Caspian Journal of Internal Medicine 2024 (Autumn); 15(4): 673-681
DOI: 10.22088/cjim.15.4.673

Original Article

Gastrointestinal bleeding following traumatic brain injury: A clinical study on predisposing factors and outcomes

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Received: 24 June 2023
Revised: 16 Aug 2023
Accepted: 6 Nov 2023
Published: 7 Sep 2024

Abstract

Background: Traumatic brain injury (TBI) is one of the most common causes of death and disability worldwide. Stress ulcers are common in critically ill patients and can lead to life-threatening gastrointestinal bleeding (GIB). This study investigates the impact of predisposing factors on GIB and outcomes of TBI patients.

Methods: This retrospective cohort study included TBI patients admitted between February 2019 and November 2021. Patients' demographic information and clinical characteristics were collected and divided into Post-TBI GIB and No-GIB groups. During clinical follow-up, the Glasgow Outcome Score (GOS) and mortality were assessed. The correlation between predisposing factors and GIB was investigated.

Results: Out of 164 eligible patients, 66.5% were males, and the mean age was 31.38 ± 13.44 years. There was a higher rate of severe TBIs ($p<0.001$), intra-axial lesions ($P=0.014$), hypotension at admission ($p<0.001$), and concurrent coagulopathies ($p<0.001$) in the Post-TBI GIB group compared to the No-GIB group. In contrast, the Glasgow Coma Scale (GCS) level upon admission and discharge ($p<0.001$) and serum hemoglobin level at admission ($p<0.001$) were lower in the Post-TBI GIB group than in the other group. Moreover, primary GCS ($P=0.017$) and hypotension at admission ($P=0.009$), spinal injury ($P=0.028$), and intra-axial brain injury ($P=0.018$) were independently associated with GIB in TBI patients.

Conclusion: Primary GCS and hypotension at admission, spinal injury, and intra-axial brain injury are independent predictors for GIB in TBI patients. The presence of GIB in TBI patients is associated with worse neurological outcomes as assessed by GOS at approximately 18 months.

Keywords: Traumatic brain injury, TBI, Gastrointestinal bleeding, Stress ulcer, Cushing ulcer.

Citation:
Mahmoodkhani M, Naeimi A, Zohrehvand A, Sabouri M, Heidari M. Gastrointestinal bleeding following traumatic brain injury: A clinical study on predisposing factors and outcomes. Caspian J Intern Med 2024; 15(4): 673-681.

Traumatic brain injury (TBI) is nondegenerative, noncongenital damage to the brain caused by an external force, which can cause a permanent or temporary impairment of cognitive, physical, and psychosocial functions, as well as altered consciousness or diminished awareness (1, 2). The effects of TBI vary from concussion to coma and death, depending on the force applied to the skull and intracranial contents (3). In the United States, TBI is responsible for over 50,000 deaths per year. In fact, TBI is one of the leading causes of death and disability worldwide (4). The annual incidence of TBI is estimated at 69 million worldwide and is increasing (5). TBI severity is usually classified based on Glasgow coma scale (GCS) scores into Mild GCS ($13\leq GCS\leq15$), moderate ($9\leq GCS\leq12$), and severe ($GCS\leq8$) (6). In addition, TBI can be classified into two subcategories: (1) primary injuries, which occur immediately following trauma and manifest as focal injuries (e.g., skull fractures, lacerations, contusions, intracranial hematomas, penetrating wounds, or diffuse axonal injuries (DAI)); and (2) secondary injuries, which occur immediately following trauma and produce long-term effects (7)

