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Outcomes and Relevant Factors Associated with Cardiac Dysfunction in Patients with Traumatic Brain Injury

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Abstract

Purpose: Cardiac dysfunction has been rarely reported in patients with traumatic brain injury (TBI). The study aimed to compare clinical outcomes in patients admitted in intensive care unit (ICU) with normal cardiac function versus cardiac dysfunction after TBI. Moreover, the association of risk factors and hospital mortality ICU or hospital length of stay was investigated. **Methods:** A retrospective study was conducted from December 2011 to April 2018 on TBI patients admitted without pre-existing cardiac diseases. Patients with TBI were grouped into secondary cardiac dysfunction (n = 112) and normal cardiac function (n = 160) groups according to the presence of abnormal echocardiography after ICU admission. Univariate and multivariate analyses were performed. **Results:** Elevated BNP and troponin levels were found in the group with cardiac dysfunction. Patients with cardiac dysfunction had significantly higher hospital mortality (16.96% vs. 8.13%), longer ICU length of stay (16.34 vs. 10.99 d) than those without cardiac events. Cardiac dysfunction was an independent predictor of hospital mortality ($p < 0.001$) and the ICU length of stay ($p < 0.001$) after adjusting confounders. Risk factors mainly associated with hospital length of stay were age ($p = 0.043$), GCS score ($p < 0.001$), and use of mechanical ventilation ($p = 0.013$). GCS score ($p < 0.001$) use of vasopressor was related factors associated with ICU length of stay ($p = 0.018$). **Conclusions:** Cardiac dysfunction in context of TBI has a negative impact on clinical outcomes, and it is an independent predictor for increasing hospital mortality and longer ICU length of stay.

Subject Areas

Emergency, Critical Care

Keywords

Intensive Care, Traumatic Brain Injury, Cardiac Function, Mortality

1. Introduction

Traumatic brain injury (TBI) is one of the most common diseases of the intensive care unit (ICU) worldwide, and over 3 - 4 million populations are affected annually in China [1] [2]. Patients with TBI are prone to develop secondary end-organ damage due to homeostasis changes, resulting in poor prognosis, increased mortality, and prolonged stay in the ICU [3] [4]. Under specific neurological conditions, brain injury may lead to brain-heart interactions and paroxysmal sympathetic hyperactivity (PSH) over the following days, even an impact on cardiac function and patients' outcomes negatively [5] [6]. Currently, such cardiac events after TBI are often thought to cause by elevated intracranial pressure (ICP) and excessive adrenergic activity, which results in increased sympathetic activity and electrocardiographic abnormalities [7] [8] [9]. Nevertheless, there are limited described neuro-cardiogenic dysfunctions in the context of TBI.

The presence of secondary cardiac dysfunction in patients with various neurological injuries is found to be associated with unfavorable clinical outcomes [10] [11] [12] [13]. One recent study demonstrated cardiac dysfunction in 22% of isolated TBI patients, including a reduced left ventricular ejection fraction (LVEF) and regional wall motion abnormalities, even correlated with increased in-hospital mortality [6]. Conversely, Najafi Pour *et al.* [14] conducted an animal study, presented that no cardiac events observed in an experimental rat model of diffuse TBI. Meanwhile, there is also evidence in a multitude of neurological conditions that the prognostic outcomes of cardiac function vary depending on multiple underlying factors, such as the severity of brain injury, relevant infections, and co-morbidity [11] [15] [16]. Therefore, the association of cardiac abnormalities after various brain injuries and patient's outcome remains controversial at present.

We retrospectively compared the clinical outcomes in patients with normal cardiac function versus cardiac dysfunction after TBI and its association with cardiac function, and further investigated risk factors associated with hospital mortality, ICU, and hospital length of stay.

