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Research Paper

Prognostic value of central venous-to-arterial carbon dioxide difference in patients with bloodstream infection

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Abstract

Background: Bloodstream infection (BSI) are prone to circulation disorders, which portend poor outcome. The central venous-to-arterial carbon dioxide difference (Pcv-aCO_2) is a biomarker for circulation disorders, but the prognostic value of Pcv-aCO_2 in BSI patients remains unclear. This study was to investigate the association of Pcv-aCO_2 with adverse events in BSI patients.

Methods: The patients with BSI between August 2014 and August 2017 were prospectively enrolled. Clinical characteristic and laboratory results were collected. We analyzed the association of the level of Pcv-aCO_2 with clinical variables and 28-day mortality.

Results: A total of 152 patients were enrolled. The Pcv-aCO_2 was positively correlated with white blood cell count (r=0.241, p=0.003), procalcitonin (r=0.471, p<0.001), C-reactive protein (r=0.192, p=0.018), lactate (r=0.179, p=0.027), Sequential Organ Failure Assessment (r=0.318, p<0.001) and Acute Physiology And Chronic Health Evaluation II score (r=0.377, p<0.001), while that was negatively correlated with central venous oxygen saturation (r=-0.242, p<0.001) and platelet (r=-0.205, p=0.011). Kaplan-Meier curves demonstrated that patients with Pcv-aCO_2 >6mmHg had a worse prognosis than those without (log rank=32.10, p<0.001). Multivariate analysis showed Level of Pcv-aCO_2 was an independent risk factor for 28-day mortality (HR: 3.10, 95% CI: 1.43-6.74, p=0.004). The area under the receiver operating characteristic curve of Pcv-aCO_2 for prediction of 28-day mortality in patients with BSI was 0.794. Pcv-aCO_2>6 mmHg had 81.1% sensitivity and 78.8% specificity for predicting 28-day mortality.

Conclusion: Pcv-aCO_2 may be a simple and valuable biomarker to assessment of 28-day mortality in patients with BSI.

Key words: central venous-to-arterial carbon dioxide difference; biomarker; prognostic factor; bloodstream infection

Introduction

Bloodstream infection (BSI) is common systemic infection in intensive care unit (ICU), affecting 189/100000 patients [1]. It is associated with increased risk of organ failure and mortality, and one-year mortality from BSI is between 8% and 48% [2]. BSI bring a huge financial burden to families and society [3]. Therefore, early accurate identification of patients at high risk of poor outcomes may have an essential role in improving prognosis.

The common pathological change of BSI is

microcirculation disorder [4]. Previously, lactate and central venous oxygen saturation ($S_{CV}O_2$) are accepted clinical indicators of organ perfusion and oxygen metabolism [5, 6]. At present, central venous-to-arterial carbon dioxide difference (Pcv-aCO_2) as a biomarker of perfusion is gradually recognized. Pcv-aCO_2 has reported to be associated with poor prognosis in critical patients suffering from shock, and Pcv-aCO_2 is recommended as a biomarker for further resuscitation interventions [7]. In addition, persistently high Pcv-aCO_2 during the early phases of resuscitation was a predictor for poor outcomes in patients with septic shock [8, 9]. However, the prognostic role of Pcv-aCO_2 in patients with BSI remains to be seen. In this study, we attempted to explore the association between Pcv-aCO_2 and 28-day mortality in patients with BSI.

Patients and methods

Study objects

We prospectively enrolled patients with BSI between August 2014 and August 2017 in Geriatric ICU, Guangdong Provincial People's Hospital, Guangzhou, China. Inclusion criterion were as follows: (1) age>18 years; (2) clinical symptoms meet systemic inflammatory response syndrome or hypotension; (3) at least one positive blood culture; (4) only a single bloodstream infection pathogen. Exclusion criteria included: (1) patients refused cardiopulmonary resuscitation or aggressive measures; (2) mismatch of the time of arterial and venous blood gas test. The eligible patients were divided into two groups based on a cut-off value of Pcv-aCO_2 of >6mmHg from previous study on septic shock [8]. The present study was approved by the Ethics Committee of Guangdong Provincial People's Hospital (No. GDREC2014006H), and written informed consent was obtained from all included patients or their relatives.

