

Clinical significance of the detection of procalcitonin and C-reactive protein in the intensive care unit

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Abstract. The identification significance of C-reactive protein (CRP) and procalcitonin (PCT) levels in the intensive care unit patients with combined infection and their prognostic effects of patients with sepsis was investigated. A total of 203 patients were divided into the sepsis (n=60) and the non-sepsis group (n=143). The predictive effects of CRP and PCT levels in patients in the intensive care unit on sepsis and their effects on the prognosis of patients with sepsis were analyzed. The results showed that CRP and PCT levels in patients in the sepsis were higher than those in the non-sepsis group ($P<0.05$); CRP and PCT levels in patients who died of sepsis at 1 week and 2 weeks after admission were not statistically different to those before admission ($P>0.05$); CRP and PCT levels in patients surviving sepsis at 1 week after admission were significantly decreased compared with those at admission ($P<0.05$). CRP and PCT levels in patients at 2 weeks after admission were significantly decreased compared with those at admission ($P<0.05$). CRP and PCT levels in patients who died of sepsis were higher than those surviving sepsis ($P<0.05$). Logistic regression analysis showed that the higher the CRP and PCT levels were, the worse the patients' conditions would be, and the higher the risk of death would be ($r=0.732$, $P=0.012$; $r=0.826$, $P=0.007$); besides, PCT had a higher value in predicting the poor prognosis of patients [PCT: Area under the curve (AUC)=0.734, CRP: AUC=0.699]; the univariate Cox regression analysis revealed that CRP, PCT and age may be the risk factors for poor prognosis in patients. CRP and PCT can be used to identify whether the patients in the intensive care unit are infected or not. The dynamic monitoring of CRP and PCT has important clinical significance in predicting the prognosis of patients with sepsis.

Introduction

Sepsis is a generalized systemic inflammatory disease with a high prevalence. There are approximately 18 million people on average suffering from sepsis per year around the world, and this number is still rising each year (1-3). Sepsis is one of the leading causes of death in the intensive care unit, and there are nearly 14,000 people worldwide die of secondary diseases on average every day (4,5). In recent years, although great strides have been made in the anti-infective treatment, the mortality rate of sepsis patients still ranges from 25 to 60% (6,7). Sepsis treatment is expensive, and the use of medical resources is also very serious (7,8). Therefore, strengthening the early diagnosis, treatment and prognosis of patients with sepsis plays a very significant role.

Recently, studies have shown that changes in C-reactive protein (CRP) and procalcitonin (PCT) levels can prompt the severity of sepsis, and CRP and PCT tests have advantages of short time and high sensitivity, which are of great significance for the diagnosis and differential diagnosis of early infection (9,10). CRP is a non-specific and inflammation-related protein that is produced in the liver and regulated by plasma interleukin-6 (IL-6). When infection or body damage occurs, the concentration of CRP will be greatly altered (11). PCT is a glycoprotein with no hormonal activity, whose sensitivity to viral and bacterial infections is high; for example, sepsis can lead to a large change in its level (12). Therefore, changes in CRP and PCT levels in patients in the intensive care unit were detected in this study, so as to explore their predictive and prognostic effects on sepsis.

Patients and methods

Study objects. A total of 203 patients aged 21-76 years admitted to the Intensive Care Unit of Qilu Hospital of Shandong University in Dongying (Dongying, China) from May 2014 to May 2016 were selected and divided into the sepsis (n=60) and the non-sepsis group (n=143). In the sepsis group, there were 21 mild-to-moderate cases, including 12 males and 9 females with an average age of 43.2 ± 21.3 years, 19 severe cases, including 11 males and 8 females with an average age of 58.5 ± 19.6 years, and 20 cases with septic shock, including 12 males and 8 females with an average age of 68.1 ± 23.5 years. In the non-sepsis group, there were 143 cases with colorectal

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cancer, including 82 males and 61 females with an average age of 35.1 ± 1.6 years. The diagnostic criteria were in line with the International Guidelines for Management of Severe Sepsis and Septic Shock (Version 2016). The study was approved by the Ethics Committee of Qilu Hospital of Shandong University in Dongying and informed consents were signed by the patients and/or guardians.

