Accuracy of serum interleukin (IL)-6 in sepsis diagnosis: a systematic review and meta-analysis

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Abstract: Objective: To systematic review and estimate the accuracy of Interleukin 6 assay in the diagnosis of sepsis by meta-analysis. Methods: With the aim to confirm this correlation, this paper performed a meta-analysis of 6 studies and the Sensitivity, specificity, positive likelihood ratio (PLR), and negative likelihood ratio (NLR) with corresponding 95% confidence intervals (CI) of each study were calculated and the pooled sensitivity was calculate using Random Effects Model and Summary receiver operating characteristic curves were constructed. Results: The pooled sensitivity for the diagnosis of sepsis was 80% (95% CI, 77% to 83%) and the specificity of 85% (95% CI, 81% to 88%). For sepsis versus health or infection, the area under the curve was 0.868. In neonate subgroup, IL-6 had a pooled sensitivity of 77.0% (95% CI, 73.0% to 81.0%) and specificity of 91.0% (95% CI, 86.0% to 94.0%) for sepsis diagnosis. In adult, IL-6 had a pooled sensitivity of 85.0% (95% CI, 80.0% to 88.0%) and specificity of 62.0% (95% CI, 55.0% to 68.0%) to identify sepsis. The AUC was 81.0%, and Q was 0.74. Conclusions: IL6 is a highly accurate diagnostic modality for the identification of sepsis, with promise for integration into routine imaging protocols for thyroid nodules.

Keywords: Sepsis, IL-6, meta-analysis, diagnosis, SROC

Introduction

Sepsis is a potentially life-threatening complication of an infection [1] and it causes millions of deaths globally each year [2], and more than 200 000 deaths each year in the United States [3]. Sepsis occurs when chemicals released into the bloodstream to fight the infection trigger inflammatory responses throughout the body [4]. This inflammation can trigger a cascade of changes that can damage multiple organ systems, causing them to fail. As a severe disease, sepsis not only lowers patient’s living quality, but also increases the mortality significantly.

Cytokines such as tumor necrosis factor, interleukin 1, and interleukin 6 can activate procoagulation factors in the cells lining blood vessels and lead to endothelial damage. The damaged endothelial surface inhibits anticoagulant properties as well as increases anti-fibrinolysis, which can lead to a systemic inflammatory response syndrome (SIRS), sepsis shock, disseminated intravascular coagulation (DIC), and multiple organ dysfunction syndrome (MODS) [5]. Now, those cytokines have been researched as potential biological markers of Sepsis Diagnosis or assessment [4, 6, 7]. But the clinical values of the biomarkers are still uncertain or controversial in diagnosis and evaluation of sepsis.

Up to now, several studies has investigated validity of Interleukin-6 (IL-6) validity for early Sepsis diagnosis. However, large sample multi-center study or meta-analysis on interleukin-6 on sepsis diagnosis is still lacking. So we performed this systematic review and meta-analysis to assess the validity of IL-6 test for early
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Methods

Data sources and search

Relevant studies without language restrictions were systematically searched by using the NCBI, Medline, Web of Science and Embase databases by two authors independently. The last retrieval date was August 14, 2014 and the search terms were “sepsis” “infected” and “interleukin-6” or “IL-6”. When more publications with duplicate samples, only the newest study was used in this research. The flow chart of the study including process was shown in Figure 1.

Inclusion and exclusion criteria

The inclusion criteria were: (1). studies which assessed the diagnostic accuracy of the IL-6 test on sepsis; (2). case-control study; (3). studies sensitivity and specificity were both provided and (4). articles that IL-6 levels were evaluated in study. The exclusion criteria were: (1). animal studies; (2). the reported data did not meet this study needed and (3). the reported data was not adaptable for our pooled study.

