

# A Study on the Predictive Value of Glial Fibrillary Acidic Protein for Prediction of Traumatic Brain Injury Severity

Esmail Fakharian, Masoumeh Abedzadeh-Kalahroudi, Mojtaba Sehat, Payam Yazdipour, Majid Nejati<sup>1</sup>

Trauma Research Center, Kashan University of Medical Sciences, Kashan, Iran, <sup>1</sup>Anatomical Sciences Research Center, Institute for Basic Sciences, Kashan University of Medical Sciences, Kashan, Iran

**ORCID:**

Esmail Fakharian: <https://orcid.org/0000-0003-0115-8398>

Masoumeh Abedzadeh-Kalahroudi: <https://orcid.org/0000-0002-7318-6294>

Mojtaba Sehat: <https://orcid.org/0000-0001-7142-4829>

Payam Yazdipour: <https://orcid.org/0000-0001-9830-6064>

Majid Nejati: <https://orcid.org/0000-0001-6024-5331>

## Abstract

**Background and Objectives:** Head injury is an increasing consequence of different kinds of trauma. It may result in release of substances such as glial fibrillary acidic protein (GFAP) within the cerebrospinal fluid or in serum, which can be used for the measurement of severity of damage. The aim of this study was to assess the predictive value of GFAP in prediction of trauma severity in head-injured patients. **Methods:** In this cross-sectional study, 98 patients with head injury admitted to Shahid Beheshti Hospital of Kashan University of Medical Sciences (KAUMS) enrolled in this study during 2020-2021. The GFAP serum level, the Extended Glasgow Coma Outcome Score (EGOS), Glasgow Coma Scale (GCS), and Rotterdam computed tomography score were assessed and then analyzed by SPSS V20. **Results:** The mean of GCS at the time of admission and discharge and EGOS and Rotterdam scores at a 3-month follow-up all were within a mild range. In addition, on the base of EGOS, all of the patients had recovered to a good state 3 months after their injury. Statistical analysis revealed a meaningful correlation between GFAP and GCS and EGOS ( $P < 0.05$ ). GFAP with sensitivity of 80.8%, specificity of 65.3%, and area under the curve of 0.804 has appropriate strength for prediction of severity of head injury. **Conclusions:** The sensitivity and specificity of GFAP revealed acceptable strength for prediction of severity of head injury, even when confounding factors are considered. The mean of EGOS and GCS and Rotterdam score were all within the range of mild injury. However, further detailed and multicenter studies are recommended for better clarification of the role of GFAP as a biomarker of traumatic brain injury.

**Keywords:** Extended Glasgow Coma Outcome Score, glial fibrillary acidic protein, Rotterdam score, traumatic brain injury

## INTRODUCTION

Traumatic brain injuries (TBIs) as one of the most common causes of mortality and somatic and mental morbidities compose about 20% of all injuries.<sup>[1]</sup> Based on statistical reports, about 70% of posttraumatic death and disabilities are secondary to head trauma.<sup>[2]</sup> Many of those saving their lives after trauma are involved with different kinds of somatic and mental difficulties affecting their quality of life, needing long-term medical care, and imposing further costs for acute and long-term follow-up.<sup>[3]</sup> There are different diagnostic facilities for the evaluation of trauma victims; they included computed tomography (CT) scan, magnetic resonance imaging, and assessment of biochemical and biomarker

released to cerebrospinal fluid (CSF) and serum following neural cell damage. One of these factors is glial fibrillary acidic protein (GFAP), which can be measured in CSF and serum.<sup>[4]</sup> GFAP is an intermediate filament structural protein known as a marker for severe central nervous system (CNS)

**Address for correspondence:** Dr. Masoumeh Abedzadeh-Kalahroudi, Trauma Research Center, Kashan University of Medical Sciences, Kashan, Iran.  
E-mail: [abedzadeh@kaums.ac.ir](mailto:abedzadeh@kaums.ac.ir)

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

**For reprints contact:** [WKHLRPMedknow\\_reprints@wolterskluwer.com](mailto:WKHLRPMedknow_reprints@wolterskluwer.com)

**How to cite this article:** Fakharian E, Abedzadeh-Kalahroudi M, Sehat M, Yazdipour P, Nejati M. A study on the predictive value of glial fibrillary acidic protein for prediction of traumatic brain injury severity. Arch Trauma Res 2023;12:44-7.

