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Changes in the levels of serum glial fibrillary acidic protein and the correlation with outcomes in severe traumatic brain injury patients

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Abstract

Purpose: Glial fibrillary acidic protein serves as a biomarker indicative of astroglial injury, particularly following instances of severe traumatic brain injury. This study aims to evaluate variations in serum glial fibrillary acidic protein levels within the first 3 days and their correlation with outcomes in patients with severe traumatic brain injury.

Subjects and methods: Thirty-nine patients with severe traumatic brain injury were enrolled in the study. Their blood samples were collected at six distinct time points: T_0 (upon admission), T_1, T_2, T_3, T_4, and T_5 (6-, 12-, 24-, 48-, and 72-h post-admission, respectively). The blood samples were run for the quantification of serum glial fibrillary acidic protein levels and other biochemical tests. All patients were closely watched and the outcomes at discharge were evaluated.

Results: Glial fibrillary acidic protein levels tend to increase gradually from the time of admission to 48 h post-admission and then decrease at 72 h post-admission. Glial fibrillary acidic protein T_2 is correlated with Acute Physiology and Chronic Health Evaluation II score, lactate, Simplified Acute Physiology Score II score and outcome. Glial fibrillary acidic protein max correlated with lactate, Acute Physiology and Chronic Health Evaluation II score, Simplified Acute Physiology Score II score, and outcome. Glasgow Coma Score at admission and glial fibrillary acidic protein T_2 (OR = 1.034; $p = 0.025$), T_3 (OR = 1.029; $p = 0.046$), T_4 (OR = 1.006; $p = 0.032$), T_5 (OR = 1.012; $p = 0.048$) and glial fibrillary acidic protein max (OR = 1.005; $p = 0.010$) were independent factors that have significant prognostic value in mortality in patients with severe traumatic brain injury. The predictive model in predicting mortality had the highest area under the curve based on glial fibrillary acidic protein T_2 and Glasgow Coma Score T_0 with an area under the curve of 0.904 and $p < 0.001$. In the multivariable regression model, glial fibrillary acidic protein max was associated with Glasgow score ($p < 0.001$; VIF = 1.585), lactate T_0 ($p = 0.024$; VIF = 1.163), Acute Physiology and Chronic Health Evaluation II score ($p = 0.037$; VIF = 1.360), and Rotterdam score ($p = 0.044$; VIF = 1.713).

Conclusion: Glial fibrillary acidic protein levels tend to increase gradually from the time of admission to 48 h post-admission then decreases at 72 h post-admission. Glial fibrillary acidic protein T_2, T_3, T_4, T_5, and glial fibrillary acidic protein max were independent factors with significant prognostic mortality values in patients with severe traumatic brain injury.

Keywords

Glial fibrillary acidic protein, biomarker, severe traumatic brain injury

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Background

Traumatic brain injury (TBI) is a significant public health concern, with an estimated 69 million new cases occurring worldwide each year. In the United States, TBI accounts for an average of 1.7 million emergency department visits annually and is a leading cause of morbidity and mortality, resulting in approximately 52,000 deaths per year.[1,2] TBI is responsible for up to one-third of all trauma deaths and is the leading cause of disability among people under the age of 40, with a yearly incidence of 15–20 per 100,000 population.[3] Despite advances in neuroimaging and neurocritical care, predicting outcomes in TBI patients remains challenging. Clinical assessment tools such as the Glasgow Coma Score (GCS) are commonly used to assess TBI severity, but they may not always accurately predict outcomes.[4]

