Original Article

Diagnostic role of soluble triggering receptor expressed on myeloid cell-1 in patients with sepsis

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BACKGROUND: Biomarkers may be helpful in risk stratification and prediction of mortality in septic patients. This study aimed to investigate the diagnostic role of soluble triggering receptor expressed on myeloid cell-1 (sTREM-1), procalcitonin (PCT), C-reactive protein (CRP) and other inflammatory markers in patients with sepsis.

METHODS: A total of 56 patients with systemic inflammation response syndrome (SIRS) who had been admitted to the ICU department of the Second Hospital of Tianjin Medical University between May 2009 and July 2010 were enrolled. They were divided into a sepsis group ($n=32$) and a SIRS group ($n=24$). Twenty-five non-SIRS patients served as controls. The sepsis group was sub-divided into a survival group and a death group according to 28-day prognosis. The values of sTREM-1, PCT, CRP, white blood cell (WBC), and neutrophil count percentage (N) were measured. Acute physiology and chronic health evaluation II (APACHE II) score were determined within 24 hours. The correlation between sTREM-1 and APACHE II score was analyzed. Quantitative data were analyzed by the F test or the Kruskal-Wallis test.

RESULTS: The plasma level of sTREM-1 in the sepsis group was significantly higher than that in the SIRS group and control group. The plasma level of sTREM-1 in the non-survival group was significantly higher than that in the survival group. In the sepsis group, the plasma sTREM-1 level was positively correlated with APACHE II score ($r_s=0.426$, $P=0.032$). The area under the ROC curve of sTREM-1 was 0.935, larger than that of PCT and CRP.

CONCLUSION: Plasma sTREM-1 is useful in the diagnosis of sepsis at early stage. The increased level of sTREM-1 during the first 24 hours may be correlated with poor outcome of patients with sepsis.

KEY WORDS: Sepsis; sTREM-1; Acute physiology and chronic health evaluation II score; Enzyme-linked immunosorbent assay; Procalcitonin; C-reactive protein

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INTRODUCTION

Sepsis is a deadly condition characterized by a whole-body inflammatory state (called a systemic inflammatory response syndrome or SIRS) and the presence of a known or suspected infection.^[1,2] The human body may develop this inflammatory response by the immune system to microbes in the blood, urine, lungs, skin, or other tissues. Sepsis is a leading cause of death in noncoronary intensive care units (ICUs) and

the 10th leading cause of death in the United States. The incidence of severe sepsis in the United States is between 650 000 and 750 000 cases.^[3,4] Biomarkers may be helpful in stratification of risk and prediction of mortality in septic patients. The study aimed to investigate the diagnostic role of soluble triggering receptor expressed on myeloid cell-1 (sTREM-1), PCT, CRP and other inflammatory markers in patients with sepsis.

METHODS

Patients

This prospective, observational study was carried out in our multidisciplinary ICU between May 2009 to July 2010. The study protocol was approved by the Ethics Committee of the Second Hospital of Tianjin Medical University. Informed consent was obtained from all patients or their relatives if they were unconscious. A total of 81 consecutive patients who had been diagnosed with severe sepsis or septic shock (according to the surviving sepsis guidelines 2004) were enrolled in this study. Newly admitted patients (<24 hours), cancer patients, and those with severe trauma or major operation were excluded from the study.

The 81 patients were divided into a sepsis group ($n=32$), a systemic inflammation response syndrome group (SIRS group, $n=24$) and a control group ($n=25$) according to the diagnostic criteria of 2001 American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference^[5]: (1) sepsis as the clinical syndrome defined by the presence of infection and a systemic inflammatory response; (2) SIRS considered to be present when patients have more than one of the following clinical findings: body temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$; heart rate $>90\text{ min}^{-1}$; hyperventilation evidenced by a respiratory rate of $>20\text{ min}^{-1}$ or a PaCO_2 of $<32\text{ mmHg}$; and a white blood cell count of $>12\,000\text{ cells L}^{-1}$ or $<4000\text{ L}^{-1}$; (3) patients in the control group who didn't meet the SIRS criteria, but had focal infection, surgery or trauma.

The sepsis group was subdivided into a survival group and a death group, according to 28-day prognosis.

Methods

Within 24 hours after hospitalization, 2 mL blood was collected and put into sterile tubes. After centrifugation, serum was kept at -80°C until assay.

Demographic data were recorded including medical history, diagnosis, pulse rate, blood pressure, respiratory rate, arterial blood gas, results of routine blood test, electrolytes, white blood cell count (WBC), neutrophil count (N), procalcitonin (PCT) and C-reactive protein (CRP). The severity of condition was measured according to APACHE-II scoring. In a 28-day follow-up, we recorded the number of patients who died of septic complications.

sTREM-1 concentration was measured by ELISA with a kit produced by the R&D Company in the United States. PCT and CRP were determined using a double antibody sandwich immunofluorescence

semi-quantitative method and immunoturbidimetry respectively. PCT was divided into 4 levels: normal $<0.5\text{ }\mu\text{g/L}$, high $\geq 0.5\text{ }\mu\text{g/L}$, higher $\geq 2.0\text{ }\mu\text{g/L}$, and highest $\geq 10.0\text{ }\mu\text{g/L}$.

