



The Value of Procalcitonin Combined with C-Reactive Protein Assay in the Early Clinical Diagnosis of Bloodstream Infection

Cheng-Hong Chen and Ling-Xian Ding*

Department of Clinical laboratory, Lijin County Central Hospital, Dongying City, Shandong Province, 257400, China.

Both authors contributed equally to this study.

ABSTRACT

This study aims to investigate the application value of procalcitonin (PCT) paired with C-reactive protein (CRP) in the early diagnosis of bloodstream infection. This study involved 298 patients with suspected bloodstream infections who were hospitalized in our hospital between March 2016 and March 2018. All patients were examined by blood culture, and the PCT and CRP levels were examined to observe the diagnostic value of PCT and CRP. Of the 108 patients with positive blood culture and 190 patients were negative. Serum PCT (12.25 ± 1.36) pg/mL and CRP (84.26 ± 2.81) mg/mL were higher in the positive group than in the negative group (1.26 ± 0.25) pg/mL, (39.12 ± 1.69) mg/mL, the difference was statistically significant ($t=16.513, 19.581, P<0.05$); PCT+CRP sensitivity was 97.22%, specificity was 90.53%, positive predictive value was 85.37%, and negative predictive value was 98.29%. To conclude the application of PCT combination with CRP detection in the early clinical diagnosis of bloodstream infection has better application value, better sensitivity and strong specificity, which can be widely used in clinical practice.

Article Information

Received 11 October 2022

Revised 20 November 2022

Accepted 04 December 2022

Available online 21 July 2023

(early access)

Authors' Contribution

CC and LD jointly conceived, designed, coordinated for this study, and wrote the manuscript.

Key words

Procalcitonin, C-reactive protein, Bloodstream infection, Early clinical diagnosis

INTRODUCTION

Bloodstream infection (BSI) is a systemic infection caused by the invasion of pathogenic microorganisms into the human body and their participation in the blood circulation, which results in the proliferation of these pathogenic microorganisms and the release of toxins and metabolites, with a high morbidity and mortality rate (Pan *et al.*, 2016). Therefore, early detection and determination of BSI and reasonable diagnosis are important to reduce the occurrence and progression of BSI (Paredes *et al.*, 2014). Blood culture has an important diagnostic value for BSI and is the gold standard for diagnosis, but this method is complicated and slow. It usually takes 5~7 days to obtain the diagnosis result, which has a negative impact on the early diagnosis and treatment of BSI and leads to a longer diagnosis and treatment period and significantly increases

medical costs, so it is important to seek a simpler and faster diagnosis method (Xu *et al.*, 2017). Procalcitonin (PCT) and C-reactive protein (CRP) are blood infection indicators that have been studied more in recent years, they each have advantages and disadvantages in reacting to blood infections. PCT is a serum protein with very low expression in normal human body, but its expression increases significantly when the body is infected with bacteria, which is often used as a marker of early bacterial infection. CRP is a non-specific inflammatory protein synthesized by the liver, and its expression increases significantly when the patient suffers from bacterial attack or tissue damage (Wang *et al.*, 2013; Milone, *et al.*, 2014).

Blood culture has been widely used as the gold standard for the diagnosis of BSI, but its detection cycle is long, which is not conducive to the timely diagnosis and treatment of clinicians. The combined detection of serum PCT and CRP is short in time and sensitive in response, which can improve the diagnostic efficiency of BSI, and can further effectively distinguish gram-positive and gram-negative bacteria, so as to provide reference advice for the medication of patients, which has a high reference value for the early diagnosis and treatment of patients with clinical BSI (Liu *et al.*, 2022). The purpose of this study was to investigate the application value of PCT combined with CRP assay in the early clinical diagnosis of bloodstream infection, which is reported as follows.

* Corresponding author: dingling88x@126.com
0030-9923/2023/0001-0001 \$ 9.00/0



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MATERIALS AND METHODS

General information

A total of 298 patients with suspected BSI were selected for this study, including 152 male patients and 146 female patients, aged 20-63 years, with a mean age of (45.26 ± 2.63) years. All patients received multiple bacterial cultures before signing the informed consent form. The blood culture detection of suspected patients with BSI was completed by Biomerieux automatic detector and supporting reagents (Biomerieux, Lyons, France). The blood culture adopted a double set method, that is, the venous blood samples of two different parts were collected, and the blood culture of aerobic bacteria and anaerobic bacteria was carried out at the same time. If the blood culture of a part of the sample is positive for bleeding, the sample is judged to be positive for blood culture, if no pathogenic bacteria are detected, it is judged to be negative. The type of pathogen was recorded in the samples with positive blood cultures.

