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Original Article

Clinical significance of serum procalcitonin and C-reactive protein in patients with septic shock

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Abstract: Objective: This study aimed to explore and analyze the clinical significance of procalcitonin (PCT) and C-reactive protein (CRP) in patients with septic shock. Method: A total of 72 patients with septic shock were enrolled and divided into death group (n = 21) and survival group (n = 51) according to treatment outcomes. Another 20 sepsis patients without septic shock were selected as control group. Examination of PCT, CRP, acute physiology and chronic health status scoring system II (APACHE II) as well as the Sequential Organ Failure Assessment (SOFA) scores were performed within 24 h of admission. PCT, CRP, SOFA, and APACHE II scores were evaluated among the three groups. Patients with septic shock were categorized as different groups according to the APACHE II and SOFA scores. The correlation between CRP, APACHE II, and SOFA scores was analyzed. The prognostic value of PCT and CRP levels in patients with septic shock was explored. Results: The death group showed the highest PCT, CRP, SOFA and APACHE II scores, followed by the survival and control groups, respectively ($P < 0.05$). PCT and CRP levels were the highest in patients with APACHE II score > 20, followed by those with score of 11-20 points and those with score 0-10 points, respectively ($P < 0.05$). Patients with SOFA score > 10 points had the highest PCT and CRP levels, followed by those with 6-10 points and those with 0-5 points, respectively ($P < 0.05$). PCT was positively correlated with APACHE II and SOFA scores ($P < 0.05$), while CRP was not correlated with APACHE II and SOFA scores ($P > 0.05$). The sensitivity and specificity of PCT in determining the prognosis of patients with septic shock were 66.8% and 45.4%, while those of CRP were 82.2% and 80.3%. Conclusion: The expression of CRP and PCT may be indicative of the prognosis of patients.

Keywords: PCT, CRP, septic shock, SOFA, APACHE II

Introduction

Sepsis is the systemic response to infection. According to the statistics, there are about 18 million new cases of sepsis worldwide each year, and its incidence is currently increasing at an annual rate of 8.0% [1]. Sepsis is characterized by acute onset and critical condition, and the mortality rate of severe sepsis is reported to be as high as 20-30%, accounting for 30-50% of the total number of hospital deaths, far exceeding the numbers of patients with myocardial death [2, 3].

Septic shock refers specifically to distributive shock due to sepsis as a result of infection, which is characterized by insufficient tissue perfusion, that is, persistent hypotension despite an adequate fluid or blood lactate concentration ≥ 4mmol/L [4]. The reason is that after pathogens invade the body, endotoxins, exotoxins and other substances produced by the pathogens act on the human body, resulting in disorders in metabolic system, microcirculation system, coagulation system, and immune system thus causing multiple organ dysfunctions and inducing shock [5, 6]. Sepsis shock is still a worldwide challenge. About 750,000 patients die from septic shock each year in the United States, and the direct medical cost is as high as 16.7 billion US dollars [7]. Early diagnosis and intervention are important prerequisites for reversing the clinical outcome and improving the prognosis of patients with septic shock. At present, the diagnostic measures for septic shock mainly rely on laboratory indicators. Both procalcitonin (PCT) and C-reactive protein (CRP) are commonly used in clinical evaluation of

inflammation, which are usually used in the assessment of inflammation level and prognostic evaluation of the body. In a survey of sepsis patients, the results showed that the levels of PCT and CRP in patients with sepsis significantly increased with the aggravation of condition of sepsis patients, and the comparison of prognostic results indicated that patients with good prognosis had lower levels of PCT and CRP. There are also a number of domestic studies on the above factors, and the results showed that PCT and CRP have a good predictive value of the disease. Current studies have found that these cytokines were highly expressed in severe shock, Systemic Inflammatory Response Syndrome (SIRS) and other diseases [1, 8]. This study aimed to analyze the expression and clinical significance of PCT and CRP in patients with septic shock, so as to provide more accurate and sensitive clinical indicators.

Materials and methods

Baseline data

A total of 72 patients with septic shock admitted to our hospital were selected as the study participants. PCT, CRP, acute physiology and chronic health status scoring system II (APACHE II) and sequential organ failure score (SOFA) scores were evaluated within 24 h of admission. According to the treatment outcomes, patients were divided into death group (DG) (n = 21) and survival group (SG) (n = 51), and another 20 sepsis patients without shock who received treatment in our hospital during the same period were enrolled as the control group.

