Can procalcitonin be used to diagnose Gram-negative bloodstream infection? Evidence based on a meta-analysis

C. HE¹, B. WANG², Y.-F. WANG¹, Y.-C. SHEN³

¹Department of Laboratory Medicine, West China Hospital of Sichuan University, Chengdu, Sichuan Province, China
²Intensive Care Unit, West China Hospital of Sichuan University, Chengdu, Sichuan Province, China
³Department of Respiratory and Critical Care Medicine, West China Hospital of Sichuan University and Division of Pulmonary Diseases, State Key Laboratory of Biotherapy of China, Chengdu, Sichuan Province, China

Abstract. – OBJECTIVE: Procalcitonin (PCT) is a useful biomarker for systemic bacterial infection, and many studies have described the correlation between high serum PCT level and Gram-negative bloodstream infection (BSI), whereas the diagnostic accuracy of PCT for this kind of episode has not been summarized. This study aimed to estimate the overall accuracy of serum PCT for diagnosing Gram-negative BSI through a meta-analysis.

MATERIALS AND METHODS: We searched PubMed, EMBASE, Web of Science, and Scopus database for studies those met the inclusion criteria. The pooled sensitivity, specificity, positive/negative likelihood ratio (PLR/NLR), and diagnostic odds ratio (DOR) were calculated using bivariate random-effects models. Summary receiver operating characteristic (SROC) curve and area under the curve (AUC) were used to summarize overall diagnostic accuracy.

RESULTS: Our meta-analysis included 13 studies involving 4,513 subjects. Summary estimates for PCT in diagnosing Gram-negative BSI were as follows: sensitivity, 0.73 (95% CI 0.68 to 0.78); specificity, 0.74 (95% CI 0.64 to 0.81); PLR, 2.77 (95% CI 2.07 to 3.70); NLR, 0.37 (95% CI 0.31 to 0.42); DOR, 7.59 (95% CI 5.31 to 10.85); AUC, 0.79 (95% CI 0.75 to 0.82). The corresponding summary performance estimates for using PCT in differentiating Gram-negative BSI from gram-positive BSI were as follows: sensitivity, 0.73 (95% CI 0.66 to 0.78); specificity, 0.70 (95% CI 0.59 to 0.78); PLR, 2.40 (95% CI 1.83 to 3.15); NLR, 0.39 (95% CI 0.33 to 0.46); DOR, 6.15 (95% CI 4.40 to 8.60); AUC, 0.77 (95% CI 0.73 to 0.81).

CONCLUSIONS: PCT may have a limited diagnostic value for Gram-negative BSI.

Key Words: Procalcitonin, Bloodstream infection, Gram-negative bacteria, Diagnosis, Meta-analysis.

Introduction

Bloodstream infection (BSI) is a life-threatening situation resulting from the presence of organisms in the blood. Gram-negative bacteria have emerged as the prevalent pathogens causing BSI¹⁻⁴. Gram-negative BSI is associated with longer length of hospital stay and high mortality (36.0%-47.9%)⁵⁻⁸. Moreover, ineffective initial antimicrobial therapy for such kind of episode was associated with poor outcome⁹⁻¹⁰. In practice, it is hard to diagnose BSI alone based on clinical manifestations. So, a reliable laboratory diagnostic method, which can guide early and accurate diagnosis of Gram-negative BSI, is crucial for patients.

Blood culture is regarded as the gold standard for laboratory diagnosis of bacterial BSI. Usually, 1-2 day is required to obtain Gram-stain result by direct smear from positive blood culture bottles. Sometimes, the result of direct smear method is not available because of its low sensitivity and specificity, and another 1-2 day is needed for obtaining the stain results from bacterial colony on the culture plate. Moreover, sensitivity of blood culture method for diagnosing BSI is relatively low¹¹ and sample contamination issue is also a challenge¹². So biomarkers, which can help to early and accurately diagnose Gram-negative BSI, are useful for appropriate initial antibiotic therapy of the patients.