2. Methods

We conducted a retrospective study of TBI patients admitted to surgical intensive care unit (SICU) at Fujian Provincial Hospital (Fujian, China) from December 2011 to April 2018. This SICU is dedicated to trauma/surgical, burn, organ transplantation, severe infection, and neurology/neurosurgery patients, and more than 600 critically ill patients admitted to this department per year. The study was approved by the institutional ethics committee of this hospital.

2.1. Patient Data

Subjects for this study were extracted automatically from a big-data intelligence database platform (YiduCloud Technology Ltd., Beijing, China) by setting the criteria of cardiac dysfunction group and normal group. The cardiac dysfunction group in TBI patients (aged 18 - 80 years old) who have were classified by presence of abnormal findings with plasma brain natriuretic peptide (BNP), Cardiac troponin (cTn), vechocardiography and electrocardiogram during the ICU stay. TBI is defined as an alteration in brain function, or other evidence include visual, neuroradiology, or laboratory confirmation of damage to the brain of brain pathology, caused by an external force. They were generally categorized as mild (GCS 13 - 15), moderate (GCS 9 - 12), and severe (GCS 3 - 8) TBI [4]. The following patients were excluded: 1) patients with pre-existing primary cardiac diseases (arrhythmia, coronary heart disease, congenital heart disease, cardiac insufficiency or heart failure condition resulted from above diseases); 2) a medical history of post-cardiac surgery or cardiac intervention surgery; 3) patients with pre-existing diabetes, hypertension, chronic kidney disease, chronic obstructive pulmonary disease, hyperthyroidism, autoimmune diseases and other diseases which already cause cardiac dysfunction; 4) patients with a prior history of intracranial diseases; 5) patients who with multiple trauma or traumatic hemorrhagic shock; 6) patients who had stayed in the ICU < 48 hours.

2.2. Data Collection and Outcome Measures

Demographic data including age, gender, and relevant risk factors (GCS score, health behaviors, CT diagnosis, and secondary infection) were collected from electronic medical records during the period of hospital admission. The following laboratory parameters were obtained during ICU admission, heart rate, respiratory rate, temperature, blood pressure (systolic and diastolic), lactate, hemoglobin (Hb), white blood cell count (WBC), blood urea nitrogen (BUN), creatinine (Cr) C-reactive protein (CRP), procalcitonin (PCT), life support modes (mechanical ventilation, inotropes or vasopressor) Moreover, cardiac enzyme data (creatine phosphokinase MB isoenzyme (CK-MB), troponin-I, B-type natriuretic peptide (BNP) were also recorded. The main clinical outcomes including ICU or hospital length of stay, hospital mortality were compared between the two groups. Risk factors contributing to hospital length of stay were also analyzed.

2.3. Statistical Analysis

All statistical analysis was conducted using SAS, version 9.4 (SAS Institute, Cary, NC). All data were expressed as mean ± SD (standard deviation) or median and interquartile range (IQR) as appropriate for continuous variables, while as percentages for categorical variables. We compared continuous variables using the Wilcoxon signed-rank test and categorical variables using chi-squared test. Variables (age, GCS score, blood urea nitrogen (BUN), creatinine (Cr), troponin-I

and BNP) with a significant difference between the two groups in univariate analysis were included into the model. A multivariable logistic (linear) regression model was developed for investigating whether secondary cardiac abnormalities were associated with length of in-hospital stay and in-hospital cure rate after adjusting all confounders. Diagnostic performance of age, GCS, troponin-I, and BNP in predicting cardiac dysfunction were evaluated using receiver operating characteristic (ROC) curves. Moreover, we calculated the odds ratios (ORs) and 95% confidence intervals (95% CIs) for mortality and ICU and hospital length of stay according to various factors using multiple logistic regression analysis. P values < 0.05 were considered statistically significant.

