Diagnostic and Therapeutic Value of Procalcitonin and D- dimer in Sepsis Study on the Expression of Procalcitonin (PCT) and D-dimer (D-D) in Serum of Sepsis Patients and Their Correlation

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Altogether 89 septic patients admitted to our hospital from February 2018 to March 2019 were selected as the experimental group, and 60 healthy people underwent physical examination during the same period were selected as the control group. The expression of PCT and D-D in serum was detected by enzyme-linked immunosorbent assay (ELISA), and the diagnostic value of PCT and D-D in septic patients was evaluated by receiver operating characteristic curve (ROC). Peason correlation coefficient was used to analyze the correlation between PCT and D-D, and the correlation among inflammatory factors interleukin- 6 (IL-6), platelet activating factor (PAF), tumor necrosis factor -α (TNF-α). Logistic regression was used to analyze the independent risk factors affecting the onset of sepsis. The expressions of serum PCT and D-D in septic patients were higher than those in the control group. AUC of patients with sepsis diagnosed by serum PCT and D-D were 0.929 and 0.905. The expression of IL-6, PAF and TNF-α in the experimental group was significantly higher than that in the control group. There was a positive correlation between PCT and D-D in the experimental group, and a positive correlation of PCT, D-D with IL-6, PAF and TNF-α. Patients with old age, high lactic acid, high CRP, high urea nitrogen, high serum creatinine, high PCT and high D-D expression have an increased risk of sepsis. Our study showed that the expression of PCT and D-D increases in septic patients, which has a satisfactory diagnostic value for septic patients, and inhibition of PCT and D-D expression can be used as a potential therapeutic target for septic patients.

Keywords: procalcitonin, D- dimer, sepsis, diagnosis

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Sepsis is one of the major causes of death in the world [1]. It is a physiological, pathological and biochemical abnormal syndrome caused by infection, and also a major public health problem [2-4]. Its characteristic is to respond to microbial infection, which leads to systemic inflammation of patients, causes dysfunction of

organs, and has become a common complication of hospitalized patients [5,6]. However, in view of the current situation, we urgently need to find a new potential target for treatment and diagnosis to further clarify the occurrence and improvement of sepsis.

PCT is produced by thyroid C cells, and its synthesis is up-regulated in bacterial infection and down-regulated in viral infection [4]. Previous studies have shown that PCT is a specific marker to distinguish bacteria from pulmonary infectious inflammation, which can be used to guide the start and duration of antibiotic therapy for patients suspected of sepsis, reduce the hospitalization time of patients, and limit the duration of antibiotic therapy [8,9]. D-D is an indirect marker of fibrinolysis and fibrin turnover. It has unique characteristics and can be used as a biomarker for hemostasis abnormalities and an indicator of thrombosis in blood vessels. Clinically, D-D can be used as an important marker for activating coagulation and fibrinolysis [10]. Protein fragments released into circulation during normal human processes or when blood clots rupture due to prescription fibrinolytic drugs can also be used to exclude high D-dimer plasma levels and venous thromboembolism [11]. Previous studies have shown that [12] D-D is a marker of adverse outcomes under various key conditions and can predict the disease severity and mortality of advanced septic shock.

At present, there are few researches on the expression of PCT and D-D in the serum of septic patients, so the expression of PCT and D-D in the serum of septic patients was detected to explore the diagnostic value and potential therapeutic methods of PCT and D-D in septic patients.

DATA AND METHODS

General Information

Altogether 89 patients with sepsis admitted to our hospital from February 2018 to March 2019 were selected as the experimental group, and another 60 people underwent physical examination during the same period were selected as the control group. There were 45 males and 44 females in the research group, aged 47-65 years with the average age of (57.68± 16.87) years, lactic acid (2.81± 1.3) mmol/L, CRP (27.91± 1.5) mg/DL, urea nitrogen (23.89± 0.9) mmol/L, creatinine (140.47±12.8) umol/L. There were 35 males and 25 females in the control group, aged 45-62 years with the average age of (55.78± 16.57) years, lactic acid (1.32± 0.9) mmol/L, CRP (9.85± 1.3) mg/DL, urea nitrogen (5.34± 0.8) mmol/L, creatinine (57.67±10.2) umol/L.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: patients met the diagnostic criteria for sepsis [13]; patients with complete clinical general data; patients aged more than 18 years; all patients were informed of the study and signed an informed consent form; the experimental process was approved by the Ethics Committee of the Hospital and was in line with the Declaration of Helsinki. Exclusion criteria were as follows: patients with chronic heart, lung, kidney and other organ systemic diseases; patients accompanied by malignant tumors; patients did not cooperate with follow-up; the survival of the patients was less than 1 month; patients lost to follow-up.

