Pcv-aCO$_2$ and procalcitonin levels for the early diagnosis of bloodstream infections caused by gram-negative bacteria

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ABSTRACT

Background: The central venous-to-arterial carbon dioxide difference (Pcv-aCO$_2$) is a biomarker for tissue perfusion, but the diagnostic value of Pcv-aCO$_2$ in bacteria bloodstream infections (BSI) caused by gram-negative (GN) bacteria remains unclear. This study evaluated the expression levels and diagnostic value of Pcv-aCO$_2$ and procalcitonin (PCT) in the early stages of GN bacteria BSI.

Methods: Patients with BSI admitted to the intensive care unit at Guangdong Provincial People's Hospital between August 2014 and August 2017 were enrolled. Pcv-aCO$_2$ and PCT levels were evaluated in GN and gram-positive (GP) bacteria BSI patients.

Results: A total of 132 patients with BSI were enrolled. The Pcv-aCO$_2$ (8.32 ± 3.59 vs 4.35 ± 2.24 mmHg $p = 0.001$) and PCT (30.62 ± 34.51 vs 4.92 ± 6.13 ng/ml $p = 0.001$) levels were significantly higher in the GN group than in the GP group. In the diagnosis of GN bacteria BSI, the area under the receiver operating characteristic curve (AUROC) for Pcv-aCO$_2$ was 0.823 (95% confidence interval (CI): 0.746−0.900). The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 71.90%, 88.00%, 74.07% and 78.21%, respectively. The AUROC for PCT was 0.818 (95% CI: 0.745−0.890). The sensitivity, specificity, PPV and NPV were 57.90%, 94.67%, 71.93% and 74.67%, respectively.

Conclusions: Pcv-aCO$_2$ and PCT have similar and high diagnostic value for the early diagnosis of BSI caused by GN bacteria.

Key Indexing Terms: Central venous-to-arterial carbon dioxide difference; Procalcitonin; Bloodstream infection; Gram-negative bacteria; Diagnosis. **[Am J Med Sci 2022;364(6):752–757.]**

INTRODUCTION

A bloodstream infection (BSI) is a serious systemic infectious disease that often leads to detrimental outcomes. BSI is associated with high mortality and morbidity.[1] Therefore, early precision anti-infective treatment is particularly important. However, the identification of BSI pathogens still depends on blood culture, which is time consuming and may delay targeted anti-infective treatment.

In recent years, some biomarkers for the early identification of pathogens have been identified, allowing the administration of targeted antibiotics as early as possible. Procalcitonin (PCT) is a helpful biomarker for early diagnosis of sepsis in critically ill patients.[2] It can differentiate gram-negative (GN) from gram-positive (GP) bacteria sepsis, especially in sepsis caused by bloodstream infection.[3–5] Recently, Pcv-aCO$_2$ has been recognized as an indicator of circulation status and oxygen metabolism balance.[6] Pcv-aCO$_2$ is defined as partial pressure difference of central venous to arterial carbon dioxide. When tissue perfusion is poor, microcirculation disorder occurs, resulting in a decrease in carbon dioxide clearance rate and an increase in Pcv-aCO$_2$, so Pcv-aCO$_2$ can effectively evaluate the status of microcirculation and tissue perfusion in patients. It is well known that BSI caused by different pathogens have different effects on hemodynamics.[7] Whether Pcv-aCO$_2$ can be used as a biomarker for the early identification of BSI pathogens

is still unclear. The objective of this study was to compare Pcv-aCO_2 and serum PCT levels in GN and GP bacteremia groups and to investigate the early diagnostic value of Pcv-aCO_2 and PCT in bacterial BSI caused by GN bacteria.

METHODS

Patients and samples

This retrospective study was carried out using clinical and routine laboratory data collected at the department of critical care medicine in Guangdong Provincial People's Hospital between August 2014 and August 2017. The inclusion criterion were as follows: (1) aged >18 years; (2) with systemic inflammatory response syndrome or hypotension; (3) more than one blood culture positive; and (4) a single microorganism was identified in the blood culture. The exclusion criteria were as follows: (1) the patient did not have Pcv-aCO_2 and serum PCT levels tested at the time blood was taken for culture; and (2) the patient had a history of a malignant tumor. The study was approved by the research ethics committee of the Guangdong Provincial People's Hospital (NO. GDREC2016372H). Patients or their relatives in the study provided informed consent to participate in the study.

