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Serum procalcitonin as a diagnostic biomarker for sepsis in burned patients: A meta-analysis

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ABSTRACT

Background: Sepsis is one of the main causes of mortality in severe burns. However, it is difficult to diagnose early. Procalcitonin (PCT) has been reported as a biomarker for sepsis with controversial results. The aim of the study is to assess the diagnostic value of serum PCT for sepsis in burn patients through a meta-analysis of published studies.

Methods: A comprehensive literature search of PubMed, Embase, Web of Science and the Cochrane Library databases for studies published up to 1st March 2014 that evaluated PCT as a marker for diagnosing sepsis in burn patients was conducted. The summary receiver operating characteristic curves served to evaulate overall test performance. Meta-Disc 1.4 software and Stata 12.1 were used to analyze the data.

Results: A total of 566 patients (samples) from nine trials were identified and analyzed. The pooled sensitivity and specificity were 0.74 and 0.88, respectively. No threshold effect was found among studies. The area under the SROC curve (AUC) was 0.92.

Conclusion: The results suggest that serum PCT is a useful biomarker (AUC = 0.92) for early diagnosis of sepsis in burn patients. However, the results should be used with caution, because of obvious heterogeneity among those studies. Further large-scale research should regard more attention to the uniform cut-off value, and laboratories test methods.

1. Introduction

Sepsis is an inflammatory response to severe infection with the existence of organ dysfunction [1,2] and is also one of the principal reasons of mortality in burned patients [3–7]. It is important but difficult to diagnose sepsis early and accurately [8–11]. However, some patients with sepsis have the similar symptoms as those with non-infectious causes of SIRS [12]. Blood microbiological cultures can help the identification of systematic bacterial infection, but the results often reported late and yield false positive or negative results [13,14]. Traditional markers such as CRP (C-reactive protein) and WBC (white blood cell) are too weak to accurately identify sepsis in the burned patient, because of the baseline inflammatory response [15] and immunopathies [16].

The 116-aminoacid polypeptide procalcitonin (PCT) has been studied as a biomarker for sepsis. PCT assay has been used to detect sepsis in critically ill patients and showed promising in differentiating sepsis from other non-sepsis situations [17–27]. Procalcitonin is also elevated in certain conditions such as major burns, trauma, surgery, and multiorgan failure as well as

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infection [28–30]. However, more recent studies have produced conflicting results [31–38] and the studies performed in the burned patients showed a diverse sensitivity and specificity [20,39–47]. Mann [29] systematically reviewed the effect of PCT in diagnosing sepsis in burn patients in 2011. Since then, some new larger-scale studies of procalcitonin or with different designs have been done and our understanding of procalcitonin is still developing.

It is necessary to assess the value of serum PCT for the diagnosis of sepsis in burned patients through a meta-analysis of published studies. Based on Mann's reviews [29] and other relative studies, we performed this meta-analysis.

2. Methods

2.1. Articles retrieval and search strategy

Four reviewers systematically reviewed PubMed, EMBASE, Web of Science, and the Cochrane Library databases up to 1st March 2014. The PubMed combined search term used was: (procalcitonin OR PCT) AND (sepsis) AND burn. The search strategy was designed for each database.

2.2. Selection of studies

Inclusion criteria: We examined the references of published articles, including data on serum PCT for diagnostic sepsis in burned patients. A study was considered eligible for inclusion if it provided both sensitivity and specificity and enough data to construct the 2×2 tables (data corresponding to true positives (TP), true negatives (TN), false positives (FP), and false negatives (FN)). The patients in the included studies principally adults. Exclusion criteria: The studies were excluded which did not afford enough data to construct the 2×2 tables even after contacting the authors. The studies including only pediatric patients were excluded. In order to assure the quality of included studies and exclude the poorly designed or executed studies, the QUADAS (quality assessment of diagnostic accuracy studies) tool [48] was used and the score was at least 10. Selection of articles was conducted separately by four researchers who have diverse educational and professional backgrounds.

2.3. Data extraction

Characteristics such as the patients' sample numbers, age, Burned Surface Area, assay method, the cut-off level of PCT, the sensitivity/specificity, and the positive/negative predictive value (PPV/NPV) of PCT for the diagnosis of sepsis in burned patients were extracted. In cases in which major discrepancies between the data reported in the included studies and the data calculated were observed, we contacted the first or last authors of the individual studies via e-mail, requesting clarification regarding the raw data of the patient groups.

2.4. Quality assessment

Quality assessment was performed based on the QUADAS (quality assessment of diagnostic accuracy studies) tool [48]. The criteria include 14 items covering several dimensions of study quality: reference independent of index test, same reference standard used, all patients verified by reference standards, short time period between reference and index test, adequate reference standard, selection criteria clearly described, representative spectrum of patients, withdraw explained, unintertable test result reports, clinical data available, blinding for index test, adequate reference test, adequate index description. Each item was assessed by scoring as "low (0 score)", "high (1 score)", or "unclear (−1 score)". The QUADAS score was the sum of the 14 items. The score of each item was discussed by the four authors. The highest score of QUADAS is 15. In order to assure the quality of included studies, all of them should meet at least 70% of the 14 items of QUADAS (QUADAS score of $\geq$10).

2.5. Statistical analysis

This meta-analysis was performed with the Meta-Disc 1.4 free software to calculate the pooled sensitivity as TP/(TP + FN), specificity as TN/(TN + FP), positive likelihood ratio (PLR) as (TP/(TP + FN))/(FP/(TN + FP)), negative likelihood ratio (NLR) as (FN/(TP + FN))/(TN/(TN + FP)) and diagnostic odds ratio (DOR) as (TP/FP)/(FN/TN) along with their 95% confidence intervals (CIs).

The summary receiver-operating characteristic (SROC) curve was constructed and the area under the curve (AUC) was then calculated. Analysis of heterogeneity between studies was done using the χ^2 test, which represents the proportion of inter-study variation that can be contributed to heterogeneity rather than to chance. When there was no significant heterogeneity between studies ($P > 0.1$, $I^2 \leq 50\%$), we used fixed-effect meta-analysis. If there was statistical heterogeneity between studies, the meta-analysis was performed using the random-effects model ($P \leq 0.1$, $I^2 > 50\%$). To probe the threshold effect, the Spearman correlation coefficient with Moses' model was calculated. A p-value less than 0.05 indicated significant threshold effect. The Deeks test [49] was performed to detect the publication bias with the Stata 12.1 software, for which a p-value less than 0.1 was suggestive of significant bias.

3. Results

The flow chart of selecting studies was shown as Fig. 1. Nine eligible articles were included. The main characteristics and relative diagnostic data are listed in Tables 1 and 2. The quality assessment was performed strictly based on the QUADAS criteria [48].

3.1. The accuracy of the PCT test in the diagnosis of sepsis in the burned patients

We also quantified the effects of heterogeneity using the I^2 test (ranges from 0 to 100%), which represents the proportion of inter-study variation that can be contributed to heterogeneity rather than to chance. I^2 values of 25, 50, and 75% indicate low, moderate, and high degrees of heterogeneity, respectively. The heterogeneity analysis revealed less homogenity for inter-study