As a result, there has been growing interest in finding biomarkers that can provide additional information on TBI severity and prognosis. One promising biomarker is glial fibrillary acidic protein (GFAP), which is released by astrocytes following brain injury.[5] GFAP is a monomeric intermediate filament protein concentrated in the astroglial cytoskeleton, specific to brain tissue and is not routinely found in peripheral blood circulation. However, GFAP is released after astrocyte death, making it an ideal candidate marker for brain injury patients.[6] Several studies have found that the serum GFAP at admission were significantly increased in TBI patients, and the correlation between serum GFAP concentrations and clinical outcomes was also reported.[7,8] In fact, several studies have shown that GFAP concentration is related to prognostic factors of TBI patients such as GCS, lactate, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Rotterdam score, SAPS II score.[9,10] During the treatment process of TBI patients, GFAP levels and some prognostic factors such as GCS, lactate, APACHE II score, Rotterdam score, and SAPS II score all change regularly. Furthermore, these indicators indirectly reflect severity or better improvement. Therefore, understanding the relationship between these indicators is a necessary clinical approach.

While there has been some research on GFAP as a biomarker for TBI, there is limited information on how GFAP levels change during the first few days after injury.[9] How the change in GFAP concentrations in the early days is related to the outcome of sTBI patients is still controversial. GFAP levels are also linked to CT pathological alterations and patient outcomes.[9,11,12] In Vietnam, TBI is complicated and is of concern to the whole society. Therefore, we performed this study to find whether changes in serum GFAP levels had a relationship with outcomes in sTBI patients.

Materials and methods

Methods

This was a prospective, descriptive study conducted at the Center of Emergency Critical Care Medicine and Clinical Toxicology, Military Hospital 103 in Hanoi, Vietnam, from January 2021 to December 2022. The study protocol was approved by the medical ethics committee of Vietnam Military Medical University.

Participants

The study enrolled sTBI patients (GCS after initial resuscitation $\leqslant 8$), $\geqslant 16$ years old, and admitted them to the hospital within 6 h after the injury. Exclusion criteria included patients diagnosed with intracranial lesions in the previous month, neurodegenerative diseases such as Alzheimer's or Parkinson's disease, mental illness, TBI in the setting of multiple trauma, patients who died before collecting enough samples, and patients or their families who did not consent to participate in the study. Demographic characteristics were collected such as age, gender, cause of the accident, GCS at the time of admission, and classified brain damage on computed tomography according to the Marshall et al.[13] and Rotterdam score.[14] Vital signs, including Glasgow score, pupillary reflex, pulse rate, blood pressure, and body temperature, were recorded at the time of sample collection. The severity of the patients was assessed by SAPS II score, and APACHE II score at the time of admission as a study of Taysser Zaytoun.[15]

Blood samples (3–5 mL red-top tube) were taken at 6 time points: T_0 (on admission), T_1 (6 h post-admission), T_2 (12 h post-admission), T_3 (24 h post-admission), T_4 (48 h post-admission), and T_5 (72 h post-admission), to quantify serum GFAP levels using the MyBioSource ELISA kit (San Diego, CA, USA). After collection, specimens were kept at room temperature for 30–60 min and centrifuged for 10 min at 4000 rpm. The supernatant was collected and stored at −80°C (<3 months) until analysis. Finally, the serum was analyzed with Human ELISA GFAP kits according to the manufacturer's protocol by enzyme linked immunosorbent assay (ELISA) apparatus, then using spectrophotometric titration to determine the results.

All patients were treated according to the latest recommendations of the American Brain Trauma Foundation.[16,17] Patients were mechanically ventilated under volume-controlled ventilation (Vt = 8 mL/kg, respiratory rate 16–20 breaths/min, I/E ratio 1/2, FiO_2 30%–40%) to maintain normal pulmonary ventilation ($SpO_2 > 95\%$ or $PaO_2 > 90$ mmHg, $PaCO_2$: 35–45 mmHg). Vasopressors were used as recommended if fluids did not maintain cerebral perfusion pressure (CPP) between 60 and 70 mmHg, with the hemodynamic goal of maintaining mean blood pressure $\geqslant 90$ mmHg and CPP between 60 and 70 mmHg. Antiepileptic drugs were given, and fluid balance, total blood counts, electrolytes, and body temperature were regularly monitored and adjusted according to guidelines. Intracranial pressure was controlled using a multimodal approach that included surgical management of intracranial lesions, maintaining posture, hyperosmotic therapy, effective anti-pain sedation, hyperventilation therapy, and other measures, with the goal of maintaining intracranial pressure below 20 mmHg.