Many complications may take place following TBI. One of the major complications following TBI is a gastrointestinal ulcer(8, 9). A stress ulcer is a medical condition following a physical stress and traumatic event. It results from impairment of mucosal integrity and gastric acid hypersecretion, with suggested mechanisms including proinflammatory states, hypoperfusion, microcirculation disturbances, ischemia, pathological luminal acidosis, hypovolemia, and shock (10, 11). Cushing's ulcer is also a gastroduodenal ulcer produced by increased intracranial pressure caused by a head injury, intracranial tumor, or other space‐occupying lesions. These ulcers usually occur in the esophagus, stomach, or duodenum and are usually deep and single. Gastrointestinal bleeding (GIB) is a serious complication of gastroduodenal ulcers, increasing mortality (12). The incidence of GIB and the mortality rate due to GIB in severe TBI patients are higher than in other cases (13-15). Various factors, including renal and hepatic failure, sepsis, hypotension, coagulopathy, especially on the first day of intensive care unit (ICU) admission, and respiratory failure (>48 hours of mechanical ventilation), are considered risk factors for stress-induced GIB (16-18). To date, several studies have contributed to improving the treatment of TBI and its complications. However, limited studies exist investigating the predictors of GIB in TBI patients. As more studies are needed to understand the role of underlying factors associated with GIB in TBI patients, this study investigates the impact of predisposing factors on GIB and clinical outcomes in TBI patients.

Methods

Study design and participants: This retrospective cohort study was conducted in Al-Zahra and Kashani Hospitals, affiliated hospitals of Isfahan University of Medical Sciences. All patients over 18 years old with a diagnosis of TBI who were admitted between 2019 and 2021 were included in the study. The exclusion criteria were as follows: (1) death within 24 hours of admission; (2) extraluminal bleeding (e.g., epistaxis, tracheal injury during intubation) in addition to GIB at hospitalization; (3) fractures of the skull base; (4) history of using anti-acid, proton-pump inhibitor (PPI), H2 antagonist, sucralfate, or misoprostol medications; (5) history of taking nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, anticoagulants, selective serotonin reuptake inhibitors (SSRIs), and antiplatelet drugs; (6) history of peptic ulcer (ICD-10-CM K250 and K270-K276), esophageal varices (ICD-10-CM I185), esophagitis (ICD-10-CM K20), gastritis (ICD-10-CM K29), helicobacter pylori (H.pylori; ICD-10-CM B98), Mallory–Weiss syndrome (ICD-10-CM K226), diverticular disease (ICD-10-CM K22, K31.4,K57, Q38-39, Q43), inflammatory bowel disease (IBD; ICD-10-CM K50-52), malignancy, colon polyps (ICD-10-CM K63.5), hemorrhoids (ICD-10-CM K64), anal fissures (ICD-10-CM K60), and proctitis (ICD-10-CM K51,K62,K93); (7) history of alcohol consumption; (8) major incomplete information in the medical record; (9) lack of consent to participate in the study. The study was approved by the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1399.1110) in accordance with the World Medical Association's code of ethics (Declaration of Helsinki, revised in Brazil 2013). Written informed consent was obtained from the patient or the next of kin when applicable.

Data collection: 6832 medical records of TBI patients were initially identified and evaluated. After applying the exclusion criteria, the records were assessed for demographical data and clinical characteristics of patients, including sex, age, primary GCS (48 hours after admission), vital signs, the severity of TBI, type of intracranial lesions or injuries (according to brain imaging), concurrent injuries (thoracic, abdominal, orthopedic, and spinal), need for cranial surgery, laboratory results in the first 24 hours of admission (including hemoglobin level (g/dl) and coagulopathy profile), upper or lower GIB specifications, endoscopy or colonoscopy findings (grade of gastroduodenal ulcer), and GCS at discharge. Next, patients were divided into two groups: (1) the Post-TBI GIB group, which included patients with evidence of GIB from the onset of TBI up to one week later (n = ۹۰), and (2) the No-GIB group, comprising all other TBI cases not classified as Post-TBI GIB (n=۹۷).

TBI management: All patients were initially evaluated by emergency specialists in the emergency department. Intracranial lesions, including extra- and intra-axial lesions, diffuse axonal injury (DAI), linear skull fracture, and depressed fracture of the skull following head trauma, were categorized as primary traumatic brain lesions. Neurosurgical lesions were treated in accordance with the Brain Trauma Foundation (BTF) (19), Advanced Trauma Life Support (ATLS) guidelines (20, 21), and regional policies. According to our institutional policy, all TBI patients received pantoprazole (Exir Co., Tehran, Iran) 0.5 mg/kg daily to prevent stress ulcers. Pantoprazole was administered intravenously in the first 48 hours and then orally for the following days of hospitalization. Moreover, depending on the patient's consciousness level and the medical-surgical status, enteral nutrition (by mouth or tube) was started in most cases.

