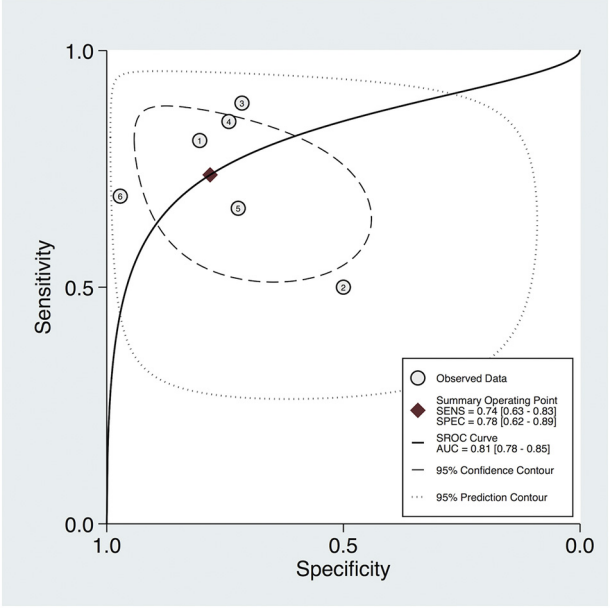

Fig. 4. Summary receiver operating characteristic curve. The area under the SROC curve was 0.81 (95% CI, 0.78–0.85).

The present study has several limitations. First, the sample size of the study was relatively small. Second, the studies included in the meta-analysis were published prior to the current sepsis definition. Additional studies with large sample sizes using the current sepsis definition will strengthen the findings of the present study.

5. Conclusions

Serum levels of IL-6 have a moderate degree of diagnostic value and the potential for clinical utility to differentiate infection in critically ill patients with suspected infection.

List of abbreviations

IL-6	Interleukin-6
PCT	procalcitonin
CRP	C-reactive protein
SIRS	systemic inflammatory response syndrome
ICU	intensive care unit
	QUADAS quality assessment of diagnostic accuracy studies
SROC	summary receiver operating characteristic
AUC	area under the curve

AKI acute kidney injury
SOFA sequential organ failure assessment

Ethics approval

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All relevant data are within the paper and its Supporting information file.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SI and TN contributed to study conception and design, acquisition of data, interpretation of data, drafting the manuscript, and critical revision of the manuscript for important intellectual content. NH, WT, and NT contributed to the acquisition and interpretation of data and critical revision of the manuscript for important intellectual content. TA contributed to statistical analysis, interpretation of data, and critical revision of the manuscript for important intellectual content. MY, TM, and SO contributed to the study conception and design and critical revision of the manuscript. All authors read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2018.05.040.

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