Study selection and data extraction

Two reviewers independently evaluated, extracted and integrated all of the studies retrieved based on pre-specified selection criteria and disagreements were resolved by consensus. Information of each papers, such as first author, year of publication, study method, region, measure method of IL-8, diagnostic cut-off point and time, sample size, cutoff (pg/mL), Sensitivity (%), Specificity (%), positive predictive value (%), negative predictive value (%), area under the curve were all exacted and rearrangement.

Statistical analysis

Meta-DiSc version 1.4 and RevMan 5.0.21 statistical software were applied to statistical analysis and publication bias. Sensitivity, specificity, positive likelihood ratio (PLR), and negative likelihood ratio (NLR) with corresponding 95% confidence intervals (CI) of each study were calculated and the pooled sensitivity was calculate using Random Effects Model. Statistical heterogeneity was measured using the I²-statistic and Q-statistic (P ≤ 0.05 was considered to be representative of statistically significant heterogeneity). Summary receiver operating characteristic curve (SROC) was constructed using data from all thresholds with the use of the Littenberg and Moses method, which showed the relationship between sensitivity and specificity (proportion of false positives). Q value was defined where the SROC curve crosses the anti-diagonal from (0; 1) to (1; 0) of the SROC space; hence TPR = 1-FPR at Q, and so the probability of an incorrect result from the test is the same for cases and non-cases.

Figure 1. Flow diagram of study selection.
Table 1. Characteristics and data extracted of the studies included in the systematic review

<table>
<thead>
<tr>
<th>Author/year of publication</th>
<th>Country</th>
<th>Age (mean ± SD or range)</th>
<th>Patients no.</th>
<th>Cut off (pg/mL)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>AUC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celik et al [8]/2013</td>
<td>Turkey</td>
<td>Neonate</td>
<td>206</td>
<td>18.9</td>
<td>82 (76-87)</td>
<td>93 (86-97)</td>
<td>97</td>
<td>67</td>
<td>91</td>
</tr>
<tr>
<td>Tsalik et al [9]/2012</td>
<td>USA</td>
<td>52 (38-65)</td>
<td>247</td>
<td>40</td>
<td>90.2 (86-94)</td>
<td>33.9 (24-45)</td>
<td>26.9</td>
<td>92.8</td>
<td>70</td>
</tr>
<tr>
<td>Jekari et al [10]/2013</td>
<td>South Korea</td>
<td>51.5 ± 22.4</td>
<td>78</td>
<td>145</td>
<td>66.7 (55-77)</td>
<td>80.3 (71-87)</td>
<td>29.4 (15.1-47.5)</td>
<td>95.1</td>
<td>75.8</td>
</tr>
<tr>
<td>Gouel-Cheron et al [11]/2012</td>
<td>France</td>
<td>37 ± 17</td>
<td>37</td>
<td>67.1</td>
<td>84.6 (68-94)</td>
<td>72.5 (60-83)</td>
<td>58</td>
<td>90</td>
<td>75 (64-84)</td>
</tr>
<tr>
<td>Dilli et al [12] 2010</td>
<td>Turkey</td>
<td>Newborns</td>
<td>35</td>
<td>24.9</td>
<td>80 (63-92)</td>
<td>91.8 (83-97)</td>
<td>82.3</td>
<td>90.6</td>
<td>89</td>
</tr>
<tr>
<td>Celik et al [13]/2010</td>
<td>Turkey</td>
<td>Newborns</td>
<td>232</td>
<td>24.65</td>
<td>72 (66-78)</td>
<td>84 (71-93)</td>
<td>95</td>
<td>42</td>
<td></td>
</tr>
</tbody>
</table>
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Meanwhile, the area under SROC curve was also calculated to show the diagnostic accuracy of IL-6 test.

Results

Literature search and study selection

The search identified a total of 242 citations, of which 59 were potentially relevant after initial evaluation. From these studies, 53 full articles were excluded. Six relevant studies with 695 Spesis and 613 adults subjects were involved in this meta-analysis based on preliminary arrangement and were analyzed (Figure 1).

Study characteristics

Table 1 showed information of the main characteristics of the selected studies. In the 6 stud-
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Figure 4. The ROC curve of neonate subgroup.