Study design

The following information was extracted from the medical file of each enrolled patient: (1) clinical and epidemiological data including age, sex, and severity of BSI as evaluated by the Sequential Organ Failure Assessment (SOFA) and Acute Physiology And Chronic Health Evaluation II (APACHE II) scores; (2) biochemical data including the Pcv-aCO_2 and PCT levels from the same time as the blood culture. When the patients were diagnosed with BSI, all the dates were collected by one researcher with the use of an electronic case report form and then confirmed by another researcher. Patients were divided into two groups according to blood culture: the GP bacteria group and the GN bacteria group. Pcv-aCO_2 levels, serum PCT levels and other variables were compared between the two groups.

Measurements of Pcv-aCO_2 and PCT levels

Arterial and central venous blood gas analysis were routinely measured at the same time as blood was taken for culture within 6 h of suspected bloodstream infection during the hospital course. The Pcv-aCO_2 level was obtained by the simultaneous analyses of arterial and central venous blood gas with a Radiometer ABL800 blood gas analyzer (Radiometer, Denmark). Serum PCT was measured with the Kryptor immunoassay (Elecsys BRAHMS PCT, Shanghai, China) in the Department of the Clinical Laboratory Center of Guangdong Provincial People's Hospital.

Statistical analyses

Statistical analyses were performed using SPSS software version 24.0 (SPSS Inc., Chicago, Illinois, USA). The continuous variables are presented as the mean ± SD and were compared using Student's t-test or analysis of variance (ANOVA) when normally distributed. Otherwise, they were compared by the Wilcoxon rank-sum test and are presented as the median and interquartile range (IQR). The discrete variables were expressed as counts (%) and compared using χ^2 or Fisher's exact tests. Receiver operating characteristic (ROC) curve analysis was used to evaluate Pcv-aCO_2 and PCT as markers of clinical success. A P value < 0.05 was considered statistically significant.

RESULTS

A total of 132 patients including 75 GP bacteria BSI and 57 GN bacteria BSI patients were enrolled in the study (Fig. 1). The baseline characteristics in the GP and GN bacteria groups are shown in Table 1. The proportions of sex, age and past disease history were similar in both groups. The SOFA (12.21 ± 3.87 vs 9.68 ± 3.37 $p = 0.001$) and APACHE II scores (28.61 ± 6.48 vs 25.07 ± 5.61 $p = 0.001$) were higher in the GN group than in the GP group. Regarding the concurrent foci of infection, there was no significant difference in the proportion of pneumonia and abdominal infection between the two groups. The proportions of urinary tract infection (10.67 vs 24.56 $p = 0.034$) and skin and soft tissue infection (14.67 vs 3.51 $p = 0.033$) in the GP group were lower and higher than those in the GN group, respectively.

The most common GP bacterial species were Staphylococcus species, including Staphylococcus aureus, coagulase-positive Staphylococcus haemolyticus and Enterococcus species. The three most common GN bacterial species were Escherichia coli, Klebsiella pneumoniae, and nonfermentative GN bacilli including Acinetobacter baumannii and Pseudomonas aeruginosa (Table 2).

The Pcv-aCO_2 (8.32 ± 3.59 vs 4.35 ± 2.24 mmHg $p = 0.001$) and PCT (30.62 ± 34.51 vs 4.92 ± 6.13 ng/ml

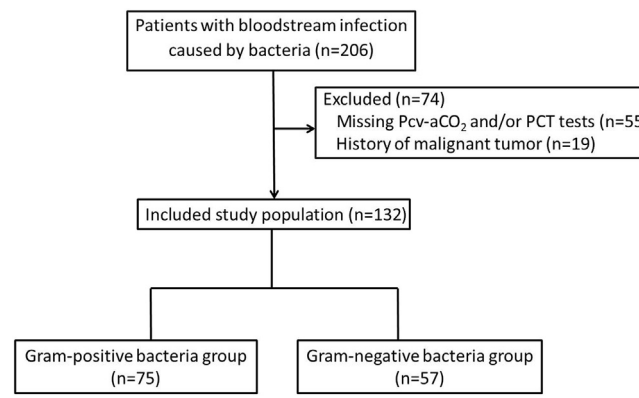

FIGURE 1. Flow chart of patient enrollment.

TABLE 1. Baseline clinical characteristics of the different groups.