Detection methods. Venous blood (3 ml x 2) was drawn from all the subjects the morning after admission, placed into a vacuum tube containing anticoagulant and then sent to the Laboratory Medicine of Qilu Hospital of Shandong University in Dongying for the detection of CRP and PCT expression levels. Fasting venous blood samples of patients in the control group were extracted for detection during the physical examination. CRP level was measured by immunoturbidimetry, and kits were provided by Beijing Strong Biotechnologies, Inc. (Beijing, China). The detection was performed by using the Beckman Coulter AU5800 automatic biochemical analyzer (Beckman Coulter, Inc., Brea, CA, USA). The standard and accusative reagents were provided by the manufacturer, and experiments were conducted in strict accordance with the kit instructions. PCT level was tested with the QMT8000 Immunoquantitative Analyzer (Getein Biotech, Inc., Nanjing, Cina), and kits were also supplied by the company.

Observation indexes. Differences in CRP and PCT levels in patients at admission between the two groups were compared; differences in CRP and PCT levels in patients who died of sepsis and those surviving from the disease at 1 and 2 weeks after admission and those at admission were analyzed; predictive effects of CRP and PCT levels on sepsis in the intensive care unit patients and their influence on the prognosis of patients with sepsis were analyzed. The latest CRP and PCT levels detected before death were taken as the standard for the dead patients with the survival time less than 1 or 2 weeks, and the data of patients at 1 or 2 weeks after admission were included, respectively.

Statistical analysis. Statistical analysis was conducted using SPSS 19.0 software [AsiaAnalytics (formerly SPSS China), Shanghai, China]. Sex and treatment effects were compared by the χ^2 test; measurement data were expressed as mean \pm SD; the non-parametric Kolmogorov-Smirnov (K-S) test was selected to compare the data between the two groups, and comparisons among various groups were conducted by using the analysis of variance. The receiver operating characteristic (ROC) curves of CRP and PCT of subjects were drawn; logistic regression analysis was used to analyze the correlation of CRP and PCT with the poor prognosis of patients. Univariate Cox regression analysis was used to analyze the related factors affecting the prognosis of patients with sepsis. A $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Clinical data. There were a total of 203 patients in the intensive care unit. In the sepsis group, there were 60 patients with colorectal cancer, including 35 males and 25 females with an

Table I. Comparisons of basic data between the two groups of patients.

Basic data	Sepsis group	Non-sepsis group	P-value
No. of cases (n)	60	143	
Sex (male/female)	35/25	82/61	0.579
Age (years)	56.6 ± 21.5	40.1 ± 11.6	0.036
Smoking history, n (%)			0.556
Yes	17 (28.33)	33 (23.08)	
No	43 (71.67)	110 (76.92)	
Place of residence, n (%)			0.372
City	41 (68.33)	82 (57.34)	
Countryside	19 (31.67)	61 (42.66)	

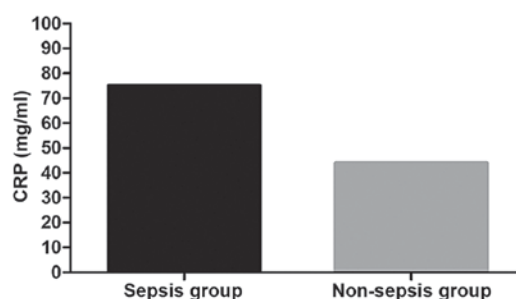


Figure 1. Detection results of CRP in the sepsis and the non-sepsis group. The average level of CRP in the sepsis group at admission is significantly higher than that in the non-sepsis group ($P < 0.05$). CRP, C-reactive protein.

average age of 56.6 ± 21.5 years; in the non-sepsis group, there were 143 patients with colorectal cancer, including 82 males and 61 females with an average age of 35.1 ± 11.6 years. There was a difference in age between the two groups ($P < 0.05$), but no differences in other basic data such as sex were found ($P > 0.05$) (Tables I-III).

Prognosis of patients with sepsis. As of May 2016, there were 26 death cases in the sepsis group, with a mortality rate of 43.33%. Septic shock occurred in most of them, with a mortality rate as high as 75%, which was significantly higher than those of patients with mild and severe sepsis ($P < 0.05$). There was no case of death in the non-sepsis group, and systemic inflammatory responses in patients were controlled and did not develop into sepsis (Table III).

