Value of Soluble TREM-1, Procalcitonin, and C-reactive Protein Serum Levels as Markers for Detecting Bacteremia among Sepsis Patients with New Fever in Intensive Care Units

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Abstract

Background

To explore the diagnostic value of soluble triggering receptor expressed on myeloid cells 1 (sTREM-1), procalcitonin (PCT), and C-reactive protein (CRP) serum levels for identifying sepsis, bacteremia, and prognosis of these sepsis patients with new fever; and to discuss the clinical application of the results.

Methods

We enrolled 144 ICU patients as subjects: 60 patients with systemic inflammatory response syndrome (SIRS) and 84 patients with sepsis complicated new fever. Tests for serum sTREM-1, PCT, and CRP levels were performed on the day of ICU admission and at the occurrence of new fever (>38.3°C) during hospitalization. Based on the results of blood culture, the subjects were divided into blood culture-positive bacteremia group (33 patients) and blood culture-negative group (51 patients). Based on 28-day survival, all the subjects, both blood culture-positive and negative, were again divided into a survivor’s group and a non-survivors’ group. Serum sTREM-1 and PCT levels were summarized as medians (interquartile ranges) and CRP levels were presented as means ± standard deviations.

Results

On ICU day 1, the sepsis group had higher serum sTREM-1, PCT, and CRP levels compared with the SIRS group ($P < 0.05$). The area under the curve (AUC) for these indicators came out
respectively as follows: 0.868 (95% CI: 0.798-0.938), 0.729 (95% CI: 0.637-0.821), and 0.679 (95% CI: 0.578-0.771). With 108.85 pg/ml as a cut-off point for serum sTREM-1, sensitivity turned out 0.83 and specificity, 0.81. There was no statistically significant difference in serum sTREM-1, PCT and CRP levels between the blood culture-positive bacteremia and blood culture-negative groups with ICU-acquired new fever. However, the non-survivors of blood culture-positive bacteremia group had higher levels of serum sTREM-1 and PCT ($P < 0.05$), with an AUC for serum sTREM-1 of 0.868 (95% CI: 0.740-0.997).

**Conclusions**

Serum sTREM-1, PCT, and CRP levels each have their role to play in the early diagnosis of sepsis. Serum sTREM-1, with its highest sensitivity and specificity of all the indicators studied, is especially worth notice. sTREM-1, PCT, and CRP levels are of no use in determining bacteremia-caused new fever in ICU patients, but sTREM-1 levels reflect the prognosis of bacteremia.

**Trial Registration**: ClinicalTrials.gov identifier NCT01410578

**Key words**

soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), fever, sepsis, bacteremia, diagnosis, prognosis

**Background**
Sepsis is one of the main causes of morbidity and mortality in the intensive care unit (ICU).

In the United States, approximately 0.5-million people die from sepsis each year [1, 2].

Owing to the prevalence of patients with fever, leukocytosis, and increased heart rate and respiratory rate in the ICU, it has been a challenge for physicians to diagnose sepsis by these criteria alone due to the lack of sensitivity and specificity [3, 4]. Blood culture has always been held to be the gold standard for sepsis diagnosis [5]. However, treatments are normally delayed during the wait for lab results. Therefore, it has been a difficult task for ICU physicians to accurately differentiate bacteremia from similar diseases and come to a rapid diagnosis. In addition, clinical studies have shown that early intervention can significantly improve the prognosis of severe sepsis and septic shock and lowers the mortality rate [6, 7].

Thus, it becomes a critical undertaking to identify any biomarker that can accurately identify infection or non-infection as well as quickly diagnose bacteremia and predict its prognosis. In this study, we evaluated the value of soluble triggering receptor expressed on myeloid cells 1 (sTREM-1), procalcitonin (PCT), and C-reactive protein (CRP) serum levels and try to assess their value for sepsis diagnosis, for identifying bacteremia-caused new fever in ICU patients, and for related prognosis.

