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Risk factors for enteral nutrition-associated diarrhea in older patients with severe traumatic brain injury: a retrospective cohort study

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Abstract

Background Severe traumatic brain injury (STBI) is one of the major causes of death and disability worldwide. The incidence and risk factors of enteral nutrition (EN)-associated diarrhea in older patients with STBI remain unclear.

Methods A cohort of adult STBI patients were retrospectively studied. The patients were stratified into an older group (≥ 65years) and a young group (< 65 years). All patients received EN for at least 48 h. Demographic, clinical and nutritional data were collected for analysis. We utilize multiple logistic regression models to evaluate predictors of diarrhea.

Results Among 292 patients with STBI aged 60.38 ± 14.89 years (mean ± standard deviation), 114 cases developed diarrhea, with an incidence of 39.04%. Older patients had a higher incidence of diarrhea than young patients (46.77% vs 33.33%, $p = 0.020$). Three variables were found to be significantly associated with diarrhea in young STBI patients. In contrast, five variables were significantly associated with this complication in older STBI patients, including acute physiology and chronic health evaluation II score (adjusted OR 1.134, 95% CI 1.019–1.272, $p = 0.025$), high-fat energy (adjusted OR 1.221, 95% CI 1.055–1.789, $p = 0.025$), EN duration (adjusted OR 1.105, 95% CI 1.005–1.223, $p = 0.044$), antibiotics total defined daily dose (DDDs) (adjusted OR 1.076, 95% CI 1.029–1.211, $p = 0.039$) and tube feeding of potassium (adjusted OR 2.525, 95% CI 1.031–6.450, $p = 0.046$).

Conclusions Enteral nutrition-associated diarrhea was prevalent among STBI patients. Older STBI patients had a higher incidence of diarrhea and more risk factors than young patients. Early management of modifiable risk factors may help reduce the incidence of diarrhea.

Keywords Traumatic brain injury, Enteral nutrition, Diarrhea, Risk factors

Introduction

Tens of millions of patients with brain trauma are hospitalized every year [1]. Patients with severe traumatic brain injury (STBI) often experience various of complications, causing an enormous burden on the society and families [2]. Patients with STBI are often unconscious and unable to consume food orally. Enteral nutrition (EN) support is one of the alternative treatment methods for STBI patients. Diarrhea is considered the most common sign of feed intolerance, which can prolong the hospitalization period and affect the prognosis [3].

With the acceleration of population aging, an increasing number of STBI patients are older individuals. EN-associated diarrhea in the older may be more harmful. Diarrhea leads to the reduction or interruption of

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nutritional support, reducing the efficiency of nutritional support and nutritional status of patients [4]. Age maybe a risk factor for the occurrence of EN-associated diarrhea. Although several risk factors for EN-associated diarrhea in patients with STBI have been reported [5], the incidence and risk factors in older STBI patients remain unclear.

The objective of this study was to determine the incidence of EN-associated diarrhea in older individuals with STBI and the risk factors to guide the management and reduce incidence of diarrhea.

Materials and methods

Study design

We conducted a retrospective cohort study at a single center in China (Emergency Department, the Second Affiliated Hospital of Zhejiang University School of Medicine) to explore the risk factors for EN-associated diarrhea in patients with STBI. The nursing staff was trained to collect medical data, including the identification of gastrointestinal intolerances, the description of stool, enteral nutritional feeding and risk factors to ensure study consistency and reduce bias. This study was approved by the Ethical Committees for Clinical Medical Research at the 2nd Affiliated Hospital of Zhejiang University.