Statistical analysis

Measurement data were expressed as mean $\pm$ standard deviation. They were compared by one-way analysis of variance (ANOVA) or the Kruskal-Wallis test. The data between the two groups were compared by Student's t test or the Mann-Whitney U test. Data were compared by the chi-square test. Spearman's rank-order correlation coefficient was used for correlation analysis. Then the receiver characteristic curve (ROC) of enrolled patients was drawn to determine the early diagnostic value of inflammatory indicators in patients with sepsis. SPSS 16.0 statistical analysis software was used for data processing. $P<0.05$ was considered statistically significant.

RESULTS

General information

In the sepsis group, 19 patients were male and 13 female, with an average age of 23-82 (64.8 ± 14.3) years. Twenty-one patients survived and 11 (34.4%) died. In the SIRS group, 14 patients were male and 10 female, and their average age was 17-80 (62.5 ± 16.0) years. In the control group, 14 patients were male and 11 female, with an average age of 20-77 (61.6 ± 13.9) years. There was no significant difference in sex and age among the three groups (sepsis group, SIRS group and control group) ($P \geq 0.05$).

Plasma level of sTREM-1

Compared to the SIRS group, sTREM-1 significantly increased in the sepsis group ($P<0.01$). Compared to the control group, sTREM-1 significantly increased in the SIRS group ($P<0.01$). When serum PCT concentration $\geq 2\text{ }\mu\text{g/L}$ was set as positive, there was a significant difference in positive rate ($\chi^2_1=25.441$, $P_1=0.000$; $\chi^2_2=40.078$, $P_2=0.000$) among the three groups (sepsis group, SIRS group and control group), while there was no significant difference in positive rate ($\chi^2=2.586$, $P=0.108$) between the SIRS group and control group. When serum PCT concentration was set $\geq 10\text{ }\mu\text{g/L}$ as positive, there was a significant difference in positive rate ($\chi^2=0.784$, $P=0.465$) between the survival group and death group, whereas there was no significant difference in CRP, WBC, N and T ($P \geq 0.05$) among the three groups (sepsis group, SIRS group and control group) (Tables 1, 2).

Table 1. Comparison of sTREM-1 and clinical parameters among the three groups

Groups	n	sTREM-1 (ng/L)	PCT $\geq$ 2.0 μ g/L (no,%)	CRP (mg/L)	WBC ($\times 10^9$ /L)	Neutrophil count	T ($^{\circ}$ C)	APACHE II
Sepsis	32	250.9 (195.8-354.3) ^{*#}	27 (84.4) ^{*#}	25.1 (11.9-39.1) [#]	13.4 $\pm$ 3.2 [#]	0.831 $\pm$ 0.112 [#]	37.7 $\pm$ 1.2 [#]	19.28 $\pm$ 4.89 ^{*#}
SIRS	24	103.6 (89.4-166.2) [#]	4 (16.7)	31.2 (21.3-34.1) [#]	11.5 $\pm$ 2.9 [#]	0.764 $\pm$ 0.073 [#]	37.6 $\pm$ 0.7 [#]	9.75 $\pm$ 3.38
Control	25	33.6 (26.2-43.0)	0 (0)	11.2 (6.85-13.1)	7.9 $\pm$ 1.6	0.694 $\pm$ 0.065	36.8 $\pm$ 0.6	9.64 $\pm$ 2.90

Compared with SIRS group, ^{*} P <0.05; compared with control group, [#] P <0.05

Table 2. Comparison of sTREM-1, clinical parameters between the survival group and death group

Groups	n	sTREM-1 (ng/L)	PCT $\geq$ 10.0 μ g/L (no, %)	CRP (mg/L)	WBC ($\times 10^9$ /L)	Neutrophil count	T ($^{\circ}$ C)	APACHE II
Survival	21	204.1(175.0-269.6)	9(42.9)	23.2(12.8-40.9)	16.3 $\pm$ 9.2	0.838 $\pm$ 0.104	37.6 $\pm$ 1.4	17.76 $\pm$ 4.01
Death	11	360.5 (262.2-434.5)	3(27.3)	25.8(9.6-38.5)	16.6 $\pm$ 8.4	0.816 $\pm$ 0.172	37.8 $\pm$ 0.9	22.18 $\pm$ 5.27
t/Z/ χ^2		-3.009	—	0.807	0.090	0.578	-0.392	2.657
P		0.002	0.465	0.826	0.929	0.486	0.698	0.013

Figure 1. Correlation between sTREM-1 levels and APACHE II score **Figure 2.** ROC curve of CRP, PCT, and sTREM-1 for diagnosis of sepsis

Correlation between plasma sTREM-1 levels and APACHE II score in sepsis patients

Spearman's rank-order correlation coefficient analysis showed that the plasma sTREM-1 level was positively correlated with APACHE II score ($r=0.426$, $P=0.032$) (Figure 1).

