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Original Article

Elevated blood pressure variability is associated with incidence of sepsis-associated encephalopathy

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Abstract: Background: Cerebral microcirculation disorder is associated with the pathophysiology of sepsis-associated encephalopathy (SAE). Blood pressure variability could be involved in the altered cerebral microcirculation due to dysfunctional cerebral autoregulation in septic patients. Methods: In this prospective study, blood pressure was monitored to analyze its variability in septic patients. The cognitive ability of these patients was assessed daily using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) test. Survivors were followed-up for a 12-month period. Results: Forty percent of sepsis patients (n = 45) presented with delirium. The cut-off value (8.94 mmHg) of BP variability was detected by ROC curve analysis. Patients with high BP variability (> 8.94 mmHg) presented with a greater degree of delirium (60.7% vs. 19.6%, $P < 0.001$) with higher Sequential Organ Failure Assessment (SOFA) scores (10.29 ± 4.82 vs. 7.7 ± 3.48, $P = 0.014$) and mortality (41.1% vs. 23.2%, $P < 0.05$). Multivariate logistic regression analysis showed that BP variability was related to delirium (OR: 1.17, 95% CI: 1.02-1.33, $P = 0.02$), and death following within 28 days (OR: 1.17, 95% CI: 1.00-1.37, $P < 0.05$), independent of mean BP and vasoactive drug usage. Conclusions: Elevated BP variability is positively related to clinical signs of SAE and mortality in septic patients.

Keywords: Blood pressure, variability, sepsis-associated encephalopathy

Introduction

Sepsis is one of the most intractable syndromes in the setting of an intensive care unit (ICU) and has perplexed critical care physicians for decades. In addition to the continuing high mortality despite the implementation of Surviving Sepsis Campaign (SSC) bundles, the social function and quality of life of many survivors are still extensively impaired by the long-term complications of sepsis [1]. As one of the most challenging complications, sepsis-associated encephalopathy (SAE) is defined by diffuse cerebral dysfunction during the course of sepsis in the absence of direct CNS infection or other types of encephalopathy [2]. SAE is characterized by an acute-onset diffuse cerebral dysfunction and a variety of clinical manifestations such as delirium, seizures, coma, and altered mental status. It occurs in more than half of patients with sepsis, and is associated with increased mortality or long-term cognitive dysfunction [3].

The pathophysiology of SAE has not been established, but several potential mechanisms have been proposed, including altered cerebral microcirculation. Cerebral autoregulation (CA) plays an important role in the intricate process by which stable cerebral perfusion is maintained against changes in arterial blood pressure (BP) [4]. However, in patients with sepsis, CA is impaired due to excessive systemic inflammation [5], with consequential influences on cerebral blood flow due to the variation in BP. Therefore, we conducted this study to investigate if variation of BP is a risk factor which contributes to the development and progression of SAE in septic patients.

Materials and methods

Subjects

We conducted a prospective, observational study in a 50-bed ICU of an academic teaching hospital over a 22-month period from March

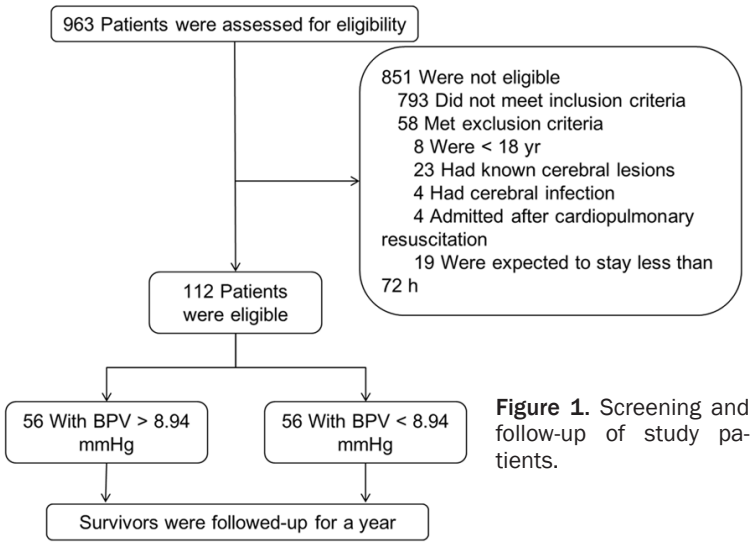

Figure 1. Screening and follow-up of study patients.