Inclusion criteria: (1) all patients diagnosed with suspected BSI with reference to the BSI diagnostic criteria (Lamy *et al.*, 2020); (2) the infected bacteria include: *Acinetobacter baumannii*, *Escherichia coli*, methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Burkholderia onioniae*, *Enterococcus faecium*, and *Staphylococcus epidermidis*; (3) the clinical information of patients were complete.

Exclusion criteria: (1) history of autoimmune disease; (2) history of diagnosed malignancy; (3) combination of acute and chronic infectious diseases; (4) recent treatment with immunosuppressive drugs or anti-inflammatory drugs; (5) patients with hematological diseases and patients with positive blood cultures for multiple bacteria. All patients were provided written informed consent to participate, and this study met ethical requirements.

Patients were examined by blood culture: extract venous blood from all patients on an empty stomach for more than 8 h, transfer the positive specimens cultured by an automatic blood bacterial culture instrument to a blood plate, culture for 12 to 20 h, and then take a single colony and configure it into 0.5 McLaughlin bacteria. The suspension was identified by an automatic bacterial identification and drug susceptibility analysis system, and if there was no positive alarm after 5 days of culture, it was regarded as negative. Patients were divided into negative and positive groups according to blood culture results.

When the fever was above 38.5°C, two sets of blood were collected from the skin puncture points of the left and right upper arms for double sets of blood culture, each set of blood culture with one bottle of anaerobic culture

and one bottle of aerobic culture, and the volume of blood collected was 16-20 mL/time, and they were placed into two blood culture bottles. 2 sets of blood cultures were drawn at intervals of less than 5 min. Positive blood cultures were identified by a fully automated bacterial identification/sensitization system. Meanwhile, CPR and PCT detected were implemented after bacterial culture. CRP (Beckman IM-MAGE800 Special Protein Analyzer) was measured by a fully automatic analyzer using latex turbidimetry with a sensitivity of 0.1 mg/mL, and positive when CRP was > 5.0 mg/L. PCT (Roche Cobas E602 Automatic Chemiluminescence Analyzer) was determined by automatic chemiluminescence immunoassay analyzer, and the detection range was 0.1~200.0 pg/mL, and PCT > 0.5 pg/mL was judged to be positive. Then, the antibacterial drugs were used for patients. Early diagnosis is made when the patient has just developed symptoms at the beginning of the disease. The combination of PCT and CRP in the early diagnosis of infectious diseases can evaluate the progress of the disease, with better sensitivity and specificity, and provide reference for the early treatment of infectious diseases. The patient's condition is accurately determined before the bacterial culture.

Observed indicators

The levels of CRP and PCT in serum were recorded. The sensitivity, specificity, positive predictive value and negative predictive value of CRP and PCT were calculated with the positive results of blood culture as the gold standard. Sensitivity = true positive/(true positive + false negative) $\times 100.00\%$; specificity = true negative/(true negative + false positive) $\times 100.00\%$; positive predictive value = true positive/(true positive + false positive) $\times 100.00\%$; negative predictive value = true negative/(true negative + false negative) $\times 100.00\%$.

Statistical methods

The data were analyzed using SPSS 20.0 statistical software, where the count data were expressed as % with χ^2 test and the measurement data were expressed as $\bar{x} \pm s$ with *t*-test, and $P < 0.05$ was considered a statistically significant difference.

RESULTS

Patient blood culture results

A total of 298 subjects were included in this study, including 152 males (51.01%) and 146 females (48.99%), with a mean age of (45.26 ± 2.63) years. Of the 298 blood culture specimens, 108 (36.24%) were positive and 190 (63.76%) were negative (Table 1).

Serum index levels of patients in both groups

According to the results, the serum PCT level of the positive group was (12.25±1.36) pg/mL, which was significantly higher than that of the negative group (1.26±0.25) pg/mL. Besides, the serum CRP level of the positive group was (84.26±2.81) mg/mL, which was markedly higher than that of the negative group (39.12±1.69) mg/mL. Therefore, we confirmed that the serum PCT and CRP levels in the positive group were both higher than those in the negative group, and the difference was statistically significant ($P < 0.05$) (Table II).

