Serum procalcitonin levels predict disseminated intravascular coagulation in patients with sepsis shock: A retrospective cohort study

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Abstract

Background

Complication of disseminated intravascular coagulation (DIC) is a determinant of the prognosis in patients with sepsis shock. Procalcitonin (PCT) has been advocated as a marker of bacterial sepsis. The purpose of this study was to evaluate the relationship between serum PCT levels and DIC with sepsis shock.

Methods

A cohort study was designed which included patients that admitted in intensive care unit (ICU) between January 1, 2015 and December 31, 2018 and the follow-up to discharge. 164 septic shock patients were divided into DIC and non-DIC groups according to international society of thrombosis and homeostasis (ISTH). PCT was measured at the admission to ICU, and all the participants received routine biochemical coagulation test subsequently.

Results

PCT levels were considerably higher in septic shock patients who developed DIC than those who did not (54.6[13.6–200] vs 12.6[2.4–53.3] ng/ml), respectively, P < 0.001). Multivariable logistic regression model revealed that PCT level was significantly associated with risk of DIC independent of conventional risk factors. In addition, curve fitting showed a linear relationship between PCT and DIC score. The Receiver Operating characteristic (ROC) curve suggested that the optimal cut-off point for PCT to predicting DIC induced by septic shock was 42.0 ng/ml, and the area under the curve (AUC) was 0.701 (95% CI [0.619–0.784], P < 0.001). More importantly, incorporating PCT with other risk factors into the prediction model significantly increased the AUC for prediction of DIC induced by sepsis shock (0.801 vs 0.706; P = 0.012).

Conclusions

Our study suggests that PCT levels on admission is significantly and independently associated with DIC development subsequently with septic shock, combining PCT levels with other risk factors could significantly improve the prediction of DIC induced by sepsis shock.

Introduction

Activation of coagulation system by multiple factors in sepsis, in addition to immune response, is recognized as a host defense strategy against infection, which is termed as immunothrombosis (1, 2). However, excessive and dysregulated activation of coagulation often leads to a very complex coagulopathy syndrome characterized by massive formation of thrombi in particular in microcirculation, termed as disseminated intravascular coagulation (DIC) (3). The occurrence of DIC is often characterized by systemic activation of coagulation, bleeding and subsequent organ dysfunctions (4). DIC is a commonly encountered life-threatening complication in 30–50% sepsis patients with mortality up to 43% (5, 6). Additionally, DIC has been identified as a potent indicator of multiple organ dysfunction syndrome (MODS) and mortality in severe septic patients (7). Treatment for DIC using anticoagulants at early stage has shown great potential to improve the patient’s outcomes (8). Thus, early detection and initiation of preventive strategies indicates tremendous clinical significance.

Conventionally, early diagnosis of DIC in septic patients largely depends on the established over-DIC diagnostic criteria released by International Society of Thrombosis and Homeostasis (ISTH) (4). The essential components of this criteria include platelet count, D-dimer, Prothrombin time, Fibrinogen, System Inflammatory Reaction Syndrome (SIRS) score, sequential organ failure assessment (SOFA) score (4). Other three score systems have also been proposed (9–11). However, these current clinical score systems are generally similar based on routine tests and often failed to detect early stage of DIC prior to apparent onsets of coagulopathy (12). Additionally, various other aspects of sepsis and coagulopathy are not covered within those components. And other parameters (such as APACHEII score (13, 14), serum lactate (15), and proinflammatory cytokines (16, 17)) have been also reported to associated DIC development. Hence, the value of those factors to predict the development of DIC in septic shock patients warrants further investigation.

Procalcitonin (PCT) is the peptide precursor of the hormone calcitonin and its plasma level is expected to be very low in normal conditions (18). However, PCT is dramatically produced and ubiquitously released with 1000-fold elevation after infection (19). Thus, it has been used as a valuable biomarker of ongoing bacterium infection and sepsis diagnosis (20). Based on earlier research, we hypothesized that PCT may be helpful alone or jointly with other risk factors to accurately predict the subsequent DIC development with sepsis shock in the early stage.