**Received:** 28-12-2022, **Revised:** 15-03-2023,  
**Accepted:** 16-03-2023, **Published:** 29-04-2023.

### Access this article online

Quick Response Code:



**Website:**  
[www.archtrauma.com](http://www.archtrauma.com)

**DOI:**  
10.4103/atr.atr\_82\_22

injury.<sup>[4-6]</sup> It also increases in patients with astrogliosis.<sup>[5]</sup> This protein, probably, passes directly from the damaged blood–brain barrier and enters circulation. Clinically, in contrast to CSF, measurement of this protein in serum is very safe in head-injured patients. Missler *et al.* have shown a correlation between the serum GFAP and severity of CNS injuries.<sup>[7]</sup> Vos *et al.* in their study have shown that serum levels of glial and neural proteins even in early stages can predict TBI.<sup>[8]</sup> Pelinka *et al.* also have confirmed that GFAP presentation increases after TBI, and can be used as a biomarker of primary injury for prediction of the outcome of brain injury.<sup>[9]</sup> Lewis *et al.* have shown that the absence of GFAP in serum cannot be ruled out TBI while its high levels are associated with brain damage.<sup>[3]</sup> Increased levels of GFAP and S100 protein and the ratio of these two biomarkers may be an indicator of mortality and morbidity after TBI.<sup>[10,11]</sup> Considering the fact that CT scan uses high doses of radiation and shows gross anatomical changes and so is blind for the minimal abnormalities, thinking about a biochemical marker helpful in the diagnosis of intracranial injuries with low costs and easier availability will be promising. The aim of this study was to assess the diagnostic value of GFAP in prediction of severity of head injury in patients admitted to Kashan Shahid Beheshti Hospital during 2020–2021.

## MATERIALS AND METHODS

### Setting

This diagnostic value study, was performed on 98 patients with head injury and Glasgow Coma Scale (GCS) scores above 8 (moderated and mild cases of head trauma) who admitted to Shahid Beheshti Hospital of Kashan University of Medical Sciences (KAUMS) and had initial brain CT scan. They enrolled using the simple sampling method after obtaining informed consent during 2020–2021. Those with any clinical or para-clinical evidence of spinal injury or neurological and cognitive problems before their trauma (e.g. brain tumors and cerebrovascular accidents) and any patient refusing completion of the informed consent were excluded from the study.

### Measurements

Blood samples for the GFAP assessment were obtained within 4 h of admission and performed using the ELISA method with a diagnostic level of more than 0.01 microgram/liter considered normal.

Computed tomographic scanning was performed for all of the patients as the gold standard,<sup>[12]</sup> interpreted by a neurological surgeon, and categorized based on the Rotterdam scoring system (48). The patients were followed up and their outcome was assessed using the Extended Glasgow Coma Outcome Score (EGOS) at the time of discharge and 3 months later.<sup>[6]</sup> Background information, including age, sex, mechanism of trauma and its severity (on the base of the GCS score of admission or at the time of intubation if performed before admission and at the time of discharge), and indication for surgical intervention, were recorded.

## Data analysis

Data were analyzed using SPSS version 20 (IBM SPSS version 20, Chicago). Descriptive statistical data were presented as mean, standard deviation, numbers, and percentage. To assess the diagnostic value of GFAP, sensitivity, specificity, and positive and negative predictive values were used. In addition, correlation between GFAP with Rotterdam score and EGOS were analyzed using Pearson's correlation coefficient. The significance level was set at  $P < 0.05$ .

## RESULTS

This study included 98 patients with mild and moderated head injury with a mean age of  $47.82 \pm 20.77$  years (range of 15–96). Most of the patients were male (82.6%), and the most common mechanism of trauma was road traffic accident (66.3%). The GCS score of the time of admission and discharge, the Rotterdam score, and EGOS at the time of discharge and 3 months later all were in a range of mild injury [Table 1]. EGOS findings showed recovery of all of the patients 3 months after their injury.

