

Original Article

The correlation between procalcitonin and D-dimer and the prognoses of emergency sepsis patients

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Abstract: Objective: To study the correlation between procalcitonin (PCT) and D-dimer (DD) levels and their impact on the prognoses of emergency sepsis patients. Methods: We included 92 sepsis patients and 50 non-sepsis patients who were diagnosed during the same period. The sepsis patients were divided into a sepsis group and a septic shock group according to disease severity and additionally divided into a survival group and death group according to 28-day survival. The levels of PCT and DD were measured after 7 days of treatment, and the severity and prognoses of the patients were compared. Results: The levels of PCT and DD were significantly higher in the sepsis patients than in the non-sepsis patients (both $P < 0.05$). The PCT and DD levels were significantly lower in the sepsis group than in the septic shock group (both $P < 0.05$). The PCT and DD levels were significantly lower in the survival group than in the death group (both $P < 0.05$). The ROC curve of PCT combined with DD was statistically different from that of PCT and DD alone ($P = 0.048$ and $P = 0.017$). Conclusions: The clinical application of PCT combined with DD is valuable in predicting the severity and prognosis of sepsis and is worthy of further study.

Keywords: Sepsis, procalcitonin, D-dimer, prognosis

Introduction

Sepsis is a severe infection with a high incidence in clinical settings and is one of the most common causes of hospitalization and death in the intensive care unit [1-3]. Each year, 31.5 million people suffer from sepsis worldwide, of whom 5.3 million die of the disease [4]. Septic infection occurs when pathogenic microorganisms enter the bloodstream and release toxic substances into the blood which damages tissue and disrupts organ function [5]. Although great breakthroughs have been made in understanding the pathogenesis of sepsis and related diagnostic techniques, the high mortality rate remains a clinical problem [6, 7]. In recent years, an increasing number of studies have focused on specific indicators for the evaluation and prognosis of sepsis patients [8]. These studies found that procalcitonin (PCT) can serve as an index reflecting the severity of infection, and many studies have confirmed that PCT is highly applicable in the diagnosis of sepsis [9]. Several studies have found that PCT

combined with other traditional indicators such as C-reactive protein, interleukin-6, and acute physiology and chronic health evaluation II is more effective at diagnosing sepsis [10-12]. D-dimer (DD) is an indicator of coagulation function. Studies have shown that coagulation dysfunction often exists in sepsis patients, especially in septic shock patients, indicating that it is related to the severity and prognosis of sepsis [13]. There are few clinical studies that combine these two indicators for the diagnosis and prognosis of sepsis. This study prospectively studied the levels of PCT and DD in sepsis patients along with the severity and prognosis of sepsis, in order to evaluate the value of PCT and DD in evaluating sepsis severity and prognosis.

Materials and methods

General data

A total of 142 patients hospitalized with infection were enrolled. Among them, 92 patients

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were diagnosed with sepsis, including 48 males and 44 females, aged 45-65 years. The other 50 patients did not have sepsis, including 28 males and 22 females, aged 44-64 years. All the patients signed an informed consent, and this study was approved by the Ethics Committee of Affiliated Hospital of Weifang Medical University.

Inclusion and exclusion criteria

Inclusion criteria: 1). The patient met the criteria for sepsis or septic shock according to the third international consensus definition of sepsis and septic shock (sepsis-3) of the European Intensive Care Medical Association in 2016, with an infection or a suspicious infection, and with a Sequential Organ Failure Assessment (SOFA) score higher than 2 points [2]. Septic shock is diagnosed when, after a patient's blood pressure is positively resuscitated with fluid, the patient still needs a vasopressor to maintain the mean arterial pressure above 65 mmHg and the blood lactic acid level above 2 mmol/L. 2). Non-sepsis patients are those who do not meet the diagnostic criteria for sepsis but have evidence of infection. 3). All subjects must be under 75 years old.

Exclusion criteria: 1). Patients without complete clinical data; 2). Patients with severe malnutrition, cancer, or other diseases; 3). Patients with severe cardiopulmonary disease or cerebrovascular disease; 4). Patients with mental illness who cannot follow the study's instructions.