Table 1. Characteristics of severe traumatic brain injury patients.

Characteristics	Median
Age (year)	49 (26–63) (from 18 to 65)
Gender	Male/Female = 32/7
At admission time point	
GCS	7 (6–8)
ICP (mmHg)	16 (12–25)
Glucose (mmol/L)	9.36 (7.59–11.43)
Creatinine (mmol/L)	80.00 (67.00–91.00)
Lactate	4.39 ± 2.37
APACHE II score	15.73 ± 4.09
SAPS II score	43.92 ± 10.86
Rotterdam score	4 (2–5)

GCS: Glasgow coma score; ICP: intracranial pressure; APACHE-II: acute physiology and chronic health evaluation-II; SAPS: simplified acute physiology score.

Early nutrition was started if there were no contraindications, with an energy target of 25–35 kcal/kg/24 h.

Patient outcomes were assessed at the time of hospital discharge. Survival was defined as patients discharged from the hospital without requiring any respiratory or circulatory support, while those who died at the hospital or were too severe to be discharged by their families were classified as non-survivors.

Data analysis

The standard normal distribution of variables was assessed using the Kolmogorov–Smirnov test. Quantitative variables displaying standard normal distribution were expressed as mean and standard deviation. For quantitative variables that do not conform to a normal distribution, median values with interquartile ranges (Q1–Q3) were reported. The association between GFAP and other factors was evaluated through Spearman correlation analysis. In addition, independent prognostic factors for mortality were analyzed using multivariable logistic regression analysis to analyze the predictive model. The Receiver Operating Characteristic curve was generated to calculate the area under the curve (AUC) for GFAP or the model for predicting mortality. Statistical significance was determined at a *p*-value less than 0.05.

Results

The median age of the participants was 49 years old. The median points of the GCS and Rotterdam score were 7 and 4, respectively. Blood lactate levels, as well as average APACHE II and SAPS II scores, were 4.39, 15.73, and 43.92, respectively (Table 1). Notably, GFAP levels at different time points did not exhibit statistical significance, with the highest recorded at time T_5 and the lowest at time T_0 (Figure 1).

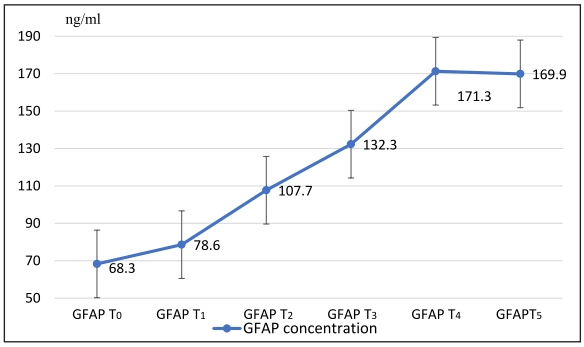

Figure 1. Variable of GFAP concentration.

Table 2. GFAP correlation with prognostic factors and outcomes in sTBI.

Correlation	r_s	*p*
GFAP T_2		
Lactate T_0	0.433	0.007
Lactate max	0.512	0.001
APACHE II score	0.687	<0.001
SAPS II score	0.332	0.044
GCS T_0	−0.146	>0.05
Rotterdam score	0.005	>0.05
Surgery (0: non, 1: yes)	0.324	0.044
Outcomes (0: survival, 1: mortality)	0.489	0.002
GFAP max		
Lactate T_0	0.372	0.002
Lactate max	0.468	0.003
APACHE II score	0.396	0.015
SAPS II score	0.538	0.001
GCS T_0	−0.297	>0.05
Rotterdam score	0.061	>0.05
Surgery (0: non, 1: yes)	0.383	0.016
Outcomes (0: survival, 1: mortality)	0.548	<0.001

GFAP: glial fibrillary acidic protein; GCS: Glasgow coma score; APACHE-II: acute physiology and chronic health evaluation-II; SAPS: simplified acute physiology score.

