RESEARCH ARTICLE

Risk factors for corticosteroid insufficiency during the sub-acute phase of acute traumatic brain injury

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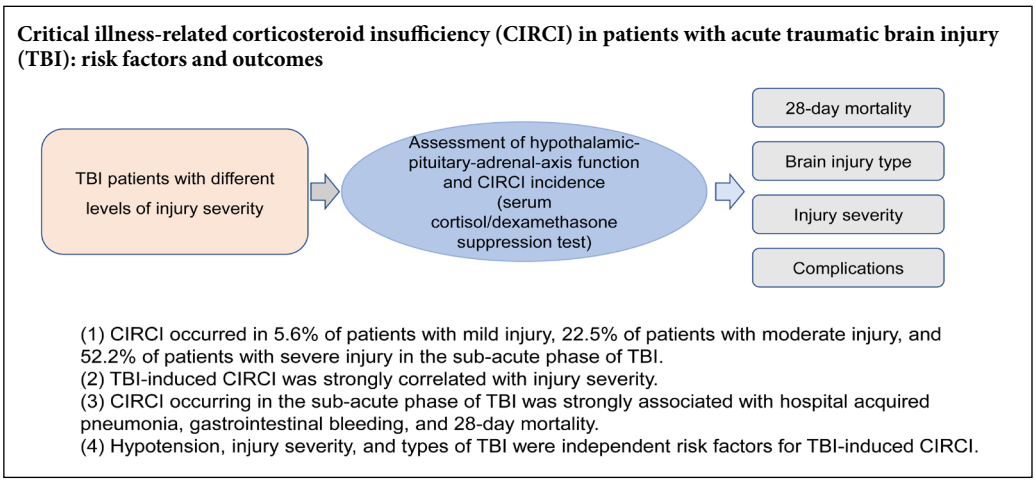
Graphical Abstract



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Abstract

Hypothalamic-pituitary-adrenal axis dysfunction may lead to the occurrence of critical illness-related corticosteroid insufficiency. Critical illness-related corticosteroid insufficiency can easily occur after traumatic brain injury, but few studies have examined this occurrence. A multicenter, prospective, cohort study was performed to evaluate the function of the hypothalamic-pituitary-adrenal axis and the incidence of critical illness-related corticosteroid insufficiency during the sub-acute phase of traumatic brain injury. One hundred and forty patients with acute traumatic brain injury were enrolled from the neurosurgical departments of three tertiary-level hospitals in China, and the critical illness-related corticosteroid insufficiency incidence, critical-illness-related corticosteroid insufficiency-related risk factors, complications, and 28-day mortality among these patients was recorded. Critical illness-related corticosteroid insufficiency was diagnosed in patients with plasma total cortisol levels less than 10 μg/dL (275.9 nM) on post-injury day 4 or when serum cortisol was insufficiently suppressed (less than 50%) during a dexamethasone suppression test on post-injury day 5. The results demonstrated that critical illness-related corticosteroid insufficiency occurred during the sub-acute phase of traumatic brain injury in 5.6% of patients with mild injury, 22.5% of patients with moderate injury, and 52.2% of patients with severe injury. Traumatic brain injury-induced critical illness-related corticosteroid insufficiency was strongly correlated to injury severity during the sub-acute stage of traumatic brain injury. Traumatic brain injury patients with critical illness-related corticosteroid insufficiency frequently presented with hemorrhagic cerebral contusions, diffuse axonal injury, brain herniation, and hypotension. Differences in the incidence of hospital-acquired pneumonia, gastrointestinal bleeding, and 28-day mortality were observed between patients with and without critical illness-related corticosteroid insufficiency during the sub-acute phase of traumatic brain injury. Hypotension, brain-injury severity, and the types of traumatic brain injury were independent risk factors for traumatic brain injury-induced critical illness-related corticosteroid insufficiency. These findings indicate that critical illness-related corticosteroid insufficiency is common during the sub-acute phase of traumatic brain injury and is strongly associated with poor prognosis. The dexamethasone suppression test is a practical assay for the evaluation of hypothalamic-pituitary-adrenal axis function and for the diagnosis of critical illness-related corticosteroid insufficiency in patients with traumatic brain injury, especially those with hypotension, hemorrhagic cerebral contusions, diffuse axonal injury, and brain herniation. Sub-acute infection of acute traumatic brain injury may be an important factor associated with the occurrence and development of critical illness-related corticosteroid insufficiency. This study protocol was approved by the Ethics Committee of General Hospital of Tianjin Medical University, China in December 2011 (approval No. 201189).