3. Results

3.1. Patients Characteristics

A total of 1404 patients with TBI between December 2011 to April 2018 were initially screened for this study. Of the enrolled 272 eligible participants, 112 TBI patients were included cardiac group, the other 160 patients were included normal group (Figure 1). Baseline characteristics of eligible patients are presented in Table 1. Patients with cardiac dysfunction after TBI were older than

Table 1. Baseline characteristics of eligible patients between the two groups.

Characteristics	Cardiac group (n = 112)	Normal group (n = 160)	*p*
Age, years (Median, range)	58 (48.5 - 68.0)	46 (33.5 - 57.0)	<0.001*
Female, n (%)	28 (25.00)	42 (26.25)	0.817
Marital status N = 95/141, n (%)	89 (79.46)	123 (76.88)	0.203
Health behaviors, n (%)			
Smoking, N = 103/153	16 (14.29)	24 (15.00)	0.450
Alcohol use, N = 104/148	11 (9.82)	15 (9.38)	0.988
GCS, N = 106/150, n (%)			0.227
Severe 3 - 8	63 (56.25)	78 (48.75)	
Moderate 9 - 12	20 (17.86)	22 (13.75)	
Mild 13 - 15	23 (20.54)	50 (31.25)	
CT diagnosis, n (%)			
Subarachnoid hemorrhage	65 (58.04)	75 (46.88)	0.070
Intracranial hematomas	88 (78.57)	108 (67.50)	0.045*
Contusion	40 (35.71)	78 (48.75)	0.033*
Infection sources, n (%)			
Pulmonary	78 (69.64)	106 (66.25)	0.556
Intracranial	7 (6.25)	11 (6.88)	0.838
Urethra	12 (10.71)	14 (8.75)	0.588
Abdomen	1 (0.89)	0	0.231

*$p < 0.05$ is considered statistically significant. Baseline characteristics of eligible patients are presented. Patients with cardiac dysfunction after TBI were older than those in the normal group (58 vs. 46, $p < 0.001$). More patients with cerebral hemorrhage ($p = 0.045$) and contusion ($p = 0.033$) were found in the normal group.

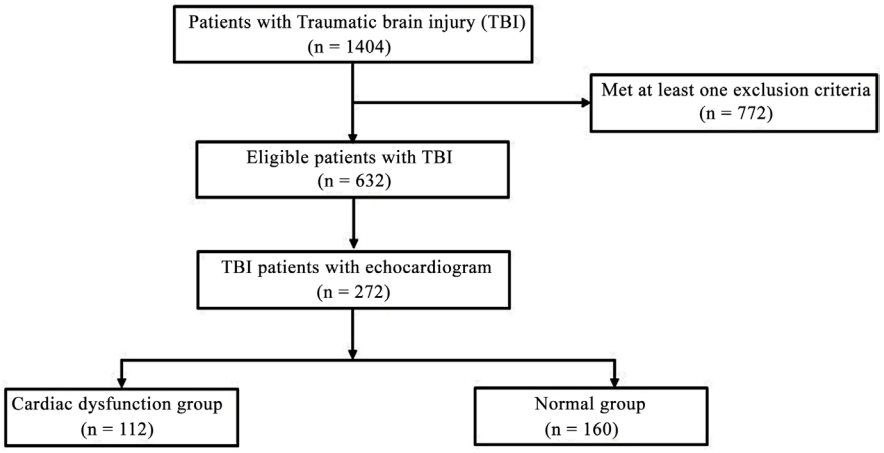

Figure 1. Patients characteristics of the flow chart of the study population.

those in the normal group (58 vs. 46, $p < 0.001$). More patients with cerebral hemorrhage ($p = 0.045$) and contusion ($p = 0.033$) were found in the normal group.

3.2. Comparison of Clinical Characteristics

Table 2 shows the comparison of clinical characteristics between the two groups. There was no difference between the two groups regarding clinical inflammatory markers (CRP, PCT, lactate), and routine blood indicators (Hb and WBC). BUN and Cr level were significantly elevated in the cardiac group ($p < 0.001$). For cardiac enzymes, the median levels of troponin ($p = 0.004$) and BNP ($p < 0.001$) in TBI patients with cardiac dysfunction were significantly higher than those without cardiac abnormalities.