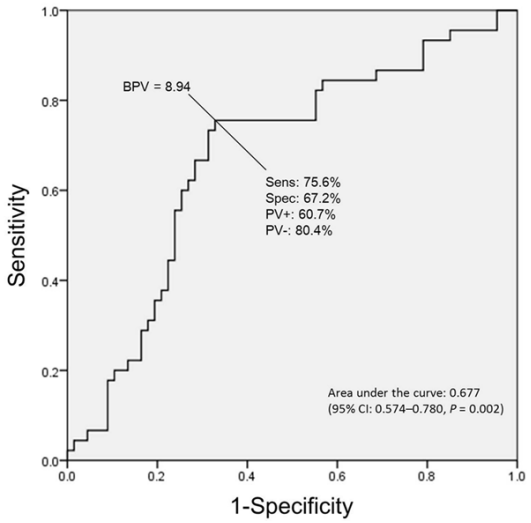

Figure 2. ROC curve analysis. ROC curve for the blood pressure variability to separate patients who presented with delirium from those who didn't.

2014 to December 2015. Patients admitted or diagnosed with sepsis in the ICU were included in the study. Sepsis was defined according to standard international criteria [6]. Severe sepsis was defined by the presence of two or more diagnostic criteria of the systemic inflammatory response syndrome, proven or suspected infection, and dysfunction of at least one organ. The Ethics Committee of the West China Hospital approved the study protocol.

Patients with one or more of the following conditions were excluded: 1) aged less than 18 years, 2) known cerebral lesions (ischemic or hemorrhagic cerebrovascular event, neoplasm), 3) cerebral infection, 4) after cardiopulmonary resuscitation, 5) expected ICU stay less than 72 h, and 6) pregnancy.

Data collection

We collected demographic information, as well as length of stay in the ICU, duration of mechanical ventilation, source of sepsis, and sedative drug usage. Clinical and laboratory data concerning organ failure and inflammation were also compiled. Survivors were followed-up for a 12-month period. The severity of illness was assessed according to the Acute Physiology and Chronic Health Evaluation (APACHE) II score and the Sequential Organ Failure Assessment (SOFA) score.

Delirium assessment

We evaluated patients twice daily to detect neurological dysfunction, inattention or altered level of consciousness using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), which is the most valid and reliable evaluation tool in delirium assessment [7]. Sedated patients were evaluated at least 4 h after the cessation of medication.

BP measurement

All the patients underwent 24-h BP monitoring after admission using a non-invasive monitor (IntelliVue MP60, Philips, Netherlands). The BP cuff was fitted to one of the participant's arms; the cuff size was determined by the upper arm circumference. BP measurements were recorded at 60-min intervals. BP variability (BPV) was calculated as the standard deviation (SD) of mean arterial pressure (MAP) on the first study day. The mean BP was calculated as an overall 24-h average of MAP for each patient.

Statistical analysis

Statistical analysis was performed with SPSS software (IBM, USA). Receiver operating characteristic (ROC) curve analysis was used to