Data collection

The demographic including sex, age were recorded and Acute Physiology And Chronic Health Evaluation II (APACHE II) score, and Sequential Organ Failure Assessment (SOFA) were calculated when the patients were diagnosed with BSI. The biochemical data, such as Pcv-aCO_2, $ScvO_2$, white blood cell (WBC) count, platelet (PLT), procalcitonin (PCT), C-reactive protein (CRP), and lactate were tested when the patients were diagnosed with BSI. We routinely performed arterial and central venous blood gas analysis while taking blood culture specimens. Pcv-aCO_2 and $ScvO_2$ were obtained by simultaneous analysis of arterial and central venous blood gases with a blood gas analyzer (ABL 800; Radiometer Medical, Denmark); other demographic and clinical characteristics of enrolled participants were collected by a researcher with the use of an electronic case report form, and then were confirmed by another researcher.

Follow-up and endpoints

All the patients were followed-up for 28 days by telephone interviews after BSI diagnosis. The primary endpoint was 28-day all-cause mortality.

Statistical analysis

Statistical analyses were performed by using SPSS 24.0 software (IBM, Armonk, NY, USA). The continuous variables were presented as mean ± standard deviation (SD), and compared using independent sample t-test when they were normally distributed; for non-normally distribution, the Wilcoxon rank-sum test was conducted, and the data presented as median and interquartile range. Categorical variables were presented as a percentage and compared using χ^2 or Fisher's exact test. Bivariate correlations were calculated by Pearson's or Spearman's correlation coefficients. Survival curves were depicted by using Kaplan-Meier analysis. Cox proportional hazards regression model was used to analyze the association between the variables and the risk of death. Multivariate Cox regression analysis was performed with the variables whose p-value was less than 0.05 in univariate logistic regression analysis for 28-day mortality. Receiver operating characteristic (ROC) curves were plotted to evaluate the predictive power of Pcv-aCO_2 for 28-day mortality. A p-value < 0.05 was considered statistically significant.

Results

Clinicopathological characteristics of patients with BSI

Finally, 152 patients were enrolled and 53 (34.9%) patients died within 28 days. All the patients were divided into two groups: Pcv-aCO_2 ≤ 6 mmHg (n=88) and Pcv-aCO_2 > 6 mmHg (n=64). The baseline characteristics were presented in **Table 1**. There were no significant differences between the two groups in terms of age, gender, concurrent foci of infection, the main history, non-infection comorbidity and CRP. The SOFA (11.89 ± 4.08 vs 9.69 ± 3.18, p<0.001), APACHE II score (28.63 ± 6.11 vs 24.78 ± 5.38, p<0.001), PCT (34.17 ± 39.52 vs 9.73 ± 21.24, p=0.001), WBC (16.90 ± 7.12 vs 14.20 ± 6.02, p=0.013), lactate (3.48 ± 3.44 vs 2.34 ± 2.67, p=0.023) were higher and platelet (114.78 ± 80.42 vs 146.23 ± 90.05, p<0.028) , $ScvO_2$ (53.15 ± 12.05 vs 70.53 ± 10.73, p<0.001) were lower in Pcv-aCO_2 > 6 mmHg group. The demand for mechanical ventilation, vasopressor and continuous

renal replacement therapy (CRRT) in Pcv-aCO_2 > 6 mmHg group is significantly greater than in Pcv-aCO_2 ≤ 6 mmHg group. Gram-positive (GP) bacteria were the predominant pathogens in Pcv-aCO_2 ≤ 6 mmHg group, while Gram-negative (GN) bacteria are the predominant pathogens in Pcv-aCO_2 > 6 mmHg group. The 28-day mortality (60.9% vs 15.9%, p<0.001) was higher in Pcv-aCO_2 > 6 mmHg group.

Table 1. Patients' baseline clinical characteristics at different levels of Pcv-aCO_2