There is a reverse correlation between GFAP and GCS at the time of admission and discharge, i.e. higher GFAP levels were seen in those with lower GCS ( $P < 0.05$ ). This reverse correlation was also visible between the GFAP and EGOS of the time of discharge and 3 months later ( $P < 0.05$ ). There was a direct correlation between GFAP and the Rotterdam score,

**Table 1: Glasgow Coma Scale, Extended Glasgow Coma Outcome Score, Rotterdam score, and glial fibrillary acidic protein level in patients**

Criteria	Frequency (%)
GCS	
Primary	
Mild	72 (73.5)
Moderate	26 (26.5)
Discharge	
Mild	79 (80.6)
Moderate	17 (17.3)
Severe	2 (2.1)
EGOS	
Discharge	
Upper moderate disability	1 (1.1)
Lower good recovery	20 (20.4)
Upper good recovery	77 (78.5)
3-month follow-up	
Lower good recovery	9 (9.2)
Upper good recovery	89 (90.8)
Rotterdam CT score	
1	20 (20.4)
2	42 (42.9)
3	21 (21.4)
4	15 (15.3)
GFAP ( $\mu\text{g/l}$ )	0.49 $\pm$ 1.33

EGOS: Extended Glasgow Coma Outcome Score, GCS: Glasgow Coma Scale, GFAP: Glial fibrillary acidic protein, CT: Computed tomography

indicating increased levels of GFAP with increased Rotterdam score [Table 2].

The results showed that GFAP with a cutoff point of 1.4 mg/L, 80.8% sensitivity and 65.3% specificity, and area under curve (AUC) of 0.804 had the capacity for the prediction of severity of TBI [Figure 1]. Results showed that confounding factors, such as age, sex, and mechanism of trauma, would not result in a significant change in AUC (0.826 in Model compared with 0.804 before adjusts for confounders) [Table 3].

## DISCUSSION

The findings of this study showed that there was a significant correlation between GFAP and GCS and EGOS. The mean of GFAP with a cutoff point of 1.4 µg/L, sensitivity of 80.8%, specificity of 65.3%, and AUC of 0.804 has the needed potential for the prediction of severity of TBI, so that even consideration of confounding factors of age, sex, and mechanism of trauma will not result in a significant change in AUC (0.826).

Aydin *et al.* in a study conducted in 2018 on a predictive value of GFAP and S100B serum protein levels on 63 patients with intracerebral hemorrhage and 30 normal persons showed a serum GFAP of 86.37 ng/ml in the former and 38.07 in the latter group. Eight of their patients (12.7%) died during their hospitalization with a mean GCS of 4.6 and mean GFAP of 127.8 ng/ml. They concluded that GFAP levels in either traumatic or nontraumatic cases of brain injury are significantly higher than normal persons and this biomarker may be used instead of brain CT scan for the diagnosis of brain injury.<sup>[13]</sup>

**Table 2: Correlation between glial fibrillary acidic protein and Glasgow Coma Scale, Extended Glasgow Coma Outcome Score, and Rotterdam score**

Criteria	GFAP	
	P	Correlation coefficient
GCS		
Primary	0.001	-0.408
Discharge	0.042	-0.206
EGOS		
Discharge	0.017	-0.241
3-month follow-up	0.001	-0.334
Rotterdam score	0.041	0.207

EGOS: Extended Glasgow Coma Outcome Score, GCS: Glasgow Coma Scale, GFAP: Glial fibrillary acidic protein