Table 1. Characteristics and laboratory results in the high and low BPV groups

	Total n = 112	BPV low group (≤ 8.94 mmHg) n = 56	BPV high group (> 8.94 mmHg) n = 56	*P* value
Age (year)	57.62 ± 16.31	55.05 ± 16.08	60.18 ± 16.29	0.097
Male	77 (68.8%)	38 (67.9%)	39 (69.6%)	0.838
APACHE II	20.18 ± 6.46	19.14 ± 6.9	21.21 ± 5.87	0.090
SOFA	8.99 ± 4.38	7.7 ± 3.48	10.29 ± 4.82	0.014
Severity				0.004
Sepsis	18 (16.1%)	14 (25.0%)	4 (7.1%)	
Severe sepsis	58 (51.8%)	31 (55.4%)	27 (48.2%)	
Septic shock	36 (32.1%)	11 (19.6%)	25 (44.6%)	
Source of sepsis				0.418
Abdomen	65 (58.0%)	31 (55.4%)	34 (60.7%)	
Lung	30 (26.8%)	14 (25.0%)	16 (28.6%)	
Other	17 (15.2%)	11 (19.6%)	6 (10.7%)	
Delirium	45 (40.2%)	11 (19.6%)	34 (60.7%)	< 0.001
Vasoactive drug usage	43 (38.4%)	14 (25.0%)	29 (51.8%)	0.004
Mean BP (mmhg)	85.85 ± 8.83	85.78 ± 9.39	85.92 ± 8.32	0.934
MAP_{max} (mmhg)	99.88 ± 10.38	96.49 ± 10.10	103.28 ± 9.60	< 0.001
MAP_{min} (mmhg)	72.38 ± 12.61	76.58 ± 9.59	68.18 ± 13.90	< 0.001
BPV (mmhg)	9.14 ± 3.49	6.7 ± 1.52	11.57 ± 3.2	-
CRP (mg/L)	148.00 (90.30, 203.00)	149.70 (81.75, 228.00)	145.50 (97.15, 195.50)	0.746
IL-6 (pg/mL)	259.00 (92.14, 865.80)	164.30 (66.79, 760.25)	343.65 (183.75, 1300.80)	0.021
PCT (ng/mL)	5.35 (1.07, 27.92)	5.17 (1.04, 26.13)	6.89 (1.37, 33.39)	0.202
Cholesterol (mmol/L)	2.23 ± 1.07	2.28 ± 1.13	2.17 ± 1.02	0.606
GCS	9.43 ± 4.08	10.05 ± 4.38	8.8 ± 3.69	0.105
RASS	-1.78 ± 1.46	-1.52 ± 1.50	2.04 ± 1.39	0.061
Midazolam (mg)*	106.38 ± 130.42	102.71 ± 144.83	110.06 ± 115.44	0.767
Propofol (mg)*	620.05 ± 1032.61	680.18 ± 1153.28	559.91 ± 902.51	0.540
Fentanyl (mg)*	2.49 ± 1.48	2.65 ± 1.50	2.33 ± 1.47	0.254

*, the data of Midazolam, Propofol and Fentanyl are the total dose during the first three days. BPV: blood pressure variability; CRP: C-reactive protein; IL-6: Interleukin 6; PCT: Procalcitonin; GCS: Glasgow Coma Score; RASS: Richmond Agitation-Sedation Scale.

Table 2. Multivariable logistic regression analysis with delirium as the dependent variable

	OR (95% CI)	Beta value	*P* value
Age	1.00 (0.97-1.03)	0.00	0.98
Vasoactive drug usage	0.96 (0.40-2.28)	-0.05	0.92
APACHE II	1.11 (1.03-1.19)	0.10	0.01
Mean BP	1.04 (0.99-1.09)	0.04	0.14
BPV	1.17 (1.02-1.33)	0.15	0.02

BPV: blood pressure variability.

assess the BPV on the first day to predict delirium and determine a cut-off value with optimal sensitivity and specificity. Patients were divided into two groups according to the cut-off value. For continuous variables, Student's *t*-test was used for normally distributed data and the Mann-Whitney U-test was used for skewed variables. Categorical variables were compared with the chi-square test or the Fisher's exact test. Risk factors for delirium, such as age and severity of illness, can also affect BPV; therefore, we performed multivariable logistic regression analysis to evaluate the independent risk factors for a positive CAM-ICU test. Survival rates were analyzed using the Kaplan-Meier test. $P < 0.05$ was considered to indicate statistical significance.

Results

A total of 112 patients with sepsis were included in this study, while 58 patients who met the exclusion criteria were excluded. **Figure 1** shows the basis for inclusion of the patients. Abdominal infection was the major source of

Table 3. Multivariable logistic regression analysis with death (28 day) as the dependent variable

	OR (95% CI)	Beta value	*P* value
Age	1.04 (1.00-1.07)	0.04	0.03
Vasoactive drug usage	2.68 (1.00-7.18)	0.99	0.05
APACHE II	1.16 (1.06-1.27)	0.15	*< 0.01*
Mean BP	0.99 (0.93-1.05)	-0.01	0.66
BPV	1.17 (1.00-1.37)	0.16	0.05#

#, P < 0.05. BPV: blood pressure variability.

sepsis (58%). Forty five patients (40.2%) presented with delirium (positive CAM-ICU test), of which 38 tested positive in the first three days.

ROC analysis

ROC curve analysis indicated that the area under the curve (AUC) for BPV to predict the presence of delirium was 0.677 (95% confidence intervals (CI), 0.57-0.78, $P < 0.01$). A cut-off value of 8.94 was set with sensitivity of 76% and specificity of 67% (**Figure 2**).