3.3. Comparisons of Clinical Outcomes

The median ICU length of stay in TBI patients with cardiac dysfunction was longer than those with normal cardiac function (16.34 vs.10.99 d) ($p = 0.048$). The hospital mortality in the cardiac group was 16.96%, while there was lower percentage of deaths (8.13%) in the control group ($p < 0.001$) (Table 3).

The effect of cardiac dysfunction on each outcome was also assessed by univariate and multivariate logistic (linear) regression through controlling variables, including age, number of cerebral hemorrhage and contusion, BUN, troponin and BNP levels (Table 4). Cardiac dysfunction in the setting of TBI was an independent factor affected hospital mortality and ICU length of stay (odds ratio [OR] = 6.660, 95% confidence interval [CI] 2.39 - 18.61, $p < 0.001$; and Exp(B) = 0.132, 95% CI 0.08 - 0.19, $p < 0.001$, respectively).

The diagnostic performances of age, GCS, levels of troponin, and BNP in predicting cardiac events are summarized in Table 5. Age was good at predicting cardiac dysfunction with an area under the receiver operating characteristic curve (AUC) of 0.70. The AUC of elevated cardiac enzymes (troponin and BNP) in predicting cardiac dysfunction was 0.61 and 0.66, respectively (Figure 2).

The factors in Table 6 associated with hospital mortality, hospital, and ICU

Table 2. Comparisons of clinical characteristics between the two groups.

Characteristics	Cardiac group (n = 112)	Normal group (n = 160)	*p*
Heart rate (per minute),	84.5 (70.0 - 103.5)	88.0 (77.0 - 101.0)	0.737
Respiratory rate (cycles/per min), N = 105/147	20.0 (18.0 - 20.0)	20.0 (18.0 - 21.0)	0.396
Temperature (˚C), N = 106/147	36.7 (36.4 - 37.2)	36.7 (36.5 - 37.2)	0.468
Blood Pressure, N = 104/142			
Diastolic pressure	74.0 (65.0 - 84.5)	76.0 (67.0 - 86.0)	0.519
Systolic pressure	132.0 (120.0 - 151.5)	131.5 (119.0 - 146.0)	0.231
$PaCO_2$ (mmHg), N = 98/133	38.66 ± 7.84	39.20 ± 6.91	0.580
Lactate, N = 97/133	2.0 (1.2 - 3.0)	1.7 (1.1 - 2.7)	0.094
HGB (g/L), N = 110/160	130.2 (115.0 - 147.0)	133.0 (115.0 - 144.0)	0.798
WBC (g/L), N = 110/160	13.1 (9.2 - 17.1)	13.4(9.0 - 17.4)	0.842
BUN (mmol/L), N = 110/159	5.3 (4.4 - 6.4)	4.4 (3.6 - 5.9)	<0.001*
Cr (ummol/L), N = 110/159	72.5 (56.0 - 89.0)	68.0(55.0 - 79.0)	0.045*
CRP (mg/L), N = 91/128	43.5 (12.1 - 122.0)	43.8 (11.8 - 98.4)	0.454
PCT (μg/mL), N = 96/134	0.28 (0.06 - 1.39)	0.31 (0.09 - 1.12)	0.851
Mechanical ventilation (n, %)	104 (92.86)	142 (88.75)	0.257
Vasopressor use, N = 111/159, (n, %)	97 (86.61)	122 (76.25)	0.086
CK - MB (U/L), N = 109/158	14.3 (10.0 - 26.5)	15.5 (11.0 - 29.1)	0.217
Troponin I(ng/ml), N = 91/118	0.02 (0.01 - 0.16)	0.01 (0.00 - 0.04)	0.004*
BNP (pg/ml), N = 95/117	255.8(108.3 - 763.1)	142.0 (54.2 - 311.7)	<0.001*

HGB: hemoglobin; WBC: White blood cell; BUN: blood urea nitrogen; Cr: Creatinine; CRP: C-reactive protein; PCT: procalcitonin; BNP: type B natriuretic peptide-B. *$p < 0.05$ is considered statistically significant.