GIB diagnosis and management: The diagnosis of GIB was made by gastroenterologists based on the clinical evidence of GIB, including hematoma, bloody discharge from the nasogastric tube, melena, rectorrhagia, positive occult blood test, and endoscopic or colonoscopy findings. As soon as the diagnosis was made, initial fluid resuscitation, blood reserves, and infusions were initiated, and all enteral nutrition and anticoagulant/antiplatelet medications were discontinued. In addition, pharmacological work-ups to assess side effects or drug interactions, as well as surgical or medical consultations to identify the source of GIB were performed in all patients. Post-traumatic coagulopathy was defined as the presence of at least two of the following laboratory findings: (1) international normalized ratio (INR)≥1.5; (2) PT≥ 13.5 seconds; (3) PTT≥65 seconds; (4) platelet count ≤100,000/dL; (5) plasma fibrinogen level≤ 200 (22).

Follow-up: After discharge, patients were followed up for a period of 18 months. Patients with GIB were concurrently under the care of a gastroenterologist, and relevant treatments were performed if necessary. During clinical follow-up at approximately 18 months after admission, the Glasgow Outcome Score (GOS) (23) and mortality were assessed. The Glasgow Outcome Score (GOS) was categorized into five levels: death, vegetative state, severe disability, moderate disability, and good recovery.

Data analysis: Descriptive statistics was used to analyze the mean ± standard deviation (SD) for continuous variables and frequency (percentage) for categorical variables. Numerical data were analyzed using one-way ANOVA, independent samples median, and Pearson correlation tests. The Pearson Chi-square test was established to examine qualitative values. Binary logistic regression was used to assess the effect of different baseline factors on the likelihood of GIB occurrence. Statistical calculations were performed using IBM SPSS Statistics for Windows, Version 26 (IBM Corp., Armonk, NYUSA), and statistical significance was evaluated at the level of 0.05.

