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Original Article

Prognostic value of soluble cluster differentiation antigen 14 subtype and platelet activating factor in patients with septic shock

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Abstract: Objective: The aim of this study was to observe and evaluate differential diagnosis and the prognostic value of serum soluble cluster differentiation antigen 14 subtype (sCD14-ST) and platelet activating factor (PAF) in septic shock. Methods: From February 2015 to February 2017, 15 patients with septic shock, 20 patients with severe sepsis, and 30 patients with sepsis, in Jiaozhou People's Hospital, were enrolled in this study. In the same period, 30 healthy subjects were selected as the control group. Serum levels of sCD14-ST, PAF, procalcitonin (PCT), C reactive protein (CRP), and white blood cell count (WBC) were measured upon patient admission. Acute physiology and chronic health status II (APACHE-II) scores were also calculated. Differences in each indicator among those groups were compared. Correlation between sCD14-ST, PAF, and APACHE-II scores was analyzed. Receiver operating characteristic curve was used to compare values of various inflammatory markers in diagnosis of septic shock. Results: Levels of sCD14-ST, PAF, PCT, CRP, and WBC as well as scores of APACHE-II in patients with sepsis, severe sepsis, and septic shock were significantly higher than those in the healthy control group (all $P<0.05$). Levels of sCD14-ST and PAF in patients with septic shock were significantly higher than in patients with severe sepsis and sepsis (all $P<0.05$). Levels of sCD14-ST and PAF in patients with septic shock were positively correlated with APACHE-II scores. Multiple Logistic regression analysis showed that increase in APACHE-II scores, sCD14-ST, and PAF was an independent risk factor for death of patients with septic shock. Conclusion: sCD14-ST and PAF can be used as diagnostic indicators of septic shock and can monitor prognosis of sepsis.

Keywords: Septic shock, soluble cluster differentiation antigen 14 subtype, platelet activating factor, prognosis

Introduction

Sepsis is a common dangerous disease found in Intensive Care Units (ICU), with a high mortality rate. Patients with poorly controlled sepsis can progress to severe sepsis, septic shock, or multiple organ failure. Therefore, early diagnosis and identification of sepsis and prompt formulation of a reasonable therapeutic regimen are of great significance for better prognosis. At present, biomarkers, for combined or individual clinical diagnosis of septic shock, include procalcitonin (PCT) and interleukin and C reactive protein (CRP). However, the sensitivity and specificity of these markers are not high enough and are unfavorable for early assessment of the disease. Research has shown that expression of PCT will also increase in non-sepsis patients with conditions such as large area trauma, organ transplantation, and pancreatitis [1]. Although blood cultures are the gold standard for diagnosis of sepsis, results often take 48 to 72 hours. This process is time-consuming and positive rates are low. Obviously, discovering an efficient and simple biological index has important clinical significance for early judgment of sepsis.

In recent years, some researchers have found that soluble cluster differentiation antigen 14 subtype (sCD14-ST) is significantly increased in peripheral blood of patients with sepsis, increasing even earlier and faster than PCT and CRP [2, 3]. Other studies have shown that platelet-activating factor (PAF) plays an important role in occurrence and development of sepsis [4]. However, at present, no studies have reported on correlation between sCD14-ST, PAF, and prognosis of patients with septic shock. Therefore, the purpose of this research was to

observe the value of sCD14-ST and PAF expression in differential diagnosis and prognosis of septic shock, with an aim of guiding clinical treatment.

Materials and methods

General information

After review and approval by the Ethics Committee of Jiaozhou People's Hospital, 65 cases of sepsis patients, admitted to Jiaozhou People's Hospital, from February 2015 to February 2017, were selected for this study.

Inclusion criteria: Clear evidence of infection; Age ≥18 years old with signed informed consent; In accordance with diagnostic standards for sepsis, jointly established by American College of Chest Physicians and Society of Critical Care Medicine in 2001 [3].

Exclusion criteria: Application of immunosuppressive agents in the past 6 months; Suffering from other immune system diseases; Age <18 years old; Combined pregnancy; Patients not eligible for this research.