GFAP T_2 correlates with the APACHE II score (r_s=0.687; $p<0.001$), lactate (r_s=0.433; p=0.007), SAPS II score (r_s=0.332; p=0.044), and outcomes (r_s=0.489; p=0.002). The maximum GFAP level (GFAP max) was correlated with blood lactate (r_s=0.372; p=0.002), APACHE II score (r_s=0.396; p=0.015), SAPS II score (r_s=0.538; p=0.001), and outcome (r_s=0.548; $p<0.001$) (Table 2). The area under the curve for mortality prediction of GFAP T_2 was 0.806 (95% CI: 0.635–0.977; p=0.003), which was lower than model 1 with an AUC of 0.904 (95% CI: 0.804–1.000; $p<0.001$) (Figure 2).

GFAP max concentration was associated with GCS ($p<0.001$; VIF = 1.585), lactate T_0 (p=0.024; VIF = 1.163), APACHE II score (p=0.037; VIF = 1.360), and Rotterdam score (p=0.044; VIF = 1.713) (Table 3).

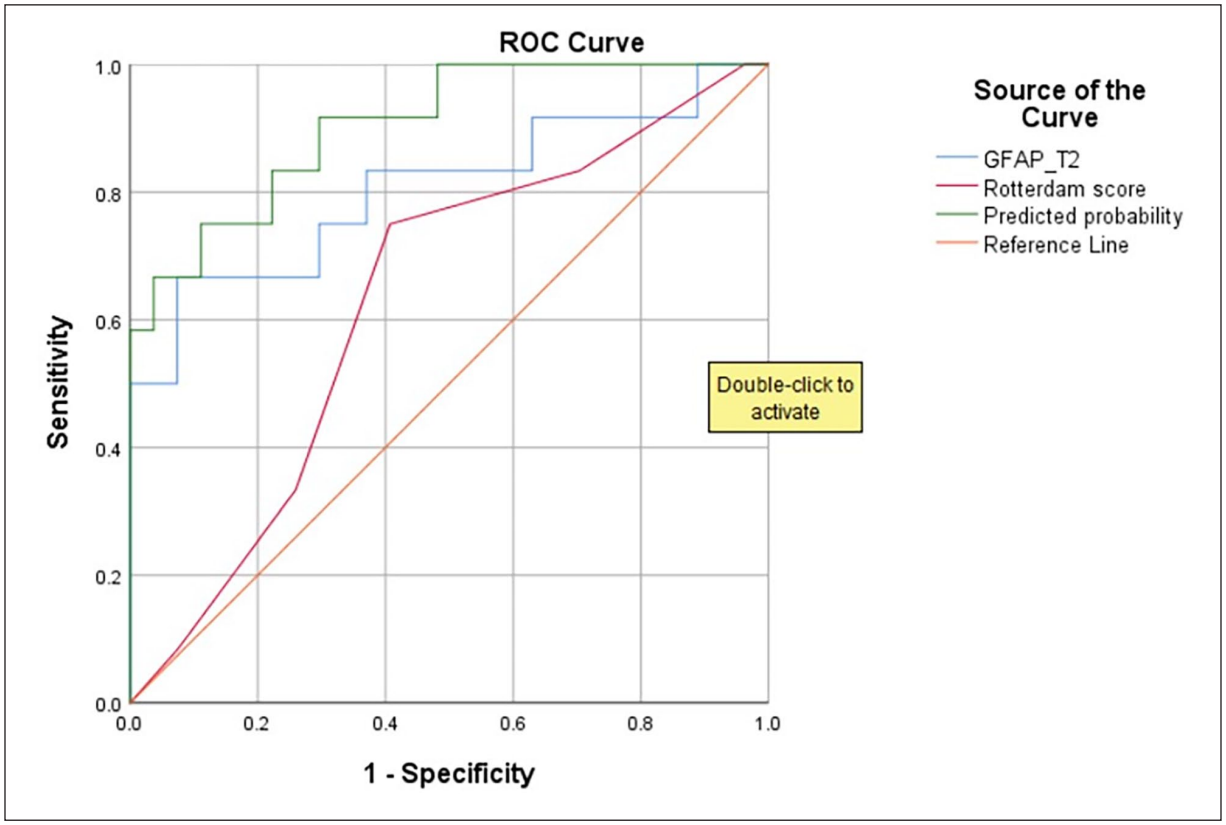

Figure 2. ROC curve predicting mortality for the prognostic model (based on GFAP T_2, Glasgow Coma Score, Rotterdam Score at admission time) and other indicative factors of trauma severity.

Table 3. Multivariable regression model relating GFAP max to prognostic factors in severe traumatic brain injury patients.

Factors	*B*	*p*	VIF
Age	1.091	0.539	1.212
GCS	−157.34	<0.001	1.585
Lactate T_0 (mmol/L)	33.463	0.024	1.163
APACHE II score	19.539	0.037	1.360
Rotterdam score	−64.166	0.044	1.713
Body weight (kg)	−9.679	0.080	1.238

GFAP: glial fibrillary acidic protein; GCS: Glasgow coma score; APACHE-II: acute physiology and chronic health evaluation-II.

GCS at admission and GFAP at T_2 (OR = 1.034; $p = 0.025$), T_3 (OR = 1.029; $p = 0.046$), T_4 (OR = 1.006; $p = 0.032$), T_5 (OR = 1.012; $p = 0.048$), and GFAP max (OR = 1.005; $p = 0.010$) were independent factors that have significant prognostic value in mortality in sTBI patients. Particularly, the predictive model based on GFAP T_2 and GCS T_0 was significant in predicting mortality with an area under the curve of 0.904 with $p < 0.001$ (Table 4).