Procalcitonin (PCT) is a 116-amino-acid peptide synthesized by the C cells in the thyroid gland. Elevated serum levels of PCT are strongly associated with systemic bacterial infections¹³. Recently, higher serum PCT level was found to be associated with Gram-negative BSI, which
suggested PCT may be a promising biomarker for diagnosing Gram-negative BSI\textsuperscript{14-17}. Therefore, we conducted a meta-analysis to evaluate the overall diagnostic accuracy of serum PCT for Gram-negative BSI.

**Materials and Methods**

**Study Selection**

Two investigators (YCS and CH) conducted an independent literature search to identify relevant studies among the articles published up to January 2017 in PubMed, EMBASE, Web of Science, and Scopus database. The following search syntax was used as Medical Headings and/or text words: “procalcitonin or PCT” and “bacteremia or bloodstream infection or sepsis” and “sensitivity or specificity or accuracy”. Reference lists of the included studies or related review articles were also checked to identify potentially eligible studies. The following inclusion criteria were applied: (1) studies were original research articles and published in English; (2) studies evaluated the accuracy of serum PCT level for diagnosing Gram-negative BSI in adults (>18 years old); (3) studies reported sufficient data for calculating the value of true positive (TP), false positive (FP), false negative (FN) and true negative (TN). Conference proceedings and studies published only as abstracts and studies involving fewer than 20 patients were excluded. Discrepancies between these two investigators were resolved by consultation with a third researcher (BW).

**Data Extraction and Quality Assessment of the Studies**

Two investigators (BW and YFW) independently extracted data from the eligible studies and conducted $2 \times 2$ tables for calculating TP, FP, FN and TN values. The following data were also extracted: name of first author, publication year, country, study setting, study design, PCT assay method, and cut-off value. The quality of these studies was assessed using Quality Assessment of Diagnostic Accuracy Studies (QUADAS)\textsuperscript{18}.

**Statistical Analysis**

Using bivariate regression model, we calculated pooled estimates of sensitivity and specificity, positive likelihood ratios (PLR), negative likelihood ratios (NLR), diagnostic odds ratios (DOR) and constructed summary receiver operating characteristic (SROC) curves\textsuperscript{18}. The area under the curve (AUC) was calculated to assess the overall diagnostic performance. Heterogeneity was assessed using the $I^2$ inconsistency test. Possible causes of heterogeneity among studies were explored through subgroup analyses: study site (European vs. Asian), sample size (< 100 subjects vs. ≥ 100 subjects), study population/setting (multi-departments vs. other), study design (prospective vs. other), assay method (immunofluorescent assay vs. other), serum PCT cut-off value (< 1 ng/mL vs. ≥ 1 ng/mL), and QUADAS score (< 10 vs. ≥ 10). Deeks’s funnel plot was used to detect publication bias\textsuperscript{19}.

**Results**

**Characteristics of Included Studies**

In our present meta-analysis, we included 13 studies\textsuperscript{20-32}, involving 4,513 subjects (2,298 BSI cases and 2,215 controls), according to the inclusion and exclusion criteria. The process of selecting studies was shown in Figure 1. All the
Can procalcitonin be used to diagnose Gram-negative bloodstream infection?

included studies have examined the ability of serum PCT to diagnose Gram-negative BSI and 8 of them determined the ability of serum PCT to differentiate Gram-negative BSI from Gram-positive BSI. The diagnosis of Gram-negative BSI was all based on the results of blood culture. The characteristics of included studies were summarized in Tables I–II.

### Diagnostic Accuracy of Serum PCT

The overall sensitivity and specificity of PCT to diagnose Gram-negative BSI were 0.73 and 0.74, respectively (Figure 2a), and AUC of SROC curve was 0.79 (95% CI: 0.75-0.82) (Figure 3a). The corresponding values of PCT to differentiate Gram-negative BSI from Gram-positive BSI were 0.73, 0.70 and 0.77, respectively (Figure 2b, 3b). The pooled parameters calculated over studies examining serum PCT to diagnose Gram-negative BSI were listed in Table III.