Figure 5. The ROC curve of adult subgroup.
ies analyzed, 3 evaluated the accuracy of IL-6 in neonatal sepsis diagnosis, and 3 evaluated in adults.

Diagnostic performance of IL-6

As Figure 2 shown, IL-6 had a pooled sensitivity of 80.0% (95% CI, 77% to 83%) and specificity of 85% (95% CI, 81% to 88%) to detect sepsis respectively. As Figure 3 shown, the Q value and AUC of SROC for sensitivity and specificity were 0.798 and 0.868 respectively in this meta-analysis.

Sensitivity analysis was performed in 2 subgroups

We divided those 6 papers into 2 subgroups based on age. In neonate subgroup, IL-6 had a pooled sensitivity of 77.0% (95% CI, 73.0% to 81.0%) and specificity of 91.0% (95% CI, 86.0% to 94.0%) for sepsis diagnosis (Figure 4). In adult, IL-6 had a pooled sensitivity of 85.0% (95% CI, 80.0% to 88.0%) and specificity of 62.0% (95% CI, 55.0% to 68.0%) to identify sepsis. The AUC was 81.0%, and Q was 0.74 (Figure 5).

Heterogeneity test

Great heterogeneity in specificity was found among studies, but not in sensitivity. In this meta-analysis, when we deleted Tsalik’s report, the value of chi-square for heterogeneity reduced from 106.30 to 16.87, indicating the heterogeneity of specificity might come from Tsalik’s report.

Discussion

Sepsis is a complex, heterogeneous disorder that is frequently misdiagnosed with significant clinical consequences [8, 9]. The research on accurate and timely diagnosis or exclude of suspected sepsis is vital to patient, which can reduce morbidity, reduces cost, and improves patient outcome. To date, multiple sepsis biomarkers have been investigated for distinguish of sepsis from infectious to non-infectious processes, but most have fallen short due to poor specificity and their results remain elusive [10].

The difficult of diagnosis of bacterial infection arose from 3 aspects: 1). routine laboratory tests is lack of sensitivity and specificity; 2). the results of confirmatory microbiologic studies can’t be applied immediately; 3). atypical clinical manifestations or even absence of elderly, pediatric, and immunosuppressed infected patients [11].

IL-6 is potent inflammatory mediator and its plasma concentration has been tested as prognostic factors in several studies [12-14]. So the aim of this study is to evaluate the accuracy of biomarker IL-6 in the serum to identify sepsis by meta-analysis. Our results show that the IL-6 has a sensitivity of 80.0%, a specificity of 75.0%, and an AUC of 0.868 for the detection of sepsis or early sepsis. Subgroup comparisons revealed that no matter neonates or adults, IL-6 always have a high sensitivity and specificity to identified sepsis. It implies that IL-6 could be extensively tested for detecting sepsis in clinic. The results of this meta-analysis are similar to the previous researches, which show IL-6 and CRP are frequently elevated in non-infectious illness and can serve as useful prognostic tools in this undifferentiated population consisting of both infected and non-infected critically ill patients [15-17].

Previously studies have demonstrated that serum concentrations of IL-6 is significant increased during sepsis, which can increase incidence of poor outcome and occurrence of shock and death [18, 19]. And Reinhart et al. recently demonstrated in septic patients that patients with IL-6 over 1000 pg/ml had a mortality of 56% compared to 40% of those below this IL-6 level [20].

Because of relatively small sample size of included studies and heterogeneity existed, further intensive researches with big sample size should be conducted, and to reduce heterogeneity for IL-6 as a diagnostic biomarker on sepsis diagnosis to make meta-analysis more convenient.

Conclusion

In a conclusion, IL-6 is a highly accurate diagnostic modality for the identification of sepsis, with promise for integration into routine imaging protocols for thyroid nodules. Due to insufficient testing data, the experiment results need continuous re-evaluation and clinical validation.
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Disclosure of conflict of interest

None.

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