Key Words: *brain herniation; corticosteroid; critical illness-related corticosteroid; dexamethasone suppression test; diffuse axonal injury; gastrointestinal bleeding; hemorrhagic cerebral contusions; hospital-acquired pneumonia; insufficiency; prognosis; traumatic brain injury*

Chinese Library Classification No. *R441; R447; R741*

Introduction

Traumatic brain injury (TBI) remains a leading cause of death and disability among adolescent males and young adults, despite extensive basic and clinical research during the last 150 years (Mollayeva et al., 2018; Clevius et al., 2019; Jang et al., 2019; King and Collins-Yoder, 2019; Lu et al., 2019; Marincowitz et al., 2019). Critical illness-related corticosteroid insufficiency (CIRCI) was coined by the American College of Society of Critical Care Medicine to describe the impairment of the hypothalamic-pituitary-adrenal (HPA) axis at any level, including at the hypothalamus, pituitary, or adrenal glands, and to describe corticosteroid resistance at the peripheral level of target tissues. The term CIRCI was recommended to replace "primary/central and secondary corticosteroid insufficiency", which only encompassed the impairment of either thalamic/pituitary or adrenal gland function. CIRCI is strongly correlated with mortality in patients with sepsis, shock, acute respiratory distress syndrome, and severe pancreatitis (Marik et al., 2008; Peng et al., 2009; Koch and Tacke, 2014; Tsai et al., 2014; Ducrocq et al., 2018; Ok et al., 2018). Recent studies have demonstrated that CIRCI is common among critically ill trauma patients and generally occurs during the early stages of injury (Yang et al., 2014; Annane et al., 2017). However, the clinical characteristics of CIRCI among patients with different levels of TBI severity have not been fully defined.

CIRCI is characterized by an exaggerated and protracted inflammatory response and corticosteroid resistance, which result in inadequate corticosteroid response to severe stress (Polito and Annane, 2011). No gold standard test currently exists for the diagnosis of CIRCI (Annane et al., 2018; Teblick et al., 2019). An adrenocorticotropic hormone stimulation test is widely used to define adrenal dysfunction in critically ill patients (Burry et al., 2013). However, this test is primarily designed to evaluate adrenal function and is limited in its ability to assess the overall functional state of the HPA axis (Teblick et al., 2019), especially in patients with TBI, for whom HPA axis dysfunction is deeply rooted in the hypothalamus and pituitary instead of the adrenal gland (Cuesta and Singer, 2012; Pastores et al., 2018).

The dexamethasone suppression test has been considered to be a clinically applicable test for the assessment of HPA-axis function (Lu et al., 2016). By evaluating the negative feedback loops of the HPA axis, via the exogenous dexamethasone-mediated suppression of corticotropin-releasing hormone and adrenocorticotropic hormone secretion, the dexamethasone suppression test may be an ideal assay for the detection of defects in hypothalamus and pituitary functions and the identification of CIRCI (Annane, 2010; Direk et al., 2016). The objective of this study was to investigate the prevalence and risk factors of CIRCI, as defined by the dexamethasone suppression test, and to evaluate the effects of CIRCI on the outcomes of patients with acute TBI.

Participants and Methods

Participants

This multicenter, prospective, cohort study was conducted among patients who were admitted by the neurosurgical departments at three tertiary-level hospitals: Tianjin Medical University General Hospital, Ordos General Hospital, and Haikou People's Hospital. The study protocol was approved by the Ethics Committee of the General Hospital of Tianjin Medical University, China (approval No. 201189) in December, 2011. Patients or their next of kin were comprehensively informed by the research team. Written informed consent was obtained from patients or their next of kin. Consecutive patients with TBI who were admitted to any of the three sites were screened from January 2012 to May 2017.

