Int J Clin Exp Med 2020;13(11):8721-8727
www.ijcem.com /ISSN:1940-5901/IJCEM0117646

Original Article

Clinical usefulness of procalcitonin and C-reactive protein as outcome predictors of septic shock

Jinshuai Lu[1], Xia Yu[2], Nan Li[3], Xia Wang[3], Ping Wang[3], Likun Xu[3]

Departments of [1]Emergency, [2]General Practice, People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, Xinjiang Uygur Autonomous Region, China; [3]Xinjiang Emergency Center, People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, Xinjiang Uygur Autonomous Region, China

Received July 6, 2020; Accepted August 9, 2020; Epub November 15, 2020; Published November 30, 2020

Abstract: Objective: We aimed to investigate the prognostic role of serum procalcitonin (PCT) and C-reactive protein (CRP) in septic shock. Methods: The clinical records of 160 patients with sepsis were retrospectively analyzed. The patients were divided into the septic shock group and the severe sepsis group (both n=80), and another 80 patients without septic shock during the same period were assigned to the control group. Results: Compared with the control group, the levels of PCT and CRP in the severe sepsis and the septic shock groups were higher at all time points. The levels of PCT and CRP in the septic shock group were higher than those in the severe sepsis group on the 3rd and 7th day after treatment (all P<0.001). In the septic shock group, the non-survived patients had a higher PCT level on the 3rd and 7th day after treatment, a higher CRP level on the 1st and 7th day after treatment, and a higher score of Acute Physiology and Chronic Health Evaluation (APACHE) II (all P<0.001). On the 7th day after treatment, the area under the curve of CRP and PCT were 0.888 (95% CI: 0.799-0.978) and 0.927 (95% CI: 0.856-0.998), respectively, and the area under the curve of Acute Physiology and Chronic Health Evaluation II score was 0.998 (95% CI: 0.992-1.000) on the 1st day after treatment. Conclusion: Both PCT and CRP have diagnostic value for septic shock and can serve essential roles in evaluating patients' prognosis and severity of the disease.

Keywords: Septic shock, procalcitonin, C-reactive protein, diagnosis, predictor

Introduction

Septic shock is a severe acute sepsis syndrome caused by microorganisms and their toxins. The disease is often accompanied with multiple organ damage and failure and has a high mortality rate, which is difficult to be treated [1, 2]. Procalcitonin (PCT), a calcitonin precursor polypeptide produced in thyroid C cells, is released in response to pro-inflammatory mediators and microbial toxins. Due to the non-specific upregulation of PCT expression in inflammatory reaction, PCT has been used as a marker of various inflammations such as severe burns, acute pancreatitis, sepsis, and postoperative infection [3-5]. C-reactive protein (CRP) is a polypeptide molecule produced by hepatocytes in response to certain pro-inflammatory cytokines. It has been identified as an important indicator of infection which can reflect the severity of the condition and prognosis of patients [6, 7]. CRP is mainly used in the clinical evaluation of disease activity and the monitoring of the efficacy to assess patients' prognosis in diseases including acute pancreatitis, pulmonary infection, malignant tumor, and gouty arthritis [8]. Acute Physiology and Chronic Health Evaluation (APACHE) II is a tool for the classification of disease severity and prognosis evaluation. It can quantitatively assess a patient's condition [9-11]. A high APACHE II score indicates a severe condition, a poor prognosis, and a high mortality rate.

It has been reported that PCT, CRP, and APACHE II score have prognostic value in patients with sepsis; however, there have been few studies on these markers in evaluating the prognosis of patients with septic shock. Therefore, in the present study, we analyzed the levels of PCT, CRP, and APACHE II score in

patients with septic shock to explore their associations with septic shock and to provide a basis for the clinical diagnosis and treatment of this disease.