Inclusion criteria: patients (1) who met the diagnostic criteria for septic shock in the guidelines for emergency treatment of septic shock in 2018 formulated by the Chinese Research Hospital Association [9]; (2) with complete medical records; (3) who aged ≥ 18 years; (4) with expected length of stay in ICU > 72 h. This study has been approved by the hospital ethics committee. The family members of patients had signed informed consent.

Exclusion criteria: patients (1) with psychiatric disorders; (2) with irreversible illness when admitted to the ICU; (3) following cardiopulmonary resuscitation; (4) with pregnancy or with immune system diseases; (5) with hematological diseases; (6) who needed long-term glucocorticoid therapy; (7) who took immunosuppressants for a long time; (8) who refused to sign the informed consent.

Intervention method

Routine treatment of septic shock was prescribed for all enrolled subjects. At the same time, 10 ml of venous blood samples were taken within 24 h of admission and centrifuged with the low-speed centrifuge at 3000 r/min to extract the serum for use. The serum was stored at -80°C and sent for detection after collection. The detection instrument was the UciCel Dxl 800 automatic chemical immunoassay analyzer (Beckman Coulter). The scattering immunoturbidimetry assay was used to detect CRP level, and the double-antibody sandwich chemiluminescence immune assay was used to detect PCT level. Each indicator was tested 3 times, and the average was taken as the final result. The scoring of APACHE II and SOFA scales was performed simultaneously for the included subjects.

Observation indicators

PCT and CRP levels: PCT and CRP levels were detected in the three groups, and the differences were analyzed.

APACHE II and SOFA scores: APACHE II and SOFA scales were performed in the three groups. APACHE II scale was used to assess disease severity. The scale is based on acute physiology score (which uses 12 physiologic values), age, and chronic health status, ranging 0-71 points. The higher score represents the more critical subject's condition. SOFA is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems. The higher score indicates the more severe subject's condition [10, 11].

PCT and CRP levels in patients with different levels of APACHE II score: According to the APACHE II score, the patients with septic shock were divided into 0-10 points (n = 22), 11-20 points (n = 35) and > 20 points (n = 15) groups, and the differences in CRP and PCT levels were compared among the three groups.

PCT and CRP levels in patients with different levels of SOFA score: According to the SOFA

Table 1. Comparison of baseline data ($\bar{x}$ ± sd)/[n (%)]

General information		Death group (n = 21)	Survival group (n = 51)	Control group (n = 20)	$F/t/X^2$	P
Gender	Male	11	25	10	1.021	0.324
	Female	10	26	10		
Average age (years)		51.28±3.33	51.31±3.29	52.61±3.11	1.261	0.288
Average weight (kg)		60.49±2.98	59.98±2.98	60.11±3.01	0.14	0.87
Average BMI (kg/m^2)		20.39±2.32	20.41±2.11	20.81±2.31	0.266	0.767
Infection site	Respiratory system	8	12	7	1.454	0.244
	Urinary system	5	12	4		
	Digestive system	4	14	5		
	Other	4	13	4		
Education level	Illiteracy	2	5	1	1.543	0.251
	Primary school	4	10	4		
	Junior high school	6	15	5		
	High school and above	9	21	10		
Marital status	Married	17	43	16	1.655	0.232
	Not married	4	8	4		
Hypertension	Yes	6	8	5	0.471	0.718
	No	15	43	15		
Diabetes	Yes	5	5	3	0.513	0.811
	No	16	46	17		

score, patients with septic shock were divided into 0-5 points (n = 20), 6-10 points (n = 30) and > 10 points (n = 22) groups, and the differences of CRP and PCT levels were compared among the three groups.

Correlation analysis of PCT, CRP, APACHE II and SOFA scores: The relationship between PCT, CRP and APACHE II and SOFA scores was explored by analyzing the values of different indicators.

Evaluation of PCT and CRP with prognosis of patients with septic shock: According to the clinical outcomes of patients with septic shock, the diagnostic performance of PCT and CRP levels on the prognosis of patients with septic shock was analyzed.

Statistical analysis

SPSS20.0 was used for statistical analysis. Measurement data ($\bar{x}$ ± sd) were tested by Student's t test. Count data [n (%)] were examined by chi-square test, and the difference between multiple groups was compared with F test. Correlation analysis was performed using Spearman correlation analysis. $P < 0.05$ means the difference is statistically significant [12].