Inclusion criteria included the following: (1) age range between 18 and 65 years; and (2) acute TBI (Carney et al., 2017; Galgano et al., 2017; Rouanet et al., 2017; Pastores et al., 2018; Caplan and Cox, 2019; Figaji, 2019); (3) a diagnosis of CIRCI was made if the baseline cortisol level was less than 10 μg/dL (275.9 nM) or if the post-test cortisol level was more than 50% of the baseline level by Dexamethasone Suppression Test (Annane et al., 2017; Annane et al., 2018).

Exclusion criteria included the following: (1) younger than 18 years of age; (2) previously diagnosed with adrenal insufficiency; (3) previous use of immunosuppression; (4) treatment with corticosteroids within the last 6 months; (5) pregnancy; (6) malignancies; (7) previously diagnosed peptic ulcer; (8) spinal cord injury with immediate methylprednisolone administration; (9) etomidate use; (10) use of nonsteroidal anti-inflammatory drugs; (11) injury to the gastrointestinal tract; (12) participation in other clinical trials within the past 30 days; or (13) consent refusal. Related clinical diagnoses were performed according to well-accepted guidelines for clinical practice.

Data collection

Each patient or guardian, assisted by a nurse coordinator, who was assigned to this study, completed a short questionnaire regarding his or her condition and then underwent physical examinations, which were conducted by an attending neurosurgeon who was masked to the treatment conditions. All data were collected onsite, by nurse coordinators, and submitted electronically to the data acquisition system. All data entries were validated by a second nurse prior to submission. The study was overseen by a data monitoring board, which was independent of the study investigators, composed of clinicians, neurosurgeons, clinical-trial experts, epidemiologists, and biostatisticians from the General Hospital of Tianjin Medical University. A total of 140 acute-TBI patients were enrolled in this study, who were allocated into mild-, moderate-, and severe-injury groups, according to admission (Glasgow Coma Scale, GCS) scores.

Brain injury type and severity

On admission, the initial post-resuscitation GCS score assessing eye opening, verbal, and motor responses was used to evaluate the level of traumatic brain injury. Brain injury types were determined by clinical signs, symptoms, and non-contrast CT scan of the head. These evaluation processes were performed according to the "4th Edition of the Brain

Trauma Foundation's guidelines" (Carney et al., 2017).

Dexamethasone suppression test

The dexamethasone suppression test was performed by administering a 1.5 mg dexamethasone tablet (Tianjin Lisheng Pharmaceutical Co., Ltd., Tianjin, China), either orally or via a nasogastric tube, at 12:00 a.m. on post-injury day 5. The total plasma cortisol level was measured at 7:00 a.m. on both post-injury day 4 (baseline) and day 5 (post dexamethasone suppression test). The total plasma cortisol level was measured using a chemiluminescence enzyme immunoassay (Siemens Medical Solutions Diagnostics, Germany). A diagnosis of CIRCI was made if the baseline cortisol level was less than 10 μg/dL (275.9 nM) on post-injury day 4 or if the post-test cortisol level was more than 50% of the baseline level on post-injury day 5.

Hospital-acquired pneumonia and gastrointestinal bleeding

A pneumonia diagnosis was considered when a patient presented with two or more of the following signs: body temperature > 38°C; leukocytosis > 12,000 cells/mL, or leukopenia < 4000 cells/mL; and purulent pulmonary secretions were present on chest X-ray, either associated with the appearance of a new infiltrate or when changes occurred in an existing infiltrate. The diagnosis was validated by laboratory tests on at least a lower respiratory tract sample (Wongsurakiat and Chitwarakorn, 2019). Hospital-acquired pneumonia was defined as pneumonia that occurred within 48 hours after admission in a patient was not incubated at the time of admission (Lanks et al., 2019). Patients with sepsis and septic shock were excluded from this study. Gastrointestinal bleeding was monitored according to signs of hematemesis, bloody or coffee-ground colored nasogastric aspirate, melena, or hematochezia (Pai and Fox, 2017).