Detection Methods

A total of 5mL fasting venous blood was collected in the next morning, centrifuged at 5000 rpm for 15min to separate the serum, and enzyme linked immunosorbent assay (ELISA) [14] was used to detect PCT (Xiamen Huijia Biotechnology Co., Ltd., Item No.: ATHJMP00030HU), D-D (Wuhan Chundu Biotechnology Co., Ltd., Item No.: CD-0207-LIN), interleukin -6(IL-6) (Wuhan Elabscience Biotechnology Co., Ltd., Item No.: E-EL-H0102c), platelet activating factor (PAF) (Shanghai Lengton Biotechnology Co., Ltd., Item No.: F00179), tumor necrosis factor-α (TNF-α) (Shanghai Hengfei Biotechnology Co., Ltd., Item No.: bs-215OR-2). The test was carried out in strict accordance with the instructions of the kit. A sample hole, a standard sample hole and a blank hole were set up. The sample hole was

added with 50μL of the sample to be tested, the standard sample hole with 50μL of the standard sample, and the blank hole was added without any reagent. The sample well and the standard well were added with 100μL of horseradish peroxidase labeled detection antibody, sealed and incubated at 37℃ for 60mim. The liquid was discarded and dried, and the well was washed for 5 times. The substrates A and B were fully mixed according to the volume of 1:1, 100μL of substrate mixed solution was added to all wells. The plates were sealed, incubated at 37℃ for 15min, and 50μL of termination solution was added to each well. The absorbance (OD value) at 450nm of each well was read by a full-automatic enzyme-labeled analyzer (Chenlian Biotechnology Development Co., Ltd., Shanghai, China, M15), and the expressions of PCT, D-D, IL-6, PAF and TNF-α were calculated.

Statistical Methods

SPSS19.0 (IBM Corp, Armonk, NY, USA) was used for statistical analysis, and Graphpad Prism6 (Graphpad Software, San Diego, USA) was used to visualize the data. Counting data was expressed by the number of cases/percentage [n(%)], and chi-square test was used for comparison of counting data between groups. The measurement data were expressed by mean ± standard deviation (mean±SD), and the comparison of measurement data between the two groups was conducted by independent-sample t test. Receiver operating characteristic curve (ROC) was used to evaluate the diagnostic value of PCT and D-D in peripheral blood for septic patients. Peason correlation coefficient was used to analyze the correlation between PCT and D-D and the correlation between PCT and inflammatory factors IL-6, PAF and TNF-α. Logistic regression was used to analyze the independent risk factors of sepsis. When $p < 0.05$, the difference was statistically significant.

RESULTS

General Information

There was no significant difference between the two groups in baseline data such as gender, age, residence, nationality, educational level, smoking history, drinking history, exercise history, systolic blood pressure, and diastolic blood pressure (P>0.05), while there were significant differences in baseline data such as lactic acid, coagulation dysfunction, CRP, urea nitrogen, creatinine (P<0.05). See Table 1.