Methods

Design, Setting, and Study population

This retrospective cohort study was designed by the investigators and performed at the Second People's Hospital of Shenzhen (20160115004). Written informed consent was obtained from each participant before enrolment.

Clinical variables and definition
All routinely collected vital signs and symptoms and laboratory values were extracted from the electronic health records retrospectively. Data included, but were not limited to, demographic data (e.g., age, gender), biochemical parameters (e.g., blood cell count, liver function, kidney function, coagulation function, blood gas analysis), mechanic ventilation and infection sources. The worst value of biochemical parameters within 24 hours admission to ICU was adopted for downstream analysis. We calculated the Acute Physiology and Chronic Health Evaluation (APACHE) II score within first 24 hours of hospitalization.

Statistical analysis

Quantitative parameters are presented as the means±standard deviations or medians and interquartile ranges (25th, 75th percentiles), and qualitative parameters are expressed as numbers and percentages. Continuous variables were compared using the independent two-sample t-test or Mann–Whitney U-test. Categorical variables were compared using the chi square test or Fisher's exact test. Univariate logistic regression analysis was performed to evaluate risk factors associated with DIC. All variables with P< 0.01 in univariate analysis were entered into a multivariate logistic regression with crude model and fully adjusted model: OR (odds ratio) and 95% confidence interval levels (95% CI). The predictive ability of PCT and other parameters for DIC was assessed using the AU-ROC curve method with MedCalc. The optimal cutoff value was determined using Youden's index. Then, we explored the relationship between PCT and DIC by smooth curve fitting after adjustment for potential confounders. Statistical analysis was performed using the statistical package SAS 9.4 (Windows, SAS Institute, Cary, North Carolina). P values (two-tailed) below 0.05 were considered statistically significant.

Results

Basic characteristics of study population

2154 patients admitted to University Hospital between January 1, 2015 and December 31, 2018. 261 sepsis shock patients hospitalized in ICU were reviewed on primary screening and only 164 patients were eventually enrolled in our study based on strict including and excluding criteria up to follow-up discharge (Fig. 1). The general characteristics of those patients with or without DIC were shown in Table 1. Among the total 164 patients, 58 patients developed DIC during hospitalization with 53.5% prevalence in our institution. Patients who developed DIC had elevated lactate level, longer length of stay in ICU and higher APACHEII score, worse liver function (higher ALT, AST and total bilirubin) and kidney function (higher creatinine and blood urea nitrogen), and significant higher PCT level (54.6 ng/ml vs 12.6 ng/ml, P < 0.001) as well as higher ISTH score (5.6 ± 0.8 vs 3.1 ± 0.7, P < 0.001), compared to those who did not develop DIC. Moreover, PCT was positively associated with ISTH score in our study (Fig. 2). Notably, age and gender did not seem to affect the development of DIC. And no difference of blood leukocyte number was observed between those two groups.

Risk factors associated with DIC induced by sepsis shock

PCT, total bilirubin, lactate and APACHEII score, but not age, gender, ALT, AST or creatinine, were identified as significant risk factors to development of DIC in septic shock patients in univariant logistic regression model. After adjustment for multivariant logistic regression model, only PCT, total bilirubin and lactate were still statistically significant risk factors to development of DIC in sepsis shock patients. Table 2.

PCT improves the prediction of DIC induced by sepsis shock

To explore other risk factors to predict DIC development subsequently with sepsis shock patients. ROC curve analysis was performed individually and combinatorically (Table3 and Fig.3A). The AUC for PCT was 0.701(95% CI [0.619-0.784], P < 0.001) and was significantly greater than those for total bilirubin, APACHEII score and lactate (P=0.01, 0.002, <0.001) respectively. The optimal cut-off point for PCT for predicting DIC induced by sepsis shock was 42.0ng/ml in our model, with a sensitivity of 54.55%, specificity of 79.27%, positive predictive value of 37.5% and negative predictive value of 88.4%. Then, prediction models incorporating clinical and biomedical risk factors were further analyzed. When using combination of lactate, total bilirubin and APACHEII score to predict the DIC development in septic shock patients, the AUC was 0.706(95% CI, 0.630-0.774), Introducing PCT into this model statistically significantly increased the AUC to 0.801 (95% CI 0.732-0.859; P = 0.012) (Table3 and Fig. 3B), which indicated that PCT could significantly improve the prediction of DIC in sepsis shock patients.