Outcomes

Demographics, medical history, and clinical information were recorded for each patient. The primary outcome was 28-day mortality, and the secondary outcomes included complications (hospital-acquired pneumonia and gastrointestinal bleeding), brain injury types (epidural hematoma, subdural hematoma, hemorrhagic cerebral contusions, diffuse axonal injury, brain herniation), and brain injury severity (mild injury, GCS ≥ 13; moderate injury, 9 ≤ GCS ≤ 12, severe injury, GCS ≤ 8; Volovici et al., 2019).

The 28-day mortality was defined as any death that occurred during the 28-day follow-up period following TBI diagnosis.

The brain injury type and injury severity were defined according to the CIRCI guidelines established by the American Neurotrauma Society (Carney et al., 2017; Galgano et al., 2017; Pastores et al., 2018; Figaji, 2019). Hypotension was considered when systolic blood pressure was less than 90 mmHg (Caplan and Cox, 2019; Volovici et al., 2019).

All clinical data were collected and analyzed by independent investigators and statisticians (Dr. Chun-Xiang Liu, Dr. Yu Guo, Dr. Zheng Zeng, Dr. Yang Gao from General Hospital of Tianjin Medical University, and Dr. Jiang-Hua Wang from Tianjin Neurological Institute), who were blinded to this study.

Statistical analysis

Data were analyzed using SPSS 20.0 software (IBM, Armonk, NY, USA). Univariate analyses of patient demographic, injury, and hospital characteristics, as confounding factors, were conducted among different groups of patients. The age, GCS, and baseline cortisol data are presented as the mean ± SD and were analyzed using either Student's *t*-test or a one-way analysis of variance, followed by the Bonferroni *post hoc* test. The gender, medical history, hypotension prior to inclusion, and baseline cortisol < 275.9 nM data are presented as percentages and were compared using Pearson's chi-squared test and Fisher's exact test. The injury type is presented as a percentage and was analyzed by the Kruskal-Wallis test. The incidence of CIRCI, pneumonia, gastrointestinal bleeding, and 28-day mortality was compared by the Kruskal-Wallis test among different injury severity groups. The incidence of pneumonia, gastrointestinal bleeding, and 28-day mortality were compared by Fisher's exact test between the CIRCI and non-CIRCI groups. Clinical and laboratory variables that were statistically significant in the univariate analysis ($P < 0.1$) were selected for the multivariate analysis, using logistic regression to obtain independent risk factors for CIRCI. All statistical tests were two-tailed. A value of $P < 0.05$ was considered to be statistically significant.

Results

Baseline characteristics

A total of 165 patients with TBI were evaluated for eligibility. Of them, 25 patients were excluded, and 140 were finally enrolled. All enrolled patients were evaluated for HPA-axis dysfunction and CIRCI incidence, according to baseline cortisol levels or dexamethasone suppression test results. Thirty-six patients were diagnosed with CIRCI during the sub-acute phase of TBI (**Figure 1**). A total of 140 TBI patients met the inclusion criteria, including 54 with mild injury (GCS ≥ 13), 40 with moderate injury (9 ≤ GCS ≤ 12), and 46 with severe injury (GCS ≤ 8). The clinical characteristics of these patients are presented in **Table 1**. Age, gender, and medical history characteristics were comparable among the three groups of patients ($P > 0.05$). More cases of hemorrhagic cerebral contusion, diffuse axonal injury, and brain herniation were found in the severe-injury group compared with the mild- and moderate-injury groups ($P < 0.05$). Hypotension was found in 21.7% of severe-injury patients, which was a significantly higher incidence than was found for the mild- or moderate-injury patients ($P < 0.01$). In addition, the baseline total plasma cortisol level was significantly higher on post-injury day 4 in patients with severe injury than in those with mild or moderate injury ($P < 0.05$; **Table 1**).