**Methods**
The study went on from September 2009 and March 2011 in the Respiratory ICU, Surgical ICU and Emergency ICU, Chinese People’s Liberation Army (CPLA) General Hospital. This study was approved by the Ethics Committee of the CPLA General Hospital (project No.20090923-001) and was registered with the U.S. National Institutes of Health Clinical Trials Register (NCT01410578). Patients or their family members were fully informed and signed informed consent forms.

**New fever in intensive care units**

Fever is a common problem in ICU patients, mainly traced to multiple infectious or noninfectious causes [8]. The definition of fever is arbitrary and depends on the purpose for which it is defined. Guidelines for evaluation of new fever in critically ill adult patients define fever in the ICU as a temperature $>38.3^\circ$C [9, 10]. Taking blood cultures from the patient is the initial step to deal with the condition (temperature $>38.3^\circ$C) [11].

**Criteria of study inclusion and exclusion**

Based on the 1991 ACCP/SCCM Sepsis Directory [12] and the diagnostic criteria advanced by the 2001 International Sepsis Definition Conference [13], patients exhibiting two or more of the following signs during their first 24 h ICU stay were eligible to be selected: (1) temperature $>38^\circ$C or $<36^\circ$C; (2) pulse rate $>90$ beats/min; (3) respiratory rate $>20$ breaths/min or hyperventilation with a partial pressure of arterial carbon dioxide (PaCO$_2$) $<32$ mmHg; (4) white blood cell (WBC) count $>12,000$ $\mu$L$^{-1}$ or $<4000$ $\mu$L$^{-1}$, or $>10\%$
immature cells. Patients were excluded for: (1) younger than 18 years of age; (2) acquired immunodeficiency syndrome; (3) reduced polymorphonuclear granulocyte counts (< 500 µL-1); (4) died within 24h after admission into the ICU, or refused to participate in the study, or declined treatment during the period of observation.

**Infection and Bacteremia Definition**

The presence of infection, defined according with clinical and microbiological criteria of the CDC definitions [14], is to be held as one of the "Gold Standards" and determined by three independent experts, who are to be blinded of CRP, PCT, WBC results [15]. Blood culture-positive bacteremia defined as growth of bacteria with recognized pathogenic capacity in 1 blood culture or as growth of common skin pathogens (i.e., coagulase-negative Staphylococcus species, diphtheroids, Bacillus species, Propionibacterium species, or micrococci) in 2 blood cultures [16].

**Clinical data and sample collection**

Demographic and disease data of the patients admitted to the ICU included: age, gender, chief complaint for admission, major diagnosis, clinical manifestation, APACHE II score, SOFA score, white blood cell (WBC) counts, CRP levels, PCT levels, sTREM-1 levels, cause of infection, initial disease status, and survival during the first 28 days. When the patients were admitted to the ICU, 3 ml of intravenous blood was collected within the first 24 h. The blood was centrifuged at 3000 rpm/min at 4°C for 15 min. Samples was collected again if the
patient’s temperature reached >38.3°C [8, 11]. According to the blood culture standards of the Clinical Laboratory Standards Institute (CLSI) [17], two sets of blood samples were collected from two different sites and were inoculated separately into a Bact/ALERT aerobic bottle and a Bact/ALERT anaerobic bottle (bioMérieux, Marcy-l’Etoile, France).

**Serological Assays and Blood Culture Procedure**

All the specimens renumbered before the experiment. Each step for researchers is relatively blind. sTREM-1 levels were determined in duplicate using a double antibody sandwich enzyme-linked immunosorbent assay (ELISA) Quantikine Human TREM-1 Immunoassay kit (R & D Systems, Minneapolis, MN, USA). PCT was measured using an enzyme linked fluorescence analysis (ELFA) VIDAS BRAHMS PCT kit (bioMérieux, Marcy-l’Etoile, France). CRP was determined using scattering turbidimetry (CardioPhase hsCRP; Siemens Healthcare Diagnostics, Deerfield, IL, USA). A BacT/ALERT 3D automation system (bioMérieux, Marcy-l’Etoile, France) was used to continuously monitor the blood samples in the blood culture bottles. As soon as bacterial growth was detected, the positive bottle was sent for single-colony subculture. Pathogens were identified manually or using the VITEK II system, and bacterial contaminations were excluded [18, 19]. All procedures were strictly conducted following the manufacturer’s instructions and standard microbiology guidelines.