Patients were divided into groups of 15 patients with septic shock, 20 patients with severe sepsis, and 30 patients with sepsis, according to severity of the sepsis. There were 41 males and 24 females, with an average age of 63.2±10.5 years old [4]. There were 40 cases of pneumonia, 10 cases of gallbladder infection, 3 cases of liver abscess, 5 cases of intestinal infection, 4 cases of urinary tract infection, and 3 cases with other infections. In the same period, 30 healthy subjects were selected as the control group. This group included 8 males and 12 females, with an average age of 61.8±10.2 years old. They had no clinical symptoms of acute or chronic disease and had not received any medical treatment. There were no significant differences in age and sex between patients with sepsis and healthy subjects (all $P>0.05$).

Determination of sCD14-ST and PAF

All patients received 10 mL of elbow vein blood extraction on the first day of admission. Blood samples were centrifuged at 3,000 rpm for 15 minutes. Extracted serum was stored in the refrigerator (-80°C) for further examination. Blood sCD14-ST levels were measured by PATHFAST chemiluminescence immune automation analyzer (Mitsubishi Corporation, Japan) and enzyme-linked immunosorbent assay kit (Diagnostica, Germany). A human PAF enzyme-linked immunosorbent assay kit (Shanghai Kai Bo Biochemical Reagent Co., Ltd.) was used to detect PAF levels.

Observation index

Main observation index: Serum levels of sCD14-ST and PAF were detected at the time of admission. Acute physiology and chronic health score II (APACHE-II) was calculated according to the worst clinical indicators within 24 hours after admission [3]. Correlation between sCD14-ST, PAF, and APACHE-II scores was analyzed. Patient survival outcome during hospitalization was recorded. Death of patients was considered poor prognosis.

Secondary observation index: Levels of PCT, CRP, and white blood cell count (WBC) were measured upon admission, respectively. Next, 5 mL of fasting elbow vein blood was collected in non-anticoagulated blood tubes and centrifuged at 4,000 rpm for 15 minutes. The upper serum remained and serum WBC and CRP levels were detected on the same day. Testing equipment was an automatic immune and biochemical analyzer from Roche Company in Switzerland. The corresponding testing kit was also provided by Roche. Immunodiffusion testing was used for determination of CRP. Changes of arterial blood PCT were detected by MICROPOINTe-308 immunodetector and hermo PCT testing kit (immunochromatographic assay).

Statistical process

Results of the observation were statistically analyzed by SPSS23.0 software package. All measurement data in line with normal distribution are expressed by mean ± standard deviation ($\overline{x} \pm sd$). Normal distribution measurement data between two groups were compared using independent sample t-test, expressed by t. Single factor variance analysis was used for comparison of measurement data in line with normal distribution among three groups and above, expressed by F. Count data are expressed by the number of cases and percentage and comparison between groups was conducted using X^2 test. Correlation of various

Table 1. Comparison of general data of patients in each group ($\bar{x} \pm sd$)

Group	Case	Age (year)	Male/female (case)	Body temperature (°C)	WBC (10^9/L)
Control group	30	61.8±10.2	18/12	36.9±2.1	9.3±2.4
Sepsis group	30	56.5±7.4	18/12	37.5±1.1	12.3±5.4
Severe sepsis group	20	61.2±8.3	13/7	37.6±1.2	16.6±8.6
Septic shock group	15	58.9±7.2	10/5	37.7±0.9	17.1±7.1
F/X^2		0.342	0.426	0.141	0.471
P		0.721	0.811	0.874	0.643

Note: WBC, white blood cell count.