Higher BPV is related to worse outcome

Demographic characteristics and laboratory results of the patients are presented in **Table 1**. Patients with high BP variability (> 8.94 mmHg) presented a higher prevalence of delirium (60.7% vs. 19.6%, $P < 0.001$) with higher SOFA scores (10.29 ± 4.82 vs. 7.7 ± 3.48, $P = 0.014$). The prevalence of septic shock was greater in patients with high BP variability (44.6% vs. 19.6%, $P = 0.004$). Vasoactive drugs were administered more frequently in the patients with high BPV (51.8% vs. 25.0%, $P = 0.004$).

Multivariate logistic regression analysis showed that BPV was related to delirium (OR (odds ratio): 1.17, 95% CI: 1.02–1.33, $P = 0.02$; **Table 2**, Table S1), and death within 28 days (OR: 1.17, 95% CI: 1.00-1.37, $P < 0.05$; **Table 3**, Table S2). The performance of mean BP in predicting delirium and death was poor.

Follow-up data analysis

The length of mechanical ventilation-free ICU stay, hospital stay and ICU stay were similar between the BPV high and BPV low groups. The same situation was found in the usage of continuous renal replacement therapy. The 28 day-mortality was much higher in the BPV high group (41.1% vs. 23.2%, $P < 0.05$; **Table 4**). Three survivors in BPV high group and two in BPV low group were lost to follow-up. The disparity in mortality between the BPV high and low groups narrowed over time, but the clinical significance was maintained (**Figure 3**).

Discussion

BP is a very powerful risk factor that should be considered in the management of critically ill patients, but much evidence suggests that instability and variability in BP are also important [8]. Autoregulation of the cardiovascular, neural and endocrine systems allows maintenance of relatively constant BP, and physiological variation with circadian rhythm. BPV can be measured in the short-term over minutes or hours, or in long-term over weeks and months. The 24-h BPV, which is the result of both external stimulation and cardiovascular control, is believed to provide evidence of cardiovascular complications and possible end-organ damage [9]. In patients with sepsis, we found a higher incidence of delirium in those with high BPV. Increased BPV was also associated with higher mortality after adjusting for age, APACHE II score, vasoactive drug usage and mean BP.

Several studies have reported that 24-h BPV is associated with target-organ damage, independent of mean BP [10-12]. Acute increases in BP, for example, may cause injury to cerebral vessels, then sometimes lead to hemorrhage. In patients with dysfunctional autoregulation of small cerebral vessels, constriction of these vessels due to a huge increases in BP might reduce the already poor perfusion of subcortical or border zone areas, especially if BP then falls. The clinical correlations between BPV and cerebral dysfunction are thought to underlie several pathophysiological mechanisms of sepsis; however, the exact mechanisms have not yet been elucidated clearly. Patients with sepsis have excessive systemic inflammation characterized by high levels of C-reactive protein, cytokines and pro-calcitonin. The inflammatory cascade in microglia is activated by mediators passing from the serum through the damaged blood-brain barrier [13]. The resulting disturbances in CA are probably due to endothelial dysfunction mediated by the excessive inflammation in the brain [5]. Variations in BP can cause spasms in large cerebral arteries, although the repeated expansion and contraction

Table 4. Outcomes in the high and low blood pressure variability groups

	Total n = 112	BPV low group (≤ 8.94 mmHg) n = 56	BPV high group (> 8.94 mmHg) n = 56	*P* value
Mechanical ventilation free ICU stay (day)	1 (0, 5)	2 (0, 7.5)	1 (0, 3.75)	0.071
CRRT	20 (17.9%)	8 (14.3%)	12 (21.4%)	0.324
ICU stay (day)	12 (5, 23.75)	10 (5, 28.75)	12 (6, 21.5)	0.998
Hospital stay (day)	18 (11, 37.75)	18.5 (11, 47.25)	17 (10.25, 30.5)	0.270
Death (28 day)	36 (32.1%)	13 (23.2%)	23 (41.1%)	0.043
Death (180 day)	50 (46.7%) n = 107	20 (37.0%) n = 54	30 (56.6%) n = 53	0.043
Death (a year)	53 (49.5%) n = 107	22 (40.7%) n = 54	31 (58.5%) n = 53	0.066

BPV: blood pressure variability; CRRT: continuous renal replacement therapy.