Discussion

TBI is a significant public health concern, and outcomes of TBI treatment remain unsatisfactory despite advances in neurosurgery and surgical critical care.[18] GFAP is a biomarker that has attracted considerable interest in recent years.[19] GFAP is a fibrous, acidic protein belonging to class III of the intermediate filaments in the astrocyte cytoskeleton in the central nervous system.[20] It plays a vital physiological role in maintaining the structure and mechanical strength of glial cells, supporting the blood-brain barrier, and neighboring cells.

In our study, GFAP levels tend to increase gradually from the time of admission to 48 h post admission then decrease by 72 h post admission. This can be explained by the pathogenesis of TBI. The result of initial damage that happens at the time of injury is referred to as a primary injury. Secondary injury develops over some time after primary injury. Secondary injury cascades including oxidative stress, endoplasmic reticulum stress, and neuroinflammation contribute to long-term brain damage and can be triggered by a variety of risk factors. The onset of secondary injury is a result of physiological and biochemical cascades that finally lead to neuronal cell death and functional impairments.[21] Several studies have shown a cascade of chemical mediators released during the first and second day after injury such as interleukin-1β,[22] interleukin-6,[23] and TGF-β.[24]

Elevated GFAP concentration has been observed in patients with moderate to sTBI, poor recovery outcomes, and abnormalities on cranial CT scans and post-traumatic cranial

Table 4. Multivariable logistic regression model decides the association between treatment outcomes and GFAP, GCS, and Rotterdam score.