Discussion

It has been generally accepted that during microorganism infection, inflammation and coagulation are involved in the development of septic complications, and mainly characterized by inflammation in early stage and obvious coagulation disorders in middle or the late stage. It may be helpful to accurately predict the coagulation condition according to the early inflammatory indicators. Our data revealed that lactate, APACHEII score and total bilirubin are independently associated with DIC development subsequently with sepsis shock, and procalcitonin improved the prediction of DIC induced by septic shock with critical ill patient. Combined procalcitonin (inflammation biomarker) with other risk factors could improve the predictive performance of disseminated intravascular coagulation (DIC) development in sepsis shock patients. Our results may offer a potential screening tool for physicians to assess the chances of DIC development at early stage of septic shock.

Notably, more than 30 million people are affected by sepsis worldwide and the incidence has been increasing over the past several decades, though the mortality has declined significantly with the advancement of diagnosis and management of sepsis (21–23). One of the most frequently encountered complications is the occurrence of DIC, which is the hallmark of the failure of hemostatic system (24). Currently, there are three guidelines for diagnosis and treatment of DIC that have been published (9–11). Although those three guidelines are generally similar, they have some key differences. Therefore, the ISTH integrated those three guidelines and published its own guidance of diagnosis and treatment for DIC(25), which has been accepted as the international
standard and was used in this study. Moreover, ISTH overt-DIC score has also been used to screen DIC on ICU day 1, which was shown to be associated significantly decreased mortality in a multicenter retrospective cohort (26). However, no single parameter has been reported to effectively predict DIC in septic shock patients.

Lactate is an anerobic metabolite that is commonly used as a marker for the function of microcirculation. During the early development of DIC, the excessive formation of microthrombi occludes the blood supply and causes tissue hypoxia, then eventually results in dysfunction of microcirculation and elevation of lactate level. Additionally, another study has shown that increased lactate level could predict the 90-day mortality of septic patients with DIC (15). Thus, lactate level elevation may reflect the early stage of DIC development, as evidenced by our finding that lactate level was an independent risk factor for DIC.

Bilirubin is a biochemical indicator of liver function. Hyperbilirubinemia (hepatic dysfunction) is not uncommonly observed in patients with severe sepsis (27). However, literatures on the study of hyperbilirubinemia in sepsis were very limited. Data from one retrospective study indicated that elevated serum bilirubin levels within 72 hours of admission were associated increased mortality in patients with severe sepsis and septic shock (28). In our study, we identified serum bilirubin as an independent risk factor for development of DIC in septic shock patients. The mechanisms of this correlation are multifaceted and warrant further investigation. One plausible explanation would be that elevated serum bilirubin is a marker of liver dysfunction which is aggravated by DIC development.

PCT was reported as a biomarker of infection and sepsis and higher level of PCT was associated with higher serum proinflammatory cytokines (16, 20), and such proinflammatory mediators could potentially contribute to occurrence of coagulopathy through various mechanisms (29). Significantly higher PCT level was also observed in septic patients with DIC compared to those without (16, 30). Our study revealed that PCT level in sepsis shock patients was significantly associated with risk of subsequent development of DIC, independent of conventional risk factors including lactate, APACHEII score and total bilirubin. More importantly, combining PCT with other risk factors significantly improve the capability to predict the subsequent development of DIC in sepsis shock patients, and close monitoring of PCT level may help to guide the use of anticoagulants in early stage of DIC for intensivists.

Several aspects of limitations present in our study should be noted. Firstly, this is a retrospective study based on a small population at single center. Secondly, although we tried to adjust the potential bias, other unknown factors may also confound our results. Thirdly, this is a preliminary study to explore the potential association between PCT and DIC development in septic shock patients and large multicenter prospective studies are needed to confirm our findings.