Table 2. Evaluation of the efficacy of various inflammatory markers in diagnosis of sepsis

Index	AUC	95% CI	P	Critical value	Sensitivity (%)	Specificity (%)
sCD14-ST	0.878	0.812-0.944		586.60 pg/mL	88.2	76.8
PAF	0.872	0.809-0.943		854.26 ng/L	87.6	75.7
PCT	0.868	0.785-0.941	<0.001#/<0.001*	0.87 ng/mL	79.3	73.6
CRP	0.675	0.576-0.768	0.002#/<0.001*	10.32 mg/mL	76.5	56.3
WBC	0.789	0.697-0.867	<0.001#/<0.001*	8.85*10^9/L	76.5	73.4

Note: sCD14-ST, soluble cluster differentiation antigen 14 subtype; PAF, platelet-activating factor; PCT, procalcitonin; CRP, C reactive protein; WBC, white blood cell count; AUC, area under the curve; CI, confidence interval. Compared with sCD14-ST, #P<0.01; compared with PAF, *P<0.01.

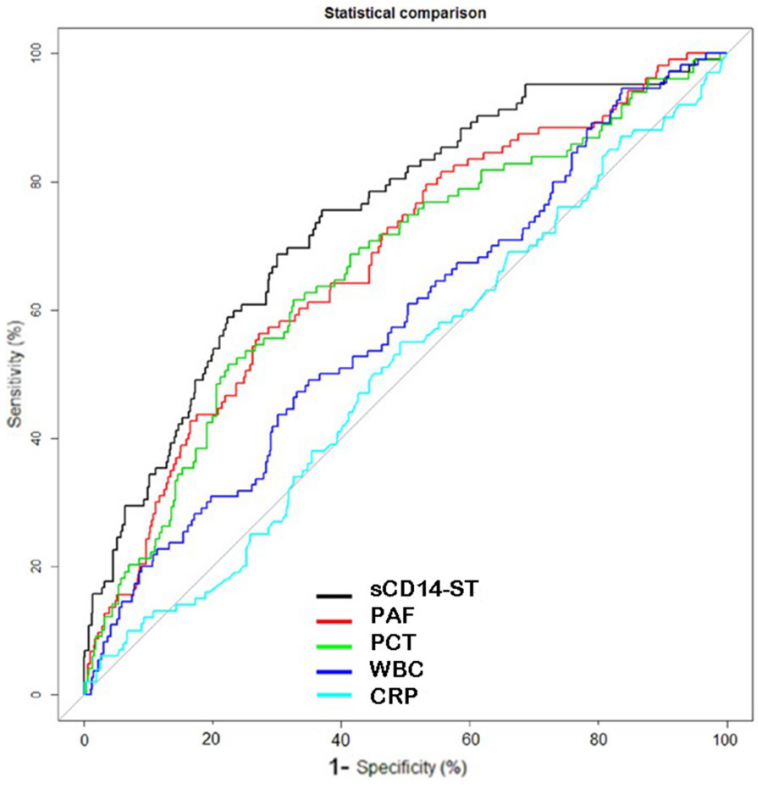

Figure 1. ROC curve of sCD14-ST, PAF, PCT, CRP, and WBC. sCD14-ST, soluble cluster differentiation antigen 14 subtype; PAF, platelet-activating factor; PCT, procalcitonin; CRP, C reactive protein; WBC, white blood cell count.

clinical indices was analyzed by Pearson's correlation analysis. Logistic regression analysis was used to analyze related factors of prognosis in patients with septic shock. Differences were considered statistically significant if P<0.05.

Results

Comparison of general data of patients in each group

There were no significant differences in age, sex, WBS, and body temperature among the control group, sepsis group, severe sepsis group, and septic shock group (all P>0.05), but all were comparable as shown in **Table 1**.

Evaluation of the efficacy of various inflammatory markers in diagnosis of sepsis

Area under receiver operating characteristic curve (AUC) of sCD14-ST was 0.878 with 586.60 pg/mL as the critical value [3]. Its sensitivity to diagnosis of septic shock was 88.2% while specificity was 76.8%. AUC of PAF was 0.872 with 854.26 ng/L as the critical

Table 3. Comparison of APACHE-II scores, sCD14-ST, and PAF levels in each group

Group	Case	APACHE-II score	sCD14-ST (pg/mL)	PAF level (ng/L)
Control group	30	0	526.23±121.57	825.97±56.42
Sepsis group	30	13.72±4.25*,#	723.16±206.83*,#	1,086.57±89.57*,#
Severe sepsis group	20	22.18±6.32*,#	1,422.86±653.27*,#	1,265.37±109.68*,#
Septic shock group	15	26.93±8.05*	2,436.57±1,438.69*	1,378.65±124.21*
P		0.001*/<0.001#	<0.001*/0.001#	0.001*/0.001#

Note: APACHE-II, acute physiology and chronic health status II; sCD14-ST, soluble cluster differentiation antigen 14 subtype; PAF, platelet-activating factor. Compared with control group, *P<0.05; compared with septic shock group, #P<0.05.