Results

Comparison of baseline data

There was no significant difference in the baseline data such as gender, age, average weight, education level, and history of diseases among the three groups ($P > 0.05$), which was comparable (**Table 1**).

PCT and CRP levels

The DG showed increased PCT and CRP levels compared with the SG, while the SG exhibited increased PCT and CRP levels compared with the control group ($P < 0.05$, **Figure 1**).

APACHE II and SOFA scores

The DG showed increased APACHE II and SOFA scores compared with the SG ($P < 0.05$), whereas, the SG showed increased APACHE II and SOFA scores compared with the control group ($P < 0.05$, **Figure 2**).

PCT and CRP levels in patients with different levels of APACHE II score

PCT and CRP levels of APACHE II score > 20 group were higher than those of 11-20 points

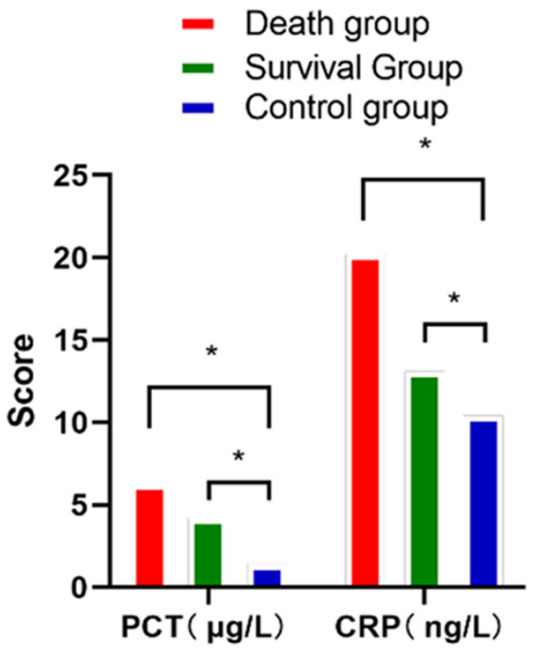

Figure 1. Comparison of the differences in PCT and CRP levels in the three groups. * indicates that the difference between groups is statistically significant.

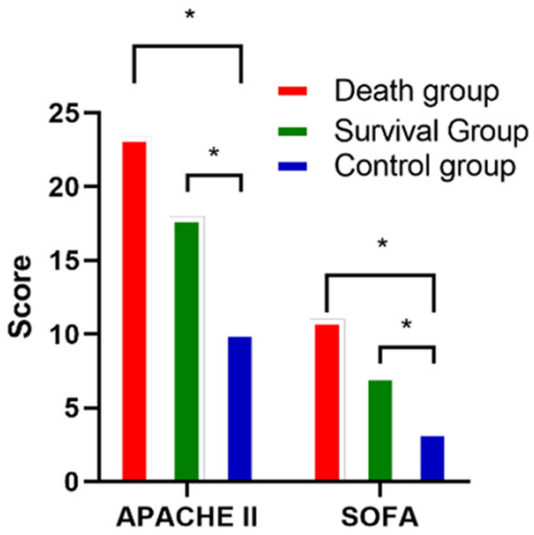

Figure 2. Comparison of the differences in APACHE II and SOFA scores in the three groups. * indicates that the difference between groups is statistically significant.

group ($P < 0.05$), and those of 11-20 points group were higher than those of 0-10 points group ($P < 0.05$) (**Figure 3**).

PCT and CRP levels in patients with different levels of SOFA score

PCT and CRP levels of septic shock patients with SOFA score > 10 were significantly higher than those with SOFA scores of 6-10 points and 0-5 points ($P < 0.05$). The 6-10 points group showed increased PCT and CRP levels compared with those with SOFA score of 0-5 points group ($P < 0.05$, **Figure 4**).

Correlation analysis of PCT, CRP, APACHE II and SOFA scores

PCT level of patients with septic shock showed a positive correlation with the APACHE II and SOFA scores ($r = 0.341$, $r = 0.334$, $P < 0.05$); while CRP levels showed negative correlation with the APACHE II and SOFA scores ($r = -0.111$, $r = -0.102$, $P < 0.05$) (**Table 2**).

Evaluation value of PCT and CRP on prognosis of patients with septic shock

It was observed that the AUC of PCT was 0.817, the sensitivity was 66.8%, and the specificity was 45.4%; the AUC of CRP was 0.522, the sensitivity was 82.2%, and the specificity was 80.3% (**Table 3**).

