Serum sTREM-1, PCT, CRP, Lac as biomarkers for death risk within 28 days in patients with severe sepsis

Abstract: This study was undertaken to evaluate the clinical efficacy of serum soluble triggering receptors expressed by myeloid cell-1 (sTREM-1), procalcitonin (PCT), C-reactive protein (CRP) and lactic acid (Lac) as biomarkers for death risk within 28 days in patients with severe sepsis. Fifty-one cases of severe sepsis from the department of ICU in Lishui People’s Hospital from May 2013 to February 2017 were retrospectively analyzed. These cases were divided into survival (n=39) and death (n=12) groups based on the outcome within 28 days of treatment. Serum levels of sTREM-1, PCT, CRP and Lac were measured on the day of admission and compared between the survival and death groups. And the death prediction value within 28 days were evaluated according to serum sTREM-1, PCT, CRP and Lac. The serum level of TREM-1 and Lac were 128.70±46.10 pg/mL, 7.02±1.56 mmol/L for the death group and 83.69±26.57 pg/mL, 4.44±0.45 mmol/L for survival group. The serum levels of sTREM-1 and Lac in death group were significantly higher than those of survival group (p<0.05). However, the serum PCT and CRP between the survival and death group were not statistically different (p>0.05). The death prediction sensitivity, specificity and AUC within 28 days were high for serum sTREM-1 (75.00%, 77.78%, 0.79) and APACHEII (74.89%, 84.62%, 0.84). However, the prediction value of serum level PCT, CRP and Lac were relatively low. A significant positive correlation was found between serum sTREM-1 and APACHEII score (r_{pearson}=0.54, p<0.001). However, no such correlation was observed between serum CRP, Lac and APACHEII scores (p>0.05).

Conclusion: Serum sTREM-1 was significantly elevated in sepsis patients who died within 28 days of admission, suggesting that this test could be a potential biomarker for severe sepsis patients, and also be used for prognostic evaluation.

Keywords: sepsis; prognosis; sTREM-1; procalcitonin; C-reactive protein; lactic acid

1 Introduction

Sepsis is a systemic inflammatory response syndrome (SIRS) caused by infection. Relevant studies have reported approximately 18 million new sepsis cases occurring annually world-wide, 750,000 of which are reported in North America [1]. The incidence of sepsis has increased by 1.5% to 8.0% annually [2]. However, no highly specific, highly sensitive, and easy-to-operate death risk prediction models are currently available, despite a very high mortality rate resulting from sepsis. Recent studies have shown the level of various serological markers, such as calcitonin and C-reactive protein (CRP) in the serum of sepsis patients were significant elevated and correlated with the severity of patients’ disease [3-5]. sTREM-1 is a member of the immunoglobulin superfamily activated receptor, and is expressed on the surface of myeloid cells. Its activation can promote the production of inflammatory mediators, such as TNF-α, IL-6, and IL-8. Thus, sTREM-1 is considered as a key marker of inflammatory disease. Compared to CRP, calcitonin, and other inflammation markers, sTREM-1 is better correlated with the severity of inflammatory disease, and could be used to evaluate the therapeutic effect and prognosis of infection [4, 6]. However, since few studies have reported on the prediction of death risk in sepsis patients by serum sTREM-1, its significance for clinical application needs further assessment. In the present work, we
present a retrospective analysis of the levels of sTREM-1, procalcitonin (PCT), CRP, and Lac in serum samples of 51 patients with severe sepsis. The feasibility of using these serum protein as biomarkers for death risk prediction during severe sepsis was explored.

2 Methods

2.1 Patients

A total of 51 severe sepsis patients admitted to the intensive care unit of the Lishui People's Hospital, Zhejiang Province from May 2013 to February 2017 were analyzed retrospectively. Patients were classified into survival (n=39) and death (n=12) groups based on the outcome within 28 days. The 51 patients were diagnosed in accordance with the sepsis diagnosis criteria formulated by SCCM and ESICM, and their diagnosis also conformed to the diagnosis criteria of severe sepsis specified in the Treatment Guideline of Sepsis and Septic Shock 2012. Patients aged 16 years and below, who died within 24h, and diagnosed with an immune-related disease, malignant tumor, or were pregnant, were excluded.

Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by Lishui People’s Hospital’s institutional review board.

2.2 Serum TREM-1, PCT, CRP and Lac detection

ELISA was performed to examine the serum PCT, sTREM by using an ELISA kit purchased from Shanghai Jinma Biotechnology Co. The automatic biochemical analyzer (American BD) was used to detect serum CRP in the peripheral blood of the severe sepsis patients. The fully automatic chemistry analyzer was used to test for Lac concentration in the serum of the included 51 patients.

2.3 Statistical analysis

Data was analyzed using STATA11.0 statistical software (http://www.stata.com), and values were expressed as a mean±standard deviation. Statistical significance was determined by Student’s t-test. Enumeration data were expressed as n (%), and was compared by chi-square test. Correlation between serum levels of sTREM-1, PCT, CRP, Lac and APACHEII score were evaluated by the Pearson correlation test. Prediction sensitivity, specificity, and the area under the ROC curve were calculated according to the equation: sensitivity=true positive/(true positive+ false negative), specificity=true negative/(true negative+ false positive). A two tailed test producing a value of p<0.05 was interpreted as a statistical difference.

3 Results

3.1 General character of the two groups

The general characteristics of the included two groups are shown in Table 1. There was no statistical difference in the age, gender and infection lesions (p<0.05) except for APACHEII score (p<0.05).

| Items               | Survival group (n=39) | Death group (n=12) | t/χ2 | p    |
|---------------------|-----------------------|--------------------|------|------|
| Age(years)          | 44.3±20.4             | 46.7±23.6          | 0.01 | 0.91 |
| Gender              |                       |                    |      |      |
| Male                | 22 (56.4)             | 7 (58.3)           |      |      |
| Female              | 17 (43.6)             | 5 (41.7)           |      |      |
| APACHEII            | 19.17±3.98            | 26.18±5.79         | 4.77 | <0.01|
| Infection lesions   |                       |                    | 0.42 | 0.98 |
| Lung infection      | 13 (33.3)             | 5 (41.7)           |      |      |
| Abdominal cavity infection | 11 (28.2)    | 3 (25.0)           |      |      |
| Septicemia          | 6 (15.4)              | 2 (16.7)           |      |      |
| Intracranial infection | 5 (12.8)         | 1 (8.3)            |      |      |
| Urinary tract infection | 4 (10.3)        | 1 (8.3)            |      |      |

3.2 Serum levels of TREM-1, PCT, CRP and Lac

The serum levels of sTREM-1 and Lac were 128.70±46.10 pg/mL, 70.2±1.56 mmol/L respectively for the death group and 83.69±26.57 pg/mL, 4.44±0.45 mmol/L respectively for the survival group. The serum levels of TREM-1 and Lac in death group were significantly higher than those of survival group (p<0.05), Figure 1. However, the serum PCT and CRP between the survival and death groups were not
Correlation between serum level of sTREM-1, PCT, CRP, Lac and APACHEII score

A significant positive correlation was found between serum sTREM-1 and APACHEII score \( r_{\text{pearson}} = 0.54, \) \( p<0.001 \). However, there was no correlation between serum CRP, Lac and APACHEII score \( p>0.05 \), Figure 3.

Death prediction value of serum sTREM-1, PCT, CRP, Lac and APACHEII

The death prediction sensitivity, specificity and AUC for death within 28 days are given in Table 2. The sensitivity, specificity and AUC were high for serum sTREM-1 (75.00%, 77.78%, 0.79) and APACHEII (74.89%, 84.62%, 0.84). However, the prediction value of serum PCT, CRP and Lac were low, Figure 2.

| Markers     | Survival group (n=39) | Death group (n=12) | t    | p    |
|-------------|-----------------------|--------------------|------|------|
| TREM-1 (pg/mL) | 83.69±26.57           | 128.70±46.10       | 4.26 | <0.001 |
| PCT (ng/mL)  | 114.50±44.03          | 131.90±59.23       | 1.10 | 0.28  |
| CRP (mg/L)   | 151.9±6.44            | 158.03±14.97       | 0.43 | 0.67  |
| Lac (mmol/L) | 4.44±0.45             | 7.02±1.56          | 2.21 | 0.03  |

Figure 1. The scatter plot of serum level of TREM-1, PCT, CRP and Lac between the two groups.

