Meta-analysis of the diagnostic value of procalcitonin in adult burn sepsis

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Abstract

Sepsis is one of the main causes of death in burn patients, and many studies have suggested that procalcitonin (PCT) is a biomarker for the early diagnosis of sepsis, but the results are controversial. The aim of this study was to evaluate the diagnostic value of serum PCT in adult burn sepsis by conducting a meta-analysis of published studies. The PubMed, Embase, Web of Science, CNKI and China Wanfang databases were searched, and studies on PCT as a marker for the diagnosis of adult burn sepsis from the establishment of the database, to February 1, 2020 were screened. The data were analyzed using Stata v. 15.0 software. A total of 10 studies and 704 patients were included. The combined sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR) were 0.67 (95% CI: 0.48–0.81), 0.87 (95% CI: 0.72–0.95), 5.20 (95% CI: 2.49–10.84), 0.38 (95% CI: 0.24–0.61) and 13.70 (95% CI: 5.72–32.82), respectively. The area under the summary receiver operating characteristic curve (SROC) was 0.85 (95% CI: 0.82–0.88), and the diagnostic threshold was the main source of heterogeneity. Results demonstrate that serum PCT may be used as a useful biomarker for the early diagnosis of burn sepsis in adults, and may be combined with other diagnostic indexes to further improve the sensitivity and specificity.

Key words: sepsis, burn, procalcitonin, meta-analysis
Background

Burns are common injuries in life and war. Although there are many strategies for the prevention and treatment of infection in burns, burn sepsis is still one of the common causes of death in patients with severe burns.1 Burns, especially severe burns, can lead to extensive damage to the skin tissue, the body’s first defense barrier, resulting in serious damage to the body’s internal homeostasis, a decrease in immunity, and a large volume of necrotic wound tissue. These changes provide good conditions for the growth and reproduction of bacteria. Therefore, infection in patients with severe burns is difficult to avoid.2,3 Septic shock and multiple organ failure can develop rapidly from burn sepsis, which can lead to death.4 Therefore, early detection of high-risk groups prone to burn sepsis, early diagnosis, and prediction of the prognosis of burn sepsis are key to reducing the mortality of patients with this condition. Bacterial blood culture is an important aspect of clinical etiological detection and diagnosis of burn sepsis, however blood culture does not enable a rapid diagnosis of burn sepsis, as it may take 3 days or more to produce a result. The use of prophylactic antibiotics in severe burn patients leads to a low positive rate of blood culture, which leads to a delay in the diagnosis of burn sepsis and an increase in antibiotic resistance.5 Patients with severe burns often have similar symptoms to infection, such as increased respiratory rate, increased heart rate, and an obvious increase of white blood cells. The commonly used clinical indicators such as blood pressure, heart rate, respiratory rate, white blood cells, neutrophils, liver, and kidney function have low specificity and sensitivity in the diagnosis of burn sepsis, and these indexes cannot accurately estimate the prognosis of burn sepsis patients. Therefore, it is necessary to identify a rapidly detectable indicator, with high specificity and sensitivity, to enable the early prediction, diagnosis, and prognosis of burn sepsis. Such an indicator would facilitate timely treatment measures, guide the use of antibiotics, and increase the survival rate of patients with burn sepsis.

In recent years, various studies have shown that serum procalcitonin (PCT) plays an important role in the diagnosis of sepsis.6,7 Serum PCT is a non-hormone active glycoprotein composed of 116 amino acids, which is a propeptide of calcitonin (CT).8 The content of serum PCT in the blood of healthy people is very low, generally less than 0.1 ng/mL.9 It has been shown that the release of serum PCT is closely related to the release of endotoxins and inflammatory mediators.10 Serum PCT level has been demonstrated to be increased in differing degrees of bacterial and fungal infections, burns, trauma, surgery, and other conditions, but the increase in patients with systemic bacterial infection was the most significant.11,12 The level of serum PCT in patients with systemic bacterial infection increased rapidly in 6–8 h and reached a peak at about 24 h. The level of serum PCT can change from low to high with severity of infection, i.e., local infection, sepsis, severe sepsis, septic shock. The level of serum PCT can always be at a high level or can increase continuously with persistent infection or aggravation of infection, so there is a significant correlation between serum PCT level and the severity of infection.11

Objectives

At present, there is still a debate regarding the significance of PCT in burn sepsis, so this study uses the method of meta-analysis to comprehensively analyze the relationship between serum PCT level and the diagnosis of sepsis in adult burn patients, to provide medical evidence for its diagnostic value.