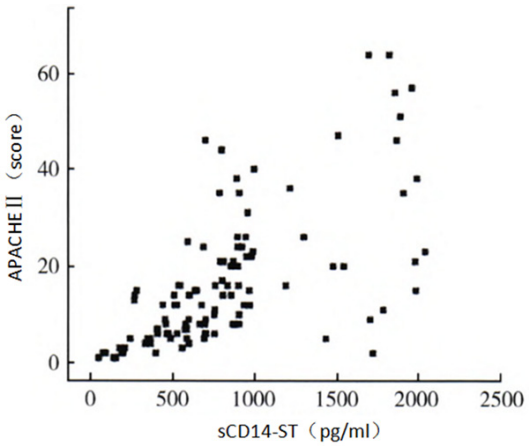

Figure 2. Correlation analysis of APACHE II and sCD14-ST. APACHE-II, acute physiology and chronic health status II; sCD14-ST, soluble cluster differentiation antigen 14 subtype.

value [4]. Its sensitivity to diagnosis of sepsis was 87.6% while specificity was 75.7%. Sensitivity and specificity of sCD14-ST and PAF were higher than those of PCT, CRP, and WBC. The differences were statistically significant (all P<0.01) as shown in **Table 2** and **Figure 1**.

Comparison of APACHE-II scores, sCD14-ST, and PAF levels in each group

Levels of sCD14-ST, PAF, and scores of APACHE-II in patients with sepsis, severe sepsis, and septic shock were significantly higher than those in the healthy control group (all P<0.05). sCD14-ST and PAF in septic shock patients were significantly higher than those in severe sepsis and sepsis group (all P<0.05). Results of Pearson's correlation analysis showed that sCD14-ST (t=12.41, r=0.68, P=0.002) and PAF levels (t=8.58, r=0.67, P=0.003) were significantly positively correlated with APACHE-II scores in septic shock patients as shown in **Table 3** and **Figures 2** and **3**.

Comparison of levels of PCT, CRP, and WBC in each group

PCT, CRP, and WBC in patients with severe sepsis and septic shock were significantly higher than those in the sepsis group (all P<0.05) as shown in **Table 4**.

Influencing factors of prognosis in patients with septic shock

Age, sex, infected area, APACHEII scores, WBC, CRP, PCT, sCD14-ST, and PAF were analyzed by single factor logistic regression analysis. Results showed that age, APACHEII scores, WBC, CRP, PCT, sCD14-ST, and PAF were statistically significant (all P<0.05), as shown in **Table 5**. A multi factor logistic regression model was introduced for gradual screening. Age, APACHEII scores, WBC, CRP, PCT, sCD14-ST, and PAF were analyzed by multi factor logistic regression analysis. These results showed that increase of APACHEII scores, sCD14-ST, and PAF was an independent risk factor for poor prognosis of septic shock as shown in **Table 6**.

Discussion

Sepsis is an infection-induced systemic inflammatory response syndrome. It is one of the leading causes of death in critically ill patients. Studies have reported that the mortality of sepsis is second only to cardiovascular disease. If conditions worsen, it can develop into severe sepsis and septic shock, combining with multiple organ dysfunction syndrome and refractory hypotension at the same time. The mortality rate is then further increased to 15-50% [5]. Early identification of high-risk patients is beneficial in developing timely treatment measures, thereby increasing cure rates for patients with sepsis. Currently, the biological indicators used to evaluate conditions and