Table 1.
General data of two groups of patients [N (%)] (x±sd)

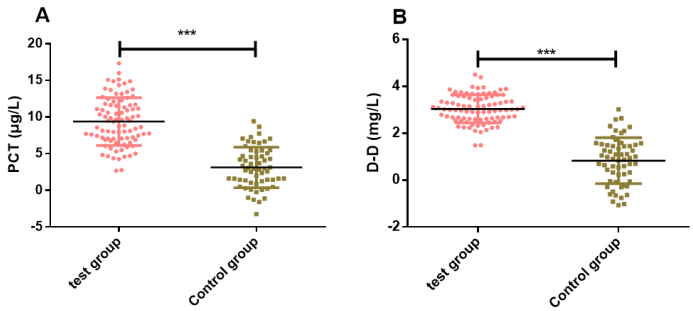
Classification	Experimental group (n=89)	Control group (n=60)	t/χ2 value	P value
Gender			0.871	0.351
Male	45(50.56)	35(58.33)		
Female	44(49.44)	25(41.67)		
Age (years)			0.679	0.498
	57.68±16.87	55.78±16.57		
Residence			0.651	0.420
City	37(41.57)	21(35.00)		
Rural	52(58.43)	39(65.00)		
Nationality			0.117	0.732

Han	39(43.82)	28(46.67)		
Minorities	50(56.18)	32(53.33)		
Educational level			0.601	0.438
≥ high school	23(25.84)	19(31.67)		
< high school	66(74.16)	41(68.33)		
Smoking history			0.049	0.825
Yes	34(38.20)	24(40.00)		
No	55(61.80)	36(60.00)		
Drinking history			0.886	0.347
Yes	39(43.82)	31(51.67)		
No	50(56.18)	29(48.33)		
Exercise history			2.099	0.147
Yes	31(34.83)	28(46.67)		
No	58(65.17)	32(53.33)		
Systolic pressure (mmHg)			0.976	0.331
	115.59±8.99	114.12±9.06		
Diastolic pressure (mmHg)			1.763	0.080
	75.04±6.88	72.98±7.16		
Lactic acid (mmol/L)			7.715	＜0.001
	2.81±1.3	1.32±0.9		
Coagulation dysfunction			77.831	＜0.001
Yes	78(87.64)	9(15.00)		
No	11(12.36)	51(85.00)		
CRP(mg/dL)			75.970	＜0.001
	27.91±1.5	9.85±1.3		
Urea nitrogen (mmol/L)			128.900	＜0.001
	23.89±0.9	5.34±0.8		
Blood creatinine (umol/L)			41.920	＜0.001
	140.47±12.8	57.67±10.2		

Expression of PCT and D-D in Serum of Experimental Group and Control Group

The expression levels of PCT in the experimental group and the control group were (9.15±3.12)μg/L, (3.12±1.76)μg/L respectively, and the expression levels of D-D in the experimental group and the control group were (3.03±0.58)mg/L and (0.51±0.52)mg/L respectively. PCT expression in the control group was significantly lower than that in the experimental group ($P < 0.001$), and D-D expression in the control group was significantly lower than that in the experimental group ($P < 0.001$). See Figure 1.

Figure 1.
Expression of PCT and D-D in serum of experimental group and control group.



The expression level of PCT in the experimental group was significantly higher than that in the control group (**A**). The expression level of D-D in experimental group was significantly higher than that in control group (**B**). Note: * * * indicates that compared with the control group, $P < 0.001$.

Diagnostic Value of PCT and D-D in Septic Patients

We visualized the ROC curve of serum PCT for sepsis patients and found that the AUC of serum PCT for sepsis patients was 0.929 (95% CI: 0.889-0.970), the cut-off value was 2.56, the sensitivity was 89.89%, and the specificity was 96.67%.The ROC curve of plasma D-D in the diagnosis of sepsis showed that the AUC of serum PCT in the diagnosis of sepsis was 0.905 (95%CI: 0.858-0.953), cut-off value was 2.35, the sensitivity was 92.13%, the specificity was 78.33%. See Table 2 and Figure 2.

Figure 2.
(**A**) ROC curve for PCT diagnosis of sepsis; (**B**) ROC curve for D-D diagnosis of sepsis.