Materials and methods

Literature search

PubMed, Emerge, Web of Science, CNKI, China Wanfang, and other databases were searched for literature related to PCT and burn sepsis, published from the establishment of each database, to February 1, 2020. The key words used were: PCT, sepsis, burn, diagnosis. The search language was limited to Chinese and English. A detailed study flow chart is shown in Fig. 1, as per PRISMA guidelines.

Inclusion and exclusion criteria

Inclusion criteria: 1) the purpose of the study was to evaluate and explore the value of PCT in the diagnosis of sepsis in burn patients over 18 years old; 2) they can directly obtain four-grid data or provide sufficient information to construct four-grid data; 3) sepsis was diagnosed using accurate definition criteria: according to the American Society of Chest Physicians (ACCP)/Society of Critical Care Medicine (SCCM) meeting definition or the American Burn Association (ABA) meeting definition; 4) there were comparative data on clinical diagnosis and blood culture results. The literature was screened independently by 2 researchers according to the inclusion criteria, and the data were extracted according to a designed data extraction table. Finally, the data extraction was cross-compared, and if any differences were solved through discussion and negotiation.

Exclusion criteria: 1) poor experimental design or implementation of the study, unable to extract accurate data to construct a 2 x 2 four-grid table; 2) the subjects included children; 3) the Quality Assessment Of Diagnostic Accuracy Studies (QUADAS) score was less than 10.
Data extraction

Literature extraction: first author, publication time, country, experimental design, sample number of patients, age, burn area, critical value of PCT, sensitivity/specificity, and other indicators for the diagnosis of burn sepsis were extracted. When we observed a significant difference between the data reported in the study and the calculated data, we contacted the first or last author of the individual study by email to request clarification of the original data for the patient group.

Document quality evaluation

The QUADAS tool was used for quality assessment, which included 14 items covering multiple dimensions of research quality. The QUADAS score was the sum of the 14 items. The scores for each item were discussed by two researchers. The highest available QUADAS score was 14, and to ensure the quality of the study, all included projects scored greater than 70% of the maximum QUADAS score (QUADAS score ≥ 10).
Statistical analyses

Stata v. 15.0 software was used to analyze the data. Cochran Q and Higgins’ I² statistics were used to test the heterogeneity between the studies. The diagnostic threshold effect was evaluated by the receiver operating curve (ROC) and the Spearman’s correlation coefficient was used to determine sensitivity and specificity. The typical shoulder-arm representation in ROC space and a strong positive correlation between the logarithm of sensitivity and the logarithm of 1-specificity were used to indicate the existence of the threshold effect. The bivariate mixed-effect regression model was used, combined with 95% confidence interval (CI), to calculate the sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR) aggregate statistics, and to draw the corresponding forest plot. Deeks’ test was used to detect publication bias, and finally, sensitivity analysis was carried out. The area under the summary receiver operating curve (SROC), (AUC) was obtained. The AUC value varies from 0.5 to 1.0, with a value close to 0.5 indicating poor diagnostic performance, and AUC close to 1.0 indicating good diagnostic performance. Where there was heterogeneity, meta-regression was used to analyze the source.

Results

Literature retrieval and quality evaluation

When retrieving statistics related to vital signs and blood samples collected at a specific time point, according to the diagnostic criteria of sepsis, each time point was defined as either sepsis or non-sepsis, and divided into a sepsis group and non-sepsis group accordingly. Initially, 227 articles were retrieved through keywords and all titles and abstracts were reviewed, resulting in exclusion of 182 articles. Full text and data integrity were then reviewed, and a further 35 were excluded. Finally, 10 studies met all the inclusion criteria, with a total of 704 patients, and 6062 time points. The information on the screening flow chart is shown in Fig. 1, which was prepared as per PRISMA guidelines. The basic characteristics and quality score of the included literature are shown in Table 1. The results of diagnostic accuracy analysis showed that significant heterogeneity was observed in the studies of sensitivity ($p = 0.00, I^2 = 93.40$), specificity ($p = 0.00, I^2 = 98.66\%$), PLR ($p = 0.00, I^2 = 97.13\%$), and DOR ($p = 0.00, I^2 = 100.0\%$). There was no obvious threshold effect in the current meta-analysis because the ROC curve was not a typical "shoulder-arm" pattern (Fig. 2). The Spearman correlation coefficient between the logarithm of sensitivity and the logarithm of 1-specificity was –0.2857, and the difference was not statistically significant. Overall, the diagnostic accuracy