Diagnostic value of plasma level of sTREM-1 in patients with sepsis

The area under the ROC curve of sTREM-1 was 0.935; sTREM-1 showed a sensitivity of 93.8% and a specificity of 84.7% in the diagnosis of sepsis, and we considered sTREM-1 $>$ 135 pg/mL as the best threshold. The area under the ROC curve of PCT was 0.891; PCT had a sensitivity of 84.4% and a specificity of 87.8% in the diagnosis of sepsis, thus we considered PCT $\geq$ 2.0 μ g/L as the best threshold. The area under the ROC curve of CRP was 0.602, indicating that CRP was unable to diagnose sepsis (Figure 2).

DISCUSSION

Sepsis is caused by an infection as a systemic inflammatory response. It may be difficult to distinguish from non-infectious systemic inflammatory response syndrome (SIRS). Hence its treatment and prognosis are different. Currently there are no diagnostic indicators for sepsis with a high specificity and a sensitivity.

Traditional inflammatory indicators include WBC, N, T, etc. In the present study, WBC and C played a role in the diagnosis of sepsis. WBC, N, T distinguished SIRS from non-SIRS, but there was no significant difference between the survival group and death group. This indicated that traditional inflammatory indicators are unable to reflect the severity of sepsis.

CRP, an acute-phase protein, is used as a non-specific inflammatory indicator, but CPR is not specific for infectious diseases.^[6] Our study revealed a significant difference in CPR among the sepsis group, SIRS group and control group; however, there was no significant

difference in CPR between the sepsis group and SIRS group or between the survival group and non-survival group. This indicated that CRP is unable to reflect the prognosis of sepsis.

PCT as the best inflammation indicator^[7,8] can accurately distinguish SIRS from sepsis if its concentration is higher in sepsis patients. It was reported that PCT had a sensitivity of 71% and a specificity of 71% in the diagnosis of sepsis, and the area under the ROC curve of PCT was 0.78; therefore PCT is not used as a diagnostic value in critical patients.^[9] Clinically semi-quantitative assay has been widely used to measure PCT. In the present study we found that if PCT ≥ 2.0 $\mu\text{g/L}$ was set as the threshold, PCT could distinguish SIRS from sepsis with a sensitivity of 84.4% and a specificity of 87.8%, but could not distinguish SIRS from non-SIRS because PCT increased significantly after occurrence of systemic infection. If PCT ≥ 10.0 $\mu\text{g/L}$ was taken as the best threshold, there was no significant difference in PCT between the survival group and death group, indicating that PCT semi-quantitative assay could not predict the prognosis of sepsis.

Triggering receptor expressed on myeloid cells-1 (TREM-1) is a sort of cell surface molecule expressed on granulocytes, monocytes and a subset of macrophages, which was discovered in 2000.^[10] It is a member of the superfamily of immunoglobulins. When the human body is infected, bacterial products such as lipopolysaccharide (LPS) activate the Toll-like receptor (Toll-like receptor, TLR) to increase the expression of TREM-1, and then TREM-1 as a key media-mediator in sepsis promotes the inflammatory response.^[11] The sTREM-1 is a protease hydrolysis product of TREM-1. It is able to bind with unknown TREM-1 ligand in blood and inhibit ligand to bind with TREM-1 in cell membrane, finally preventing the inflammatory signal transduction. This may be one of the regulating ways for TREM-1 activating inflammatory signaling pathways.

Recent studies have shown that sTREM-1 is promising for the diagnosis of sepsis and the prediction of prognosis.^[12-14] When sTREM-1 of plasma is >60 $\mu\text{g/L}$ in ICU sepsis patients, it is more accurate than any other clinical or laboratory indicators in predicting infection and sepsis with a sensitivity of 96% and a specificity of 89%.^[15] A study found that sTREM-1 concentration was significantly lower at admission in non-survivors than in survivors.^[16] In our study, plasma sTREM-1 concentration in the early course was higher in the sepsis group than in the SIRS group and control group, and sTREM-1 concentration was higher in the survivors than

in the non-survivors. The area under the ROC curve of sTREM-1 was 0.935; if sTREM-1 > 135 $\mu\text{g/mL}$ was set as the best threshold, there were a sensitivity of 93.8% and a specificity of 84.7% in the diagnosis of sepsis. The area under the ROC curve of sTREM-1 was similar to that of PCT, thus both sTREM-1 and PCT are of high value in the early diagnosis of sepsis, but PCT is unable to reflect the prognosis of sepsis. SOFA score is an effective indicator to show the severity and prognosis of sepsis.^[17] In the present study, the plasma sTREM-1 level was positively correlated with APACHE II score, indicating that plasma sTREM-1 can reflect the severity of sepsis to some extent. Combined sTREM-1 and SOFA score might be more valuable to predict the prognosis of patients with sepsis.

Experiments showed that injecting sTREM-1 homologous synthetic peptide can reduce the inflammatory response in septic mice and also improve the prognosis.^[18] But research is still preliminary. Further study is needed to explore whether targeted therapy associated with sTREM-1 can be a new way to treat sepsis.

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Conflicts of interest: No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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