Detection results of CRP. At admission, the average level of CRP in the sepsis was obviously higher than that in the non-sepsis group ($P < 0.05$). In the sepsis group, the average CRP level in patients with septic shock was higher than that in patients with severe sepsis and mild sepsis ($P < 0.05$); the average CRP level in patients with severe sepsis was higher than that in patients with mild sepsis ($P < 0.05$). Comparisons of CRP levels in patients who died of sepsis at 1 and 2 weeks after admission and those at admission showed that there were no changes ($P > 0.05$); CRP level in patients surviving sepsis at 1 week after admission was clearly decreased compared

Table II. Subgroups of the sepsis group (n=60).

Subgroups	Mild sepsis	Severe sepsis	Septic shock	P-value
No. of cases (n)	21	19	20	
Sex (male/female)	12/9	11/8	12/8	0.732
Average age (years)	43.2±21.3	58.5±19.6	68.1±23.5 ^a	0.664

^aCompared with those in patients with mild sepsis, there is a difference in the average age ($t=3.125$, $P=0.032$).

Table III. Prognosis of patients with sepsis.

Item	Mild sepsis	Severe sepsis	Septic shock	P-value
No. of cases (n)	21	19	20	
Survival, n (%)	19 (90.48)	10 (52.63)	5 (25.00)	0.029
Death, n (%)	2 (9.52)	9 (47.37)	15 (75.00)	

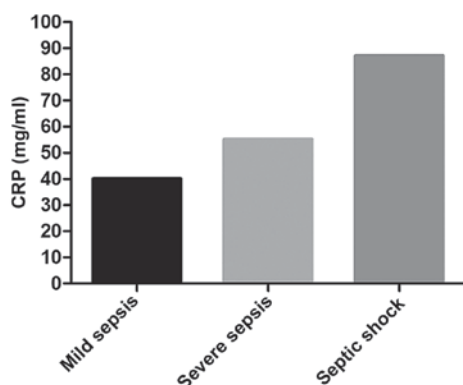


Figure 2. Detection results of CRP in each subgroup of patients in the sepsis group. In the sepsis group, the average CRP level in patients with septic shock is higher than those in patients with severe sepsis and mild sepsis ($P<0.05$), and the average CRP level in patients with severe sepsis is higher than that in patients with mild sepsis ($P<0.05$). CRP, C-reactive protein.

with that at admission ($P<0.05$); CRP level in those at 2 weeks after admission was significantly reduced compared with that at admission ($P<0.05$). The average level of CRP of patients who died of sepsis was higher than that of those who survived ($P<0.05$) (Figs. 1 and 2 and Table IV).

Detection results of PCT. The average PCT level in the sepsis group was significantly higher than that in the non-sepsis group ($P<0.05$). In the sepsis group, the average level of PCT in patients with septic shock was higher than that in patients with severe sepsis and mild sepsis ($P<0.05$); the average PCT level in patients with severe sepsis was higher than that in patients with mild sepsis ($P<0.05$). Comparison of the average PCT level in patients who died of sepsis at 1 week and 2 weeks after admission and that at admission showed there were no changes ($P>0.05$). PCT level in patients surviving from sepsis at 1 week after admission was overtly lowered compared with that at admission ($P<0.05$); PCT level in those at 2 weeks after admission significantly declined compared with that at

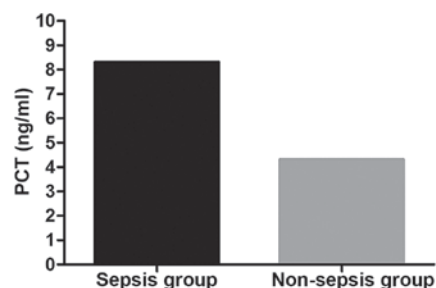


Figure 3. Detection results of PCT in the sepsis and the non-sepsis group. The average PCT level in the sepsis is significantly higher than that in the non-sepsis group ($P<0.05$). PCT, procalcitonin.

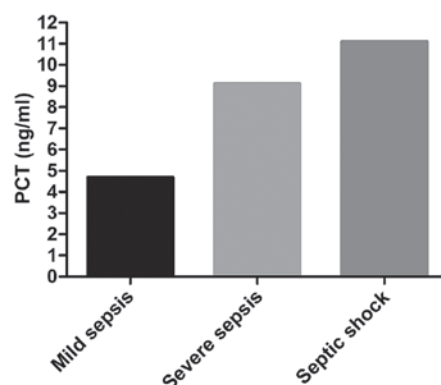


Figure 4. Detection results of PCT in each subgroup of patients in the sepsis group. In the sepsis group, the average level of PCT in patients with septic shock is higher than those in patients with severe sepsis and mild sepsis ($P<0.05$), and the average PCT level in patients with severe sepsis is higher than that in patients with mild sepsis ($P<0.05$). PCT, procalcitonin.

admission ($P<0.05$). The average level of PCT in patients who died of sepsis was higher than that in patients surviving from it ($P<0.05$) (Figs. 3 and 4 and Table V).