Methods

The patients with sepsis and septic shock were treated with anti-infection therapy, rehydration, anti-shock, and other symptomatic treatments, while the patients with non-sepsis infections received anti-infection therapy and symptomatic treatment.

Determination of PCT and DD: after 7 days of the above treatment, two tubes (5 mL each) of venous blood were collected from each patient and stored in a sterile tube with ethylene diamine tetraacetic acid. The blood samples were stored in the refrigerator at 4°C for 15 minutes. Serum and plasma were separated by centrifugation at 3,300 rpm. The separated plasma was mixed with a phosphate buffer solution containing 40 µL protease inhibitor and frozen at -80°C for storage until later use.

The PCT levels were determined using an enzyme-linked immune sorbent assay using an automatic microplate reader (Thermo, US), and the DD levels were determined using immunoturbidimetry. The patients were divided into a sepsis group (n=67) and a septic shock group (n=25) according to the severity of the sepsis. Patient survival was recorded after 28 days, and the patients were divided into a survival group and a death group accordingly.

Statistical analysis

The data were analyzed using SPSS 17.0 statistical software. Continuous variables were assessed for normality using a Kolmogorov test. The data that conformed to a normal distribution were expressed as the means \pm standard deviations ($\bar{x} \pm sd$), and tested using an independent sample *t* test if the data conformed to the homogeneity of variance. Otherwise the data were tested using a rank sum test which was expressed by *Z*. The counting data were assessed using a chi-squared test which was expressed by χ^2 . The area under the ROC curve, specificity, sensitivity, and cut-off value were used to evaluate the prognostic value of PCT, DD, and PCT combined with DD in treating sepsis. $P < 0.05$ was considered statistically significant.

Results

Comparison of the general data

No significant differences were observed among the sepsis group, the septic shock group, and the non-sepsis group in terms of gender, age, infection site, complications, white blood cell count, platelet count, prothrombin time, and serum creatinine (all $P > 0.05$). However, there were significant differences among the three groups in mean arterial pressure, respiratory rate, serum albumin, and SOFA scores, which were related to shock, low blood pressure, fast breathing, poor nutritional status, and the overall critical condition of the septic shock patients (all $P < 0.05$, **Table 1**).

Comparison of the PCT and DD levels

Our comparison of the PCT and DD levels between the sepsis patients and the non-sepsis patients revealed that the levels of PCT and DD in the sepsis patients were significantly higher than those in the non-sepsis patients

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Table 1. Comparison of the general and baseline information ($\bar{x} \pm sd, n$)

	Sepsis group (n = 67)	Septic shock group (n = 25)	Non-sepsis group (n = 50)	χ^2/F	P
Gender (Male: female)	34:33	14:11	28:22	0.390	0.823
Age (year)	62.6±10.3	63.6±8.4	63.2±9.3	0.512	0.765
Infection site				1.114	0.573
Lung	30	10	24		
Abdomen	12	4	10		
Urinary system	9	3	7		
Traumas	16	8	9		
Complications					
Hypertension				0.482	0.786
Yes	26	8	20		
No	41	17	30		
Diabetes				1.494	0.474
Yes	14	3	12		
No	53	22	38		
Cerebrovascular disease				0.815	0.665
Yes	10	2	6		
No	57	23	44		
Chronic obstructive pulmonary disease				0.333	0.847
Yes	14	4	9		
No	53	21	41		
Mean arterial pressure (mmHg)	78.14±17.45	71.25±14.25	82.60±12.36	4.562	<0.001
Respiratory rate (time)	21.10±4.89	25.23±8.41	20.36±3.67	3.647	<0.001
White blood cell count (10 ⁹ /L)	14.26±9.58	14.89±9.47	13.98±8.23	0.325	0.624
Blood platelet count (10 ⁹ /L)	95.62±72.36	100.25±82.36	100.36±71.36	0.687	0.424
Prothrombin time (s)	13.48±2.36	14.36±2.41	12.85±2.37	0.519	0.523
Serum creatinine (μmol/L)	117.36±42.65	131.25±6.21	119.51±43.48	0.698	0.312
Serum albumin (g/L)	29.42±7.69	26.24±6.24	30.15±6.89	3.125	0.012
SOFA score	4.23±2.69	9.14±4.54	0.74±0.24	5.698	<0.001

Note: SOFA, Sequential organ failure assessment.