Table 3. Comparison of clinical outcomes between the cardiac dysfunction and normal groups.

Characteristics	Cardiac group (n = 112)	Normal group (n = 160)	*p*
hospital length of stay (days) (Median, range)	53.0 (30.0 - 90.0)	47.0(25.5 - 87.0)	0.690
ICU length of stay (days)	16.34 (6.84 - 31.17)	10.99 (4.86 - 28.96)	0.048*
hospital Mortality, n (%)	16 (16.96)	13 (8.13)	<0.001*

*$p < 0.05$ is considered statistically significant. The median ICU length of stay in TBI patients with cardiac dysfunction was longer than those with normal cardiac function (16.34 vs.10.99 d) ($p = 0.048$). The hospital mortality in the cardiac group was 16.96%, while there was lower percentage of deaths (8.13%) in the control group ($p < 0.001$).

Table 4. Multivariate logistic (linear) regression analysis of abnormal echocardiography associated with hospital mortality and length of stay.

Characteristics	Adjusted OR or Exp (B)	95% confidence interval	*p*
Hospital mortality	6.660	2.39 - 18.61	<0.001*
Hospital length of stay	0.015	−0.02 - 0.04	0.343
ICU length of stay	0.132	0.08 - 0.19	<0.001*

OR: Odds ratio; Exp (B): Coefficients; *$p < 0.05$ is considered statistically significant. Adjusted for age, the number of cerebral hemorrhage and contusion, BUN, troponin and BNP level.

Table 5. Predictors for in-hospital mortality, length of in-hospital stay and ICU stay.

Predictors	Mortality in hospital (OR (95% Cl))		Length of in-hospital stay (Exp(B) (95% Cl))		Length of in ICU stay (Exp(B) (95% Cl))	
	Multivariable	*p*	Multivariable	*p*	Multivariable	*p*
Age	1.00 (0.98 - 1.02)	0.982	0.36 (−0.01 - 0.71)	0.043*	0.03 (−0.15 - 0.20)	0.765
Cardiac function	3.17 (1.44 - 6.95)	0.004*	−8.43 (−19.37 - 2.50)	0.130	−0.32 (−5.79 - 5.14)	0.908
GCS	0.94 (0.86 - 1.03)	0.189	−1.97 (−3.16 - −0.78)	0.001*	−1.49 (−2.09 - −0.89)	<0.0001*
Mechanical ventilation	0.77 (0.20 - 2.92)	0.696	21.89 (4.59 - 39.18)	0.013*	4.02 (−5.38 - 13.43)	0.400
Vasopressors use	0.17 (0.01 - 3.88)	0.268	−16.81 (−72.59 - 38.96)	0.553	−33.42 (−60.97 - −5.86)	0.018*

OR: Odds ratio; Exp (B): Coefficients; *$p < 0.05$ is considered statistically significant. Adjusted for age, gender, smoking, alcohol use, the number of stones, WBC level at hospital admission.

Table 6. Predictors for hospital mortality, hospital and ICU length of stay.