### Heterogeneity Examination and Publication Bias of the Studies

High $I^2$ values of sensitivity and specificity suggest substantial heterogeneity among included studies (Figure 2, all $p < 0.05$), so we performed a meta-regression to investigate the possible sources of heterogeneity. The results of meta-regression based on 7 covariates were summarized in Table IV, which indicated none of them was the source of heterogeneity (all $p > 0.05$). The slope coefficient of Deeks’ funnel plot asymmetry test was associated with $p$-values of 0.07 and 0.53, suggesting symmetry in the data and low likelihood of such bias (Figure 4).

### Discussion

The early and accurate diagnosis of Gram-negative BSI was associated with better clinical outcome. Serum PCT is biomarker for diagnosing systematic bacterial infection, while its overall accuracy in differential diagnosis of Gram-negative BSI remains unclear. In our study, we summarized the overall diagnostic performance of PCT for Gram-negative BSI through a meta-analysis, and our results suggested that the value of PCT in diagnosing Gram-negative BSI may be limited.

The sensitivity and specificity of PCT in diagnosing Gram-negative BSI were 0.73 and 0.74, respectively, suggesting a relatively high rate of missed diagnoses (27%) and misdiagnoses.
PLR > 10 and NLR < 0.1 are considered as strong indicators to rule in or rule out a diagnostic test, respectively. In our meta-analysis, PLR was 2.77 and NLR was 0.37, suggesting relatively low ability to diagnose Gram-negative BSI, consistent with the AUC in SROC analysis was 0.79. Additionally, it appears the PCT is not robust enough on its own to diagnose Gram-negative BSI with a low pooled DOR of 7.59, suggesting that the diagnostic accuracy of PCT combination with other biomarkers, such as CRP37,38, presepsin37,38, interleukin-1 receptor 215, should be evaluated. It is reported that serial evaluations of PCT seem to be more accurate to diagnose BSI in cancer patients39, which suggested that further work might aim to determine whether continuously monitoring serum PCT level increases the sensitivity and specificity of diagnosing Gram-negative BSI or not. Also, diagnostic performance of PCT for BSI in immunocompromised/neutropenic patients was lower than that in patients without immunosuppression31,36. Studies in different populations (such as patients in intensive care unit, cancer patients, and transplant patients, etc.) should be performed to get a definite conclusion.

It is reported that Gram-negative bacteria and Gram-positive bacteria may activate different Toll-like receptor signaling pathways, resulting in the production of distinct pro-inflammatory cytokines that stimulate PCT release. Gram-negative bacteria can produce endotoxins that can also be released upon cell death, leading to persistently high levels of PCT40. Our meta-analysis found that the diagnostic performance of PCT in discriminating Gram-negative BSI from Gram-positive BSI is also not so good, with pooled sensitivity of 0.73, specificity of 0.70, and AUC of 0.77.

Our study has identified significant heterogeneity among included studies, while we didn’t find the source of heterogeneity through a meta-regression analysis regarding the study site, sample size, study population/setting, study design, assay method, serum PCT cut-off value, and QUADAS score. Whereas, it is needed to pay attention to that cut-off value of PCT in diagnosing Gram-negative BSI ranged from 0.015 ng/mL to 10.8 ng/mL, such variation in cut-off value partly reflects differences in study context: assay method31, study populations31, bacterial species29, etc. Although we didn’t identify cut-off value of PCT as a source of heterogeneity in the meta-regression analysis.
Can procalcitonin be used to diagnose Gram-negative bloodstream infection?

Specific cut-off values for different populations and bacterial species might give more useful information for clinical practice.

The findings of this meta-analysis should be interpreted with caution due to a few limitations. First, with our strict inclusion criteria, the number of included studies is limited. Second, we omitted unpublished studies and studies not indexed in our set of databases, which may bias for our results.

Conclusions

Our present meta-analysis suggests that PCT may play a limited role in diagnosing Gram-negative BSI. Further prospective work related on PCT combination with other biomarkers, dynamic evaluation of PCT, and PCT variation in different populations and species, might obtain a more definite conclusion.

Table III. Accuracy of procalcitonin for diagnosing Gram-negative bloodstream infection (BSI).