Materials and methods

Study design and enrollment

A total of 160 patients with sepsis who were admitted to People's Hospital of Xinjiang Uygur Autonomous Region were retrospectively analyzed. According to the degree of infection, the patients were divided into the severe sepsis group (n=80, 38 males and 42 females, age: 44.77±4.21) and the septic shock group (n=80, 41 males and 38 females, age: 45.11±3.14). Meanwhile, 80 patients with systemic inflammatory response syndrome who were hospitalized during the same period were assigned to the control group (n=80, 45 males and 35 females, age: 45.21±3.63). The patients in the septic shock group were further divided into the non-survival group and the survival group according to the survival status in a one-month follow-up. The study was approved by the Ethics Committee of People's Hospital of Xinjiang Uygur Autonomous Region and the patients and their families signed informed consent.

The patients were given rehydration at a volume of 30 mL/kg/h, and the dosage was adjusted according to the patients' blood pressure, heart rate, and urine volume. If the patients' blood pressure was still low after sufficient liquid supplement, intravenous infusion of noradrenaline was administered to increase the blood pressure. Moreover, the patients were treated with ulinastatin in a timely manner for anti-inflammation, and in some severe cases, blood purification was applied to remove the inflammatory mediators.

Inclusion and exclusion criteria

Inclusion criteria were as follows: 1) Patients diagnosed with severe sepsis or septic shock according to the *International Guidelines for the management of Severe Sepsis and Septic Shock, 2012* [9]; 2) Patients over 18 years old; 3) Patients who had complete medical records; 4) Patients who participated in this study voluntarily.

Exclusion criteria: 1) Patients with complications such as acute respiratory distress syndrome, acute lung injury, stress ulcer, deep vein thrombosis, metabolic acidosis, and diffuse intravascular coagulation; 2) Patients who took drugs that may affect serum factors' levels; 3) Patients who were pregnant or lactating; 4) Patients who had malignant tumors or immune disorders; 5) Patients with severe mental illness; 6) Patients who had poor compliance.

Measurement of indicator

In the severe sepsis and the septic shock groups, routine supportive treatment was performed according to the treatment guidelines for sepsis, whereas the control group received anti-infective treatment and nutritional support. When the patient was admitted to the hospital, 5 mL of venous blood was taken within 24 hours and centrifuged at 3,000× g for 15 min. After discarding the supernatant, dry immunofluorescence quantitative analysis was performed to measure the serum PCT level using the test kits (Diagnostica, Berlin, Germany). The serum CRP level was detected by immunoturbidimetry with an automatic biochemical analyzer (Beckman Coulter, USA). The levels of PCT and CRP were measured on the 1st, 3rd, and 7th day after treatment using the same protocols. APACHE II scoring system consisted of three parts, which were acute physiology score, age score, and chronic health. The patients with septic shock were scored by medical staff according to the criteria of APACHE II.

Statistical analysis

SPSS software (version 22.0, SPSS Inc., Chicago, IL, USA) was applied for statistical analysis. Data are expressed as mean ± standard deviation ($\bar{x}$ ± sd). Student's t-test or one-way analysis of variance was used to compare the distributions of continuous variables. Bonferroni test was utilized to compare the differences among multiple groups. Categorical data are expressed as number (percentage) and compared by Pearson's chi-square test or Fisher's exact test if applicable. The receiver operating characteristic (ROC) curve was plotted and the area under the curve (AUC) was compared using the Z test. All statistical analyses were two-sided, and the significance level was set at 0.05.