In conclusion, our study revealed an unappreciated clinical value of PCT in prediction of DIC development in septic shock patients. Better predictive performance could be obtained by integrating the PCT with conventional risk factor.

**Declarations**

**Authorship Contributions**

Drs X He and H Zhan had full access to all of the data in the study and take responsibility for the integrity of the data;

Statistical analysis: X He, H Li;
Concept and design: M Wu

Drafting of the manuscript: G Fu

Critical revision of the manuscript for important intellectual content: Y Luan, M Wu

Administrative, technical, or material support: Y Chen, Z Yang, J Huang, Y Feng

Drs X He and H Li contributed equally and share first authorship. Drs Y Luan contributed equally to this article.

Obtained funding: Y Feng, Y Luan, M Wu

Supervision: M Wu

**Disclosure Statement**

The authors have no conflicts of interest to declare.

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**References**


### Table 1: Baseline characteristics of non-DIC and DIC patients with sepsis shock

<table>
<thead>
<tr>
<th>Variables</th>
<th>ALL n=164</th>
<th>Non-DIC n=106</th>
<th>DIC n=58</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (S.D.)</td>
<td>64.1±18.9</td>
<td>65.7±17.7</td>
<td>61.2±20.9</td>
<td>0.19</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td>0.44</td>
</tr>
<tr>
<td>male N (%)</td>
<td>97</td>
<td>65/61.3%</td>
<td>32/55.2%</td>
<td></td>
</tr>
<tr>
<td>Female N (%)</td>
<td>67</td>
<td>41/38.7%</td>
<td>26/44.8%</td>
<td></td>
</tr>
<tr>
<td>WBC (10^3/L)</td>
<td>13.4(7.9,20.2)</td>
<td>13.4(7.7,20.4)</td>
<td>13.3(8.5,19.9)</td>
<td>0.89</td>
</tr>
<tr>
<td>Hemoglobin (g/L) (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocyte(1×10^9/L) (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil(1×10^9/L) (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP (mg/dl) (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tb (umol/L) (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT (U/L) (IQR)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>AST (U/L) (IQR)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Creatinine (umol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUN (mmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lac (mmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PO2/FiO2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical Ventilation</td>
<td></td>
<td></td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>yes N (%)</td>
<td>91</td>
<td>56/52.8%</td>
<td>35/60.3%</td>
<td></td>
</tr>
<tr>
<td>no N (%)</td>
<td>73</td>
<td>50/47.2%</td>
<td>23/39.7%</td>
<td></td>
</tr>
<tr>
<td>Infection sources</td>
<td></td>
<td></td>
<td></td>
<td>0.41</td>
</tr>
<tr>
<td>Lungs N (%)</td>
<td>52</td>
<td>37/34.9%</td>
<td>15/25.9%</td>
<td></td>
</tr>
<tr>
<td>Urinary tract N (%)</td>
<td>23</td>
<td>14/13.2%</td>
<td>9/15.5%</td>
<td></td>
</tr>
<tr>
<td>Blood N (%)</td>
<td>5</td>
<td>2/1.9%</td>
<td>3/5.2%</td>
<td></td>
</tr>
<tr>
<td>Abdominal cavity N (%)</td>
<td>42</td>
<td>25/23.6%</td>
<td>17/29.3%</td>
<td></td>
</tr>
<tr>
<td>Skin and soft tissue N (%)</td>
<td>7</td>
<td>3/2.8%</td>
<td>4/6.9%</td>
<td></td>
</tr>
<tr>
<td>Two or more N (%)</td>
<td>35</td>
<td>25/23.6%</td>
<td>10/17.2%</td>
<td></td>
</tr>
<tr>
<td>LOS ICU, median (IQR) (d)</td>
<td>8(3,18)</td>
<td>9(3,8,20.3)</td>
<td>4(2,13.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>APACHE-II score</td>
<td>23.5±9.4</td>
<td>21.8±8.4</td>
<td>26.6±10.3</td>
<td>0.003</td>
</tr>
<tr>
<td>ISTH score</td>
<td>4.0±1.4</td>
<td>3.1±0.7</td>
<td>5.6±0.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

WBC: White blood cell; CRP: C reactive protein; PCT: procalcitonin; Tb: Total bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; Lac: Lactic acid; LOS, Length of stay; APACHE-II, Acute Physiology and Chronic Health Evaluation score; ISTH: international society of thrombosis and homeostasis.