Discussion

Sepsis is a life-threatening disease complicated with multiple organ dysfunctions [13], which occurs when the pathogen stimulates the body's innate immune regulatory system, leading to systemic inflammatory reactions. This process is often accompanied by the excessive reactions to pathogens, breaking the balance of pro-inflammatory and anti-inflammatory factors, inducing a large amount of apoptosis of T lymphocytes, and finally making the body's immune response dysregulated [14]. Data show that the annual incidence of adult sepsis around the world is about 300 cases per 100,000, and the mortality rate is about 19.3-47.2%. Clinical practice has found that patients with sepsis often face unaffordable medical costs, and the average person needs to spend 11,000 RMB per day, which brings a heavy burden to patients' families and society [15, 16]. Early diagnosis and intervention are vital measures to reduce patient mortality and improve patient prognosis [17].

Laboratory indicators are a common method for assessing the severity of clinical symptoms in patients with sepsis. A number of studies have pointed out that laboratory indicators are widely used to assess patients' conditions, predict patients' prognosis, and quantify treat-

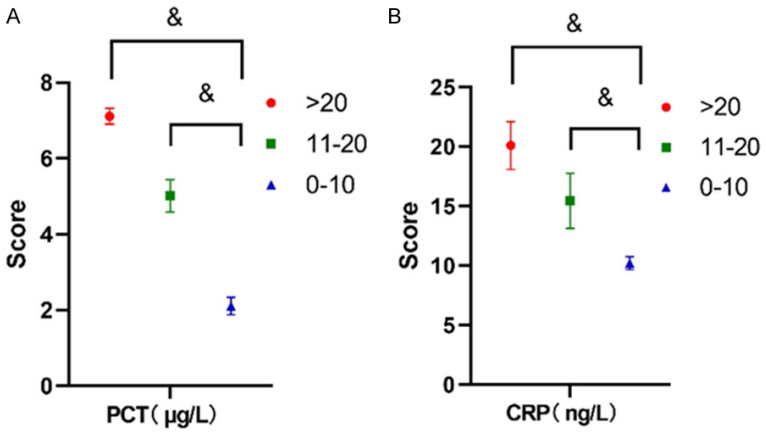

Figure 3. Comparison of differences in PCT and CRP levels in patients with different levels of APACHE II scores. & indicates that the difference between groups is statistically significant.

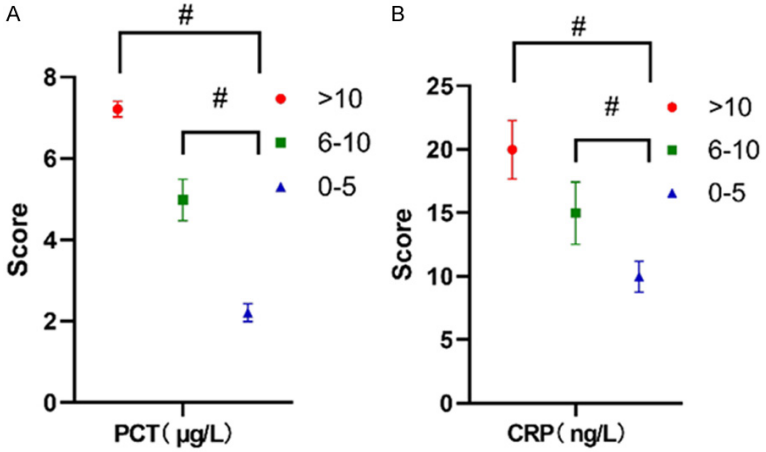

Figure 4. Analysis of differences in PCT and CRP levels of patients with different levels of SOFA scores. # indicates that the difference between groups is statistically significant.