**Statistical analysis**
SPSS statistical software v16.0 (SPSS, Chicago, IL, USA) was used for data analysis. The normally distributed variances were expressed as the mean ± SD. The Student t-test was used to compare mean values between two groups. The data that were not normally distributed were expressed as median (interquartile ranges) and analyzed using the rank sum test. Unordered categorical variables were expressed as percentages, and the difference in proportion between two groups was analyzed using the chi-square test. A receiver operating characteristic (ROC) curve was employed to evaluate the effects of sTREM-1, PCT, and CRP levels on sepsis diagnosis, bacteremia-caused new fever and the prognosis of bacteremia patients.

Results

Patient Characteristics

For the study, a total of 372 patients met the inclusion criteria, and 195 were excluded (Figure 1). 177 patients were further divided into 57 SIRS suspected and 120 sepsis suspected, and then, group according to microbial culture results, classified into a SIRS (n=60) and a sepsis complicated new fever (n=84). 84 sepsis patients were placed respectively into a blood culture-positive bacteremia group (n=33) and a blood culture-negative (n=51) group, based on blood culture tests at the occurrence of new fever. Based on 28-day survivals, blood culture-positive bacteremia patients were further divided into a survivor group, 22 persons
and a non-survivor 11 persons. So were the blood culture-negative patients (29 survivors and 22 non-survivors).

The patients’ baseline data at admission are shown in Table 1. The temperature, APACHE II and SOFA scores of the patients was notably higher in the sepsis group than that of the SIRS group ($P < 0.001$); however, the initial temperature, APACHE II and SOFA scores demonstrated no correlation with blood culture-positive. As for the source of infection, the percentage of catheter-related infections was considerably higher in the blood culture-positive than the blood culture-negative group ($P = 0.006$). However, pulmonary infection, abdominal infection, urinary tract infection, and trauma/postoperative infection were not significantly different between these two groups. As far as predisposing factors were concerned, the immunocompromised rate was higher in the sepsis group than in the SIRS group ($P = 0.011$). Conversely, the presence or absence of immunosuppression at the initial stage did not correlate with positivity of blood culture. Furthermore, there was no significant difference in all of the other predisposing factors among the three groups (SIRS, sepsis with blood culture-positive bacteremia, and sepsis with blood culture-negative). In terms of mortality rate, it was much higher in the sepsis group than in the SIRS group ($P < 0.001$), but this did not correlate with blood culture positivity. No statistical difference was noted for age or gender among the three groups.

sTREM-1, CRP, and PCT: early diagnosis of sepsis on the day of enrolment in ICU
sTREM-1, CRP, and PCT levels and APACHE II scores on the day of enrolment in ICU are shown in Figure 2. For the sepsis group, these values (sTREM-1, CRP, and PCT levels and APACHE II scores) are significantly higher, compared to the SIRS group (149.06 pg/ml vs. 59.97 pg/ml, \( P < 0.001 \); 2.86 ng/ml vs. 0.33 ng/ml, \( P < 0.001 \); 11.4 mg/dl vs. 8.3 mg/dl, \( P = 0.001 \); 18 vs. 11, \( P < 0.001 \), respectively). On the other hand, there was no difference in WBC counts (13.32×10^9/L vs. 12.54×10^9/L, \( P = 0.373 \)). The ROC curves were obtained for sTREM-1, PCT, and CRP levels and APACHE II scores, which were significantly different between the SIRS and sepsis groups (Figure 3). The area under the curve (AUC) for sTREM-1, PCT, CRP levels and APACHE II scores were 0.868 (95% CI: 0.798-0.938), 0.729 (95% CI: 0.637-0.821), 0.679 (95% CI: 0.578-0.771), and 0.745 (95% CI: 0.656-0.833), respectively. When 108.85 pg/ml was set as the cut-off value for sTREM-1, the sensitivity was 0.83 and specificity was 0.81 (Table 2).