Model	Factors	Multivariable logistic regression		ROC curve	
		OR (95% CI)	*p*	AUC	*p*
1	GFAP T_0 (μg/L)	1.002 (0.992–1.012)	0.671	0.769	0.008
	GCS T_0	0.421 (0.196–0.905)	0.027		
	Rotterdam score	0.877 (0.429–1.796)	0.721		
2	GFAP T_1 (μg/L)	1.004 (0.998–1.010)	0.222	0.775	0.007
	GCS T_0	0.464 (0.213–1.013)	0.054		
	Rotterdam score	0.978 (0.462–2.071)	0.954		
3*	GFAP T_2 (μg/L)	1.034 (1.004–1.065)	0.025	0.904	<0.001
	GCS T_0	0.328 (0.112–0.960)	0.042		
	Rotterdam score	0.844 (0.341–2.088)	0.713		
4	$GFAP_{max}$ (μg/L)	1.005 (1.001- 1.010)	0.010	0.840	0.001
	GCS T_0	0.732 (0.292 -1.832)	0.505		
	Rotterdam score	1.077 (0.457–2.536)	0.865		
5	GFAP T_3 (μg/L)	1.029 (1.001–1.059)	0.046	0.919	<0.001
	GCS T_0	0,383 (0.141–1.040)	0.060		
	Rotterdam score	0.732 (0.271–1.981)	0.540		
6	GFAP T_4 (μg/L)	1.006 (1.001–1.012)	0.032	0.806	0.084
	GCS T_0	0.719 (0.294–1.756)	0.468		
	Rotterdam score	1.087 (0.483–2.446)	0.840		
7	GFAP T_5 (μg/L)	1.012 (1.000–1.023)	0.048	0.890	<0.001
	GCS T_0	0.753 (0.283–2.000)	0.569		
	Rotterdam score	1.036 (0.424–2.529)	0.938		

GFAP: glial fibrillary acidic protein; GCS: Glasgow coma score; sTBI: severe traumatic brain injury.

MRI.[25] GFAP levels increase in the cerebrospinal fluid and serum/plasma within 3–34 h following sTBI, and its increase is related to the severity of the injury. GFAP has emerged as the most powerful biomarker in the prognosis of TBI. However, increased GFAP concentration has also been observed in other brain diseases, such as neurodegenerative disease, multiple sclerosis, and stroke.[26–28]

According to our results (Table 4), GFAP concentrations at T_2, T_3, T_4, T_5, and GFAP max were independent factors that had significant prognostic value in mortality in sTBI patients. In particular, the prognostic model based on GFAP concentration T_2 and GCS T_0 was significant in predicting mortality with an area under the curve of 0.904, $p < 0.001$. Takala et al.[29] found a negative correlation between GFAP concentrations at admission time and days 1–2 and GOS levels with Spearman correlation coefficient of −0.349, $p < 0.001$; −0.433, $p < 0.001$ and −0.311, $p < 0.001$, respectively. The negative correlations between GFAP concentration and GOS-E were also found at admission time and days 1–2 with Spearman correlation coefficients of −0.335, $p < 0.001$, −0.417, $p < 0.001$ and −0.305, $p < 0.001$, respectively. However, multivariable regression did not prove that GFAP concentrations had a prognostic value in mortality. Another study by Anderson et al.[30] carried out on 243 moderate and sTBI patients found that GFAP concentration combined with pre-hospital prognostic factors compared to merely those factors significantly improved AUC in all models (ICH, 0.82 vs. 0.64; 48-h mortality, 0.84 vs. 0.71; 28-day mortality, 0.84 vs. 0.66; GOS-E, 0.78 vs. 0.69).

After 48 h, an increase in the inflammatory response process occurs, potentially due to cerebral anemia, bleeding, cytoplasm discharge, and diffuse axon damage[31] leads to increased cerebral edema, accompanied by stimulating responses of glial cells to promote regeneration and phagocytosis of dead cells.[32] The secondary lesion mechanism leads to increased GFAP concentration, but over time, the natural elimination process and the effects of treatment reduce this concentration. The results of this study were similar to those found by Nylén et al.[7] in their study of 59 patients with sTBI. The authors saw that the concentrations of GFAP were highest in the early days, ranging from days 0 to 4, before gradually decreasing. Over 50% of the patients returned to a normal range of serum GFAP concentration between the 11th and 14th days.