Participants

Participants were eligible if they were aged at least 18 years; diagnosed with STBI; GCS score of 3–8 and using nutritional therapy by jejunal feeding. TBI was defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force [6]. According to the definition by the Critical Care Nutrition, diarrhea was considered to have 3–5 water bowel movements or total stool volume ≥ 750 ml/24 h. The type of EN formula was polymeric. All nutritional formulas are isotonia. The calories and protein targets were 25 ~ 30 kcal kg^{-1} d^{-1} and 1.2 ~ 2.0 g kg^{-1} d^{-1}, respectively. The target value of enteral nutrition was achieved progressively within 4 days, and the infusion rate was 20–30 ml/h up to a maximum of 150 ml/h. Patients with the following conditions were excluded: (a) receiving an enteral diet for less than 48 h; (b) patients had diarrhea on admission or with past medical history of diarrheal disease, such as inflammatory bowel disease, colon cancer et al.; and (c) gastrointestinal bleeding and infectious diarrhea, such as *Clostridium difficile*-associated diarrhea.

Risk factors

Data were collected using a pre-established questionnaire from the patient admission to the Emergency department until the patient left the ward or died. Demographic, clinical and nutritional data were documented. Potential diarrhea predictors were determined based on previous studies [3, 5, 7] and our own experience, including gender (male/female), age (years), Glasgow Coma Scale (GCS) score (3–15), acute physiology and chronic health evaluation II (APACHE II) score (0–71), hypertension (yes/no), diabetes (yes/no), body mass index (BMI), fasting time, daily nutrient solution, high-fat energy (yes/no), EN duration, serum albumin, use of antibiotics, prokinetic and potassium drugs (yes/no). GCS was divided into two groups: 3–5 and 6–8. Hypertension was defined as having a past history of high blood pressure. Fasting time referred to the interval of activating enteral nutrition after trauma. High-fat energy is defined as a percentage of fat energy greater than 35% of total EN energy. The time of serum albumin testing was within 24 h after admission. The antibiotic consumption was calculated as total defined daily dose (DDDs). DDDs was defined as accumulated dose of antibiotics used for its main indication [8]. For patients with hypokalemia, potassium chloride was given by tube feeding with a dosage of 2–3 g daily, until the serum potassium level was normal.

Statistical analysis

The incidence of diarrhea was defined as the proportion of patients who developed diarrhea after the start of EN. The *t* test was used for normally distributed quantitative data and Chi-square test was used for qualitative data. For non-normally quantitative data, Mann–Whitney test was used to compare the groups. We first examined univariate associations. Only predictors that were statistically significant ($p < 0.05$) were included in the multivariable logistic regression analysis models. Adjusted odds ratios (OR) were used to estimate effects. Receiver operating characteristic (ROC) curve was used for analysis of a predictive model. Overall sensitivity and specificity were assessed as areas under the curve (AUC). The threshold for statistical significance was $p < 0.05$ and the statistical analysis was performed using GraphPad Prism 9.0 (GraphPad Inc., La Jolla, CA, USA).

Results

Patient characteristics

From January 2018 to December 2023, 351 STBI patients from the Emergency department were retrospectively analyzed, 292 of whom were included in this study. Among these patients, 168 cases were young patients (age < 65years) and 124 were older patients (age ≥ 65years) (Fig. 1). The mean age was 60.38 [standard deviation (SD) = 14.89] years and 73.97% (216/292) were male. Median GCS score was 6 (4, 7) (interquartile range, IQR). APACHE II score was 16.76 (SD = 5.29) (Table 1).