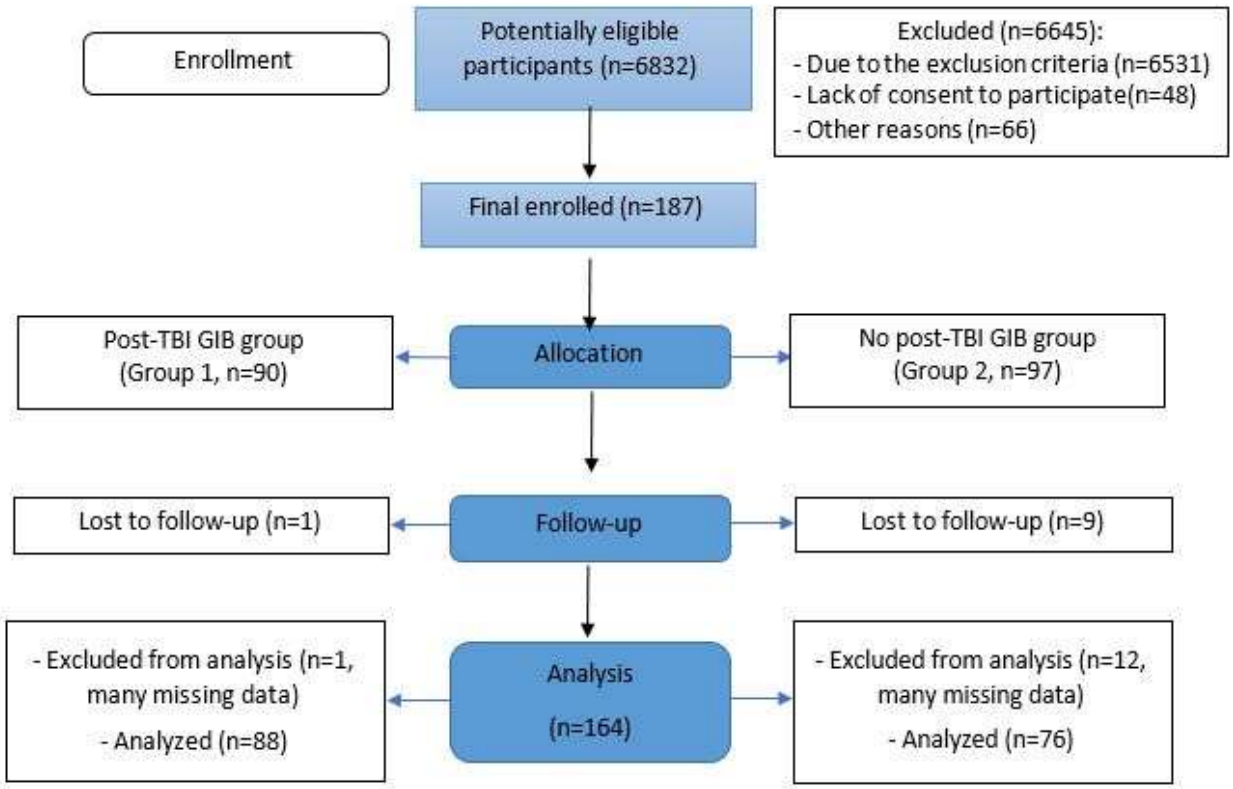

Figure 1. Flow diagram summarizing the study in a step-by-step fashion

Results

Comparison of baseline and clinical characteristics between Post-TBI GIB and No-GIB groups: Out of 164 eligible patients, 109 (66.5%) patients were males, and the mean age of patients was 31.38 ± 13.44 years. The post-TBI GIB group included more severely injured TBI (59.1%) patients compared to the No-GIB group (26.3%, p<0.001), while the number of patients with moderate TBI was higher in the No-GIB group (p<0.001). Moreover, in the Post-TBI GIB and No-GIB groups, extra-axial (48.2%) and intra-

axial lesions (23.2%) were the most common intracranial lesions. Besides, extra-axial and intra-cranial lesions significantly differed between the study groups (p<0.001 and P=0.014, respectively). More detailed information is provided in Table 1. The mean of primary GCS in the Post-TBI GIB group (8.31 ± 3.52) was significantly lower than the other group (10.30±3.05, p<0.001). Among the occurrence of other concurrent injuries other than TBI, spinal injuries (18.3%) and abdominal injuries (15.9%) were the most common types in the studied groups, with no significant differences between the groups (P=0.240 and P=۰.191, respectively). No significant difference was also found between the Post-TBI GIB and No-GIB groups regarding gender distribution (P=0.616), age (P=0.641), mild TBI severity(P=0.685), DAI (P=0.607), depressed (P=0.371) and linear fractures (P=0.850), the need for cranial surgery (P=0.087), and follow-up period (P=0.658).

Comparison of GIB-related factors: According to endoscopy reports, 56 out of 88 patients in the post-TBI GIB group (63.7%) had endoscopic evidence of stress ulcers. The prevalence of grade 1, grade 2, grade 3, and grade 4 gastroduodenal ulcers were 11.3%, 32.9%, 14.7%, and 4.5%, respectively (Table 1). The presence of hypotension on admission and concurrent coagulopathy were both significantly higher in the Post-TBI GIB group compared to the other group (p<0.001 for each). Moreover, the mean hemoglobin level taken during admission was significantly lower in the Post-TBI GIB (10.24 ± 1.13 (mg/dL)) than in the No-GIB (13.22 ± 1.80 (mg/dL)) group (p<0.001, R = -0.710) (Table 1).