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>PCT cut-off</th>
<th>Age [years]</th>
<th>TBSA [%] burned</th>
<th>Time points</th>
<th>Sample size</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>QUADAS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heimburg et al.</td>
<td>1998</td>
<td>Germany</td>
<td>PS</td>
<td>3</td>
<td>37.3 (18–65)</td>
<td>51 (20–91)</td>
<td>27</td>
<td>27</td>
<td>2</td>
<td>0</td>
<td>16</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Bargues et al.</td>
<td>2007</td>
<td>France</td>
<td>PS</td>
<td>0.534</td>
<td>40 ±14</td>
<td>40 ±17</td>
<td>359</td>
<td>25</td>
<td>39</td>
<td>29</td>
<td>53</td>
<td>237</td>
<td>11</td>
</tr>
<tr>
<td>Lavrentieva et al.</td>
<td>2007</td>
<td>Greece</td>
<td>PS</td>
<td>1.5</td>
<td>45.6 ±20.1</td>
<td>41.4 ±22</td>
<td>934</td>
<td>43</td>
<td>93</td>
<td>72</td>
<td>21</td>
<td>748</td>
<td>13</td>
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<tr>
<td>Larventieva et al.</td>
<td>2012</td>
<td>Greece</td>
<td>PS</td>
<td>1.5</td>
<td>48.2 ±18.3</td>
<td>38.8 ±18</td>
<td>145</td>
<td>145</td>
<td>64</td>
<td>5</td>
<td>9</td>
<td>67</td>
<td>13</td>
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<tr>
<td>Cakir et al.</td>
<td>2013</td>
<td>Turkey</td>
<td>PS</td>
<td>0.759</td>
<td>40 ±17</td>
<td>36.1 ±23.4</td>
<td>611</td>
<td>37</td>
<td>181</td>
<td>79</td>
<td>59</td>
<td>292</td>
<td>11</td>
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<tr>
<td>Seoane et al.</td>
<td>2014</td>
<td>Spain</td>
<td>RS</td>
<td>1.7</td>
<td>52.5 ±17.2</td>
<td>37.6 ±22.9</td>
<td>34</td>
<td>34</td>
<td>4</td>
<td>0</td>
<td>12</td>
<td>18</td>
<td>10</td>
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<tr>
<td>Paratz et al.</td>
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<td>Australia</td>
<td>PS</td>
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<td>40.16 (18–60)</td>
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<td>344</td>
<td>54</td>
<td>38</td>
<td>190</td>
<td>10</td>
<td>106</td>
<td>11</td>
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<td>Mokline et al.</td>
<td>2015</td>
<td>Tunisia</td>
<td>PS</td>
<td>0.69</td>
<td>37 ±17</td>
<td>23 ±17</td>
<td>121</td>
<td>121</td>
<td>39</td>
<td>12</td>
<td>5</td>
<td>65</td>
<td>11</td>
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<tr>
<td>Cabral et al.</td>
<td>2017</td>
<td>Portugal</td>
<td>RS</td>
<td>0.5</td>
<td>40.8 ±79.0</td>
<td>160–38.8</td>
<td>3419</td>
<td>150</td>
<td>463</td>
<td>1062</td>
<td>189</td>
<td>1705</td>
<td>12</td>
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<tr>
<td>Zhou M et al.</td>
<td>2020</td>
<td>China</td>
<td>PS</td>
<td>4.05</td>
<td>30.93–54.31</td>
<td>40.6–53.7</td>
<td>68</td>
<td>68</td>
<td>14</td>
<td>7</td>
<td>4</td>
<td>43</td>
<td>10</td>
</tr>
</tbody>
</table>

TP – true positive; FP – false positive; FN – false negative; TN – true negative; QUADAS – Quality Assessment Of Diagnostic Accuracy Studies; PS – prospective; RS – retrospective; TBSA – total body surface area; PCT – procalcitonin.
of PCT in adult burn sepsis was: combined sensitivity = 0.67 (95% CI: 0.48–0.81), combined specificity = 0.87 (95% CI: 0.72–0.95), PLR = 5.20 (95% CI: 2.49–10.84), NLR = 0.38 (95% CI: 0.24–0.61), DOR = 13.70 (95% CI: 5.72–32.82). The forest plot of DOR is shown in Fig. 3A, the sensitivity and specificity of the forest plot are shown in Fig. 3B, and the forest plot of PLR and NLR are shown in Fig. 3C. The SROC is shown in Fig. 2 (AUC = 0.85, 95% CI: 0.82–0.88). Fagan’s nomogram result showed that when the pre-test probability ratio was 20%, the post-test probability of PLR was 57% and
the post-test probability of NLR was 9% (Fig. 3D). This shows that PCT has a good diagnostic performance for adult burn sepsis. The Deeks’ funnel plot in Fig. 4 shows that the p-value was 0.61, which can be considered as a lack of publication bias. The results of the meta-regression analysis are shown in Table 2, which shows that the ethnicity of the study population and experimental design did not affect the source of heterogeneity, and the diagnostic threshold was the main source of heterogeneity.