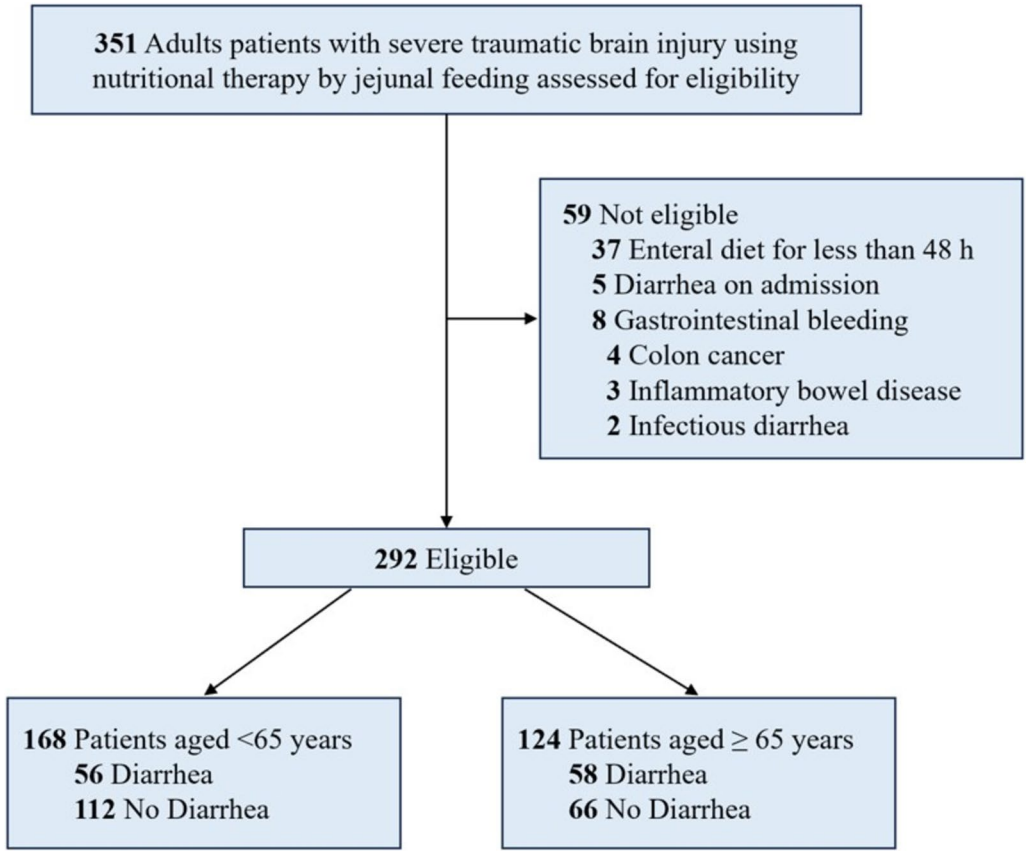

Fig. 1 Patient screening process and data

Incidence of diarrhea

Based on the definition of Critical Care Nutrition, 114 of 292 patients developed diarrhea, for an incidence of 39.04%. The incidence differed between young and older patients. We found that older patients had a higher incidence of diarrhea than young patients (46.77% vs 33.33%, $p=0.020$) (Table 1).

Factors associated with diarrhea

In young STBI patients, we found that there was a significant association between diarrhea and APACHE II score, EN duration, serum albumin level and antibiotics DDDs ($p<0.05$). In older STBI patients, five variables were positive: GCS, APACHE II score, high-fat energy, EN duration, antibiotics DDDs and tube feeding of potassium (Table 1). No statistically significant association was found between diarrhea and sex, hypertension, diabetes, BMI, fasting time, daily nutrient solution intake and prokinetic drug use.

In the multiple logistic regression model, the findings showed that three variables were significantly associated with diarrhea in young STBI patients, including APACHE II score (adjusted OR 1.144, 95% CI 1.061–1.241, $p=0.001$), EN duration (adjusted OR 1.117, 95% CI 1.028–1.222, $p=0.012$) and antibiotics DDDs (adjusted OR 1.110, 95% CI 1.035–1.204, $p=0.006$). The association of serum albumin with diarrhea was excluded.

In older STBI patients, in addition to the above three variables, including APACHE II score (adjusted OR 1.134, 95% CI 1.019–1.272, $p=0.025$), EN duration (adjusted OR 1.105, 95% CI 1.005–1.223, $p=0.044$) and antibiotics DDDs (adjusted OR 1.076, 95% CI 1.029–1.211, $p=0.039$), other two independent diarrhea factors were found. The patients with higher fat energy (adjusted OR 1.221, 95% CI 1.055–1.789, $p=0.025$) and tube feeding of potassium (adjusted OR 2.525, 95% CI 1.031–6.450, $p=0.046$) were more likely to have diarrhea (Table 2).