Table 1. Patient's demographic information and clinical characteristics

Variable		Post-TBI GIB*	No-GIB	Total	P-value
Demographic characteristics					
Age (Years), mean±SD*		30.92 ± 13.59	31.91 ± 13.34	31.38 ± 13.44	0.641
Gender, n (%)	Male	60 (68.2)	49 (64.5)	109 (66.5)	
	Female	28 (31.8)	27 (35.5)	55 (33.5)	0.616
	M: F	2.14: 1	1.81: 1	1.98:1	
Clinical characteristics					
TBI severity, n (%)	Mild	16 (18.2)	12 (15.8)	28 (17.1)	0.687
	Moderate	20 (22.7)	44 (57.9)	6٤ (39)	**<0.001**
	Severe	52 (59.1)	20 (26.3)	72 (43.9)	**<0.001**
Concurrent injury, n (%)	Spinal	19 (21.6)	11 (14.5)	30 (18.3)	0.240
	Abdominal	17 (19.3)	9 (11.8)	26 (15.9)	0.191
	Orthopedic	12 (13.6)	7 (9.2)	19 (11.6)	0.377
	Thorax	11 (12.5)	4 (5.3)	15 (9.1)	0.109
	None	29 (33)	45 (59.2)	74 (45.1)	**0.001**
Intracranial lesion, n (%)	Extra-axial	26 (29.5)	53 (69.7)	79 (48.2)	**<0.001**
	Intra-axial	27 (30.7)	11(14.5)	38 (23.2)	**0.014**
	DAI	5 (5.7)	3 (3.9)	8 (4.9)	0.607
	Depressed fracture	4 (4.5)	6 (7.9)	10 (6.1)	0.371
	Linear fracture	4 (4.5)	3 (3.9)	7 (4.3)	0.850

Variable		Post-TBI GIB*	No-GIB	Total	P-value
GCS* at admission, mean±SD		8.31 ± 3.52	10.30 ± 3.05	9.23 ± 3.45	**<0.001**
Need for cranial surgery, n (%)		25 (28.4)	13 (17.1)	38 (23.2)	0.087
GIB related factors					
Hemoglobin level (g/dl, mean ± SD)		10.24 ± 1.13	13.22 ± 1.80	11.62 ± 2.10	**<0.001**
Concurrent coagulopathy		39 (44.3)	15 (19.7)	54 (32.9)	**<0.001**
At admission hypotension		25 (28.4)	2 (2.6)	27 (16.5)	**<0.0٠1**
Grade of gastro-duodenal ulcer	1	10 (11.3)	N/A		N/A
	2	29 (32.9)			
	3	13 (14.7)			
	4	4 (4.5)			
	None	32 (36.3)			
Clinical outcomes					
GCS at discharge, Mean±SD		10±3.06	12.89 ± 2.58	11.35 ± 3.18	**<0.001**
Mortality, n (%)		9 (10.2)	3 (3.9)	12 (7.3)	0.124
GOS*, n (%)	Dead	9 (10.2)	3 (3.9)	12 (7.3)	0.124
	Persistent vegetative state	13 (14.8)	3 (3.9)	16 (9.8)	0.020
	Severe disability	16 (18.2)	10 (13.2)	26 (15.9)	0.380
	Moderate disability	21 (23.9)	17 (22.4)	38 (23.2)	0.821
	Good recovery	29 (33)	43 (56.6)	72 (43.9)	**0.002**
Follow-up period (months, Mean ± SD)		17.81 ± 6.28	17.37 ± 5.45	17.60 ± 5.88	0.658

*SD: standard deviation, TBI: traumatic brain injury, GIB: gastrointestinal bleeding, GCS: Glasgow Coma Scale, Glasgow Outcome Score; P-value<0.05 is statistically significant

Evaluation of the predictive role of different factors in the occurrence of post-TBI GIB: To ascertain the effect of various factors on the likelihood of post-TBI GIB, a binominal logistic regression model, adjusted for age, sex, primary GCS at admission, cranial surgery, concurrent coagulopathy, hypotension at admission, concurrent injury (abdominal, chest, orthopedic, spinal), and brain injury (extra-axial, intra-axial, DAI, linear and depressed fracture) were performed. The logistic regression model revealed that lower primary GCS (B=-0.18, P=0.017), hypotension upon admission (B=2.35, P=0.009), spinal injury (B=1.26, P=0.028), and intra-axial lesion (B=1.21, P=0.018) were associated with an increased likelihood of post-TBI GIB (Table 2).