Clinical variables	Gram-positive bacteria group (*n* = 75)	Gram-negative bacteria group (*n* = 57)	*p*-value
Age (years)	81.65 ± 7.97	80.54 ± 8.14	0.434
Women, n (%)	23 (30.67)	18 (31.58)	0.911
SOFA score	9.68 ± 3.37	12.21 ± 3.87	0.000
APACHEIIscore	25.07 ± 5.61	28.61 ± 6.48	0.001
Comorbidities, n (%)			
Diabetes	23 (30.67)	18 (31.58)	0.911
Hypertension	45 (60.00)	26 (45.61)	0.101
Cerebral infarction	30 (40.00)	15 (26.32)	0.100
COPD	21 (28.00)	10 (17.54)	0.160
CAD	15 (20.00)	9 (15.79)	0.534
Previous cardiovascular surgery	7 (9.33)	4 (7.02)	0.633
NYHA III–IV	21 (28.00)	13 (22.81)	0.499
Chronic renal insufficiency	8 (10.67)	6 (10.53)	0.979
Concurrent foci of infection, n (%)			
Pneumonia	51 (68.00)	33 (57.89)	0.232
Urinary tract infection	8 (10.67)	14 (24.56)	0.034
Abdomen infection	4 (5.33)	6 (10.52)	0.264
Skin and soft tissue infection	11 (14.67)	2 (3.51)	0.033
Others	1 (1.33)	2 (3.51)	0.809
28-day mortality, n (%)	23 (30.67)	28 (49.12)	0.031

The data are expressed as the mean ± standard deviation, and p ≤0.05 indicates a significant difference.
APACHEII, Acute Physiology And Chronic Health EvaluationII; COPD, chronic obstructive pulmonary disease; CAD, Coronary atherosclerotic cardiopathy; SOFA, Sequential Organ Failure Assessment; NYHA, New York Heart Association..

p = 0.001) levels at the onset of BSI were significantly higher in the GN group than in the GP group (Fig. 2). The corresponding ROC curve was constructed to measure the overall diagnostic value. Pcv-aCO_2 and PCT have similar diagnostic value for BSI caused by GN bacteria (Fig. 3). The area under the ROC curve (AUROC) for Pcv-aCO_2 was 0.823 (95% confidence interval (CI): 0.746 −0.900). Considering a Pcv-aCO_2 cutoff value of 6.70 mmHg, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 71.90%, 88.00%, 74.07% and 78.21%, respectively. The AUROC for PCT was 0.818 (95% CI: 0.745−0.890), and the optimal cutoff value was 12.6 ng/mL; The sensitivity, specificity, PPV and NPV were 57.90%, 94.67%, 89.19% and 74.73%, respectively.

DISCUSSION

The present study demonstrated that the levels of Pcv-aCO_2 and PCT were higher in BSI caused by GN bacteria than by GP bacteria. The Pcv-aCO_2 and PCT can improve the accuracy of early diagnosis of BSI caused by GN bacteria.

BSI represents a common complication among critical patients and is a leading cause of morbidity and mortality.[8] BSI may have serious adverse outcomes without timely and effective treatment. Studies have shown that the correct use of antibiotics in patients with severe infection is important for reducing mortality and morbidity.[9] Therefore, the identification of pathogens within 6 h of admission is closely associated with the clinical outcome of patients with severe infections.[10] However, the pathogens of BSI is mainly determined by time-consuming blood culture, which making it difficult to identify

TABLE 2. Pathogen distribution of bloodstream infection.

Pathogen	*n* (%)
Gram-positive bacteria	
Staphylococcus aureus	15 (11.36)
Staphylococcus epidermidis	20 (15.15)
Staphylococcus hominis	16 (12.12)
Staphylococcus capitis	9 (6.82)
Enterococcus faecium	6 (4.55)
Enterococcus faecalis	4 (3.03)
Staphylococcus wallis	2 (1.52)
Staphylococcus auricularis	1 (0.76)
Staphylococcus lugdunensis	1 (0.76)
Streptococcus constellation	1 (0.76)
Gram-negative bacteria	
Escherichia coli	17 (12.88)
Pseudomonas aeruginosa	11 (8.33)
Klebsiella pneumoniae	15 (11.36)
Acinetobacter baumannii	7 (5.30)
Alcaligenes xylosoxidans	1 (0.76)
Stenotrophomonas maltophilia	1 (0.76)
Clostridium	2 (1.52)
Bacteroides thetaiotaomicron	2 (1.52)
Enterobacter cloacae	1 (0.76)