Table I. Basic information of 298 patients.

Information	n(%)/ $\bar{x}\pm s$
Gender	
Man	152 (51.01%)
Woman	146 (48.99%)
Age	45.26±2.63
Underlying illness	
Sepsis	154 (51.7%)
Septic shock	49 (16.4%)
Pneumonia	95 (31.9%)
Blood culture results	
Negative	190 (63.76%)
Positive	108 (36.24%)

Table II. Comparison of serum index levels between two groups of patients ($\bar{x}\pm s$).

Group	PCT (pg/mL)	CRP (mg/mL)
Positive group (n=108)	12.25±1.36	84.26±2.81
Negative group (n=190)	1.26±0.25	39.12±1.69
<i>t</i> value	16.513	19.581
<i>P</i> value	<0.05	<0.05

PCT, procalcitonin; CRP, C-reactive protein.

Table III. Analysis of clinical diagnostic value of serum indicators (%).

Indicators	Sensitivity	Specificity	Positive predictive value	Negative predictive value
PCT	75.00 (81/108)	78.95 (150/190)	69.94 (81/121)	84.75 (150/177)
CRP	96.30 (104/108)	16.32 (31/190)	39.92 (105/263)	88.57 (31/35)
PCT-CRP	97.22% (105/108)	90.53% (172/190)	85.37% (105/123)	98.29% (172/175)
<i>t</i> value		16.513		19.581
<i>P</i> value		<0.05		<0.05

PCT, procalcitonin; CRP, C-reactive protein.

Sensitive and specific of CPR-PCT

The sensitivity, specificity, positive predictive value and negative predictive value of PCT-CRP were higher than those of PCT alone, and the specificity, positive predictive value and negative predictive value of PCT-CRP were higher than those of CRP alone, and the differences were statistically significant ($P < 0.05$) see Table III.

DISCUSSION

Patients with BSI often have a systemic inflammatory response, which can lead to severe sepsis and septic shock. Blood culture is the gold standard in the diagnosis of BSI and plays an important role in clinical practice, but this method takes a long time to diagnose, and if some patients have already taken anti-infection treatment, it will have a certain impact on the rate of positive detection of pathogenic bacteria. Even if a positive test is found, the patient may have a serious infection, resulting in the patient's condition not being effectively treated in a timely manner, which may result in the patient's death. To a certain extent, Gram negative bacterial BSI has more serious pathological changes than Gram positive bacterial BSI, especially bacterial bloodstream infections caused by *Escherichia coli* and *Staphylococcus aureus*, and if a positive blood culture result is detected earlier, the morbidity and mortality rate is significantly lower than that of patients with later detection results. Therefore, early diagnosis of BSI facilitates timely and effective treatment of the disease and has a significant control effect on the progression of the disease (Liu *et al.*, 2022). Several previous studies have shown that PCT-CRP can be used for clinical diagnosis, and in this study, based on previous studies, clinical data from local hospitals were used for analysis (Ding *et al.*, 2016; Chen *et al.*, 2015; Tang *et al.*, 2013; Tan, 2017). The results are an important guide for the diagnosis of patients with BSI in local hospitals.

It was found that the serum PCT and CRP levels in the positive group were higher than those in the negative group, and the difference was statistically significant. The results of the study pointed out that the specificity of PCT was higher than that of CRP (78.95% vs 16.32%), which was similar to the results of the study by Philipp (Schuetz *et al.*, 2018). However, van der Does *et al.* (2018) showed that the accuracy of PCT was lower than that of CRP in the diagnosis and suspected infection. The positive predictive value of PCT was 69.94%, higher than that of CRP (39.92%). The negative predictive value of PCT was 84.75%, lower than that of CRP (88.57%), which was consistent with Simon *et al.* (2005). PCT+CRP sensitivity was 97.22%, specificity was 90.53%, positive predictive value was 85.37%, and negative predictive value was

98.29%. The results of [Tang et al. \(2013\)](#) showed that the sensitivity of PCT+CRP was 67.6%, specificity was 88.6%, positive predictive value was 82.1%, and negative predictive value was 78.0%, and the specificity and positive predictive value were consistent with the results of this paper, but the sensitivity and negative predictive value of the combined diagnosis were lower, considering that it might be related to the atypical sample selection and the difference in the sample selection size.