Sensitivity analysis

The result of the sensitivity analysis is shown in Fig. 5. Goodness-of-fit and bivariate normal analysis (Fig. 5A,B) show that the bivariate mixed-effect model was robust for meta-analysis. Also, through sensitivity analysis (Fig. 5C) and outlier detection (Fig. 5D), a study that deviated from the others was identified, that may affect the robustness of meta-analysis. After excluding this study, in the overall analysis with or without outliers, there was no significant change in sensitivity (0.67 vs 0.73), specificity (0.87 vs 0.84), PLR (5.20 vs 4.60), NLR (0.38 vs 0.32), DOR (13.70 vs 14.00) and AUC (0.85 vs 0.85), indicating that the meta-analysis of diagnostic value in this study was robust.

Discussion

Burns are tissue injuries caused by thermal, chemical, electrical, or radiation factors, which can damage the physiological barriers of the body surface of burn patients. When an extensive area of this physiological barrier is destroyed, the resulting large wound becomes a suitable medium for the growth of bacteria, and as the body surface has the temperature and humidity suitable for the reproduction and growth of bacteria, the proliferation of bacteria is promoted within the wound. The immune function of the patient after burns is impaired and maladjusted, and the anti-infection ability of the whole body is low. Therefore, burn patients have a higher incidence of sepsis. Severe sepsis and septic shock are common causes of death in burn patients, accounting for 30% of hospital mortality.25

Fig. 5. The results of sensitivity analysis
Although interventions for the treatment of sepsis have been improving, such as anti-infective treatment and efforts to follow the development of supportive methods such as immunotherapy from the surviving sepsis guidelines, prognosis remains not optimistic for patients with sepsis. 26 Burn sepsis is a severe systemic inflammatory response syndrome (SIRS) reaction caused by a bacterial infection, which occurs and develops rapidly. When the course of burn sepsis progresses to septic shock or multiple organ dysfunction syndrome (MODS), there are no clear, effective, and specific treatment measures, and this condition carries a poor prognosis and high mortality. Early diagnosis of sepsis and appropriate treatment can reduce the mortality of burn sepsis. 27 Therefore, the early diagnosis of sepsis in burn patients becomes particularly critical, and there is an urgent need for more effective markers for early diagnosis. Mann et al. 28 in 2011 and Ren et al. 29 in 2015 systematically reviewed the relationship of PCT and the diagnostic value of burn sepsis, until then there was little systematic analysis on the topic. Therefore, we carried out a meta-analysis to comprehensively evaluate the diagnostic value of PCT in adult burn sepsis.

The date of literature retrieval included in this study was from the establishment of each relevant database to February 1, 2020. A total of 10 studies, 704 patients, and 6062 time points were included. There were strict inclusion and exclusion criteria for the included literature. To ensure the quality of the literature, each paper was scored by QUADAS, and studies with a score of less than 6 were excluded. To more accurately evaluate the role of PCT in the diagnosis of adult burn sepsis, this study also imposed a strict age limit, with all subjects being over 18 years old, which reduced the heterogeneity to some extent. Besides patient age, there are many factors that may affect the heterogeneity of the diagnostic value of PCT, such as detection method, burn severity etc. Therefore, this study conducted a meta-analysis including ethnicity of the study, experimental design and diagnostic threshold to analyze the source of heterogeneity. The results of this study showed that the AUC was 0.85, and combined sensitivity and specificity of SROC were 0.67 and 0.87 respectively. In terms of sensitivity, the ability of serum PCT to detect sepsis in adult burn patients was weaker, and the ability to detect non-sepsis in adult burn patients was stronger. The PLR was 5.20 and the NLR was 0.38. Where the likelihood ratio is more than 1, it means that the result of the diagnostic test is related to the disease; and where the likelihood ratio is less than 1, it means that the result of the diagnostic test is not related to the disease. In our results, the PLR was 5.20, which means that sepsis patients with positive diagnostic tests were 5.20 times more likely to develop sepsis than non-sepsis patients with positive diagnostic tests. The results of the likelihood ratio showed that serum PCT could be used to distinguish adult burn patients with sepsis from those without sepsis. DOR combines the results of sensitivity and specificity, which is an ideal independent index. When the lower limit of 95% CI of its value is more than 1, the difference is considered statistically significant, and the larger the value is, the more obvious the diagnostic effect is. In our study, DOR = 13.70 (95% CI: 5.72–32.82), therefore this showed that serum PCT had good accuracy in the diagnosis of adult burn sepsis. The analysis of publication bias showed that there was no obvious publication bias in this study. The results of the sensitivity analysis showed that the results of this study were robust.