<table>
<thead>
<tr>
<th>Aims</th>
<th>No. of studies</th>
<th>Cases</th>
<th>Controls</th>
<th>AUC (95% CI)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PLR (95% CI)</th>
<th>NLR (95% CI)</th>
<th>DOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>2298</td>
<td>2215</td>
<td>0.79 (0.75-0.82)</td>
<td>0.73 (0.68-0.78)</td>
<td>0.74 (0.64-0.81)</td>
<td>2.77 (2.07-3.70)</td>
<td>0.37 (0.31-0.42)</td>
<td>7.59 (5.31-10.85)</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>2044</td>
<td>1713</td>
<td>0.77 (0.73-0.81)</td>
<td>0.73 (0.66-0.78)</td>
<td>0.70 (0.59-0.78)</td>
<td>2.40 (1.83-3.15)</td>
<td>0.39 (0.33-0.46)</td>
<td>6.15 (4.40-8.60)</td>
</tr>
</tbody>
</table>

Aim 1: diagnosing Gram-negative BSI; Aim 2: differentiating Gram-negative BSI from Gram-positive BSI; AUC: Area under the curve; CI: Confidential interval; PLR: Positive likelihood ratio; NLR: Negative likelihood ratio; DOR: Diagnostic odds ratio.
Table IV. Meta-regression of potential heterogeneity among the included studies.

<table>
<thead>
<tr>
<th>Covariates</th>
<th>No. of studies</th>
<th>Coefficient</th>
<th>SE</th>
<th>RDOR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>9</td>
<td>0.48</td>
<td>0.37</td>
<td>1.61 (0.57-4.54)</td>
<td>0.27</td>
</tr>
<tr>
<td>Asian</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 100</td>
<td>4</td>
<td>-0.63</td>
<td>0.44</td>
<td>0.53 (0.16-1.81)</td>
<td>0.23</td>
</tr>
<tr>
<td>≥ 100</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study population/setting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multi-departments</td>
<td>5</td>
<td>0.35</td>
<td>0.25</td>
<td>1.42 (0.71-2.83)</td>
<td>0.23</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study design</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective</td>
<td>5</td>
<td>-0.79</td>
<td>0.35</td>
<td>0.45 (0.17-1.21)</td>
<td>0.09</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assay</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFA</td>
<td>9</td>
<td>-0.65</td>
<td>0.24</td>
<td>0.52 (0.27-1.03)</td>
<td>0.06</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cut-off</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1.0 ng/mL</td>
<td>5</td>
<td>0.26</td>
<td>0.25</td>
<td>1.29 (0.65-2.56)</td>
<td>0.36</td>
</tr>
<tr>
<td>≥ 1 ng/mL</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QUADAS score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10</td>
<td>4</td>
<td>-0.29</td>
<td>0.33</td>
<td>0.75 (0.30-1.87)</td>
<td>0.43</td>
</tr>
<tr>
<td>≥ 10</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SE: Standard error; RDOR: Relative diagnostic odds ratio; CI: Confidential interval; QUADAS: Quality assessment for diagnostic accuracy studies.

Figure 3. Summary receiver operating characteristic (SROC) curve for procalcitonin as a diagnostic test for Gram-negative bloodstream infection (BSI). The SROC curves with confidence and prediction regions around mean operating sensitivity and specificity point analyses. AUC, area under the curve; SENS, Sensitivity; SPEC, Specificity. A, Diagnosing Gram-negative BSI; B, Differentiating Gram-negative BSI from Gram-positive BSI.
Can procalcitonin be used to diagnose Gram-negative bloodstream infection?

Acknowledgements
This work was supported by grants No.81201342 from the National Natural Science Foundation of China, and projects No.16PJ325 from Health and Family Planning Commission of Sichuan province. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of Interest
No conflict of interests to disclose.

References


12) Bloos F, Senderek M, Bauer M. Sensitivity of blood culture vs polymerase chain reaction for skin con-
serum procalcitonin as a diagnostic marker of infection in solid tumors. Medicine (Baltimore) 2015; 94: e1774.


Can procalcitonin be used to diagnose Gram-negative bloodstream infection?