Table 1. Baseline characteristics of the patients

Factor	Control group (n=80)	Severe sepsis group (n=80)	Septic shock group (n=80)	χ^2	P
Sex (male/female)	45/35	38/42	41/39	1.235	0.539
Age (year)	45.21±3.63	44.77±4.21	45.11±3.14	0.306	0.737
Temperature (°C)	38.26±0.35	38.32±0.29	38.31±0.27	0.747	0.475
Underlying disease (n, %)					
Hypertension	15 (18.75)	13 (16.25)	16 (20.00)	0.390	0.823
Diabetes	10 (12.50)	9 (11.25)	8 (10.00)	0.250	0.882
Coronary heart disease	4 (5.00)	3 (3.75)	2 (2.50)	0.693	0.707
Source of infection (n, %)					
Respiratory system infection	32 (40.00)	29 (36.25)	34 (42.50)	0.662	0.718
Urinary system infection	23 (28.75)	25 (31.25)	21 (26.25)	0.488	0.783
Central nervous system infection	5 (6.25)	2 (2.50)	3 (3.75)	1.461	0.482
Digestive tract infection	8 (10.00)	6 (7.50)	9 (11.25)	0.673	0.714
Others	12 (15.00)	17 (21.25)	13 (16.25)	1.212	0.545

Table 2. Serum CRP and PCT levels in patients before treatment

	CRP (mg/L)	PCT (ng/mL)
Control group (n=80)	23.24±6.14	0.30±0.04
Severe sepsis group (n=80)	98.07±19.27$^{###}$	1.79±0.10$^{###}$
Septic shock group (n=80)	101.21±28.91$^{###}$	13.08±2.95$^{###,***}$
F	375.667	1344.918
P	<0.001	<0.001

Note: $^{###}$P<0.001 vs. the control group; ***P<0.001 vs. the severe sepsis group. CRP: C-reactive protein; PCT: procalcitonin.

Results

Patients' characteristics

There were no intergroup differences in gender, age, body temperature, underlying diseases, and source of infection (all P>0.05), indicating that the results were comparable. See **Table 1**.

PCT and CRP levels before treatment

Before treatment, the CRP and PCT levels in the severe sepsis group and the septic shock group were higher than those in the control group; moreover, the septic shock group had a higher serum PCT level than the severe sepsis group (all P<0.001). See **Table 2**.

PCT and CRP levels at different time points after treatment

The PCT and CRP levels in the septic shock group and the severe sepsis group were higher than those in the control group on the 1st, 3rd, and 7th day after treatment (all P<0.001). The PCT and CRP levels in the septic shock group were higher than those in the severe sepsis group on the 3rd and 7th day after treatment (both P<0.05). See **Figure 1**.

PCT and CRP levels and APACHE II score in the septic shock group

Based on the survival outcome, the patients in the septic shock group were further divided into the survival group (n=60) and a non-survival group (n=20). The PCT level in the non-survivor group was higher than that in the survival group on the 3rd and 7th day after treatment, and the CRP level in the non-survival group was higher than that in the survival group on the 1st and 7th day after treatment (all P<0.001). The survival group had a lower APACHE II score than the non-survival group on the 1st, 3rd, and 7th day (all P<0.001). See **Figure 2**.

ROC curve

The ROC curves of CRP, PCT and APACHE II for diagnosis of sepsis shock at different time points after treatment are shown in **Figure 3**. The AUC values of CRP and PCT on the 7th day after treatment were 0.888 (95% CI: 0.799-0.978) and 0.927 (95% CI: 0.856-0.998), respectively, which were the highest. The AUC of APACHE II was 0.998 (95% CI: 0.992-1.000) on the 1st day after treatment. See **Table 3**.