**sTREM-1, PCT, and CRP: bacteremia in sepsis patients with new fever**

Eighty-four patients with sepsis had new fever (>38.3°C) during their ICU stay. Thirty-three samples were positive for bacteremia (39.2%). The causes of bacteremia are shown in Figure 4. Of the 33 bacteremia-positive samples, a total of 40 different pathogens were discovered through culturing, including 22 Gram-positive bacteria: *Staphylococcus aureus* (27.5%), coagulase negative *Staphylococcus* (25%), and *Enterococcus* (2.5%); 12 Gram-negative bacteria: *Acinetobacter baumannii* (10%), *E. Coli* (10%), and *Klebsiella*
pneumoniae (7.5%); and 4 Candida albicans (10%). In addition, 7 patients had co-infection of two or more pathogens (17.5%). Serum sTREM-1, PCT, and WBC counts come out as 155.43 (123.36) pg/ml vs. 131.57 (194.81) pg/ml, \( P=0.724 \); 2.39 (8.1) ng/ml vs. 2.71 (25) ng/ml, \( P=0.693 \); 12.98 \( \pm \) 7.58 \( \times \) 10\(^{9}\)/L vs. 11.3 \( \pm \) 5.01 \( \times \) 10\(^{9}\)/L, \( P=0.264 \), respectively. But a comparison of WBC level between the two groups is devoid of such significance 13.19 \( \pm \) 8.03 mg/dl vs. 9.55 \( \pm \) 6.52 mg/dl, \( P<0.033 \) (Figure 5).

**sTREM-1, PCT, and CRP: prognostic value**

We compared all the parameters of the 22 survivors and the 11 nonsurvivors in the blood culture-positive state (Table 3). It was found that body temperature and WBC count as well as sTREM-1, PCT, and CRP levels of the non-survivors were all higher than those of the survivors, although only sTREM-1 and PCT levels between the groups were significantly different. However, in the blood culture-negative group, difference in all these indicators between survivors and non-survivors is insignificant. Furthermore, we worked out ROC curves for sTREM-1 and PCT levels to predict bacteremia prognosis (Figure 6), and the AUC values for sTREM-1 and PCT levels were 0.868 (95% CI: 0.740-0.997) and 0.789 (95% CI: 0.624-0.995), respectively. With 126.94 pg/ml as the cut-off value for sTREM-1, the sensitivity and the specificity were 1 and 0.68, respectively (Table 4). Multivariable logistic regression was employed to assess possible risk factors to bacteremia. The variables taken into account included serum sTREM-1 and PCT. Finally, only serum sTREM-1 was able to
enter the regression equation, with a regression coefficient=0.007, OR=1.007, Wald
coefficient=5.716, and 95% CI 1.001-1.013 ($P=0.017$).

**Discussion**

TREM-1 was recently discovered and is a member of the immunoglobulin superfamily of
receptors that is specifically expressed on the surfaces of neutrophils and monocytes.

sTREM-1 is a soluble form of TREM-1 and is released into the body fluid when TREM-1 is
upregulated. Many studies indicate that sTREM-1 could be a valuable diagnostic biomarker
for various of infectious diseases [20-27]. Dynamic changes in sTREM-1 levels could predict
survival and mortality of patients at the early stage of sepsis[28, 29]. PCT expression is
related to the severity of bacterial infection; hence, it is one of the biomarkers for infection
[30, 31]. PCT measurements along with other clinical tests for infection might be valuable for
determining the prognosis of patients [32, 33]. CRP is a biomarker involved in variety of
inflammatory diseases. Although the majority of hospitals can widely implement CRP
analysis in sepsis diagnosis and prognosis [34, 35], it is still controversial whether CRP is a
good biomarker for early diagnosis of sepsis or bacteremia [36, 37]. Our study found that
sTREM-1,PCT and CRP levels indicate infection, while sTREM-1 and PCT levels predict
prognosis. However, none of them bring to light the cause of new fever. Moreover, sTREM-1
is the best indicator to the diagnosis sepsis and assess prognosis of blood culture-positive bacteremia.