Risk prediction model of enteral nutrition-related diarrhea

In the risk prediction model of EN-associated diarrhea of young STBI patients, the sensitivity of the prediction model was 71.05%, the specificity was 77.69%, and the area under ROC curve was 0.820 (95%CI 0.754–0.886) (Fig. 2A). In the order STBI patients, the sensitivity was

Table 1 Clinical features and univariate associations with diarrhea in STBI patients

Variables	Age < 65 (*n* = 168)			Age ≥ 65 (*n* = 124)		
	Diarrhea (*n* = 56)	No Diarrhea (*n* = 112)	*p* value	Diarrhea (*n* = 58)	No Diarrhea (*n* = 66)	*p* value
Age (years)	52.61 ± 9.86	49.90 ± 12.09	0.249	73.53 ± 7.87	73.18 ± 6.71	0.961
Sex (M/F)	45/11	82/30	0.310	46/12	43/23	0.081
GCS			0.742			**0.021**
3–5	24	51		34	25	
6–8	32	61		24	41	
APACHE II	17.57 ± 6.02	13.91 ± 4.38	**0.000**	20.45 ± 4.90	17.67 ± 3.63	**0.002**
Hypertension (%)	12(21.43%)	20(17.86%)	0.578	28(48.28%)	36(54.55%)	0.486
Diabetes (%)	4(7.14%)	6(5.36%)	0.645	10(17.24%)	8(12.12%)	0.419
BMI (Kg/m^2)	23.76 ± 3.12	23.20 ± 2.96	0.259	23.02 ± 3.97	22.67 ± 3.03	0.571
Fasting time (days)	1.27 ± 0.82	1.08 ± 0.75	0.205	1.21 ± 0.95	1.29 ± 1.08	0.614
Daily nutrient solution (mL)	1239 ± 258	1186 ± 270	0.198	1267 ± 254	1274 ± 275	0.794
High fat energy (%)	45(80.36%)	80(71.43%)	0.211	53(91.38%)	47(71.21%)	**0.005**
Enteral nutrition duration (days)	13.89 ± 9.28	8.77 ± 4.09	**0.000**	14.59 ± 6.01	9.36 ± 5.55	**0.000**
Serum albumin (g/L)	34.04 ± 7.20	36.70 ± 6.17	**0.009**	36.31 ± 5.67	36.51 ± 6.47	0.857
Antibiotics DDDs	15.86 ± 8.17	9.25 ± 5.07	**0.000**	15.53 ± 8.28	9.11 ± 5.64	**0.000**
Use prokinetic drugs (%)	46(82.14%)	87(77.68%)	0.502	45(77.59%)	50(75.76%)	0.810
Tube feeding of potassium (%)	32(57.14%)	52(46.43%)	0.190	38(65.52%)	27(40.91%)	**0.006**

Values are mean ± SD

STBI Severe Traumatic Brain Injury, *GCS* Glasgow Coma Scale, *APACHE II* Acute Physiology and Chronic Health Evaluation II, *BMI* Body Mass Index, *DDDs* Total Defined Daily Dose of Antibiotics

Table 2 Multivariate logistic regression analysis of enteral nutrition-associated diarrhea in STBI patients

Variables	Age < 65 (*n* = 168)			Variables	Age ≥ 65 (*n* = 124)		
	p value	Adjusted OR	95% *CI*		*p* value	Adjusted OR	95% *CI*
APACHE II	**0.001**	1.144	1.061–1.241	GCS	0.161	0.494	0.180–1.313
Enteral nutrition duration	**0.012**	1.117	1.028–1.222	APACHE II	**0.025**	1.134	1.019–1.272
Serum albumin	0.120	0.955	0.899–1.012	High fat energy	**0.025**	1.221	1.055–1.789
Antibiotics DDDs	**0.006**	1.110	1.035–1.204	Enteral nutrition duration	**0.044**	1.105	1.005–1.223
				Antibiotics DDDs	**0.039**	1.076	1.029–1.211
				Tube feeding of potassium	**0.046**	2.525	1.031–6.450