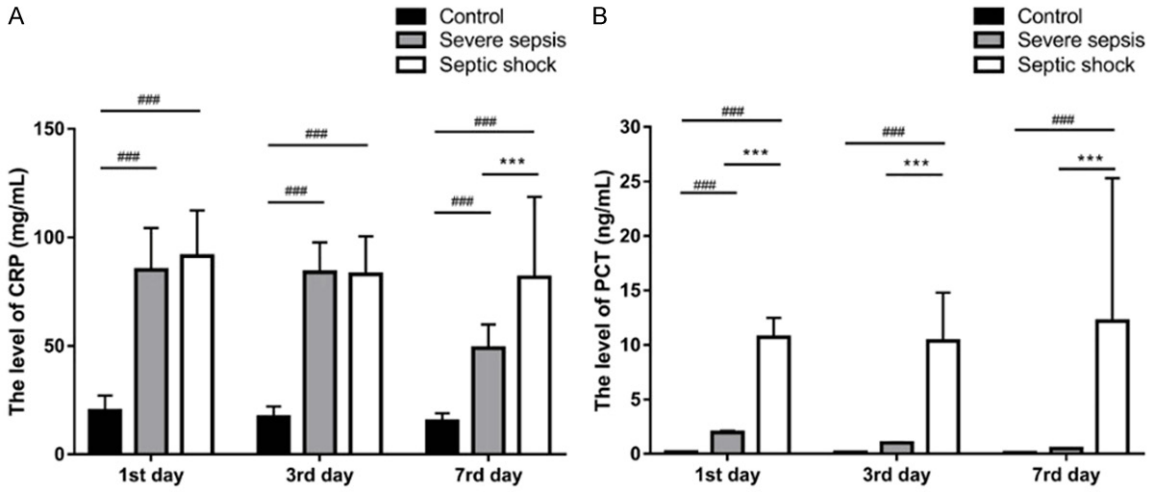

Figure 1. CRP and PCT levels at different time points after treatment. A: CRP level; B: PCT level. ###P<0.001 vs. the control group, ***P<0.001 vs. the severe sepsis group. CRP: C-reactive protein; PCT: procalcitonin.