CRP is a non-specific marker of acute phase protein formed in the liver of infected patients and elevated when the body experiences an inflammatory response. Under normal conditions, serum CRP levels are low; when the body becomes infected, CRP synthesized by the liver increases dramatically. PCT is a pre-titanium analog of calcitonin produced by the thyroid gland, and under normal conditions, the body produces very low levels of PCT, but when bacterial infections occur, endotoxin-induced production of PCT in parenchymal tissue cells increases and it enters the bloodstream, often resulting in serum PCT concentrations up to 1000 times the normal value within 24 h ([Tan, 2017](#)). Some studies have pointed out that early PCT evaluation can improve the overall in-hospital survival rate of febrile patients in the emergency room, and has a higher prognostic effect on the patients finally diagnosed with bloodstream infection. At the same time, it may be related to the lower mortality rate of patients over 85 years old with severe acquired pneumonia or high comorbidities ([Covino et al., 2020, 2021](#)). From the results of this study, it is clear that the combination of PCT and CRP has a better sensitivity, specificity and more accurate results. The results of this study showed that: among the 298 blood culture specimens, there were 108 positive cases and 190 negative cases, and the serum PCT and CRP levels in the positive group were higher than those in the negative group, and the difference was statistically significant ($P < 0.05$), indicating that the expression levels of inflammatory factors were significantly higher in patients with BSI compared with those in the healthy population, suggesting that PCT and CRP have some value in the diagnosis of BSI. This was also confirmed in a study by [Liu et al. \(2022\)](#) in which serum PCT and CRP levels in patients with BSI, were significantly higher than patients without BSI, suggesting that serum PCT and CRP levels were abnormally elevated in patients with BSI. In healthy individuals, serum PCT levels are very low. PCT is not affected by hormones or renal function in the body during secretion. PCT is usually expressed in neuroendocrine cells of the thyroid and lung and is cleaved to produce calcitonin; in patients with BSI, pro-inflammatory cytokines can lead to PCT expression in tissue cells of the body. It has also been suggested that the rate of positive

serum PCT increases significantly in comparison with the rate of positive microbiological cultures, and that the rate of positive microbiological cultures increases with the increase in PCT levels ([Zhu et al., 2018](#)). When patients have viral infections and allergic reactions, they usually do not cause an increase in PCT levels; when they have localized infections, they have a mild increase in PCT; when they have severe systemic bacterial infections, they often result in a significant increase in PCT levels ([Wang and Yan, 2017](#)). Moreover, the increased PCT levels due to bacterial infections usually originate from macrophages and monocytes in various organs. In vitro testing of patients for inflammatory factors such as serum PCT and CRP is relatively simple, but when blood culture is used for testing, it takes a longer time, resulting in a delay in obtaining results, and is prone to contamination. Although inflammatory factors such as PCT and CRP can effectively diagnose whether a patient has a BSI, the type of pathogenic bacteria cannot usually be determined, and it is difficult to determine the selection of cooperative antimicrobial drugs for symptomatic treatment with these results, so blood culture and drug sensitivity tests cannot be replaced by inflammatory factor tests such as PCT and CRP. Therefore, when testing patients with BSI, the effective combination with dynamic blood culture testing is usually used, which can improve the clinical diagnostic accuracy and shorten the testing time, allowing patients to be treated earlier. Studies have shown that serum PCT and CRP levels are of high diagnostic value for Gram-negative bacteria BSI ([Yang et al., 2017](#)). However, the specificity and sensitivity of PCT and CRP tests to different strains are still unclear. We will conduct further research to explore the differences in detection sensitivity among different strains. In conclusion, this study: (1) verified the value of PCT combined with CRP test in the early clinical diagnosis of BSI; (2) combined with local hospital data, this method can be promoted and used in the clinical diagnosis of local hospitals. There are some limitations to this study, such as the sample size of the two groups is too different, the results may be biased. This study does not limit the strain, which may make it difficult to replicate the results of this study.

CONCLUSION

The application of PCT combination with CRP detection in the early clinical diagnosis of bloodstream infection has better application value, better sensitivity and stronger specificity than those of PCT alone or CRP alone. This method can be widely used in clinical practice.

Funding

Not applicable.

IRB approval

The study was approved by the Ethics Committee of Lijin County Central Hospital.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Lijin County Central Hospital, Informed consent was also obtained from all of the patients.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article

Statement of conflict of interest

The authors have declared no conflict of interest.

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