Incidence and related complications of CIRCI

CIRCI occurred in 5.6% of patients with mild injuries,

Table 1 Demographic data and clinical characteristics of traumatic brain injury patients at admission

Variables	Mild injury (n = 54)	Moderate injury (n = 40)	Severe injury (n = 46)	P-value
Age (yr)	42.0±17.5	42.9±15.5	45.7±18.7	0.567
Male	31(57.4)	27(67.5)	30(65.2)	0.558
Medical history				
Diabetes mellitus	4(7.4)	3(7.0)	2(4.2)	0.771
Hypertension	2(3.7)	2(5.0)	2(4.3)	0.954
Chronic pulmonary disease	2(3.7)	0	2(4.3)	0.431
Injury type				
Epidural hematoma	16(29.6)	20(50.0)	6(13.0)	0.001
Subdural hematoma	8(14.8)	8(20.0)	4(8.7)	0.324
Hemorrhagic cerebral contusions	10(18.5)	13(32.5)	30(65.2)	< 0.001
Diffuse axonal injury	0	1(2.5)	8(17.4)	0.001
Brain herniation	0	0	18(39.1)	< 0.001
Hypotension prior to inclusion	0	6(15.0)	10(21.7)	0.002
GCS (scores)	14.3±0.9	10.3±1.2	5.7±1.8	< 0.001
Baseline cortisol (nM)	742.2±204.2	802.9±253.8	990.5±339.4	< 0.001
Baseline cortisol < 275.9 nM	0	2(5.0)	3(6.5)	0.183

Age, GCS and cortisol are expressed as the mean ± SD; the other data are expressed as the n(%). A total of 140 traumatic brain injury patients were enrolled, including 54 with mild injury, 40 with moderate injury, and 46 with severe injury. The age, gender, and medical history were comparable among three groups of patients (P > 0.05). There were more cases of hemorrhagic cerebral contusion, diffuse axonal injury, and brain herniation in severe-injury group as compared to those in mild- and moderate-injury groups (P < 0.05). Hypotension was found in 21.7% of severely injured patients, significantly higher than those in mildly or moderately injured patients (P < 0.01). The baseline total plasma cortisol level was significantly higher on post-injury day 4 in patients with severe injury as compared to those with mild or moderate injury. Univariate analysis was conducted among different groups of patients. The data of age, GCS, and baseline cortisol were presented as the mean ± SD (one-way analysis of variance followed by Bonferroni *post hoc* test). The data of male, medical history, injury type, hypotension prior to inclusion, and baseline cortisol < 275.9 nM were presented as percentage and compared with Pearson's chi-squared test and Fisher's exact test. The data of injury type were presented as percentage (Kruskal-Wallis test between different groups). GCS: Glasgow Coma Scale.

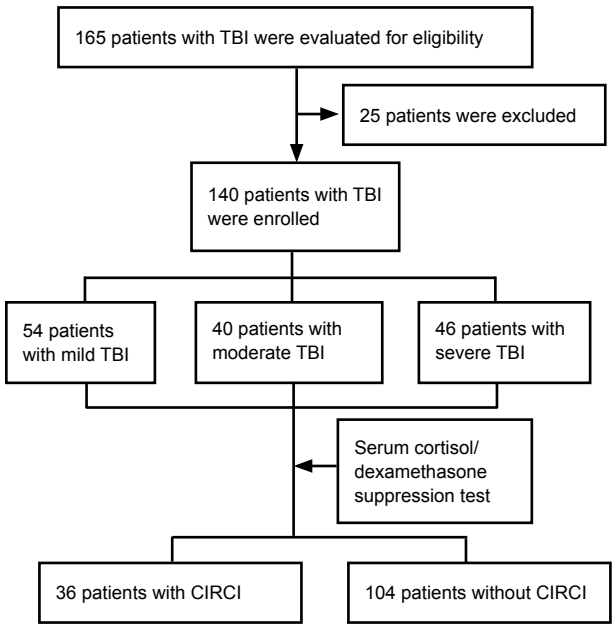

Figure 1 Flow chart of the study protocol.
CIRCI: Critical illness-related corticosteroid insufficiency; TBI: traumatic brain injury.

22.5% of patients with moderate injuries, and 52.2% of patients with severe injuries, during the sub-acute phase of TBI (**Table 2**). The incidence of CIRCI was strongly associated with injury severity. During the 28-day follow-up period, the incidences of pneumonia (58.7%) and gastrointestinal bleeding (56.5%) were significantly higher in patients with severe injury than in those with mild and moderate injuries (P < 0.01). Fifteen patients with severe TBI died during the 28-day follow-up period (**Table 2**).