The diagnostic criteria of sepsis are defined by the ACCP/SCCM, but in patients with burn sepsis, there is a higher incidence of local bacterial colonization and more obvious SIRS, which will affect the diagnosis of burn sepsis. The ABA meeting in 2007 proposed new diagnostic criteria for SIRS and sepsis in burn patients, which were more suitable for this group of patients. 29,30 Meta-regression analysis showed that the main source

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Category</th>
<th>Studies</th>
<th>Sen (95% CI)</th>
<th>p-value for Sen</th>
<th>Spe (95% CI)</th>
<th>p-value for Spe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity</td>
<td>Non-Caucasian</td>
<td>2</td>
<td>0.85 (0.64–1.00)</td>
<td>0.22</td>
<td>0.86 (0.62–1.00)</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>Caucasian</td>
<td>8</td>
<td>0.62 (0.43–0.81)</td>
<td>0.80</td>
<td>0.88 (0.76–0.99)</td>
<td></td>
</tr>
<tr>
<td>Design</td>
<td>RS</td>
<td>2</td>
<td>0.48 (0.07–0.89)</td>
<td>0.29</td>
<td>0.88 (0.65–1.00)</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>PS</td>
<td>8</td>
<td>0.71 (0.55–0.88)</td>
<td>0.87</td>
<td>0.87 (0.75–0.98)</td>
<td></td>
</tr>
<tr>
<td>PCT cut-off</td>
<td>&gt;1.5 ng/mL</td>
<td>3</td>
<td>0.35 (0.09–0.62)</td>
<td>0.02</td>
<td>0.97 (0.90–1.00)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>≤1.5 ng/mL</td>
<td>7</td>
<td>0.77 (0.65–0.89)</td>
<td></td>
<td>0.80 (0.67–0.93)</td>
<td></td>
</tr>
</tbody>
</table>

Sen – sensitivity; Spe – specificity; PS – prospective; RS – retrospective; PCT – procalcitonin.
of heterogeneity may be the threshold of PCT, and was not related to race or experimental design. The criteria of Bargues et al.\textsuperscript{14} for the diagnosis of sepsis were based on the ACCP/SCCM consensus, in which the proportion of respiratory system infection and wound infection was higher, which tend to mislead or exaggerate the diagnosis of sepsis, combined with the relatively conservative diagnostic threshold of 0.534 ng/mL. There was reason to suspect that the subjects were patients with mild to moderate infection rather than severe burns, so it was recommended to adopt the ABA sepsis criteria in future studies to avoid exaggerating the diagnosis of sepsis.

The results of this study suggest that PCT may not be the most ideal biomarker for early diagnosis of burn sepsis in adult patients. In fact, an ideal biomarker may not exist, due to the complex pathophysiological processes in sepsis that cannot be described by a single biomarker. However, it may be a useful and promising biomarker of sepsis in burn patients. In practical application, PCT may be combined with other biomarkers to aid in the early diagnosis of burn sepsis, which may achieve higher diagnostic accuracy.

Limitations

Of course, inevitably, this study had some limitations: 1. There were relatively few studies included, and only 10 articles met the criteria. We aimed to collect all studies that met the requirements, but some of them were of low quality or the data was not accurate, which were therefore excluded from our study. 2. There is a certain heterogeneity in the study. Although we have carried out meta-regression according to the diagnostic threshold, ethnicity and experimental design, and come to the conclusion that the diagnostic threshold has the greatest influence on the heterogeneity, it is still inevitable that there is still a certain heterogeneity, which may be caused by different ages or burn areas, but cannot be further stratified. As a result, it is impossible for us to conduct further research on it. 3. This study only considers published studies in Chinese and English, which may mean important data obtained from unpublished studies and studies written in other languages was excluded.

Conclusions

Procalcitonin is useful in the diagnosis of burn sepsis in adult burn patients. This index can be used in early diagnosis of adult burn sepsis. At the same time, it is necessary to combine PCT with other diagnostic indexes to further improve the diagnostic sensitivity and specificity of burn sepsis. Sepsis leads to a complex inflammatory response, and clinicians should understand the diagnostic efficiency and limitations of PCT and other inflammatory indicators.

Combination of a variety of inflammatory indicators for comprehensive evaluation is often more reliable than relying solely on one diagnostic threshold.

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**References**