Clinical variables	Pcv-aCO_2≤6mmHg (n=88)	Pcv-aCO_2>6mmHg (n=64)	p
Age (years)	80.55 ± 7.62	82.58 ± 8.24	0.119
Women, n (%)	31(35)	19(30)	0.200
SOFA	9.69± 3.18	11.89± 4.08	<0.001
APACHE II	24.78± 5.38	28.63± 6.11	<0.001
Concurrent foci of infection(%)			
Pneumonia	64(72.7)	38(59.3)	0.084
Urinary tract infection	15(17.0)	10(15.6)	0.600
Abdomen infection	3(3.4)	7(10.9)	0.129
Skin and soft tissues infection	4(4.5)	7(10.9)	0.236
Others	1(1.1)	2(3.1)	0.780
History, n (%)			
Diabetes	30(34.1)	20(31.3)	0.713
Hypertension	51(57.9)	33(51.6)	0.434
Cerebral infarction	30(34.1)	15(23.4)	0.155
COPD	28(31.8)	12(18.8)	0.071
CAD	16(18.2)	7 (10.9)	0.192
Previous cardiovascular surgery	9(10.2)	6(9.4)	0.862
Chronic renal insufficiency	10(11.4)	5(7.8)	0.469
Non-infection comorbidity, n (%)			
NYHA III–IV	21(23.9)	11(17.2)	0.319
Surgical treatment	9(10.2)	6(9.4)	0.862
Massive haemorrhage	6(6.8)	2(3.1)	0.523
Traumatic brain injury	7(8.0)	2(3.1)	0.369
PCT (ng/ml)	9.73 ± 21.24	34.17± 39.52	<0.001
WBC($x10^3/mm^3$)	14.20 ± 6.02	16.90± 7.12	0.013
Plateles ($x10^3/mm^3$)	146.23 ± 90.05	114.78 ± 80.42	0.028
CRP(mg/L)	122.60 ± 61.37	130.35± 52.86	0.417
Lactate (mmol/L)	2.34 ± 2.67	3.48 ± 3.44	0.023
$ScvO_2$(%)	70.53± 10.73	53.15± 12.05	<0.001
Microbiology			
Gram-positive bacteria, n (%)	54(61.4)	21(32.8)	<0.001
Gram-negative bacteria, n (%)	15(17.0)	42(65.6)	<0.001
Fungus, n (%)	18(20.5)	2(1.6)	<0.001
Mechanic ventilation, n (%)	60(68.2)	58(90.6)	0.001
Vasopressor, n (%)	50(56.8)	50(78.1)	0.006
CRRT, n (%)	20(22.7)	32(50.0)	<0.001
28-day death (%)	14(15.9)	39(60.9)	<0.001

SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology And Chronic Health Evaluation II; COPD, chronic obstructive pulmonary disease; CAD, Coronary Artery Disease; PCT, procalcitonin; WBC, white blood cell; CRP, C-reaction protein; $ScvO_2$, central venous oxygen saturation; CRRT, continuous renal replacement therapy; NYHA, New York Heart Association.

Correlation of Pcv-aCO_2 with other parameters

We found that Pcv-aCO_2 was positively correlated with WBC (r=0.241, p=0.003), PCT (r=0.471, p<0.001), CRP (r=0.192, p=0.018), lactate (r=0.179, p=0.027), SOFA (r=0.318, P<0.001), and APACHE II score (r=0.377, p<0.001), while that was negatively correlated with $ScvO_2$ (r =-0.242, p<0.001) and PLT (r =-0.205, p=0.011) (**Table 2**).

Table 2. Spearman's correlation analysis between Pcv-aCO_2 and other clinical variables among all patients included in the study (n=152)

	r	p
WBC	0.241	0.003
Platele	-0.205	0.011
PCT	0.471	<0.001
CRP	0.192	0.018
$ScvO_2$	-0.242	0.003
Lactate	0.179	0.027
SOFA	0.318	<0.001
APACHE II	0.377	<0.001

WBC, white blood cell; PCT, procalcitonin; CRP, C-reaction protein; $ScvO_2$, central venous oxygen saturation; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology And Chronic Health Evaluation II.

Pcv-aCO_2 and 28-day mortality

The survival curves were shown in **Figure 1**. Kaplan–Meier survival curves show that patients with Pcv-aCO_2 > 6 mmHg had a worse prognosis than those with Pcv-aCO_2 ≤6 mmHg (log-rank=32.10, p< 0.001).