STBI Severe Traumatic Brain Injury, *APACHE II* Acute Physiology and Chronic Health Evaluation II, *GCS* Glasgow Coma Scale, *DDDs* Total Defined Daily Dose of Antibiotics, *CI* Confidence Interval, *OR* odds ratio

82.00%, the specificity was 77.03%, and the area under ROC curve was 0.846 (95%CI 0.775–0.917) (Fig. 2B).

Discussion

EN-associated diarrhea is prevalent among STBI patients. This study showed that older patients had a higher incidence of diarrhea (46.77%) and more risk factors than young patients, including APACHE II score, EN duration, antibiotics DDDs, high-fat energy and tube feeding of potassium.

EN is an important nutritional support for many severe patients. Diarrhea is a common manifestation of enteral nutritional intolerance with a high incidence [3]. There are two main approaches for EN support: nasogastric and small intestinal feeding. Compared with nasogastric feeding, small intestinal feeding has the advantage of reducing gastric retention and aspiration pneumonia [9]. For coma patients with STBI, nutritional support by small intestinal feeding is more recommended [10]. All patients in this study were provided with nutritional support via small intestinal feeding. The risk factors for diarrhea caused by EN support differ among different diseases [4]. STBI patients often present with a coma or various neurological functional defects, swallowing function disorders, autonomic nerve function disorders or gastrointestinal motility. STBI patients are more

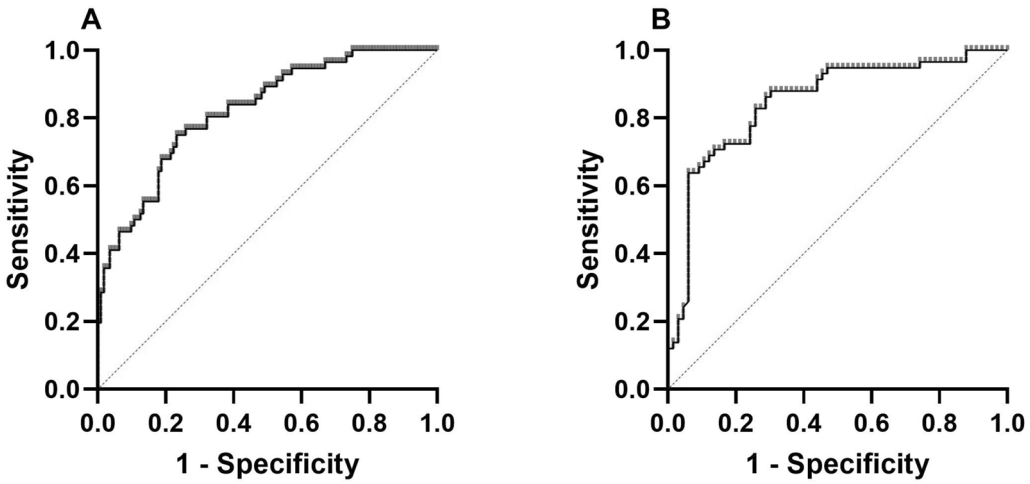

Fig. 2 ROC curve of enteral nutrition-associated diarrhea in young patients (**A**) and older patients (**B**) with severe traumatic brain injury

dependent on EN support. The incidence of diarrhea supported by EN varies greatly among different nervous diseases [7, 11]. The incidence of diarrhea in this study was 39.04%, which is lower than that reported in other studies [5, 11]. A possible reason for this is that we took preventive measures in advance, such as using probiotics to reduce the imbalance of intestinal flora caused by the use of broad-spectrum antibiotics [12].