Evaluation of outcomes: GCS at discharge, mortality, and GOS at a follow-up visit were assessed to evaluate TBI patient outcomes. The mean follow-up period was approximately 17.60 ± 5.88 months. According to the comparison of mean GCS at discharge among the studied groups, the mean GCS in the Post-TBI GIB group (10±3.06) was significantly lower than in the No-GIB group (12.89±2.58, p< 0.001, R = -0.454, Table 1). Moreover, the mortality rate was 10.2 % in the Post-TBI GIB group compared to 3.9% in the No-GIB group, which was not statistically different (P=0.124). Finally, a better GOS outcome was found for the No-GIB group compared to the other one (p<0.002, Table 1).

Table 2. Binominal logistic regression for predicting factors associated with GIB

						95% CI or OR*		
	B	SE*	Wald	df	P-value	OR	Lower	Upper
Age	-0.005	0.016	0.107	1	0.743	0.995	0.963	1.027
Sex (male)	-0.412	0.460	0.802	1	0.370	0.662	0.269	1.631
GCS* at admission	-0.182	0.076	5.718	1	**0.017**	0.834	0.718	0.968
Hypotension at admission	2.352	0.897	6.870	1	**0.009**	10.502	1.810	60.952
Cranial surgery	0.839	0.516	2.649	1	0.104	2.314	0.843	6.358
Concurrent coagulopathy	-0.059	0.534	0.012	1	0.912	0.943	0.331	2.684
Concurrent injury			7.336	4	0.119			
Abdominal	1.001	0.626	2.556	1	0.110	2.720	0.798	9.276
Chest	1.341	0.815	2.710	1	0.100	3.825	0.774	18.888
Orthopedic	1.024	0.693	2.183	1	0.140	2.785	0.716	10.840
Spinal	1.258	0.574	4.803	1	**0.028**	3.520	1.142	10.846
Brain injury (Extra-axial)			6.557	4	0.161			
Intra-axial	1.206	0.512	5.551	1	**0.018**	3.339	1.225	9.104
DAI*	0.477	0.999	0.228	1	0.633	1.611	.227	11.413
Linear fracture	-0.166	0.870	0.036	1	0.849	.847	0.154	4.661
Depressed fracture	1.077	0.937	1.320	1	0.251	2.936	0.468	18.433
Constant	0.367	0.951	0.149	1	0.700	1.443		

*SE: standard error, CI: confidence interval, OR: odds ratio, GIB: gastrointestinal bleeding, GCS: Glasgow Coma Scale, DAI: diffuse axonal injury; P-value<0.05 is statistically significant.

Discussion

In this study, primary evaluation of a variety of demographic and clinical factors in TBI patients indicated that there was a higher rate of severe TBIs, intra-axial lesions, hypotension at admission, and concurrent coagulopathies in the Post-TBI GIB group compared to the No-GIB group, whereas the GCS level upon admission and discharge and serum hemoglobin level in the Post-TBI GIB group were lower than those in the other group. So far, some studies have investigated the role of different factors in TBI patients experiencing GIB. In this regard, some authors indicated a relationship between the severity of the TBI and the incidence of GIB (24, 25). Kamada et al., in a study on 433 TBI patients, found that patients with severe TBI had a higher rate of GIB (15). Moreover, in another study on 41 TBI patients admitted to a neurosurgical intensive care unit, nearly 40% of patients with a GCS score ≤ 9 developed GIB (14). Consistent with this, our investigation demonstrated that TBI severity is strongly associated with higher rates of GIB following TBI. Hence, a lower GCS level is expected in TBI patients with GIB. On the other hand, our research also delineated that lower Hb levels on admission can predict GIB occurrence over the following days (p<0.001). In line with this, Wei et al. showed that low hemoglobin level in the first days of hospitalization is a risk factor and can have predictive value for post-traumatic GIB (14).