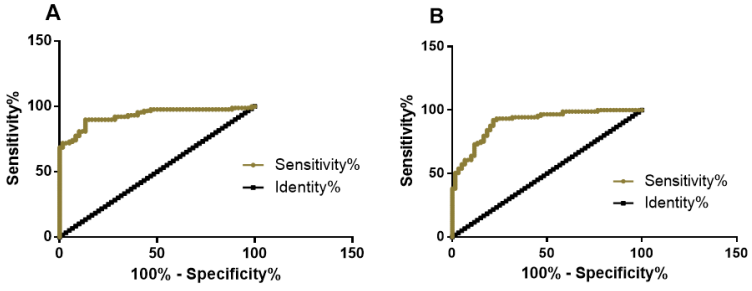


Table 2.
ROC parameters of PCT and D-D for sepsis patients

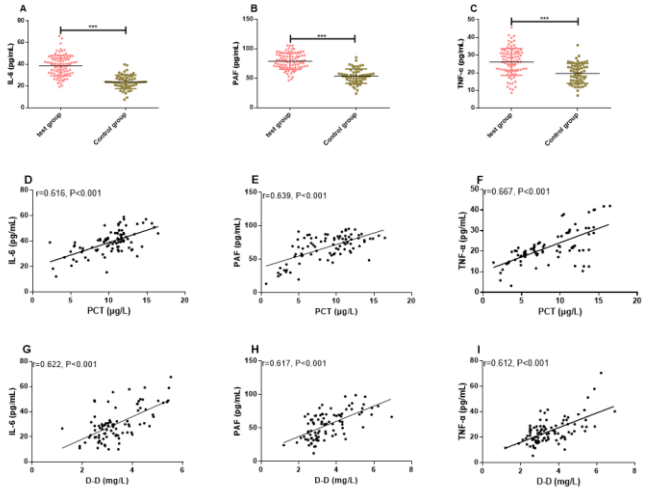
Group	AUC	95%CI	S.E	Cut-off	Sensitivity(%)	Specificity(%)

PCT	0.929	0.889-0.970	0.021	2.56	89.89	96.67
D-D	0.905	0.858-0.953	0.024	2.35	92.13	78.33

Expression of Inflammatory Factors IL-6, PAF and TNF-α in Two Groups of Patients and Their Correlation with PCT and D-D

The expression levels of inflammatory factor IL-6 in experimental group and control group were (39.52±9.52)pg/mL, (20.46±6.39)pg/mL respectively. The expression levels of PAF in experimental group and control group were (80.13±10.15)pg/mL, (57.32±10.11)pg/mL respectively, and the expression levels of TNF-α in experimental group and control group were (26.08±7.36)pg/mL, (19.52±5.44)pg/mL respectively. The expression of inflammatory factors IL-6, PAF and TNF-α in the control group were significantly lower than that in the experimental group ($P < 0.05$). Peason correlation coefficient was used to analyze the correlation between PCT\D-D and inflammatory factors IL-6, PAF and TNF-α. The results showed that PCT, D-D and inflammatory factors IL-6, PAF and TNF-α were positively correlated (r=0.616, P< 0.001, r=0.639, P< 0.001, r=0.667, P< 0.001, r=0.622, P< 0.001, r=0.617, P< 0.001, r=0.612, P< 0.001). See Figure 3.

Figure 3.
Expression of inflammatory factors IL-6, PAF and TNF-α in two groups of patients and their correlation with PCT and D-D.

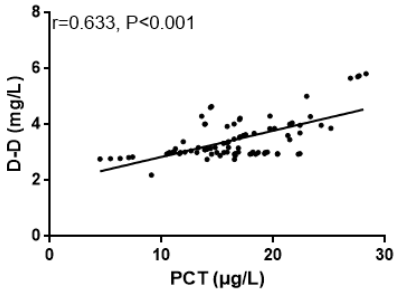


The expression of inflammatory factor IL-6 in experimental group was significantly higher than that in control group (**A**). The expression of inflammatory factor PAF in experimental group was significantly higher than that in control group (**B**). The expression of inflammatory factor TNF-α in experimental group was significantly higher than that in control group (**C**). PCT was positively correlated with inflammatory factor IL-6 (r=0.616, P< 0.001) (**D**). PCT was positively correlated with inflammatory factor PAF (r=0.639, P< 0.001) (**E**). PCT was positively correlated with inflammatory factor TNF-α (r=0.667, P< 0.001) (**F**). D-D was positively correlated with inflammatory factor IL-6 (r=0.622, P< 0.001) (**G**). D-D was positively correlated with inflammatory factor PAF (r=0.617, P< 0.001) (**H**). D-D was positively correlated with inflammatory factor TNF-α (r=0.612, P< 0.001) (**I**).