**Table 3: Predictive value of glial fibrillary acidic protein for the severity of traumatic brain injuries**

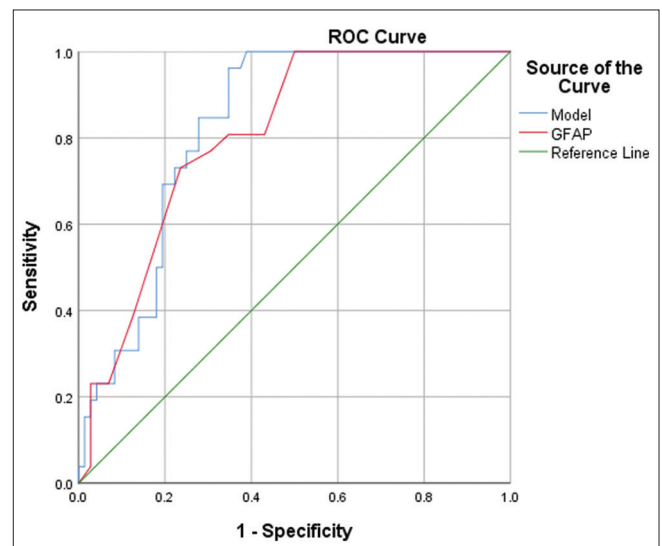
Criteria	TBI severity on the base of GCSS		Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	-LR	+LR	AUC (95% CI)
	Mild (n=72)	Moderate (n=26)								
GFAP	1.2±0.49	1.71±0.26	1.4	80.8	65.3	90.4	90.4	2.33	0.29	0.804 (0.877-0.712)
Model*	-	-	-	84.6	72.2	92.9	92.9	3.05	0.21	0.826 (0.895-0.736)

AUC: Area under curve, TBI: Traumatic brain injury, PPV: Positive predictive value, NPV: Negative predictive value, CI: Confidence interval, GCSS: Global customer service system, GFAP: Glial fibrillary acidic protein, LR: Likelihood ratio

Okonkwo *et al.* in a study conducted in 2013 assessed the predictive value of GFAP-breakdown product (BDP) on 215 TBI patients (including 83% mild, 4% moderate, and 13% severe) with acute traumatic lesions. Fifty-four percent of the cases, according to the AUC, showed an 88% diagnostic value of GFAP-BDP, and in spite of emphasizing the value of this method for the diagnosis of brain injury, a larger clinical trial is recommended for further scrutinization of this biomarker as a routine diagnostic tool.<sup>[14]</sup> This finding is concordant with our results.

In another study in 2015, Lei *et al.* measured the serum GFAP using the ELISA method in 67 patients with severe TBI at the time of admission and in 5 consequent days and compared it with EGOS after a 6-month follow-up and showed increased GFAP levels in all samples. The AUC analysis also revealed its ability to predict a final neurological outcome after 6 months. GFAP was also able to predict death with a 76.1% sensitivity at the time of admission and disability with an AUC equal to 0.823.<sup>[6]</sup> Although our study has not considered mortality, the findings are similar regarding a predictive value of GFAP in TBI.

We found a significant inverse correlation between GFAP and GCS of admission and discharge and EGOS of discharge and a 3-month follow-up and also we found a direct correlation between GFAP and the Rotterdam score.



**Figure 1: ROC curve related to the GFAP criterion for predicting the severity of TBI. GFAP: Glial fibrillary acidic protein, ROC: Receiver operator characteristic, TBI: Traumatic brain injury**

Pelinka *et al.* in 2015 showed an inverse correlation between the GFAP/S100B ratio with GCS and EGOS.<sup>[9]</sup> Although it is different from the current study in consideration of S100B protein, this concept may be used in future studies.

McMahon *et al.* in a prospective study, on TBI patients with a age range of 16–93 years, measured serum GFAP-BDP in 24 h and concluded that GFAP has 51% accuracy for prediction of intra cranial injuries in comparison to the brain CT scan Rotterdam score. Furthermore, GFAP-BDP had a significant direct relationship with the Rotterdam score. This study found that GFAP-BDP assay as an adjunct to current screening methods may help prevent unnecessary CT scans without reducing sensitivity.<sup>[15]</sup> The findings of this study in terms of correlation between GFAP and Rotterdam score are similar to the findings of the present study.

This study had several limitations. Inclusion of the patients from one center, although it is the only center in the district for the admission and care for the TBI patients, small volume of the study cases, and intentional exclusion of patients with a significant facial injury and normal brain CT scans are the limitations of this study. Considering the brain CT scan as the gold standard and performing an initial CT scan for all patients can be regarded as the strengths of this study.

## CONCLUSIONS

Serum GFAP as a specific brain protein has an acceptable sensitivity and specificity in prediction of severity of TBI. It is recommended to consider this protein and other brain biomarkers for the diagnostic and prognostic assessment of TBI in more extensive clinical trials.