Rivera-Chavaz et al. [38] performed a study among 93 patients in the ICU with SIRS symptoms and suspected infection. The patients were classified as having SIRS (no infection; n = 37) or sepsis (n = 56) according to the diagnosis of the physician in charge and clinical evidence. Patients with sepsis had significantly higher sTREM-1 concentrations than those with SIRS. At a cut-off of 30 pg/mL, sTREM-1 correctly identified patients suffering from infection with 96% sensitivity and 91% specificity. Porfyridis et al. [39] enrolled 68 patients with acute respiratory illness. A total of 34 patients were diagnosed with community acquired bacterial pneumonia and 34 with nonbacterial pulmonary disease. sTREM-1 levels were significantly higher among the pneumonia group than the nonbacterial pulmonary disease group, and this analysis was more sensitive and specific than CRP levels. Yong J et al. [40] performed a meta-analysis of 13 clinical studies that fulfilled the inclusion criteria (980 patients, 557 patients with bacterial and 423 with nonbacterial infections). They found that sTREM-1 levels for the diagnosis of infection in the AUC of the summary ROC was 0.86, with a sensitivity of 0.82 and a specificity of 0.86. This finding confirmed that sTREM-1 is a reliable biomarker of bacterial infection. However, other studies argue that sTREM-1 is of no value for infection diagnosis [41-43]. Some experts have suggested that CRP and PCT levels are more sensitive biomarkers for bacterial infection diagnosis than sTREM-1 [44, 45]. Our
study, on the other hand, found that on the day of ICU admission the sepsis group had higher sTREM-1, PCT, and CRP levels and APACHE II scores than the SIRS group. The indicators above, to different degrees, have values in sepsis identification or diagnosis, of which sTREM-1 proves most efficient. Data obtained through our study are quite similar to those previously reported.

There have been numerous studies on PCT. Stefan et al. [46] enrolled 295 patients whose blood culture samples were collected at the emergency department. Based on the blood culture results, the patients were categorized into blood culture positive, blood culture negative, and blood culture contaminated groups. The results indicated that PCT is the most valuable biomarker for the diagnosis of sepsis and bacteremia for patients in the emergency department. Kim et al. [47] and Lai et al. [37, 48] also arrived at the same conclusion that PCT levels are the most meaningful parameter for bacteremia diagnosis and for cases of bacteremia with a high fever in the emergency department. On the contrary, CRP levels have no value for diagnosing cases of bacteremia with a high fever in the emergency department. However, Blijleven et al. [49] questioned the value of PCT levels in the sepsis diagnosis. Besides, Ruiz-Gonzalez et al. [50] have recently suggested that sTREM-1 levels are valuable for diagnosing cases of bacteremia with community-acquired pneumonia. Since fewer studies have shown the value of sTREM-1 in the diagnosis of bacteremia, we divided feverish ICU patients into blood culture-positive bacteremia and blood culture-negative groups based on
their blood culture results. We found that sTREM-1 and PCT levels from the two group were very comparable. Interestingly, CRP levels were significantly higher in the blood culture-negative group than in the bacteremia group \((P = 0.033)\). We speculate that this occurs because of the rise of CRP reactivity rather than of bacteremia itself. Our study implies that sTREM-1, CRP, and PCT levels may possess no clinical value in determining whether a given sepsis patient is complicated with bacteremia on the grounds of a new fever.

Gibot el al. [29] studied sTREM-1 levels in 63 patients with severe sepsis and found that decreased sTREM-1 plasma levels had a positive correlation with a better prognosis. Thus, sTREM-1 is an excellent biomarker for the prognosis of sepsis. Furthermore, Zhang et al. [28, 29] studied sTREM-1, PCT, and CRP levels in 52 patients with sepsis, and found that compared to PCT and CRP levels, dynamic changes in sTREM-1 levels predict the prognosis of sepsis better. However, no studies have reported whether sTREM-1, PCT, and CRP levels are good parameters for the prognosis of bacteremia. Here, we showed that sTREM-1 and PCT levels were useful for prognosis of blood culture-positive bacteremia. For example, sTREM-1 and PCT levels were significantly higher in the nonsurvivor group than in the survivor group among bacteremia group. However, we failed to find any prognostic value of sTREM-1 and PCT for blood-culture-negative sepsis. Moreover, according to the ROC curves of sTREM-1 and PCT levels, sTREM-1 is a more ideal predictor for the prognosis of
blood-culture-positive bacteremia. As such, physicians are expected to pay close attention to patients with high levels of sTREM-1.