### Table 2: Risk factors associated with DIC induced by septic shock in univariable and multivariable regression model

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariable OR (95%CI)</th>
<th>P value</th>
<th>Multivariable OR (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.988(0.971,1.004)</td>
<td>0.149</td>
<td>0.987(0.956,1.006)</td>
<td>0.128</td>
</tr>
<tr>
<td>Male</td>
<td>1.288(0.673,2.464)</td>
<td>0.444</td>
<td>1.491(0.635,3.505)</td>
<td>0.359</td>
</tr>
<tr>
<td>PCT (ng/ml)</td>
<td>1.009(1.004,1.013)</td>
<td>&lt;0.001</td>
<td>1.010(1.005,1.016)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tb (umol/L)</td>
<td>1.009(1.001,1.017)</td>
<td>0.022</td>
<td>1.010(1.001,1.02)</td>
<td>0.032</td>
</tr>
<tr>
<td>ALT(U/L)</td>
<td>1.005(1.002,1.009)</td>
<td>0.003</td>
<td>1.000(0.995,1.005)</td>
<td>0.920</td>
</tr>
<tr>
<td>AST(U/L)</td>
<td>1.004(1.001,1.007)</td>
<td>0.004</td>
<td>1.002(0.999,1.005)</td>
<td>0.215</td>
</tr>
<tr>
<td>Creatinine (umol/L)</td>
<td>1.002(1.000,1.004)</td>
<td>0.004</td>
<td>1.001(0.999,1.004)</td>
<td>0.256</td>
</tr>
<tr>
<td>Lac (mmol/L)</td>
<td>1.290(1.126,1.477)</td>
<td>&lt;0.001</td>
<td>1.186(1.005,1.399)</td>
<td>0.043</td>
</tr>
<tr>
<td>APACHE-II score</td>
<td>1.059(1.021,1.108)</td>
<td>0.002</td>
<td>1.046(0.99,1.105)</td>
<td>0.111</td>
</tr>
</tbody>
</table>

PCT: procalcitonin; Tb: Total bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; Lac: Lactic acid; APACHE-II, Acute Physiology and Chronic Health Evaluation score; Fully adjusted model: Age, Gender
Table 3: Predicting DIC induced by septic shock with ROC curve

<table>
<thead>
<tr>
<th>Variables</th>
<th>AUC (95% CI)</th>
<th>Cut-off value</th>
<th>Sensitivity, specificity</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT (ng/ml)</td>
<td>0.701 (0.619-0.784)</td>
<td>42.1</td>
<td>60.34% 72.64%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lac (mmol/L)</td>
<td>0.669 (0.579-0.759)</td>
<td>4.2</td>
<td>51.70% 77.40%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tb (umol/L)</td>
<td>0.621 (0.525-0.717)</td>
<td>31.8</td>
<td>37.93% 86.79%</td>
<td>0.010</td>
</tr>
<tr>
<td>APACHE</td>
<td>0.643 (0.550-0.736)</td>
<td>28.5</td>
<td>53.45% 74.53%</td>
<td>0.002</td>
</tr>
<tr>
<td>Lact + APACHE + Tb</td>
<td>0.706 (0.630-0.774)</td>
<td>N/A</td>
<td>65.5% 80.20%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCT + Lact + APACHE + Tb</td>
<td>0.801 (0.732-0.871)</td>
<td>N/A</td>
<td>74.1% 76.4%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

PCT: procalcitonin; Lac: Lactic acid; Tb: Total bilirubin; APACHE-II, Acute Physiology and Chronic Health Evaluation score;

Figures

![Flow diagram of study subjects](image)

Figure 1

Flow diagram of study subjects
Figure 2

The relationship between PCT and DIC (ISTH) by smooth curve fitting
Figure 3

The ROC curve of PCT, Lac, Tb and APACHEII scores