A study by Pelinka et al.[33] showed that among 114 TBI patients with or without multiple injuries, serum GFAP concentrations were highest within the first 12–36 h after the accident, gradually decreasing thereafter. Lumpkins et al.[34] demonstrated that a continuous increase in GFAP levels on the second day after injury is a predictive sign of death. Czeiter et al.[35] found that GFAP was better than five other biomarkers in predicting brain lesions on computed tomography scans within the first 24 h after injury. A systematic review in 2017 noted that GFAP concentration appeared to

be diminished over time after injury in some studies, while others found that GFAP increased up to 16–24 h after injury. However, the review suggested that the differences in GFAP concentrations between the studies may be due to the lack of standardization in the biomarker concentration test kits.[36]

Wiesmann et al.[37] also found that GFAP concentrations in the molarity group or vegetative state group were higher than in severely disabled patients (GOS 3; $p < 0.05$); good recovery group (GOS 4–5; $p < 0.05$), or healthy control group. In addition, GFAP concentration in the first 6 h was a good factor in predicting patient outcome ($r_s = 0.47$; $p = 0.04$). Nylén et al.[7] also found that GFAP concentrations were highest on the first day, then gradually decreased. Patients with unfavorable outcomes had significantly higher maximum GFAP values ($p < 0.001$) during the acute phase compared with patients with favorable outcomes. In addition, all patients who had GFAP concentrations >15.04 µg/L died (reference level < 0.15 µg/L).

Yates[38] also found that patients who died during the study period had GFAP concentrations 33.4 times higher than those who were alive after 6 months. The mean GFAP concentrations in the unfavorable neurological outcome group (GOS-E 1–4) were 19.8 times higher than the group with favorable neurological outcome (GOS-E 2–8).[8] Korley et al.[39] demonstrated that the AUC of GFAP to predict mortality, unfavorable outcome, and incomplete recovery after 6 months were 0.87 (95% CI: 0.83–0.91), 0.86 (95% CI: 0.83–0.89) and 0.62 (95% CI: 0.59–0.65), respectively.

Our study had some limitations. First, the participants in our study were mostly men with sTBI, showing diverse and heterogeneous injury patterns. Second, the sample size of the study was relatively small, lacked control variables, and had a short follow-up duration. Third, all sTBI patients enrolled in the study were included in the study, so no sample size calculation formula was used. Finally, the fluctuations of GFAP levels were influenced by various factors, encompassing both the morphological and biochemical aspects of the injured brain, as well as the effects of treatment interventions.

Conclusion

GFAP levels increased gradually from the time of admission to 48 h post admission then decreased to 72 h post admission. GFAP was a reliable indicator of brain damage and a potential predictor of mortality. GFAP max was associated with some prognostic factors of TBI patients (Glasgow score, lactate T_0, APACHE II score, and Rotterdam score).

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Author contributions

Kien Nguyen Trung and Tuan Dinh Le oversaw the concept, design, data analysis, and manuscript revision. Manh Dang Le, Ba Van Dang, Cong Van Pham, Hoang Duong Huy, and Hai Anh Vu contributed to data analysis and drafting of the article. Tien Viet Tran and Thuc Luong Cong helped edit the manuscript. Son Tien Nguyen, Tam Chi Nguyen, Huy Quang Nguyen, and Anh The Vu contributed to data collection. All authors read and approved the final manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics approval

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethical Review Committee of Military Hospital 103 (Reference No. 58/2023/HĐĐĐ, date 23 September 2022).

Informed consent

Written informed consent was obtained from all legal representatives of the patients before inclusion.

Trial registration

Not applicable.

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