Our study was, however, limited by the following factors: (1) A small sample size, as only 33 patients with a positive blood culture were enrolled. (2) Only those who developed new fever (>38.3°C) in the ICU were enrolled. Therefore, we cannot exclude the possibility that patients who did not have a high fever also had bacteremia, but unfortunately, no such patients were involved in our analyses. (3) The incidence of opportunistic infections is higher in the ICU, and many pathogens circulate in the wards. Consequently, the possibility of false-positive blood cultures could not be excluded. Furthermore, the patients receive regular antibiotics treatment, and side-effects of such a long-term treatment should not have been ignored. (4) It is well known that more than two thirds of patients with severe bacterial sepsis have negative blood cultures[51, 52], but this fact (blood-culture- negative bacteremia) has not been properly dealt with in the study.

Conclusions

sTREM-1, PCT, and CRP levels are of substantial value for the early diagnosis of sepsis. In addition, sTREM-1 levels can reflect the infection more accurately and more specifically than CRP and PCT levels. However, none of these three parameters could be used to determine whether the fever of patients with sepsis was caused by bacteremia. Finally, sTREM-1 and
PCT levels could aid in predicting the prognosis of bacteremic patients. Regrettably the sample size of this study was small; larger studies are thus needed to further evaluate the value of sTREM-1, PCT, and CRP levels in the diagnosis of bacteremia.

**Competing interests**

All authors declare that they have no competing interests.

**Authors' contributions**

LS designed the study, performed the data analysis, and wrote the first manuscript draft. CJ, JD and YJ carried out the study in the SICU, EICU and the RICU, respectively. Before the experiment started, BH was responsible for sorting out the samples and having them re-numbered; LL & CJ tested sTREM-1 concentration; DF performed the statistical work. LX was responsible for protocol revisions, data analysis, and final draft revision. All authors have read and approved the final manuscript.

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Written consent for publication was obtained from the patient or their relative.

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References


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Table 1 Clinical and biological data at ICU admission according to the SIRS and sepsis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SIRS negative blood culture N=60</th>
<th>SIRS positive blood culture N=51</th>
<th>Sepsis positive blood culture N=33</th>
<th>P value</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>51±21</td>
<td>59±18</td>
<td>54±20</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (n, %)</td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>36 (60)</td>
<td>31 (60.8)</td>
<td>25 (75.8)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>24 (40)</td>
<td>20 (39.2)</td>
<td>8 (24.2)</td>
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<tr>
<td>temperature (℃)</td>
<td>37.2±0.9</td>
<td>38.4±0.9</td>
<td>38.0±1.2</td>
<td>&lt;0.001</td>
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<tr>
<td>APACHE II score</td>
<td>11±7</td>
<td>18±8</td>
<td>17±8</td>
<td>&lt;0.001</td>
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<td>SOFA score</td>
<td></td>
<td>8±4</td>
<td>8±4</td>
<td>NS</td>
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<tr>
<td>Etiological factors (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary infection</td>
<td></td>
<td>40(78.4)</td>
<td>23(69.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Abdominal infection</td>
<td></td>
<td>11(21.6)</td>
<td>6(18.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td></td>
<td>10(19.6)</td>
<td>8(24.2)</td>
<td>NS</td>
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<tr>
<td>Trauma/postoperative infection</td>
<td></td>
<td>16(31.4)</td>
<td>14(42.4)</td>
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<tr>
<td>Catheter-related infections</td>
<td></td>
<td>3(5.9)</td>
<td>9(27.3)</td>
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<tr>
<td>Others</td>
<td></td>
<td>4(3)</td>
<td>1(3)</td>
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### Predisposing factors (n, %)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Group 1 (n, %)</th>
<th>Group 2 (n, %)</th>
<th>Group 3 (n, %)</th>
<th>Significance</th>
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</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>15 (25)</td>
<td>19 (37.3)</td>
<td>10 (30.3)</td>
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<tr>
<td>Diabetes</td>
<td>4 (6.7)</td>
<td>10 (19.6)</td>
<td>4 (12.1)</td>
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<td>COPD</td>
<td>2 (3.3)</td>
<td>6 (11.8)</td>
<td>3 (9.1)</td>
<td>NS</td>
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<td>Coronary heart disease</td>
<td>7 (11.7)</td>
<td>7 (13.7)</td>
<td>2 (6.1)</td>
<td>NS</td>
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<td>Immunosuppressed</td>
<td>0 (0)</td>
<td>5 (9.8)</td>
<td>3 (9.1)</td>
<td>0.011</td>
</tr>
<tr>
<td>Nervous system disease</td>
<td>3 (5)</td>
<td>5 (5.9)</td>
<td>2 (6.1)</td>
<td>NS</td>
</tr>
<tr>
<td>CKD</td>
<td>2 (3.3)</td>
<td>3 (5.9)</td>
<td>3 (9.1)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Mortality rate (n, %)</strong></td>
<td>4 (6.7)</td>
<td>22 (43.1)</td>
<td>11 (33.3)</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