The risk of death was significantly correlated with the levels of Pcv-aCO_2 (hazard ratio (HR): 4.90, 95% confidence interval (CI): 2.66-9.05, p<0.001), PLT (HR: 3.90, 95% CI: 2.16-7.03, p<0.001), PCT (HR: 2.87, 95% CI: 1.62-5.07, p<0.001), lactate (HR: 2.53, 95% CI: 1.46-4.45, p=0.001), $ScvO_2$ (HR: 2.04, 95% CI: 1.17-3.53, p=0.011), SOFA (HR: 3.25, 95% CI: 1.81-5.86, p<0.001) and APACHE II score (HR: 2.61, 95% CI: 1.44-4.75, p=0.002) . Multivariate Cox regression analysis was used to analyze the associations of the risk of death and adjustment of Pcv-aCO_2, PLT, PCT, lactate, $ScvO_2$, SOFA and APACHE II score. The levels of Pcv-aCO_2 (HR: 3.10, 95% CI: 1.43-6.74, p=0.004) and PLT (HR: 2.08, 95% CI: 1.08-3.98, p=0.028) were independent risk factors for 28-day mortality in patients with BSI (**Table 3**).

Table 3. Univariate and multivariate Cox regression analyses of the 28-day mortality

Variables	Univariate Cox regression			Multivariate Cox regression		
	HR	95% CI	p	HR	95% CI	p
Pcv-aCO_2	4.90	2.66-9.05	<0.001	3.10	1.43-6.74	0.004
WBC	3.18	0.77-13.07	0.108			
Platele	3.90	2.16-7.03	<0.001	2.08	1.08-3.98	0.028
PCT	2.87	1.62-5.07	<0.001	1.39	0.72-2.69	0.327
CRP	1.40	0.81-2.43	0.229			
$ScvO_2$	2.04	1.17-3.53	0.011	0.72	0.38-1.36	0. 311
Lactate	2.53	1.46-4.45	0.001	1.57	0.85-2.88	0.147
SOFA	3.25	1.81-5.86	<0.001	1.86	0.91-3.82	0.89
APACHE II	2.61	1.44-4.75	0.002	1.28	0.62-2.64	0.507

Pcv-aCO_2, central venous-to-arterial carbon dioxide difference; WBC, white blood cell; PCT, procalcitonin; CRP, C-reaction protein; $ScvO_2$, central venous oxygen saturation; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology And Chronic Health Evaluation II.

The predictive accuracy for 28-day mortality

The ROC curve of Pcv-aCO_2 predicting 28-day mortality in patients with BSI, as shown in **Figure 2**, revealed that the area under the ROC curve was 0.794. Furthermore, Pcv-aCO_2 greater than 6 mmHg was the best threshold for predicting 28-day mortality, with a sensitivity of 81.1% and specificity of 78.8%.

Discussion

The present study demonstrated that increased Pcv-aCO_2 at the time of blood culture was independently associated with 28-day mortality in patients with BSI. In addition, Pcv-aCO_2>6 mmHg was a valuable predictor of the increased risk of 28-day mortality. In this study, the 28-day mortality was 34.9%, which were higher than previous studies [10]. It might be due to the advanced age of the patients in our study, because age is one of the risk factors for poor prognosis [11]. The other reasons should be considered was more serious patients enrolled in our study. Patients included in this study had higher SOFA and APACHE II score than previous studies [10].

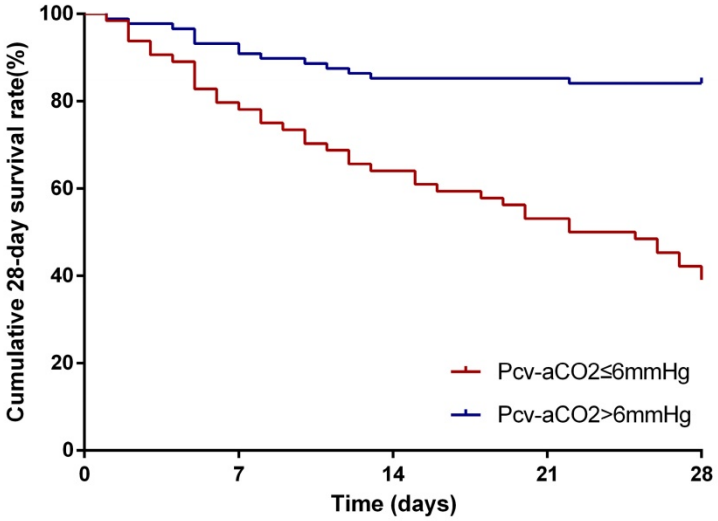

Figure 1. Kaplan-Meier analysis for depicting the curves of the 28-day cumulative survival rates. Comparing patients in the groups of Pcv-aCO_2 ≤ 6 mmHg and Pcv-aCO_2>6 mmHg showed that the 28-day survival rates were significantly lower in patients with Pcv-aCO_2>6 mmHg than those with Pcv-aCO_2 ≤ 6 mmHg (p<0.001)