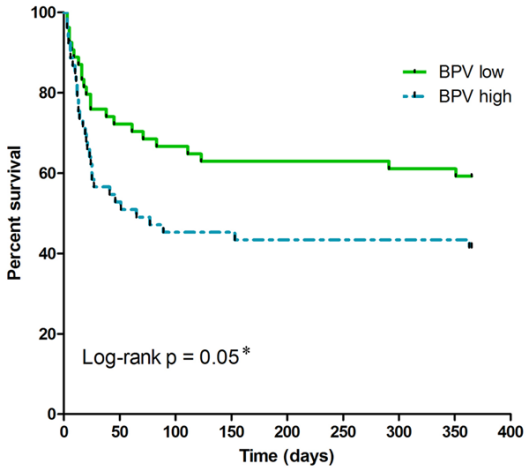

Figure 3. Survival curves of the high and low blood pressure variability groups. The Kaplan-Meier analysis of the probability of death at a year for patients with BPV high and low; BPV low group (BPV ≤ 8.94 mmHg), BPV high group (BPV> 8.94 mmHg); *, P > 0.05 by the log-rank test for the between-group difference.

of small vessels due to fluctuations in BP is a more likely cause of altered cerebral microcirculation, which is a critical pathological feature of cerebral dysfunction during sepsis. In this study, we identified a significant correlation between BPV and delirium in patients with sepsis.

A plurality of large sample surveys have shown that increased BPV is positively associated with cardiovascular events and death [14-16]. A recent meta-analysis [17] of 77, 299 patients supported the relationship between BPV and mortality. After adjusting for age and mean BP, the relative risk of all-cause mortality and cardiovascular event-related mortality associated with BPV was 1.03 (95% CI, 1.02-1.04; $P < 0.001$) and 1.10 (95% CI, 1.02-1.17; $P < 0.001$). In a small survey [18] conducted in patients with sepsis, a significant correlation was found between BPV and APACHE II score ($r = 0.732$, $P < 0.001$), making it a potential risk factor for predicting the survival rate of patients with sepsis. In our study, BPV was identified as an independent predictor of mortality in patients with sepsis.

Mean BP was not found to be related to delirium or death in our study. Similarly, mortality did not differ significantly among patients with septic shock who were treated to reach target MAPs of 80 mmHg or 65 mmHg [19]. When the MAP is in a reasonable range (i.e. greater than 65 mmHg), patients with sepsis seem to be more sensitive to BPV rather than mean BP. We found that 24-h BPV was associated with clinical signs of SAE and death in patients with sepsis, independent of mean BP. Therefore, clinicians should focus on stabilizing BP in the management of patients with sepsis.

The vasoactive drugs that are frequently administered to sepsis patients, not only cause fluctuations in BP, but are also related to increased mortality. Vasopressor therapy indicates the development of septic shock, which is associated with extremely high mortality (mean mortality, 46.5% [95% CI, 42.7%-50.3%], with a variation from 23.0% to 81.8%) [20]. Therefore, the use of vasoactive drugs is an important confounder in inv estigations of the correlation between BPV and mortality in patients with sepsis. Multivariate logistic regression revealed that BPV was an independent predictor of delirium and death in sepsis patients after adjusting for vasoactive drug use and other confounders.

Our study has some limitations. First, the study was not blinded: the researcher who administered the CAM-ICU test was aware of the BP

level of the patient. Nevertheless, since BPV was calculated subsequently by a statistician, it is unlikely that knowledge of the patient's BP could affect the judgment of the researcher. Second, although invasive arterial pressure monitoring was performed for some of the patients, non-invasive BP data was used in this study. Non-invasive blood pressure monitoring has been shown to be as effective in detecting BP fluctuations as invasive blood pressure monitoring in clinical practice [21]; therefore, it can be assumed that this method has little influence on our results. Third, we only assessed the clinical symptoms associated with SAE, without any neuroradiological or neurophysiological results (e.g., electroencephalograms or magnetic resonance imaging). Furthermore, patients included in present study were diagnosed as sepsis, severe sepsis and septic shock, that has been revised by the third international definitions for sepsis and septic shock which were published after wise [22]. However, we believe that patients diagnosed with "old" sepsis went through the similar pathophysiological process and were still representative to a certain degree.