NS, not significant. Quantitative data of normal distribution are presented as mean±SD. Quantitative data of non-normal distribution are presented as median (interquartile range). Qualitative data are presented as n( %).

Respiratory Intensive Care Unit, RICU; Surgical Intensive Care Unit, SICU; Emergency Intensive Care Unit, EICU; APACHE II score, Acute Physiologic Assessment and Chronic Health Evaluation II scores; SOFA score, Sequential Organ Failure Assessment scores; Chronic Obstructive Pulmonary Disease; CKD, chronic kidney disease.
Table 2 Area under ROC curve as means of differentiating sepsis from SIRS

<table>
<thead>
<tr>
<th>variable</th>
<th>AUC</th>
<th>Std. Error</th>
<th>P value</th>
<th>Asymptotic 95% Confidence Interval</th>
<th>Cut</th>
<th>sen</th>
<th>spe</th>
<th>PPV</th>
<th>NPV</th>
<th>PLR</th>
<th>NLR</th>
<th>YI</th>
</tr>
</thead>
<tbody>
<tr>
<td>sTREM-1</td>
<td>0.868</td>
<td>0.036</td>
<td>&lt;0.001</td>
<td>0.798 0.938</td>
<td>108.85</td>
<td>0.83</td>
<td>0.81</td>
<td>0.86</td>
<td>0.65</td>
<td>2.9</td>
<td>0.31</td>
<td>0.64</td>
</tr>
<tr>
<td>PCT</td>
<td>0.729</td>
<td>0.047</td>
<td>&lt;0.001</td>
<td>0.637 0.821</td>
<td>2.07</td>
<td>0.55</td>
<td>0.83</td>
<td>0.82</td>
<td>0.42</td>
<td>2.14</td>
<td>0.51</td>
<td>0.38</td>
</tr>
<tr>
<td>CRP</td>
<td>0.675</td>
<td>0.049</td>
<td>0.001</td>
<td>0.578 0.771</td>
<td>16.5</td>
<td>0.35</td>
<td>0.98</td>
<td>0.96</td>
<td>0.35</td>
<td>2.85</td>
<td>0.76</td>
<td>0.33</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>0.745</td>
<td>0.045</td>
<td>&lt;0.001</td>
<td>0.656 0.833</td>
<td>19.5</td>
<td>0.49</td>
<td>0.89</td>
<td>0.86</td>
<td>0.4</td>
<td>3.49</td>
<td>0.62</td>
<td>0.39</td>
</tr>
</tbody>
</table>
Table 3 Prognostic value of temperature, WBC, sTREM-1, CRP, and PCT levels