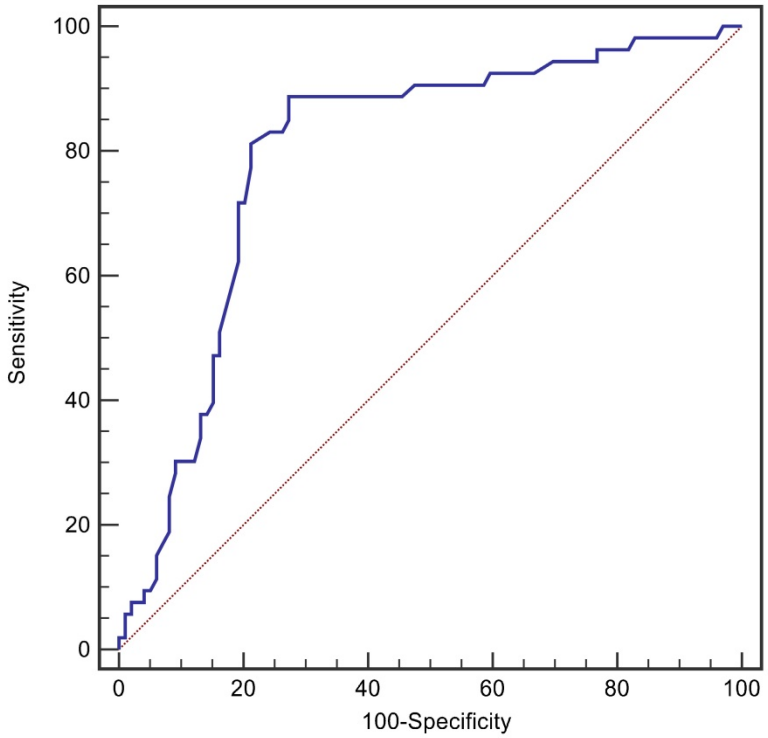

Figure 2. The receiver operating characteristic curves for Pcv-aCO_2 levels in predicting 28-day mortality of the patients with BSI.

It is well-known that BSI often cause circulatory disorder, which associated with poor outcomes [12]. In recent years, Pcv-aCO_2 is considered one of indicator for monitoring of tissue perfusion [13]. A previous study reported that a significant increase in Pcv-aCO_2 during cardiac arrest results from cardiovascular stagnation [14]. Similarly, another research showed that Pcv-aCO_2 is inversely proportional to cardiac output in animal models of hemorrhage, hypovolemia, and obstructive shock [15-17]. When cardiac output reduce, the blood flow is slow and the elution ability of CO_2 is impaired; therefore, more CO_2 is accumulated in the tissue, and the Pcv-aCO_2 increases as the CO_2 diffuses easily and quickly [18]. In the early fluid resuscitation of septic shock, a persistent increase in Pcv-aCO_2 suggests a poor prognosis, and monitoring Pcv-aCO_2 during early fluid resuscitation is a helpful indicator for assessing the adequacy of tissue perfusion [8, 19]. As an indicator of tissue perfusion, Lactate is the goal of early fluid resuscitation in septic shock [20]. There was a correlation between Pcv-aCO_2 and lactate in our study. In Pcv-aCO_2 > 6 mmHg group, the lactate level, circulatory disorders and vasopressor used were more, which suggest that Pcv-aCO_2 can be an good indicator of tissue perfusion and prognosis.