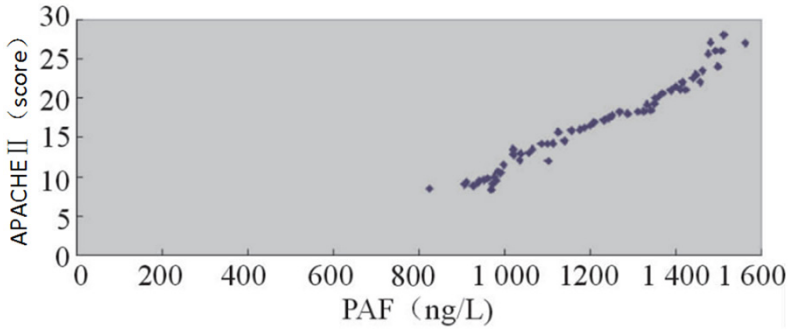

Figure 3. Correlation analysis of APACHE II and PAF. APACHE-II, acute physiology and chronic health status II; PAF, platelet-activating factor.

Table 4. Comparison of PCT, CRP, and WBC levels in each group

Group	Case	PCT (ng/mL)	CRP (mg/L)	WBC (*10^9/L)
Control group	30	0.31±0.11	7.08±1.04	9.07±1.34
Sepsis group	30	0.86±0.36	33.65±4.87	11.26±2.64
Severe sepsis group	20	2.34±0.84*	35.78±5.02*	15.76±2.08*
Septic shock group	15	3.47±1.26#	37.93±6.28#	18.69±3.16#
F		7.943*/6.293#	8.164*/8.036#	8.741*/6.533#
P		0.003*/0.008#	0.004*/0.003#	0.003*/0.003#

Note: PCT, procalcitonin; CRP, C reactive protein; WBC, white blood cell count. Severe sepsis group compared with sepsis group, *P<0.05; septic shock group compared with sepsis group, #P<0.05.

Table 5. Single factor logistic regression analysis of prognostic factors in patients with septic shock

Factor	P	OR	95% CI
Age	0.021	3.99	0.63-2.92
Gender	0.086	0.99	0.15-0.93
Infection Site	0.084	1.01	0.11-1.37
APACHE-II scores	<0.001	4.71	0.45-9.49
WBC	0.021	1.45	0.53-2.16
CRP	<0.001	2.28	1.39-5.26
PCT	<0.001	2.76	0.85-6.73
sCD14-ST	0.043	1.53	1.00-1.69
PAF	<0.001	7.99	3.39-12.33

Note: APACHE-II, acute physiology and chronic health status II; WBC, white blood cell count; CRP, C reactive protein; PCT, procalcitonin; sCD14-ST, soluble cluster differentiation antigen 14 subtype; PAF, platelet-activating factor; OR, odds ratio; CI, confidence interval.

the prognosis of patients are PCT, CRP, and WBS. Of these, PCT has been the most widely studied and used. The diagnostic value of PCT for infection and sepsis is significantly better than traditional inflammatory markers including CRP, WBS, and interleukin-6. Also, there is correlation between PCT and APACHE-II scores [5]. However, other studies have reported that the diagnostic efficiency of PCT is low, with specificity and sensitivity for diagnosis of sepsis at 71%. PCT cannot be used singularly as a differential diagnosis of sepsis in critically ill patients. Other indicators must be taken into consideration, as well [6]. Other studies have shown that severe trauma and postoperative patients have a significant increase in PCT concentrations [7]. Prognosis of sepsis and differential diagnosis, based solely on indicators such as PCT, will often result in missed diagnosis or misdiagnosis. Clinical diagnosis of sepsis often takes blood cultures as the gold standard. Results of blood culturing are usually ready within 48-72 hours. This takes a long time with low positive rates, thus, clinicians often give empirical treatment to sepsis patients. Early diagnosis and treatment is very important in improving prognosis of patients with sepsis. Discovery of effective biological indicators to monitor sepsis patients is also very important.