Table 2 Comparison of clinical characteristics and complications between different groups

Variable	Mild injury (n = 54)	Moderate injury (n = 40)	Severe injury (n = 46)	P
CIRCI incidence	3(5.6)	9(22.5)	24(52.2)	0.001
Pneumonia	0	4(7.5)	23(58.7)	< 0.001
Gastrointestinal bleeding	0	3(10)	27(56.5)	< 0.001
28-Day mortality	0	0	15(32.6)	< 0.001

CIRCI occurred in 5.6% of patients with mild injury, 22.5% with moderate injury, and 52.2% with severe injury in the sub-acute phase of traumatic brain injury. The incidence was strongly correlated with injury severity. During the 28-day follow-up, the incidences of pneumonia (58.7%) and gastrointestinal bleeding (56.5%) in patients with severe injury were significantly higher than those with mild and moderate injuries (P < 0.01). Univariate analysis was conducted among different groups of patients. The incidence of CIRCI, pneumonia, and gastrointestinal bleeding, and 28-day mortality were analyzed by Kruskal-Wallis test between different groups. CIRCI: Critical illness-related corticosteroid insufficiency.

Risk factors and mortality of CIRCI

According to the univariate analysis, baseline total plasma cortisol levels were comparable between CIRCI and non-CIRCI patients (P > 0.05; **Table 3**), but the development of CIRCI was associated with the injury type (hemorrhagic

Table 3 Comparison of clinical characteristics between CIRCI and non-CIRCI patients

Variable	CIRCI (n = 36)	Non-CIRCI (n = 104)	P
Age (yr)	41.4±18.9	44.5±16.8	0.351
Male	26(72.2)	62(59.6)	0.23
Medical history			
Diabetes mellitus	4(10.0)	5(4.8)	0.264
Hypertension	2(5.6)	4(4.8)	0.647
Chronic pulmonary disease	1(2.8)	3(2.9)	1
Injury type			
Epidural hematoma	9(25.0)	33(31.7)	0.53
Subdural hematoma	4(11.1)	16(14.0)	0.784
Hemorrhagic cerebral contusions	24(66.7)	29(27.9)	< 0.001
Diffuse axonal injury	7(19.4)	2(1.9)	< 0.001
Brain herniation	17(47.2)	1(1.0)	< 0.001
Hypotension prior to inclusion	10(27.8)	6(5.8)	0.001
GCS (scores)	6.6±3.1	11.6±3.2	< 0.001
Baseline cortisol (nM)	813.9±405.6	852.5±237.3	0.484
Baseline cortisol < 275.9 nM	5(13.9)	0	< 0.001

Age, GCS and cortisol are expressed as the mean ± SD; the other data are expressed as the n(%). The baseline total plasma cortisol level was comparable between CIRCI and non-CIRCI patients (P > 0.05), but the development of CIRCI was associated with injury type (hemorrhagic cerebral contusions, diffuse axonal injury, and brain herniation) and severity of traumatic brain injury and the presence of hypotension (P < 0.01). The data of age, GCS, and baseline cortisol are presented as the mean ± SD (Student's t-test). The data of male, medical history, hypotension prior to inclusion, and baseline cortisol < 275.9 nM are presented as percentage (Pearson's chi-squared test and Fisher's exact test). The data of injury type are presented as percentage and analyzed by Kruskal-Wallis test between CIRCI and non-CIRCI groups. A value of P < 0.05 was considered statistically significant. CIRCI: Critical illness-related corticosteroid insufficiency; GCS: Glasgow Coma Scale.

cerebral contusions, diffuse axonal injury, and brain herniation), the severity of TBI, and the presence of hypotension (P < 0.01). According to the multivariate analysis, hemorrhagic cerebral contusions, diffuse axonal injury, brain herniation, hypotension, and injury severity were independent risk factors for CIRCI (P < 0.01; **Tables 3** and **4**). The rates of pneumonia, gastrointestinal bleeding, and mortality were significantly higher in CIRCI patients than in non-CIRCI patients during the 28-day follow-up period (P < 0.01; **Table 5**).