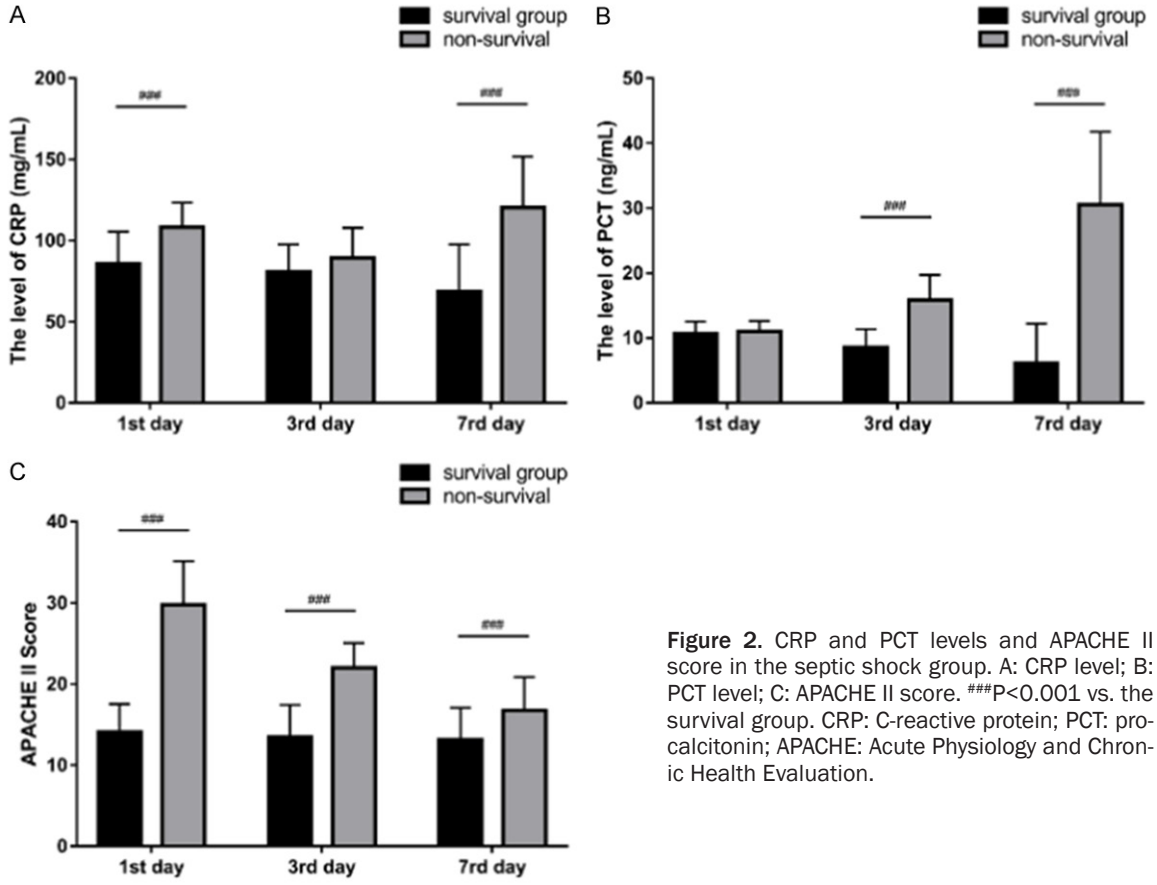

Figure 2. CRP and PCT levels and APACHE II score in the septic shock group. A: CRP level; B: PCT level; C: APACHE II score. ###P<0.001 vs. the survival group. CRP: C-reactive protein; PCT: procalcitonin; APACHE: Acute Physiology and Chronic Health Evaluation.

Discussion

Septic shock is a common critical illness with complicated pathogenesis, which can induce multiple organ dysfunction syndrome. The progression of septic shock is rapid and the short-term mortality rate is high [12-14]. Thus, early diagnosis and effective treatment are crucial to reducing mortality and improving prognosis [15, 16].

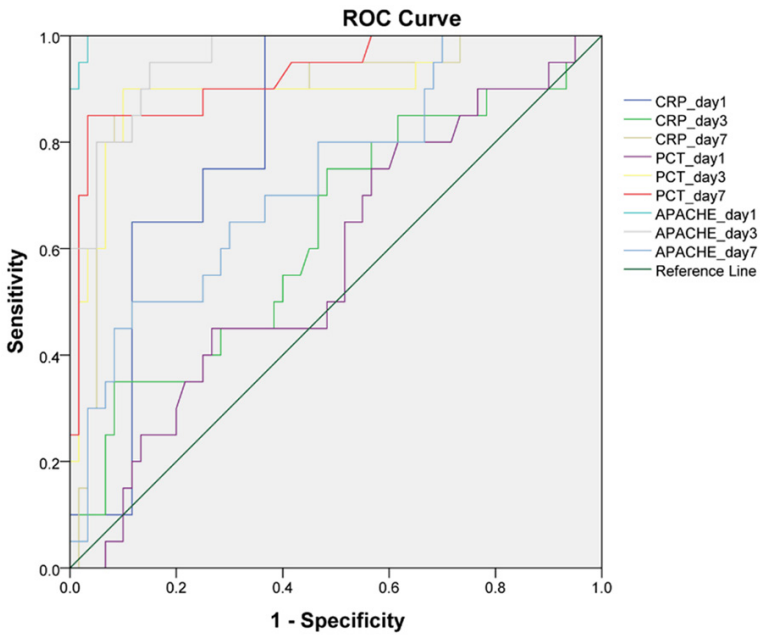

Figure 3. ROC curve. ROC: receiver operating characteristic; CRP: C-reactive protein; PCT: procalcitonin; APACHE: Acute Physiology and Chronic Health Evaluation.

A recent retrospective study on 188 patients with sepsis found that PCT value was higher in the non-survival group (median 34.0 μg/L, 5.0-71.9) than that in the survival group (median 6.4 μg/L, 4.1-13.1) and a high level of PCT was associated with poor prognosis in patients with sepsis [17]. Moreover, another retrospective cohort study on patients with infection, sepsis, and septic shock was performed to verify the predictability of PCT for diagnosing sepsis and reported that the optimal cut-off value of PCT is 0.41 ng/dL (sensitivity: 74.8% and specificity: 63.8%; AUC: 0745) and the optimal cut-off value of septic shock is 4.7 ng/dL (sensitivity: 66.1% and specificity: 79.0%; AUC: 0.784), indicating that PCT can be a reliable marker to predict sepsis and septic shock due to its sensitivity [18]. In the present study, patients with septic shock had a higher PCT level than the other groups, and the PCT level was higher in the non-survival group than in the survival group. These results demonstrate that the PCT levels are significantly elevated in patients with septic shock and the level of PCT is correlated with the severity of infection.