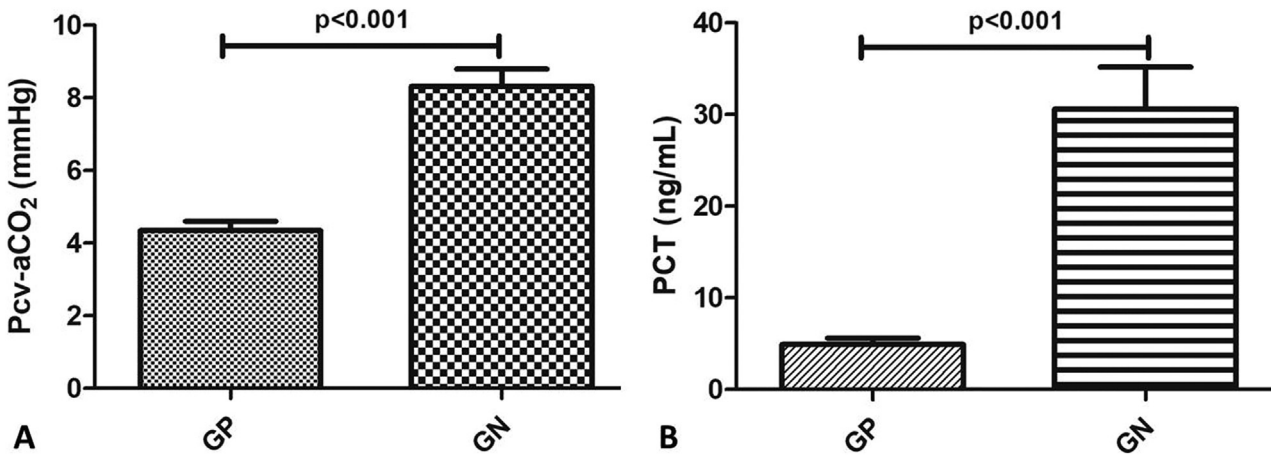

FIGURE 2. The differences between the GN and GP groups in Pcv-aCO_2 and serum PCT levels: A, Pcv-aCO_2 levels in the two groups: the Pcv-aCO_2 levels were significantly higher in the GN group than in the GP group ($p < 0.001$); B, PCT levels in the two groups: the PCT levels were significantly higher in the GN group than in the GP group ($p < 0.001$). *Abbreviations*: GN, gram-negative; GP, gram-positive; Pcv-aCO_2, central venous-to-arterial carbon dioxide difference; PCT, procalcitonin.

pathogens in the early stage. Moreover, due to the small number of pathogenic microorganisms in circulating blood, the extensive requirements for culture conditions for specific pathogens, and the use of antibiotics before blood culture, the positivity rate of blood culture is not high, which may eventually lead to delayed use of targeted antibiotics.[11] As a common indicator of clinical infection, PCT plays an important role in the early diagnosis and prognosis of infectious diseases.[12] PCT combined with C-reactive protein (CRP) has important predictive value for the prognosis of septic shock.[13] The

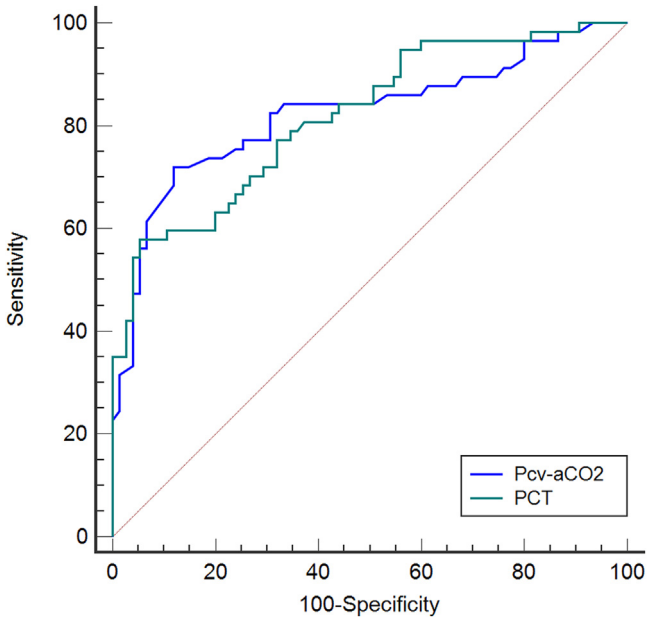

FIGURE 3. ROC curve of Pcv-aCO_2 and serum PCT levels in early diagnosis of gram-negative bacteria bloodstream infection. *Abbreviations*: Pcv-aCO_2, central venous-to-arterial carbon dioxide difference; PCT, procalcitonin; ROC, Receiver Operating Characteristic Curve.