<table>
<thead>
<tr>
<th>Parameter</th>
<th>blood culture-positive bacteremia</th>
<th>P value</th>
<th>blood culture-negative bacteremia</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>survivors (n=22)</td>
<td>non-survivors (n=11)</td>
<td>survivors (n=29)</td>
<td>non-survivors (n=22)</td>
</tr>
<tr>
<td>Temperature (mean±SD, °C)</td>
<td>38.8±0.5</td>
<td>38.9±0.7</td>
<td>38.96±0.46</td>
<td>38.82±0.39</td>
</tr>
<tr>
<td>WBC (mean±SD, ×10^9/L)</td>
<td>10.8±3.6</td>
<td>12.2±7.2</td>
<td>12.68±8.01</td>
<td>13.38±7.14</td>
</tr>
<tr>
<td>sTREM-1 (median-interquartile range, pg/ml)</td>
<td>105.63(90.81)</td>
<td>273.6(350.61)</td>
<td>137.1(159.18)</td>
<td>168.28(150.19)</td>
</tr>
<tr>
<td>PCT (median-interquartile range, ng/ml)</td>
<td>1.18(11.44)</td>
<td>19.94(61.65)</td>
<td>2.55(6.82)</td>
<td>1.83(9.59)</td>
</tr>
<tr>
<td>CRP (median-interquartile range, mg/dl)</td>
<td>8.9±7.1</td>
<td>10.9±5.2</td>
<td>12.63±7.9</td>
<td>13.9±8.33</td>
</tr>
</tbody>
</table>
Table 4 Area under ROC curve as means of differentiating non-survivors from blood culture-positive

<table>
<thead>
<tr>
<th>variable</th>
<th>AUC</th>
<th>Std. Error</th>
<th>P value</th>
<th>Asymptotic 95% Confidence Interval</th>
<th>Cut point</th>
<th>sen</th>
<th>spe</th>
<th>PPV</th>
<th>NPV</th>
<th>PLR</th>
<th>NLR</th>
<th>YI</th>
</tr>
</thead>
<tbody>
<tr>
<td>sTREM-1</td>
<td>0.868</td>
<td>0.066</td>
<td>0.001</td>
<td>Lower limit: 0.74 Upper limit: 0.997</td>
<td>126.94</td>
<td>1</td>
<td>0.68</td>
<td>0.61</td>
<td>1</td>
<td>3.33</td>
<td>0.13</td>
<td>0.68</td>
</tr>
<tr>
<td>PCT</td>
<td>0.789</td>
<td>0.085</td>
<td>0.012</td>
<td>Lower limit: 0.624 Upper limit: 0.955</td>
<td>2.26</td>
<td>0.9</td>
<td>0.63</td>
<td>0.55</td>
<td>0.86</td>
<td>2.57</td>
<td>0.27</td>
<td>0.53</td>
</tr>
</tbody>
</table>
Figure legends

Figure 1 Trail profile for patients enrolled in our study.

Figure 2 sTREM-1, CRP, PCT levels, WBC count and APACHE II score on day of enrollment in ICU. The dots denote individual values, and the bars, medians or means.

Figure 3 ROC curves for sTREM-1, CRP, PCT levels and APACHE II score for distinguishing sepsis from SIRS.

Figure 4 Causes of bacteremia. The relative proportions of causes of bacteremia from 33 positive blood culture.

Figure 5 Comparison diagnostic value of sTREM-1, CRP, PCT and WBC count for bacteremia. The dots denote individual values, and the bars, medians or means.

Figure 6 ROC curves for sTREM-1 and PCT for distinguishing non-survivors from blood culture-positive.
eligible patients
n=372
Excluded: younger than 18 years, 23; acquired immunodeficiency syndrome, 9; reduced polymorphonuclear granulocyte counts, 28; refused to participate, 103; died within 24hrs, 32

SIRS suspected
n=57
no new fever
n=6
SIRS
n=43
Sepsis + new fever
n=8
blood culture-positive bacteremia
n=33
survivors
n=22

sepsis suspected
n=120
no new fever
n=27
Sepsis + new fever
n=76
blood culture-negative
n=51
non-survivors
n=11
Diagonal segments are produced by ties.
Figure 4
Figure 6

ROC Curve

Source of the Curve
- serum sTREM-1 (pg/ml)
- PCT (ng/ml)
- Reference Line