Figure 2. The scatter plot of serum level of sTREM-1, PCT, CRP and Lac between the two groups.

Figure 3. The scatter plot of serum level of TREM-1, PCT, CRP and Lac between the two groups.

Table 2. Serum level of TREM-1, PCT, CRP and Lac comparison between the two groups

3.3 Death prediction value of serum sTREM-1, PCT, CRP, Lac and APACHEII

statistically different \( p>0.05 \), Table 2.

3.4 Correlation between serum level of sTREM-1, PCT, CRP, Lac and APACHEII score


Figure 2. The ROC curve of serum TREM-1, PCT, CRP, Lac and APACHEII for prediction death within 28 days in sepsis patient.

Figure 3. Scatter plot of correlation between serum level of TREM-1, PCT, CRP, Lac and APACHEII score.
4 Discussion

The mortality rate of resulting from sepsis remains high despite extensive studies on the pathological physiology of severe sepsis [7-9]. Numerous new concepts and new methods, such as early targeted therapy, low tidal volume ventilation, intensive insulin treatment, and blood purification technology [10-12], have been applied clinically [13]. Biochemical markers are also being increasingly applied for the early diagnosis and management of sepsis. Ideal biochemical markers are characterized by the following features: they could be easily and widely applied clinically; provide opportunities for intervention and rapid improvement of prognosis; and provide information on prognosis as well as, or better than presently utilized evaluation methods serum levels of PCT [14], CRP, and Lac [15, 16] have been widely used as clinical indicators to evaluate the severity of infectious diseases, and these markers reflect the level of inflammation in the body. While, PCT, CRP, and Lac present in the serum reflect the degree of inflammatory response during sepsis, they are not sufficient to predict the prognosis of sepsis.

Human TREM-1 is a type of transmembrane glycoprotein composed of a 194 amino acid residue extracellular domain, 29 amino acid transmembrane domain, and 5 amino acid cytoplasmic domain. TREM-1 has a relative molecular weight of 30×10³ [17]. The TREM-1 gene located on chromosome-6p21.2, and includes 4 exons, and specifically expressed on the membrane surface of the neutrophils and monocytes in the blood. It is selectively expressed on the macrophage surface in the lung alveolar fluid, intestinal fluid, and other body fluids.

As the spliced form of TREM-1, sTREM-1 is a secretory subtype without the transmembrane domain. This molecule is released to the blood and body fluids during infections. TREMs are receptor proteins widely expressed on the surface of myeloid cells and are membrane recognition receptors in the immunoglobulin superfamily [18]. TREM-1 is also closely related to inflammatory response [19]. The soluble TREM-1 (sTREM-1) is a secretory subtype of TREM-1. Upon upregulation of TREM-1 expression, sTREM-1 content in the blood increases significantly, reflecting the activation of TREM-1 to some extent. This phenomenon is also positively correlated with the severity of the infection and threat to visceral organs. Previous studies [4, 20, 21] have previously suggested that the serum level of sTREM-1 is correlated with the severity of infection observed in sepsis patients, and could be used as the early indicator to assist the diagnosis of sepsis. However, the use of sTREM-1 as an indicator for the prognosis of sepsis patients is rarely reported and remains controversial. Thus, 51 severe sepsis patients admitted to our hospital were analyzed retrospectively. The patients were grouped into the survival and death groups according to the outcome within 28 days. The value of sTREM-1 as prognosis indicator was analyzed to evaluate the patients’ death risks. Our findings showed that serum TREM-1 was elevated significantly in patients who died within 28 days. Our results support the use of sTREM-1 as an indicator for evaluating the death risk of patients with severe sepsis with high sensitivity and specificity. However, this study was a retrospective analysis including only 51 sepsis patients. Consequently, the study design and small sample size limited the statistical power. Looking forward, multicenter prospective randomized clinical controlled studies are need to further evaluate the clinical value of serum sTREM-1, PCT, CRP, Lac as biomarkers for death risk within 28 days in patients with severe sepsis.

Conflict of interest: Authors state no conflict of interest.

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