infections caused by GN bacteria result in higher levels of PCT than those resulting from infections caused by GP bacteria and fungi, and the PCT level can provide guidance for the choice of antibiotics;[14] therefore, PCT levels can be used for the early diagnosis of sepsis caused by GN bacteria.[15] PCT and CRP kinetics are predictors of early clinical stability of BSI caused by GN bacteria.[16] In fact, PCT also plays an important role in the initial identification of pathogens in patients with BSI. Our study showed that serum PCT levels were significantly higher in the GN group than in the GP group, which is similar to previous research.[17] The reason for the apparent increase in PCT level caused by GN bacteria may be related to activation of signaling pathways by endotoxins. Therefore, PCT is a useful indicator for the identification of pathogens in patients with BSI and provides important clues for the early selection of appropriate antibiotic regimens.[18]

In this study, we first found that the Pcv-aCO_2 level in patients with BSI caused by GN bacteria was significantly higher than that caused by GP bacteria. This may be due to different pathogen infections cause different circulation disorders,[7] and GN bacteria infections are more prone to circulatory failure, leading to poor tissue perfusion.[19] As we know, Pcv-aCO_2 has been considered an evaluation indicator of tissue perfusion.[20] Weil et al. found that Pcv-aCO_2 was significantly elevated in patients who underwent cardiac arrest, which is clearly associated with poor tissue perfusion.[21] Similarly, Pcv-aCO_2 gradually increased with decreasing cardiac output in animal hemorrhage, hypovolemia, and obstructive shock models.[22] Because Pcv-aCO_2 is closely related to cardiac output, Pcv-aCO_2 is a good predictor of death after cardiac surgery.[23,24] In addition, by monitoring Pcv-aCO_2, we can observe the balance between tissue oxygen supply and demand under low blood volume conditions.[25] Pcv-aCO_2 is not consistent with the changes in cardiac output in patients with septic shock, suggesting that changes in the

Pcv-aCO_2 level are related not only to cardiac output but also to the tissue oxygen supply and demand balance.[26] Therefore, the role of Pcv-aCO_2 in the diagnosis and treatment of septic shock is important.[27] During early fluid resuscitation in septic shock patients, the improvement in Pcv-aCO_2 is closely related to the prognosis and can be used as an indicator of adequate fluid resuscitation.[28–30] The high ratio of Pcv-aCO_2 to arterial-central venous oxygen partial pressure is associated with poor lactate clearance and is an independent predictor of ICU death in septic shock patients.[31,32]

BSI as a serious infection may lead to pathological changes such as tissue perfusion disorders and oxygen metabolism imbalance in patients in the ICU.[33] Since Pcv-aCO_2 can reflect tissue perfusion and oxygen metabolism, it can be used as an indicator of BSI severity and pathogen identification. In this study, the level of Pcv-aCO_2, SOFA score and APACHEII score in GN bacteria group was significantly higher than in GP bacteria group. Furthermore, we evaluated the diagnostic value of Pcv-aCO_2 and PCT for BSI caused by GN bacteria with a ROC curve. Pcv-aCO_2 and PCT have similar predictive value for the diagnosis of bloodstream infection caused by GN bacteria. We found that they can provide clues for the identification of pathogens in the early stage of BSI and improve the diagnostic efficiency of BSI caused by GN bacteria.

CONCLUSIONS

Pcv-aCO_2 and PCT levels were higher in the GN group than in the GP group. They have similar and high diagnostic value for the early diagnosis of GN bacteria BSI.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Zhong-hua Wang: Writing – review & editing, Conceptualization, Visualization, Writing – original draft. **Xue-biao Wei:** Writing – review & editing, Conceptualization, Visualization, Writing – original draft. **Xiao-long Liao:** Writing – review & editing, Data curation. **Sheng-long Chen:** Writing – review & editing, Formal analysis. **Wei-xin Guo:** Writing – review & editing, Data curation. **Pei-hang Hu:** Writing – review & editing, Data curation. **Yan Wu:** Writing – review & editing, Data curation. **You-wan Liao:** Writing – review & editing, Data curation. **Tie-he Qin:** Writing – review & editing. **Shou-hong Wang:** Writing – review & editing.

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