Predictors	Hospital mortality (OR (95% CI))		hospital length of stay (Exp(B) (95% CI))		ICU length of stay (Exp(B) (95% CI))	
	Multivariable	*p*	Multivariable	*p*	Multivariable	*p*
Age	1.00 (0.98 - 1.02)	0.982	0.36 (−0.01 - 0.71)	0.043*	0.03 (−0.15 - 0.20)	0.765
Cardiac function	3.17 (1.44 - 6.95)	0.004*	−8.43 (−19.37 - 2.50)	0.130	−0.32 (−5.79 - 5.14)	0.908
GCS	0.94 (0.86 - 1.03)	0.189	−1.97 (−3.16 - −0.78)	0.001*	−1.49 (−2.09 - −0.89)	<.0001*
Mechanical ventilation	0.77 (0.20 - 2.92)	0.696	21.89 (4.59 - 39.18)	0.013*	4.02 (−5.38 - 13.43)	0.400
Vasopressors use	0.17 (0.01 - 3.88)	0.268	−16.81 (−72.59 - 38.96)	0.553	−33.42 (−60.97 - −5.86)	0.018*

OR: Odds ratio; Exp (B): Coefficients; *$p < 0.05$ is considered statistically significant. Adjusted for age, gender, smoking, alcohol use, WBC level at hospital admission.

length of stay using univariable and multivariable regression analyses. Factor associated with hospital mortality were cardiac function (OR = 3.17, 95% CI 1.44 - 6.95, $p = 0.004$). Factors mainly associated with length of stay in hospital were age (Exp(B) = 0.36, 95% CI 0.01 - 0.71, $p = 0.043$), GCS score (Exp(B) = −1.97, 95% CI 3.16 - −0.78, $p < 0.001$), and use of mechanical ventilation (Exp(B) = 21.89, 95% CI 4.59 - 39.18, $p = 0.013$). GCS score (Exp(B) = −1.49, 95% CI 2.09 - −0.89, $p < 0.001$), and use of vasopressor (Exp(B) = −33.42, 95% CI 60.97 - −0.86, $p = 0.018$) were related factors associated with ICU length of stay.

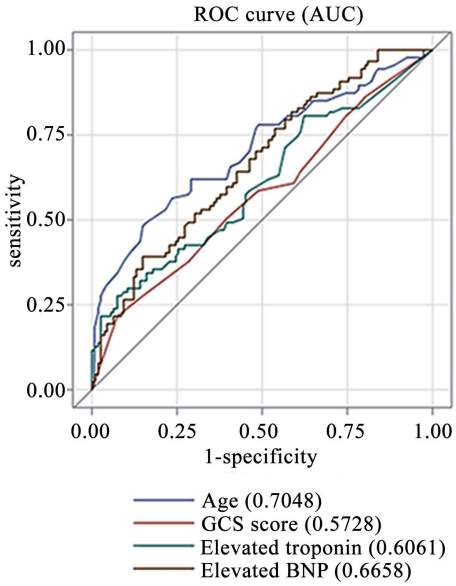

Figure 2. Age was good at predicting cardiac dysfunction with an area under the receiver operating characteristic curve (AUC) of 0.70. The AUC of elevated cardiac enzymes (troponin and BNP) in predicting cardiac dysfunction was 0.61 and 0.66, respectively.

4. Discussion

Neuro-cardiogenic dysfunction that follows brain injury can generally result in several complications such as electrolyte disturbance, related infection and prolonged ventilation, which can negatively impact prognosis of brain trauma and increase mortality and financial burden [13] [17] [18]. This retrospective study confirmed that worse clinical outcomes and longer ICU length of stay are common among patients with cardiac dysfunction after TBI, and cardiac abnormality was found to be an independent factor of clinical outcomes after adjusting confounders. The elevated cardiac enzymes (troponin-I and BNP) can be predicted cardiac dysfunction to a certain extent. Moreover, Age, GCS, and mechanical ventilation seem to be the main related factors for hospital length of stay, while ICU length of stay was associated with GCS and use of vasopressors. TBI patients who had cardiac dysfunction during ICU admission were associated with higher hospital mortality.