Logistic regression analysis and ROC analysis. Logistics regression analysis showed that PCT and CRP levels in patients in the intensive care unit were closely related to the severity of sepsis and the prognosis of patients. The higher the PCT and CRP levels were, the more severe the sepsis and the worse the prognosis would be ($r=0.826$, $P=0.007$; $r=0.732$, $P=0.012$). With death as the end of the prognosis of patients, the values of PCT and CRP in predicting the death of patients were relatively great, and their areas under the curve (AUC) were 0.734 and 0.699, respectively, and 95% confidence intervals (95% CIs) were 0.665-0.874 and 0.601-0.792, respectively (Fig. 5).

Table IV. Comparisons of the detection results of CRP between patients surviving sepsis and those who died (mg/ml).

Time	Patient surviving sepsis	Patient died of sepsis	t-value	P-value
No. of cases (n)	34	26		
At admission	52.2±11.3	64.5±10.9	2.365	0.047
1 week after admission	42.1±8.4 ^a	68.2±10.4 ^c	2.933	0.036
2 weeks after admission	35.2±7.7 ^b	69.5±9.4 ^d	3.114	0.027

^{a,b}Compared with that at admission, level is decreased ($P<0.05$); ^{c,d}compared with that at admission, there is no change ($P>0.05$). CRP, C-reactive protein.

Table V. Comparisons of the detection results of PCT between patients surviving sepsis and those who died (ng/ml).

Time	Patient surviving sepsis	Patient died of sepsis	t-value	P-value
No. of cases (n)	34	26		
At admission	5.8±1.2	7.8±1.6	2.269	0.038
1 week after admission	3.4±0.9 ^a	8.9±2.1 ^c	3.012	0.024
2 weeks after admission	2.1±0.4 ^b	8.1±1.4 ^d	3.985	0.015

^{a,b}Compared with that at admission, level is decreased ($P<0.05$); ^{c,d}compared with that at admission, there is no change ($P>0.05$). PCT, procalcitonin.

Table VI. Univariate Cox regression analysis.

Factors	Univariate analysis	
	HR (95% CI)	P-value
Sex (male vs. female)	0.734 (0.247-2.356)	0.792
Age (<50 vs. ≥50 years)	2.145 (1.549-4.566)	0.012
CRP (low vs. high)	2.141 (1.269-2.724)	0.013
PCT (low vs. high)	3.044 (1.258-7.336)	0.011

CRP, C-reactive protein; PCT, procalcitonin; HR, hazard ratio; CI, confidence interval.

Univariate Cox regression analysis. PCT level at 6.9 ng/ml represented that the specificity and sensitivity of the poor prognosis of patients with sepsis were 73.6 and 77.5%, respectively, so PCT=6.9 ng/ml was taken as the critical point between high concentration and low concentration. CRP concentration at 55.7 mg/l indicated that the specificity and sensitivity of the poor prognosis of patients were 64.6 and 77.4%, respectively, so CRP=55.7 mg/l was taken as the critical point between high concentration and low concentration. Univariate Cox regression analysis revealed that CRP, PCT and age might be risk factors for the poor prognosis of patients with sepsis (Table VI).

Discussion

Sepsis is one of the major causes of patient's death in the intensive care unit. It leads to the body's use of a large amount of sugar, lipids and proteins, thus changing the energy metabolism