## Acknowledgment

This study was derived from the doctoral thesis on neurosurgery (grant no.: 99125). We express our thanks to the deputy of research of Kashan University of Medical Sciences, and staff of Trauma Research Center and Shahid Beheshti Hospital for their cooperation.

## Authors' contributions

All authors contributed in all stages of research and read and approved the final manuscript.

## Financial support and sponsorship

This study was funded by the deputy of research in Kashan University of Medical Sciences (grant no: 99125).

## Conflicts of interest

There are no conflicts of interest

## REFERENCES

- Kiening K, Unterberg A. Trauma care in Germany: A European perspective. *Clin Neurosurg* 2007;54:206-8.
- Ansari M, Bayan L, Gorji A. The impact of road accidents on brain injury. *Neurosci J Shefaye Khatam* 2016;4:103-10.
- Ratan SK, Pandey RM, Kulsreshtha R, Ratan J. Risk factors for mortality within first 24 hours of head injury. *Indian J Pediatr* 2002;69:573-7.
- Fraser DD, Close TE, Rose KL, Ward R, Mehl M, Farrell C, *et al.* Severe traumatic brain injury in children elevates glial fibrillary acidic protein in cerebrospinal fluid and serum. *Pediatr Crit Care Med* 2011;12:319-24.
- Jones A, Jarvis P. Review of the potential use of blood neuro-biomarkers in the diagnosis of mild traumatic brain injury. *Clin Exp Emerg Med* 2017;4:121-7.
- Lei J, Gao G, Feng J, Jin Y, Wang C, Mao Q, *et al.* Glial fibrillary acidic protein as a biomarker in severe traumatic brain injury patients: A prospective cohort study. *Crit Care* 2015;19:362.
- Missler U, Wiesmann M, Wittmann G, Magerkurth O, Hagenström H. Measurement of glial fibrillary acidic protein in human blood: Analytical method and preliminary clinical results. *Clin Chem* 1999;45:138-41.
- Vos PE, Lamers KJ, Hendriks JC, van Haaren M, Beems T, Zimmerman C, *et al.* Glial and neuronal proteins in serum predict outcome after severe traumatic brain injury. *Neurology* 2004;62:1303-10.
- Pelinka LE, Kroepfl A, Leixnering M, Buchinger W, Raabe A, Redl H. GFAP versus S100B in serum after traumatic brain injury: Relationship to brain damage and outcome. *J Neurotrauma* 2004;21:1553-61.
- Bazarian JJ, Biberthaler P, Welch RD, Lewis LM, Barzo P, Bogner-Flatz V, *et al.* Serum GFAP and UCH-L1 for prediction of absence of intracranial injuries on head CT (ALERT-TBI): A multicentre observational study. *Lancet Neurol* 2018;17:782-9.
- Wiesmann M, Steinmeier E, Magerkurth O, Linn J, Gottmann D, Missler U. Outcome prediction in traumatic brain injury: Comparison of neurological status, CT findings, and blood levels of S100B and GFAP. *Acta Neurol Scand* 2010;121:178-85.
- Luoto TM, Raj R, Posti JP, Gardner AJ, Panenka WJ, Iverson GL. A systematic review of the usefulness of glial fibrillary acidic protein for predicting acute intracranial lesions following head trauma. *Front Neurol* 2017;8:652.
- Aydin I, Algin A, Poyraz MK, Yumrutas O. Diagnostic value of serum glial fibrillary acidic protein and S100B serum levels in emergency medicine patients with traumatic versus nontraumatic intracerebral hemorrhage. *Niger J Clin Pract* 2018;21:1645-50.
- Okonkwo DO, Yue JK, Puccio AM, Panczykowski DM, Inoue T, McMahon PJ, *et al.* GFAP-BDP as an acute diagnostic marker in traumatic brain injury: Results from the prospective transforming research and clinical knowledge in traumatic brain injury study. *J Neurotrauma* 2013;30:1490-7.
- McMahon PJ, Panczykowski DM, Yue JK, Puccio AM, Inoue T, Sorani MD, *et al.* Measurement of the glial fibrillary acidic protein and its breakdown products GFAP-BDP biomarker for the detection of traumatic brain injury compared to computed tomography and magnetic resonance imaging. *J Neurotrauma* 2015;32:527-33.