In both young and older patients with STBI, common risk factors were APACHE II score, EN duration, and cumulative antibiotic use. Diarrhea is related to the disease severity. APACHE II score (0–71) is a commonly used tool to assess the severity of critically ill patients in intensive care units, including acute physiological score, age score and chronic health status score. The higher the APACHE II score is, the more critical the patient's condition is. In critically ill patients, the stress response of the gastrointestinal tract is strong, and the barrier function of the intestinal mucosa is damaged, which makes it easy to cause the accumulation of harmful intestinal substances, disturbances in the internal environment, increased intestinal mucosal permeability, electrolyte imbalance, water and nutrient absorption disorders, and so on, resulting in diarrhea [13]. The GCS score reflected the degree of traumatic coma. In this study, GCS score was found to be a risk factor for diarrhea in older trauma patients through a univariate model analysis. However, the logistics regression analysis showed no statistical significance. It is suggested that the use of GCS as a variable to assess EN intolerance in patients with STBI is limited, whereas the APACHE II score evaluates the systemic status of patients more comprehensively.

The longer the duration of EN, the more likely diarrhea occurs [14]. The specific mechanism is still unclear, and it may be because EN can cause intestinal mucosal atrophy and a decline in absorption function [14, 15]. However, further basic research and pathological studies are required to define the mechanisms. Most studies have confirmed that antibiotic use is an independent risk factor for EN-associated diarrhea. The type, quantity, and duration of antibiotics are variables that affect diarrhea [5], and most studies have used only one of these indicators. DDDs was used as a comprehensive index in this study to fully reflect the intensity of antibiotic use and ensure the accuracy of the study [8].

With the aggravation of the aging society, EN-associated diarrhea in the older patients may be more harmful. This study showed a higher incidence of diarrhea in older patients, and some studies have suggested that age is a risk factor for EN-associated diarrhea [16]. We found that older patients had more risk factors than young patients, including the use of high-fat EN and nasal potassium intake. The intestines of the older have difficulty absorbing high-fat nutrients. Potassium preparations may cause diarrhea by damaging the intestine and increasing intestinal peristalsis. Our finding in this report suggests that EN strategies should differ among older patients with STBI. High-fat EN preparations should be avoided, and the nasal feeding of potassium preparations should be restrained.

Previous studies have shown that fasting duration and the use of gastrointestinal motility medications are risk factors for diarrhea [5]. However, we did not observe this co-relationship. The negative results of this study may be related to the shorter fasting duration in our enrolled patients, most of whom started early EN support within 1–2 days of admission. Gastrointestinal motility drugs can improve gastrointestinal motility and function.

Several studies have shown that it is not a risk factor for diarrhea in severe patients [17], which is consistent with our findings.

There are some limitations to this study: (1) this was a retrospective study, and some risk factors were not included, such as continuous and intermittent enteral support and routine diet, which need to be confirmed by further research; (2) This study is a single-center study in China, and further confirmation is needed for other regions and ethnicities.

Conclusion

We studied the incidence and risk factors of EN-associated diarrhea in patients with STBI. This study revealed that older STBI patients had a higher incidence of diarrhea and more risk factors than younger patients. EN-associated diarrhea remains a common problem in clinical practice and attention must be paid to modifiable risk factors. However, further studies on management and outcome of diarrhea in STBI patients are warranted.

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Author contributions
All authors gave approval for the final version of manuscript. L-Z.W. conceptualized the study. X-X. S., Q.L., X-D. L., L.F. J-J. J. X–Y. T. and Q-S. H. contributed to acquisition of data. X-X. S., Q-L. Z. and L-Z.W. contributed to interpretation of data. X-X. S. drafted the manuscript and L-Z.W. critically revised the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee for Clinical Medical Research at the 2nd Affiliated Hospital of Zhejiang University (IH2020001042).

Competing interests
The authors declare no competing interests.

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