Correlation Analysis of PCT and D-D

We analyzed the correlation between PCT and D-D by Peason correlation coefficient. The results showed that PCT and D-D in the study group had positive correlation (r=0.633, P< 0.001). See Figure 4.

Figure 4.
PCT was positively correlated with D-D (r=0.633, P< 0.001).



Multivariate Logistic Regression Analysis on Sepsis

Multivariate Logistic regression analysis was conducted on the factors with differences. The results showed that age (P=0.002), lactic acid (P=0.009), CRP (P=0.001), urea nitrogen (P=0.001), creatinine (P=0.001), PCT(P=0.004), and D-D(P=0.001) were independent risk factors for sepsis. Patients with old age, high lactic acid, high CRP, high urea nitrogen, high serum creatinine, high PCT and high D-D expression have increased risk of sepsis. See Table 3-4.

Table 3.
Logistic multivariate regression analysis assignment

Classification	Experimental group (n=89)	Control group (n=60)	t/χ2 value	P value
Gender			0.871	0.351
Male	45(50.56)	35(58.33)		
Female	44(49.44)	25(41.67)		
Age (years)			0.679	0.498
	57.68±16.87	55.78±16.57		
Residence			0.651	0.420
Urban	37(41.57)	21(35.00)		
Rural	52(58.43)	39(65.00)		
Nationality			0.117	0.732
Han	39(43.82)	28(46.67)		
Minorities	50(56.18)	32(53.33)		
Educational level			0.601	0.438
≥ high school	23(25.84)	19(31.67)		
< high school	66(74.16)	41(68.33)		

Smoking history			0.049	0.825
Yes	34(38.20)	24(40.00)		
No	55(61.80)	36(60.00)		
Drinking history			0.886	0.347
Yes	39(43.82)	31(51.67)		
No	50(56.18)	29(48.33)		
Exercise history			2.099	0.147
Yes	31(34.83)	28(46.67)		
No	58(65.17)	32(53.33)		
Systolic pressure (mmHg)			0.976	0.331
	115.59±8.99	114.12±9.06		
Diastolic pressure (mmHg)			1.763	0.080
	75.04±6.88	72.98±7.16		
Lactic acid (mmol/L)			7.715	＜0.001
	2.81±1.3	1.32±0.9		
Coagulation dysfunction			77.831	＜0.001
Yes	78(87.64)	9(15.00)		
No	11(12.36)	51(85.00)		
CRP(mg/dL)			75.970	＜0.001
	27.91±1.5	9.85±1.3		
Urea nitrogen (mmol/L)			128.900	＜0.001
	23.89±0.9	5.34±0.8		
Blood creatinine (umol/L)			41.920	＜0.001
	140.47±12.8	57.67±10.2		

Table 4.
Multivariate logistic regression analysis on the incidence of sepsis

Variable	B	S.E	Wals	P	OR	95% CI
Age	0.143	0.048	9.394	0.002	1.153	1.054-1.619
Coagulation dysfunction	0.634	0.599	1.145	0.280	1.901	0.571-6.152

Hospital infection	0.174	0.080	5.001	0.021	1.897	1.003-1.343
Lactic acid	0.101	0.473	0.045	0.009	1.106	0.429-2.819
CRP	0.338	0.108	9.935	0.001	1.245	1.050-1.476
Urea nitrogen	0.634	0.599	1.145	0.001	1.901	0.635-0.827
Serum creatinine	0.945	0.703	1.732	0.001	2.563	0.601-0.799
PCT	1.345	0.475	8.617	0.004	4.029	1.598-10.217
D-D	1.612	0.471	11.658	0.001	5.005	1.942-12.618

DISCUSSION

The development of sepsis has become the key factor of organ failure in patients clinically [15], and with the increase of the number of patients, sepsis has become the difficulty and focus of clinical treatment. The symptoms are highly variable, so it is difficult to diagnose and evaluate the severity of the disease [16,17]. However, studies have shown that biomarkers can identify the pathological and physiological characteristics of sepsis and may become the key to personalized targeted therapy in the future clinical management of sepsis [18].