In our study, the occurrence of coagulopathy on the first day of hospitalization was significantly higher in TBI patients who experienced post-traumatic GIB compared to others. In general, coagulopathy can occur following TBI,

especially in severe TBI, and is considered a predictor of GIB occurrence (16, 26). In a prospective multicenter study on 847 critically ill patients, coagulopathy and respiratory failure were determined as two strong independent risk factors for gastrointestinal bleeding (27). Therefore, the authors recommended continuing stress ulcer prophylaxis for critically ill patients who develop coagulopathy or require mechanical ventilation. In the current study, after adjusting for related cofounders, we found that primary GCS at admission, hypotension on admission, spinal injury, and intra-axial brain injury are predictors for post-TBI GIB. To date, some studies have investigated the correlation between GIB and concurrent injuries or intracranial lesions in patients with TBI. In this regard, some researchers have shown the association between acute spinal injury and GIB (28, 29).

Besides, some other studies stated that GIB could rarely occur following blunt abdominal trauma (30). In our research, while abdominal injury was not correlated with GIB, spinal injury was found to be associated with it (P=0.028). On the other hand, in a study by Zheng et al., the incidence of GIB in intracerebral (ICH) and intraventricular (IVH) hemorrhage after brain trauma was considered higher compared to other types of brain lesions (31). Consistent with their study, the crude analysis of our study demonstrated more elevated numbers of intra-axial injuries in TBI patients with GIB compared to those without (P=0.014).

Moreover, according to the regression model, intra-axial injuries were found to be correlated with GIB. The underlying mechanism of developing GIB in TBI patients is not fully understood. However, it is stated that proinflammatory states, splanchnic hypoperfusion, and impaired microcirculation can cause mucosal ischemia and reperfusion damage and impair mucosal integrity (3, 32-34). Besides, intracranial lesions or brain edema can increase the intracranial pressure (ICP), which can stimulate the parasympathetic centers in the hypothalamus and vagus nuclei and result in a gastric hypersecretory state (35-37). Hence, among neurosurgical patients, hypersecretion of gastric acid and pepsin is presumed as the major pathophysiology of ulceration (38).

In the present study, the patients were followed-up for about 17.60 ± 5.88 months and their outcomes were evaluated. In our investigation, although the rate of mortality did not differ between the study groups, the occurrence of GIB had a deleterious effect on GOS outcomes. Therefore, TBI patients with GIB had a less good recovery than those without (P=0.002). In line with our findings, Li et al. in a prospective cross-sectional study on 68 patients with severe head injuries, delineated that GIB has a negative impact on favorable clinical outcomes (9). Furthermore, some other authors reported that GIB is associated with longer ICU stays (39),

extended hospital length of stay (40, 41), and a higher mortality rate (39-41) in critically ill patients. However, our findings did not support the negative effect of GIB on the mortality rate of TBI patients (p>0.05). The present study had some limitations. This study was single-center research with a limited number of patients. As the current study was conducted during the COVID-19 pandemic, many patients were excluded due to COVID-19 infection, which may have resulted in simultaneous confounding errors due to the small sample size. Therefore, more multicenter studies involving diverse populations are recommended. Primary GCS and hypotension at admission, spinal injury, and intra-axial brain injury are independent predictors for the occurrence of GIB in TBI patients. The presence of GIB in TBI patients is associated with worse neurological outcomes as assessed by GOS at approximately 18 months. Identifying predictors of GIB in TBI patients might allow better early management of these patients to reduce the risk of GIB.

Acknowledgments

Not applicable.

Funding: No funding was received to conduct this study.

Ethics approval: The study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1399.1110) in accordance with the World Medical Association's code of ethics (Declaration of Helsinki, revised in Brazil 2013).

Conflict of interests: The authors have no competing interests to declare that are relevant to the content of this article.

Authors' contribution: M.M. and M.S. contributed to the study's conception and design. M.H. and A.N. contributed to material preparation and data collection. Statistical analysis was performed by A.N. and M.H. The first draft of the manuscript was written by A.N. and M.H. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data, Materials, and/or Code availability: The datasets supporting the conclusions of this article are available from the corresponding author upon reasonable request.

Consent to participate and publish: Written informed consent was obtained from all individual participants. No personal data leading to the identification of samples were reported.

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