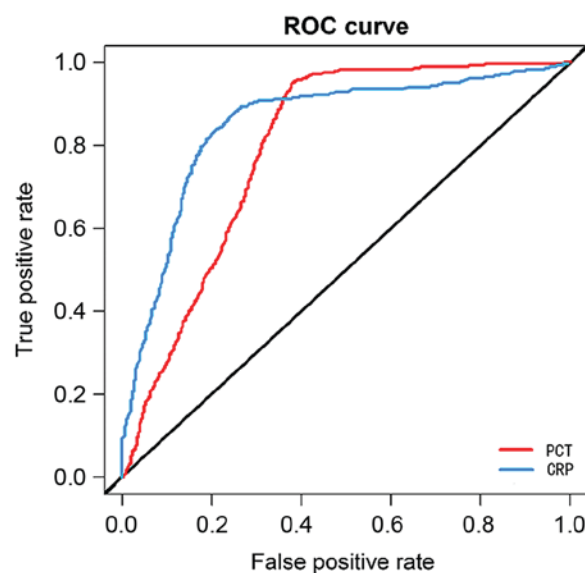


Figure 5. ROC regression analyses of PCT and CRP. With death as the end of the prognosis of patients, the values of PCT and CRP in predicting the death of patients are relatively great, and their AUC are 0.734 and 0.699, respectively, and 95% CIs are 0.665-0.874 and 0.601-0.792, respectively. ROC, receiver operating characteristic; PCT, procalcitonin; CRP, C-reactive protein; AUC, area under the curve.

mode and the rate of energy utilization of patients, which will cause an additional burden and may also cause concurrence with hypoproteinemia in patients (13,14). Moreover, the body's resistance to sepsis-induced tissue damage and inflammatory responses can further undermine the body's metabolic balance, and even cause organ failure (15,16). Therefore, it is very important to predict the occurrence of sepsis in patients

in the intensive care unit, control and treat sepsis in patients in the intensive care unit, and improve patients' quality of life and survival time. In this study, the predictive values of PCT and CRP for sepsis in patients in the intensive care unit and the prognostic values for patients with sepsis were explored by examining changes in PCT and CRP levels in patients in the intensive care unit.

In this study, changes in PCT and CRP levels in 203 intensive care unit patients were measured, and the results revealed that patients with sepsis had higher levels of PCT and CRP than non-sepsis patients, suggesting that PCT and CRP may be related to the occurrence of sepsis. However, no patients without sepsis was found to develop into patients with sepsis in this study. Therefore, whether changes in PCT and CRP levels have values in predicting sepsis needs to be further investigated. The study of Su *et al* (17) found that PCT cannot be completely used to predict the risk of sepsis after transplantation. The most sensitive indicator for neonatal sepsis diagnosis is CRP (18). However, there are few studies on whether CRP can be used as a predictor for sepsis, so more studies are needed to analyze whether these two markers can be predictors for sepsis.

In our study, patients with sepsis were further subdivided in detail according to different components, which showed that with the aggravation of sepsis in patients, PCT and CRP levels were also increased. Therefore, logistics regression analysis was used to analyze the relationships of PCT and CRP levels with the severity of sepsis, which revealed that the higher the PCT and CRP levels were, the more severe the sepsis in patients would be. Univariate Cox regression analysis also manifested that PCT and CRP might be risk factors for the poor prognosis of patients with sepsis. Studies of Savva *et al* (19), and Ashour *et al* (20) proved that soluble triggering receptor expressed on myeloid cells 1 (sTREM-1) and PCT have very good effects in assessing the severity of sepsis. Currently, there is little research on the value of CRP in assessing the severity of sepsis. However, Huo *et al* (21) found that autophagy-related 16-like 1 (ATG16L1) gene polymorphism is closely related to the severity of sepsis. Whether ATG16L1 affects PCT and CRP levels is worth further investigation.

During this study, there were 26 cases of death (43.33%). The prognosis of patients with sepsis was also analyzed. Logistic regression analysis showed that the higher the PCT and CRP levels were, the higher the risk of poor prognosis would be. Further ROC curve analysis revealed that PCT and CRP have good values in the prognosis of patients with sepsis. PCT is a good indicator for the diagnosis and prognosis of sepsis, and PCT and CRP levels are closely related to the severity of infection and organ dysfunction (22). A study of Franekova *et al* (23) also revealed that serum PCT and CRP can predict the prognosis of children with sepsis, which is consistent with our results. A study of Sonawane *et al* (24) indicated that CRP can also be used as an early predictor of sepsis in patients with thermal burns. Therefore, PCT and CRP are good indicators for the diagnosis and prognosis of sepsis, but their joint diagnostic values remain to be further explored.

In conclusion, the detection of changes in CRP and PCT levels has great clinical value in assessing the prognosis of patients with sepsis. High-level CRP and PCT indicate a poor prognosis in patients with sepsis.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

QL contributed to design of the study and was responsible for detection of CRP and PCT levels. He also drafted and revised the manuscript. XG analyzed and interpreted statistical analysis. Both authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Qilu Hospital of Shandong University in Dongying (Dongying, China) and informed consents were signed by the patients and/or guardians.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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