Discussion

In this multicenter, prospective, cohort study, we investigated the prevalence, risk, and mortality associated with CIRCI in patients with acute TBI. We made the following observations. First, TBI-induced CIRCI was strongly associated with TBI severity during the sub-acute phase of TBI, diagnosed in 5.6% of patients with mild injuries, 22.5% of patients with moderate injuries, and 52.2% of patients with severe injuries, and was an independent risk for death. Second, CIRCI occurrence during the sub-acute phase of TBI was strongly associated with increased rates of hospital-acquired pneumonia, gastrointestinal bleeding, and 28-day mortality.

Table 4 Analysis of risk factors for CIRCI patients

Variable	Odds ratio	95% CI	β	P
Hemorrhagic cerebral contusions	3.283	1.796–6.000	1.1888	< 0.001
Diffuse axonal injury	3.513	2.186–5.646	1.2565	0.001
Cerebral herniation	6.064	3.953–9.305	1.8024	< 0.001
Hypotension prior to inclusion	2.981	1.789–4.967	1.0923	0.001
GCS ≤ 8	4.087	2.251–7.421	1.4078	< 0.001

The five variables that had P values less than 0.1 in the univariate analysis in Table 3 were selected for the multivariate analysis using a Logistic regression to obtain independent risk factors for CIRCI. The hemorrhagic cerebral contusions, diffuse axonal injury, brain herniation, hypotension, and injury severity were found to be independent risk factors for CIRCI (P < 0.01). CIRCI: Critical illness-related corticosteroid insufficiency; GCS Glasgow Coma Scale.

Table 5 Comparison of clinical outcome [n(%)] between CIRCI and non-CIRCI patients

Variable	CIRCI (n = 36)	Non-CIRCI (n = 104)	P
Pneumonia	16(44.4)	11(10.6)	< 0.001
Gastrointestinal bleeding	17(47.2)	13(12.5)	< 0.001
28-Day mortality	9(25.0)	6(5.8)	0.003

The rates of pneumonia, gastrointestinal bleeding, and mortality in CIRCI patients were significantly higher than in non-CIRCI patients during the 28-day follow-up (P < 0.01). The incidence of pneumonia, gastrointestinal bleeding and 28-day mortality were compared by Fisher's exact test between CIRCI and non-CIRCI groups. CIRCI: Critical illness-related corticosteroid insufficiency.

Third, hypotension, severe hemorrhagic cerebral contusions, diffuse axonal injury, and brain herniation were independent factors that predicted the incidence of TBI-induced CIRCI.

Increasing evidence has strongly indicated that CIRCI can occur in a variety of critically ill patients (Roquilly et al., 2011; Teblick et al., 2019). However, the exact mechanism underlying the development of CIRCI during the acute phase of TBI remains largely unknown. Structural damage to the HPA axis might be the underlying cause for CIRCI development among patients with TBI because HPA dysfunction primarily derives from hypothalamic or pituitary inadequacies in TBI patients (Seravalli, 2009) instead of adrenal insufficiency, as observed in patients with other critical illnesses. In this study, severe hemorrhagic cerebral contusions, diffuse axonal injuries, and brain herniations, which are strongly correlated with structural damage to the HPA axis, were independent factors that predicted TBI-induced CIRCI. We and others have previously shown that hypothalamic hemorrhage or infarction occurs in 40% of TBI patients, and adenohypophysial hemorrhage and necrosis have been found in 43% of patients who die within 1 week after TBI (Edwards and Clark, 1986; Salehi et al., 2007; Diaz-Arrastia et al., 2012). The breakdown of the blood-brain barrier, followed by neuronal apoptosis in the paraventricular nucleus of the hypothalamus, is considered to be a pathological characteristic of TBI-associated HPA-axis dysfunction (Chen

et al., 2013, 2014; Wang et al., 2019). The downregulation of glucocorticoid receptor-α and the upregulation of glucocorticoid receptor-β at target tissues, which is considered to be the basis for glucocorticoid resistance, might also contribute to the progress of CIRCI development; however, this hypothesis remains to be further validated in acute TBI patients (Chen et al., 2013; Wang et al., 2019).