The results of our study show that BPV is correlated with the clinical signs of SAE, probably by altering cerebral microcirculation in the early stage of sepsis. A cut-off value of BPV > 8.94 mmHg could be used in clinical practice to predict the risk of delirium in patients with sepsis. Increased BPV is also independently associated with increased mortality. Further studies are warranted to confirm the results of our study and evaluate the value of monitoring BPV in the clinical management of sepsis patients.

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Disclosure of conflict of interest

None.

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Table S1. Univariate analysis of patients with and without delirium

	Total n = 112	Delirium n = 45	Non-delirium n = 67	*P* value
Age (year)	57.62 ± 16.31	59.31 ± 16.47	56.48 ± 16.23	0.370
Male	77 (68.8%)	30 (66.7%)	47 (70.1%)	0.697
APACHE II	20.18 ± 6.46	22.29 ± 5.77	18.76 ± 6.55	0.004
SOFA	8.99 ± 4.38	10.69 ± 4.35	7.85 ± 4.05	0.001
Severity				0.007
Sepsis	18 (16.1%)	2 (4.4%)	16 (23.9%)	
Severe sepsis	58 (51.8%)	23 (51.1%)	35 (52.2%)	
Septic shock	36 (32.1%)	20 (44.4%)	16 (23.9%)	
Vasoactive drug usage	43 (38.4%)	20 (44.4%)	23 (34.3%)	0.280
Mean BP (mmhg)	85.85 ± 8.83	86.79 ± 8.33	85.22 ± 9.16	0.358
BPV (mmhg)	9.14 ± 3.49	10.14 ± 3.68	8.46 ± 3.22	0.012
CRP (mg/L)	148.00 (90.30, 203.00)	148.00 (84.50, 204.50)	150.00 (92.00, 204.00)	0.574
IL-6 (pg/mL)	259.00 (92.14, 865.80)	221.25 (84.59, 904.28)	275.80 (110.60, 519.80)	0.844
PCT (ng/mL)	5.35 (1.07, 27.92)	5.12 (1.04, 27.60)	7.02 (1.27, 28.57)	0.423
GCS	9.43 ± 4.08	8.07 ± 3.61	10.34 ± 4.14	0.003
Death (28 day)	36 (32.1%)	22 (48.9%)	14 (20.9%)	0.002

BPV: blood pressure variability; CRP: C-reactive protein; IL-6: Interleukin 6; PCT: Procalcitonin; GCS: Glasgow Coma Score.

Table S2. Univariate analysis of survival and non-survival patients

	Total n = 112	Non-survivor (28D) n = 36	Survivor (28D) n = 76	*P* value
Age (year)	57.62 ± 16.31	64.86 ± 15.48	54.18 ± 15.65	0.001
Male	77 (68.8%)	29 (80.6%)	48 (63.2%)	0.064
APACHE II	20.18 ± 6.46	24 ± 5.97	18.37 ± 5.89	0.000
SOFA	8.99 ± 4.38	11.42 ± 3.86	7.84 ± 4.16	0.000
Severity				0.015
Sepsis	18 (16.1%)	1 (2.8%)	17 (22.4%)	
Severe sepsis	58 (51.8%)	19 (52.8%)	39 (51.3%)	
Septic shock	36 (32.1%)	16 (44.4%)	20 (26.3%)	
Vasoactive drug usage	43 (38.4%)	21 (58.3%)	22 (28.9%)	0.003
Mean BP (mmhg)	85.85 ± 8.83	84.19 ± 7.69	86.64 ± 9.26	0.172
BPV (mmhg)	9.14 ± 3.49	10.52 ± 4.61	8.48 ± 2.6	0.003
CRP (mg/L)	148.00 (90.30, 203.00)	144.00 (92.20, 199.70)	149.00 (88.50, 208.00)	0.947
IL-6 (pg/mL)	259.00 (92.14, 865.80)	356.40 (166.98, 500.80)	205.80 (86.75, 1037.50)	0.568
PCT (ng/mL)	5.35 (1.07, 27.92)	4.94 (1.86, 28.00)	5.49 (1.06, 28.41)	0.940
GCS	9.43 ± 4.08	7.28 ± 3.42	10.45 ± 3.98	0.000
Delirium	45 (40.2%)	22 (61.1%)	23 (30.3%)	0.002

BPV: blood pressure variability; CRP: C-reactive protein; IL-6: Interleukin 6; PCT: Procalcitonin; GCS: Glasgow Coma Score.