It has been found that the serum CRP level can effectively reflect the severity of infection in patients [19, 20]. In our study, the serum CRP levels in the septic shock group and the severe sepsis group were higher than that in the control group at all time points, and the CRP level in the septic shock group was higher than that in the severe sepsis group on the 7th day after treatment. In the septic shock group, the survival group had a lower CRP level than the non-survival group on the 1st and 7th day after treatment, indicating that the serum CRP level has a certain significance in the initial identification of the clinical manifestations caused by infective factors and may guide the diagnosis and treatment of septic shock to some extent.

Ryoo et al. conducted a study on 1,772 patients with septic shock to evaluate the prognostic value of PCT and CRP and demonstrated that high levels of CRP and PCT are associated with a high mortality [21]. In this study, the ROC curve showed that the AUC values of PCT and CRP have good sensitivity and specificity. The AUC value of APACHE II on the 1st day after treatment was the highest, indicating that APACHE II score can be used in prognostic prediction in early stage of hospitalization.

Although the prognostic roles of CRP, PCT and APACHE II score were investigated in patients with septic shock, there are still some limitations in the study. First of all, the sample size was small, which may lead to biased results; also, the study was a single-center study with only a one-month follow up period, and the long-term prognosis of the patients was not accurately assessed. Thus, a multicenter study with a larger sample size and longer follow-up time needs to be carried out in the future. Moreover, the correlation among these indicators and the combined assessment of prognosis using these markers need to be further studied.

In conclusion, PCT, CRP and APACHE II can serve as important markers for the diagnosis of

Table 3. ROC curve analysis of CRP and PCT levels and APACHE II score at different time points in the diagnosis of septic shock

Factor	AUC (95% CI)	SE	P	Sensitivity	Specificity	Cut-off Value
CRP day 1	0.819 (0.727-0.911)	0.047	<0.001	100.0	63.3	87.68
CRP day 3	0.630 (0.485-0.774)	0.074	0.084	75.0	51.7	80.74
CRP day 7	0.888 (0.799-0.978)	0.046	<0.001	85.0	91.7	100.71
PCT day 1	0.573 (0.430-0.715)	0.073	0.331	75.0	43.3	10.16
PCT day 3	0.901 (0.809-0.993)	0.047	<0.001	90.0	90.0	10.79
PCT day 7	0.927 (0.856-0.998)	0.036	<0.001	85.0	96.7	27.63
APACHE II day 1	0.998 (0.992-1.000)	0.003	<0.001	100.0	96.7	21.23
APACHE II day 3	0.957 (0.916-0.997)	0.021	<0.001	95.0	85.0	17.48
APACHE II day 7	0.732 (0.605-0.858)	0.065	0.002	50.0	88.3	17.64

Note: CRP: C-reactive protein; PCT: procalcitonin; APACHE: Acute Physiology and Chronic Health Evaluation; ROC: receiver operating characteristic; AUC: area under the curve; SE: standard error; CI: confidence interval.

septic shock and for the assessment of the severity of this disease.

Disclosure of conflict of interest

None.

Address correspondence to: Likun Xu, Xinjiang Emergency Center, People's Hospital of Xinjiang Uygur Autonomous Region, No. 91 Tianchi Road, Tianshan District, Urumqi 830001, Xinjiang Uygur Autonomous Region, China. Tel: +86-0991-8562861; E-mail: xulikun83xj@163.com

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