(both $P < 0.05$). Further, comparing the PCT and DD levels between the sepsis group and the septic shock group showed that PCT and DD levels were lower in the sepsis group than in the septic shock group (both $P < 0.05$, **Tables 2 and 3**).

Comparison of 28-day survival in sepsis patients

Our comparison of the 28-day survival of the included patients showed that 17 patients in the sepsis group died, giving a mortality rate of 25.37%, and 13 patients in the septic shock group died, giving a mortality rate of 52.00%. This difference was statistically significant ($P < 0.05$). It indicated that a worse condition at admission was associated with a worse prognosis (**Table 4**).

Comparison of the PCT and DD levels between the survival and death groups

The PCT and DD levels in the survival group were significantly lower than those in the death group (both $P < 0.05$, **Table 5**).

The predictive value of PCT and DD in the death of sepsis patients

The area under the ROC curve of PCT, DD, and PCT combined with DD was 0.939, 0.832 and 0.947, respectively; the 95% confidence interval was 89.4%-98.3%, 74.0%-92.4%, and 90.4%-98.9% respectively; the cut-off value of PCT and DD was 4.13 ng/mL and 3.85 mg/L respectively; the Youden index was 0.741, 0.557, and 0.738 respectively; the sensitivity

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Table 2. Comparison of PCT and DD between the sepsis and non-septic patients ($\bar{x} \pm sd$)

	Sepsis patients (n = 92)	Non-septic patients (n = 50)	t	P
PCT (ng/mL)	4.75±2.82	2.05±1.33	6.381	<0.001
DD (mg/L)	3.61±1.42	2.82±0.97	3.905	<0.001

Note: PCT, procalcitonin; DD, D-dimer.

Table 3. Comparison of PCT and DD between the sepsis and septic shock groups ($\bar{x} \pm sd$)

	Sepsis group (n = 67)	Septic shock group (n = 25)	t	P
PCT (ng/mL)	3.94±2.31	6.92±2.96	5.076	<0.001
DD (mg/L)	3.24±1.31	4.62±1.25	4.568	<0.001

Note: PCT, procalcitonin; DD, D-dimer.

Table 4. Comparison of the 28-day survival in patients with sepsis

	Sepsis group (n = 67)	Septic shock group (n = 25)	χ^2	P
Death	17 (25.37%)	13 (52.00%)	5.874	0.015
Survival	50 (74.63%)	12 (48.00%)		

Table 5. Comparison of PCT and DD between the survival and death groups ($\bar{x} \pm sd$)

	Survival group (n = 62)	Death group (n = 30)	t	P
PCT (ng/mL)	3.31±1.57	7.74±2.68	8.943	<0.001
DD (mg/L)	3.07±1.13	4.73±1.33	6.206	<0.001

Note: PCT, procalcitonin; DD, D-dimer.

Table 6. The predictive value of PCT and DD in the deaths of sepsis patients

	Area under ROC curve	Youden index	Sensitivity	Specificity
PCT	0.939	0.741	0.967	0.774
DD	0.832	0.557	0.767	0.790
PCT + DD	0.947	0.738	0.867	0.871

Note: PCT, procalcitonin; DD, D-dimer.

was 0.967, 0.767, and 0.867 respectively; the specificity was 0.774, 0.790, and 0.871 respectively (Table 6).

The ROC curves of PCT and DD were not statistically different ($P=0.578$), but the ROC curve of PCT combined with DD was statistically different from that of PCT and DD alone, respectively ($P=0.048$ and $P=0.017$, Figure 1).