Cardiac dysfunction has been occurred and described in a variety of models of brain injury, such as subarachnoid hemorrhage (SAH) [5], stroke [19], and emotional stress [20], etc. The proposed mechanism for this neuro-cardiogenic dysfunction is thought to be excessive catecholamine level and inflammatory cascade [21] [22]. The clinical manifestations cardiac are varied by the existence of echocardiographic abnormalities and elevated cardiac enzymes are critical clues for early detection of cardiac dysfunction [6]. The present study reveals a tendency of abnormal echocardiograms for TBI patients who are older and have elevated levels of troponin-I and BNP. Similarly, another study showed that nearly half of the patients developed cardiac dysfunction as recorded by elevated troponin [13]. Meanwhile, a few published studies have revealed a strong clinical

relationship between episodes of secondary neuro-cardiogenic dysfunction and the worst clinical outcome [23] [24]. The findings of our study are consistent with Ahmed *et al.* [13] who demonstrated a significantly higher in terms of mortality in patients with cardiac dysfunction after TBI. Hospital and ICU length of stay in the cardiac group tended to be longer, Furthermore, our data is in line with previous studies suggesting that secondary cardiac dysfunction after TBI was a risk factor for clinical outcomes [6] [25] [26]. Therefore, the presence of cardiac dysfunction most likely reflects a severe brain injury and predicts a poor outcome. Meanwhile, our result is consistent with recent studies demonstrating that elevated BNP and troponin were associated with poor cardiac prognosis [15] [27]. Early detection of troponin and BNP levels for cardiac dysfunction has a certain degree of warning. However, King *et al.* [28] reported that there was no significant correlation between troponin levels and clinical outcomes. Taken together, BNP or troponin could not guarantee a reliable prediction of clinical outcome in critically ill patients, and a comprehensive clinical assessment is essential.

We also investigated several variables affecting clinical outcomes. In the present study, cardiac function was considered the candidate influential factor for cure rate. The consciousness of the presence of cardiac dysfunction after TBI in these patients and its impact on clinical outcome might attract attention toward cardiac protection. Finding in our study, which mirrors that of David *et al.* and others [29] [30], is that age and GCS were significant predictors of mortality and discharge. GCS has been considered as a tool to classify the severity of neurologic disorders. In addition, age may affect the association between the severity of TBI and the neurologic conditions measured by GCS [31]. For Mechanical ventilation use, Lim *et al.* [32] suggested that life-saving interventions were not significant related with clinical outcomes. However, mechanical ventilation is commonly used in critically ill patients for requiring to support ongoing organ failure. Hospital length of stay is often prolonged due to inadequate mechanical ventilation. Therefore, this result needs more validation in larger studies.

The present study had several possible limitations that should be acknowledged. First, it is limited by its retrospective observational design. Second, the size of the study population was small. Strictly exclusion of patients might affect the generalizability of our study. Therefore, further larger prospective studies and intervention trials should be undertaken to confirm this causal association and to understand the underlying pathophysiology.

5. Conclusion

In summary, TBI patients with secondary cardiac dysfunction appear to be longer ICU length of stay, the higher hospital mortality. Cardiac dysfunction in the setting of TBI was found to be an independent risk factor of clinical outcomes through controlling confounding factors. Moreover, age, GCS, and mechanical ventilation seem to be the main related factors for hospital length of stay. GCS and use of vasopressors were associated with ICU length of stay.

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Data Availability

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

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Statement of Ethics

The study protocol was approved by the hospital ethics committee.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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Abbreviations

TBI: Traumatic Brain Injury; ICU: Intensive Care Unit; PSH: Paroxysmal Sympathetic Hyperactivity; ICP: Elevated Intracranial Pressure; LVEF: Left Ventricular Ejection Fraction; SICU: Surgical Intensive Care Unit; GCS: Glasgow Coma Scale; HGb: Hemoglobin; CRP: C-Reactive Protein; WBC: White Blood Cell count; PCT: Procalcitonin; CK-MB: Creatine phosphokinase MB isoenzyme; BNP: B-type Natriuretic Peptide; BUN: Blood Urea Nitrogen; Cr: Creatinine.