In severe infections, oxygen supply-demand imbalance often leads to increased mortality [21]. In fact, Pcv-aCO_2 monitoring not only can reflect cardiac output and tissue microcirculation perfusion, but also show a balance between tissue oxygen supply and demand, thereby objectively reflecting tissue oxygen metabolism [22]. A study showed that the changes of cardiac output were not consistent with those of Pcv-aCO_2 during septic shock, suggesting that hemodynamic changes cannot be used to explain an increase in Pcv-aCO_2 in this case, which may be associated with poor tissue oxygen supply and increased oxygen consumption [23]. Kocsi *et al* [24] found that Pcv-aCO_2 is an important indicator to monitor an imbalance between tissue oxygen supply and demand caused by low blood volume. The oxygen supply and demand of tissue can be timely detected by monitoring dynamic changes of Pcv-aCO_2 in case of insufficient blood volume.The ratio of Pcv-aCO_2 to arteriovenous oxygen contentis difference is a better marker of global anaerobic metabolism than lactate in septic shock patients [25]. Furthermore, we found that Pcv-aCO_2 was negatively correlated with $S_{CV}O_2$ which is an indicator of the balance of oxygen metabolism, suggesting that Pcv-aCO_2 is an appropriate indicator for tissue perfusion and oxygen metabolism.

The mortality of bloodstream infections caused by different pathogen is different [26]. Furthermore, different pathogen infections may cause different circulation disorders [27], which indicated by Pcv-aCO_2. Since Pcv-aCO_2 can reflect tissue perfusion, it may be used for the identification of BSI pathogens. As we know, PCT plays an important role in the diagnosis of BSI [28]. It helps identify pathogens and guides the choice of antibiotics [29]. In this study, Pcv-aCO_2 and PCT were found to be significantly correlated, suggesting that Pcv-aCO_2 may contribute to the identification of pathogens. Moreover, we found the pathogen distribution was different in different groups presented based on the level of Pcv-aCO_2, and there was more GN bacteria infection in the higher level of Pcv-aCO_2 group. This shows that Pcv-aCO_2 can provide a clue to identify pathogens and predict outcomes.

Additionally, we found that Pcv-aCO_2 has a significant correlation with $S_{CV}O_2$, lactate, PCT, CRP, SOFA and APACHE II score in patients with BSI. PCT and CRP plays an important role in the early diagnosis and prognosis of BSI patients [30, 31]. $S_{CV}O_2$ and lactate guides early fluid resuscitation can effectively predict the prognosis of patients with sepsis [32, 33]. Pcv-aCO_2, $S_{CV}O_2$, and lactate are taken as important indicators for treatment and prognosis of sepsis [34]. In our study, the patients with different levels of Pcv-aCO_2 showed significant differences in $S_{CV}O_2$, lactate, PCT, PLT, SOFA, APACHE II score, and prognosis. The use of mechanical ventilation, vasopressor, and CRRT were significantly more in Pcv-aCO_2 >6mmHg group than those in Pcv-aCO_2 ≤6mmHg group. Therefore, Pcv-aCO_2 can properly reflect the illness severity of the patient. We also further analyzed the association between Pcv-aCO_2 and the risk of death by using Cox regression analysis, which indicated that Pcv-aCO_2 was an independent risk factors for 28-day mortality. After that, ROC curves were plotted to evaluate the predictive power of Pcv-aCO_2 for the occurrence of 28-day mortality. We found that the Pcv-aCO_2 is an important predictive factor for 28-day mortality in patients with BSI.

Limitation

This was a retrospective analysis based on prospectively collected data. There are several limitations in this study. One limitation is that there was no dynamic monitoring of Pcv-aCO_2, that may ignore the impact of different treatments on clinical outcomes. In addition, the use of basic drugs, especially sodium bicarbonate, in patients during the study was not fully clarified, which may affect the accuracy of the results of Pcv-aCO_2 monitoring. Moreover, this is a single-center study, that included limited research samples, therefore further

multi-center large-scale studies need to be conducted.

Conclusion

Our results demonstrated that increased Pcv-aCO_2 while blood culture was an independent predictor of 28-day mortality in patients with BSI, even after adjusting a previous risk model. Furthermore, patients with Pcv-aCO_2 greater than 6mmHg were more likely to have poor outcomes. The use of Pcv-aCO_2 as a prognostic marker provides valuable information for risk stratification.

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Author Contribution

Zhonghua Wang and Xuebiao Wei contributed equally to this article. Zhonghua Wang and Xuebiao Wei conceived and designed the study, and drafted the article. Xiaolong Liao, Weixin Guo, Peihang Hu, Yan Wu, Jie Li, Youwan Liao collected the clinical data. Shenglong Chen analyzed statistically the data. Tiehe Qin and Shou-hong Wang conceived and designed the study, revised the article, and all authors approved the final version of the article. All authors meet the ICMJE authorship criteria.

Competing Interests

The authors have declared that no competing interest exists.

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