Discussion

Studies have found that PCT in sepsis patients begins to increase at the early stages of infection and even before the increases in other inflammatory factors [14]. PCT elevation is consistent with the severity of sepsis. The mean PCT level of sepsis patients was 3.63, while the mean PCT level of the severe sepsis patients was 11.06, which represents a significant increase [15]. Another study reached a similar conclusion [16]. A study of DD found that the abnormal coagulation mechanism and the DD elevation are common in sepsis patients [17]. In our study, the PCT and DD levels in the sepsis patients were significantly higher than those in the non-sepsis patients. Further comparisons between the sepsis patients and the more severe septic shock patients showed that the PCT and DD levels were significantly higher in the septic shock patients than in the sepsis patients, which is consistent with the above findings.

In terms of mortality, the mortality of sepsis patients worldwide is around 30-50% [18]. In our study, 30 of 92 patients died within 28 days, for a total mortality rate of 32.61%. Among them, 17 patients in the sepsis group died and 13 patients in the septic shock group died, giving mortality rates of 25.37% and 52.0%, respectively. The mortality rate was higher in the septic shock group than in the sepsis group, which was primarily related to the patients' conditions at admission. The mortality rate in this study was consistent with previous studies. A prior study which divided sepsis patients into a low PCT group and a high PCT group according to their PCT level found that the 28-day mortality rate was 4.6% in the low PCT group and 13.5% in the high PCT group, with a significant difference [12]. In a study of DD, patients with sepsis often had diffuse intravascular coagulation, which led to an increase in 28-day mortality [19]. In this study,

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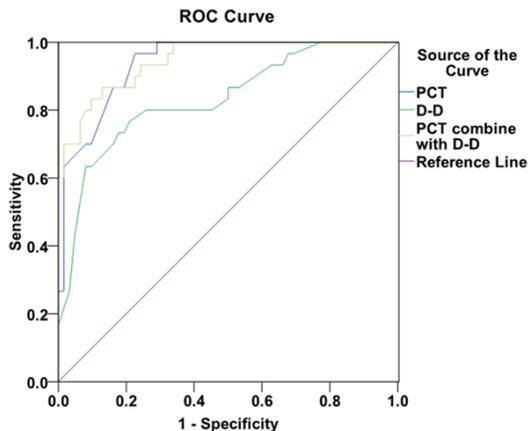


Figure 1. The predictive value of PCT and DD in the deaths of sepsis patients. PCT, procalcitonin; DD, D-dim.

the PCT and DD levels in the survival group were significantly lower than the levels in the death group, which is consistent with the above results.

In a meta-analysis of the prognostic value of PCT in sepsis patients, the area under the ROC curve of PCT was 0.85, and the sensitivity and specificity of PCT were both higher than those of the traditional inflammatory factors [20]. However, some studies have found that PCT alone does not have a high diagnostic value for the prognosis of sepsis, and that the level of PCT on admission day was especially unreliable [21]. Thus, PCT levels after 7 days of treatment were selected as predictors in this study. In addition, PCT is often combined with other indicators for diagnosis, which can improve the diagnostic efficiency. A study found that the combination of PCT and CRP increased specificity but decreased sensitivity [22]. Another study used PCT in combination with the SOFA score to diagnose sepsis, which was found to increase the specificity to 0.98 [23]. In the present study, when PCT alone was used to predict the prognosis, the area under the ROC curve was 0.939, the sensitivity was 0.967, and the specificity was 0.774; when DD alone was used to predict prognosis, the area under the ROC curve was 0.832, the sensitivity was 0.767, and the specificity was 0.790; when PCT and DD were combined to predict prognosis, the area under the ROC curve was 0.947, the sensitivity was 0.867, and the specificity was 0.871. Thus, combining the two indicators improved the specificity.

The sample size of this study was relatively small and should be further expanded. Moreover, this study was a retrospective rather than a prospective study. Additional multi-center prospective studies need to be conducted to examine the application value of PCT combined with DD in sepsis patients.

In this study, we found that the clinical application of PCT combined with DD is valuable in predicting the severity and prognosis of sepsis and is worthy of further study and application.

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Disclosure of conflict of interest

None.

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