The widely used adrenocorticotropic hormone stimulation test assumes that HPA axis dysfunction arises from adrenal gland insufficiency (Seki et al., 2018). However, HPA dysfunction is primarily caused by hypothalamic or pituitary inadequacies in patients with TBI (Seravalli, 2009). No gold standard test is currently available for the diagnosis of HPA-axis dysfunction in TBI patients (Annane et al., 2018; Pastores et al., 2018). Therefore, we used the dexamethasone suppression test to measure the negative feedback of the hypothalamus and pituitary gland in response to exogenous dexamethasone (Lu et al., 2016). As their levels increase in peripheral blood, corticosteroids trigger the negative feedback of the hypothalamus, resulting in decreased corticotropin-releasing hormone production, and the pituitary gland, resulting in decreased adrenocorticotropic hormone secretion, which combine to reduce blood cortisol levels. Consequently, the disappearance of this negative feedback loop indicates compromised HPA axis function and the presence of CIRCI (Fleseriu and Loriaux, 2009; Direk et al., 2016; Lu et al., 2016; Findling and Raff, 2017; Teblick et al., 2019).

The incidence of CIRCI varies considerably among different types of critical illnesses, and its presence has consistently been associated with mortality (Meduri et al., 2007; Marik, 2009; Peng et al., 2009; Triantos et al., 2011; Cuesta and Singer, 2012; Jung et al., 2012; Vella et al., 2017). Recent clinical trials have demonstrated that HPA-axis-dysfunction can be found in 50% to 70% of trauma patients, with approximately 34% mortality, independent of therapies (Walker et al., 2011). We found that 52.2% of patients with severe TBI suffered from CIRCI, and TBI-associated CIRCI was strongly correlated not only with increased mortality but also with more frequent complications, such as pneumonia and gastrointestinal bleeding, which have also been associated with poor outcomes in TBI patients. However, significantly more patients with CIRCI developed pneumonia and gastrointestinal bleeding than those without CIRCI, even though patients with sepsis were excluded from this study. This study was not powered to investigate the causal relationship between CIRCI and pneumonia or gastrointestinal bleeding; however, the interface among TBI, HPA function, and infection requires further investigation because their interactions may influence the treatment and outcomes of TBI patients, especially those with severe injuries. Consistent with the epidemiological findings, the use of a stress-dose of hydrocortisone decreased the rate of hospital-acquired pneumonia in multiple-trauma patients and was associated with a low incidence of CIRCI and mortality in experimental-TBI rats (Bronchard et al., 2004; Schneider et al., 2007; Roquilly et al., 2011, 2013; Chen et al., 2013). Together, these findings indicated that patients with CIRCI might have reduced HPA axis function and are more likely to develop pneumonia and gastrointestinal bleeding, resulting in higher rates of mortality.

The study had several limitations. First, this study was limited in its ability to determine whether similar findings can also be observed at other time points following injury. These findings might be associated with changes in cytokine levels in the brain or blood, which can directly influence hypothalamopituitary function, or with changes in the partial arterial oxygen and carbon dioxide pressures, which are key factors during the evolution of brain injuries. Second, the univariate analysis was used to conduct subgroup analyses, which may not be sufficiently powered to indicate which factors affect injury severity. Despite these limitations, this study suggested that CIRCI is common during the sub-acute phase of TBI and is strongly associated with poor prognosis.

Our findings have several clinical implications. First, much attention must be paid to the HPA axis function among patients with severe TBI, especially those with hypotension, hemorrhagic cerebral contusions, diffuse axonal injury, and brain herniation. Second, the dexamethasone suppression test might be an applicable assay for the clinical evaluation of HPA axis function during the sub-acute phase of TBI. Third, appropriate corticosteroid supplementation might be necessary to improve the survival rates of TBI patients with CIRCI. Therefore, these results call for more studies regarding the underlying mechanisms associated with CIRCI and the early detection and treatment of CIRCI in TBI patients.

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