Table 2. Correlation analysis of PCT, CRP, APACHE II and SOFA scores

Observation indicators	APACHE II score		SOFA score	
	r	*P*	*r*	*P*
PCT	0.341	< 0.01	0.334	< 0.05
CRP	-0.111	0.534	-0.102	0.231

Table 3. PCT and CRP in the prognostic evaluation of patients with septic shock

Index	Cutoff value	AUC	95% CI	Sensitivity (%)	Specificity (%)
PCT	3.37	0.817	0.801-0.934	66.8%	45.4%
CRP	14.17	0.522	0.411-0.622	82.2%	80.3%

ment effectiveness. PCT is a precursor of calcitonin [18]. Normally, the level of calcitonin in an individual's blood sample is extremely low or negative, but when an individual is infected with bacteria or viruses, the immune response is activated, releasing a series of inflammatory mediators. PCT is an inflammatory mediator with high sensitivity and specificity for sepsis. Generally, abnormally elevated PCT levels can be detected in the blood circulation within 3 to 4 h of endotoxin stimulation [19]. CRP is an acute phase reaction protein produced by the body during inflammation, infection or injury. It has been widely used in the early diagnosis, differential diagnosis and monitoring of the recovery period of multiple infectious diseases, the determination of anti-infective efficacy and the assessment of patient prognosis, and the test is fast and convenient [20].

This study analyzed the expression and clinical significance of PCT and CRP in septic shock patients by setting up different groups. The results showed that PCT and CRP levels in the DG were significantly higher than those in the SG, and the levels of the SG were also significantly higher than those of the control group, suggesting that the levels of PCT and CRP also increased significantly with the worsening of sepsis. A retrospective analysis of 201 sepsis patients suggested that the average PCT level and CRP level of sepsis patients with clinically dead outcomes were 11.03 μg/L and 110.94 mg/L, while the PCT level and CPR level of the SG was 1.39 μg/L and 56.93 mg/L, respectively [21]. In this study, it is believed that PCT and CRP are commonly used clinical laboratory indicators that can reflect the body's inflammatory res-

ponse, of which an abnormally elevated level often indicates a significant state of inflammation in the body of subjects. When the body has an inflammatory response, under the action of inflammatory factors and bacterial toxins, PCT will be produced by the lungs, kidneys and other parts and enters the blood circulation. It will be detected in the blood samples within 2-4 h of the occurrence of infection, and reach its peak within 6-24 h [22, 23]. CRP is a phase protein with acute sensitivity and high sensitivity. It is also sensitive to the inflammatory response of the body. Therefore, PCT and CRP levels will vary in blood samples of septic shock patients with different clinical outcomes [24]. In this study, the differences in the APACHE II and SOFA scale scores of patients with septic shock were also analyzed. The difference in the scores of the three groups of patients in the study also confirms the authenticity of the differences in the PCT and CRP levels of the three groups of patients.

This study also compared the differences in PCT and CRP levels in septic patients with different APACHE II and SOFA scores. The results showed that higher APACHE II and SOFA scores indicated higher PCT and CRP levels. In the retrospective analysis of 90 patients with sepsis, APACHE II and SOFA scale scores were administered to the enrolled subjects before intervention, and PCT and CRP levels were measured at the same time; the patients were divided into death and survival groups according to the outcomes, and the intergroup comparisons showed that the death group had higher APACHE II and SOFA scores, as well as higher PCT and CRP levels than the survival group [25]. APACHE II and SOFA scales are clinical scoring systems for the evaluation of the prognosis of critically ill patients in the ICU. There are few studies on the correlation between these scales and PCT and CRP levels. The results of this study showed that the APACHE II and SOFA scales are significantly positively correlated with PCT levels, but not significantly correlated with CRP levels. The reason may be that PCT is a relatively stable infection marker and is not affected by factors such as neutropenia, immunodeficiency, and glucocorticoids. As the disease progresses, its level rises steadily. Although CRP is very sensitive to inflammation, there will be a sharp increase in CRP levels in early infection. Even systemic inflammatory response syndrome caused by non-infection factors will also lead to an increase in CRP levels. Therefore, CRP is more easily interfered, and there is a great difference between CRP and PCT in relation to the disease [26]. The above indicators can be considered as a reference for the clinical intervention of patients with septic shock, and can be used as a routine monitoring indicator for critically ill patients.

In summary, the expression of CRP and PCT has a significant correlation with the severity and prognosis of patients, which can be used as important indicators to reflect the prognosis of patients. The innovation of this study lies in the association of CRP and PCT with the APACHE II and SOFA scores, confirming the feasibility of CRP and PCT as indicators for prognosis of patients with septic shock. The shortcoming is that the sample size is small, resulting in a lack of comprehensiveness of the results. Besides, there was no long-term follow-up. In the future, we will carry out clinical studies with a larger sample size, longer follow-up time, and more indicators, so as to provide a better reference for improving the clinical outcome of patients with septic shock.

Disclosure of conflict of interest

None.

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