Soluble cluster differentiation antigens are associated with the disappearing or emerging cell surface molecules of hematopoietic stem cells during differentiation and maturation into different lineages and different stages of differentiation, as well as during the activation process [8]. CD14 is a receptor for lipopolysaccharides and lipopolysaccharide binding proteins, found in the form of soluble CD14 and membrane CD14 in the body [8]. In recent years, studies have shown that sCD14-ST has certain advantages in the diagnosis and prognosis evaluation of sepsis, as a new type of biomarker [9]. Research has shown that levels of sCD14-ST significantly increase in the peripheral blood of patients with sepsis, beginning within 6 hours after onset of sepsis [8, 9]. This increase is earlier and faster compared to pre-

Table 6. Multi factor logistic regression analysis of prognostic factors in patients with septic shock

Factor	P	β	OR	95% CI
Age	0.082	0.04	1.04	0.62-2.91
Gender	0.095	-0.01	0.99	0.53-1.39
Infection Site	0.091	-0.00	0.99	0.63-1.27
APACHE-II scores	<0.001	1.04	2.82	2.13-3.56
WBC	0.443	0.33	1.39	0.93-1.78
CRP	0.264	-0.28	0.75	0.46-1.08
sCD14-ST	<0.001	0.79	2.20	1.79-2.80
PAF	<0.001	0.87	2.38	1.97-2.91

Note: APACHE-II, acute physiology and chronic health status II; WBC, white blood cell count; CRP, C reactive protein; sCD14-ST, soluble cluster differentiation antigen 14 subtype; PAF, platelet activating factor; OR, odds ratio; CI, confidence interval.

vious serum biological markers like CRP and PCT [10]. This study demonstrated that sCD14-ST of patients in sepsis, severe sepsis, and septic shock groups was significantly higher than in the healthy control group, with statistical differences. Increased sCD14-ST might be related to lysis of lysosomal enzymes in phagocytic bacteria during the process of infection with bacteria and other microorganisms. This is basically consistent with previous research reports [11, 12]. The optimal critical value of sCD14-ST was 586.60 pg/mL, with specificity of 76.8% and sensitivity of 88.2%. These results were basically in line with results of foreign research [13]. Correlation analysis showed a significantly positive correlation between sCD14-ST and APACHE-II scores. Analysis indicated that sCD14-ST was closely linked with progression of sepsis. Multi-factor logistic regression analysis showed that increased APACHEII scores, sCD14-ST, and PAF were independent risk factors for poor prognosis of sepsis and could be used as indicators for prognosis.

PAF is a powerful bioactive phospholipid produced by a wide variety of cells and tissues from WBC, platelets, endothelial cells, lungs, liver, and kidneys [14, 15]. PAF can also promote secretion of inflammatory factors such as tumor necrosis factor-1 and interleukin [16]. Research has shown that accumulation of PAF in the body will further aggravate inflammatory response, resulting in organ damage [17]. Other studies have shown a correlation between PAF and severity of infectious diseases in ICU patients [18]. Results of this study showed that PAF levels in patients with septic shock were higher than those in other groups, possibly due to PAF's involvement in septic shock caused by gram-positive bacteria and endotoxins, as well as ischemia-reperfusion injury during septic shock, stimulating synthesis of PAF [19]. It has been reported that there is a correlation between plasma PAF and severity of infectious diseases in ICU. Plasma PAF levels in sepsis patients have been correlated with serum calcitonin levels and SOFA scores, but correlation with APACHE-II scores was deemed insignificant. APACHE-II scores can be used as predictors of mortality in patients with sepsis [20]. Results of ROC curve showed that PAF was of great value in differential diagnosis of sepsis patients, having a significantly positive correlation with APACHE-II scores. Therefore, PAF might become one of the indicators guiding future evaluation of patients.

In conclusion, sCD14-ST and PAF can be used as diagnostic indicators of sepsis. They can also monitor the prognosis of sepsis. Combined detection of both can help improve the accuracy of diagnosis and prognosis assessment of sepsis. However, the sample size of this research was relatively small. Also, it was a single-center study with a limited source of cases. Therefore, including larger sample sizes and multi center cooperation are necessary for future research.

Disclosure of conflict of interest

None.

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