PCT is a host reaction marker that can be up-regulated by microbial toxins and certain pro-inflammatory mediators (tumor necrosis factor-α, interleukin -6) and down-regulated during recovery. The dynamics of PCT have also shown to predict mortality and septicemia with treatment failure [19]. Some studies have shown that PCT can diagnose early and stage accurately, guide sepsis and reduce mortality [20]. D-D is sensitive enough in patients with clinical manifestations and septicemia to exclude organ dysfunction, ICU demand and mortality, and higher D-D level can predict organ dysfunction [21]. Previous studies have shown that D-D can predict the existence of bacteremia in septicemia patients and is related to the severity of septicemia [22]. Liu D et al. showed that the increase of PCT concentration and the unclear PCT in septicemia patients are closely related to all-cause mortality [23]. In the research of neonatal sepsis by Kumar P et al., it was showed that D-D is a sensitive predictor of neonatal septicemia with high sensitivity and negative predictive value [24]. However, in this study, the expression of serum PCT and D-D in septic patients was significantly up-regulated compared with the control group, and the AUC of serum PCT and D-D in diagnosing septic patients was 0.929 and 0.905, which indicated that serum PCT and D-D have good diagnostic value for septic patients and can be used as biomarkers for predicting septic patients.

IL-6 is an effective inflammatory mediator. Its plasma concentration has been tested and can be used as a prognostic factor for severe intraperitoneal septicemia, and has extremely high sensitivity and specificity to the identified septicemia [25,26]. PAF is an effective phospholipid-derived medium. Its central role has been fully established in non-immune mediated and immune mediated allergic reaction experimental models, and it is also considered as a mediator of allergic and non-allergic inflammatory diseases [27]. TNF-α is an inflammatory cytokine secreted by immune cells, which plays an important role in the pathophysiological process of sepsis [28]. In the study of Debonde et al., the combination of TNF-α and IL-6 levels has high specificity and sensitivity in the diagnosis of neonatal septicemia [29]. In the study of patients with severe sepsis by Dhainaut J F A et al., PAF antagonist is a safe and promising treatment for patients with severe gram- negative sepsis [30]. The results of this study on inflammatory factors showed that the expressions of inflammatory factors IL-6, PAF and TNF-α in the experimental group were significantly higher than those in the control group. PCT and D-D were positively correlated

with inflammatory factors IL-6, PAF and TNF-α, indicating that high expression of PCT and D-D in inflammatory environment may be related to the occurrence and development of sepsis. In the study of Nasa P on inflammatory sepsis and septic shock in the elderly [31], age, elevated serum lactic acid and organ failure are all pathogenic factors of sepsis. Logistic regression analysis results of multiple factors that affect the onset of sepsis in this study showed that age, high lactic acid, high CRP, high urea nitrogen, high serum creatinine, high PCT and high D-D expression are risk factors for the onset of sepsis, among which high PCT and high D-D expression have the greatest risk multiples, indicating that knocking down PCT and D-D expression may reduce the onset risk of sepsis. Moreover, PCT and D-D in the experimental group have significant positive correlation, indicating that PCT and D-D may play a synergistic role in the development of sepsis patients, but the specific regulatory mechanism needs to be further determined by cytological function research.

In this study, the subjects were screened strictly according to the inclusion and exclusion criteria. There was no significant difference between the experimental group and the control group in general clinical baseline data of gender and age, which ensured the rigour and reliability of the study. Although this study confirmed that there is a positive correlation between PCT and D-D, both of which are over-expressed in the serum of septic patients and are also positively correlated with inflammatory factors IL-6, PAF and TNF-α. There are still some deficiencies for improvement. We can supplement basic experiments to further understand the regulatory mechanism of PCT and D-D on septic patients and study the prognosis of septic patients, thus further supporting the results of this study.

To sum up, our research showed that the expression of PCT and D-D increases in septic patients, which has satisfactory diagnostic value for septic patients, and inhibition of PCT and D-D expression can be used as a potential therapeutic target for septic patients.

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