Glial fibrillary acidic protein level on admission can predict severe traumatic brain injury in patients with severe multiple trauma: A single-center retrospective observational study

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ARTICLE INFO

Keywords:
Biomarker
Prediction
Multiple trauma
Traumatic brain injury
GFAP

ABSTRACT

Objective: This study aimed to clarify whether the glial fibrillary acidic protein (GFAP) and soluble protein-100β (S100β) can predict severe traumatic brain injury (TBI) in patients with severe multiple trauma.

Methods: This is a single-center retrospective observational study of 179 patients with severe multiple trauma. The GFAP and S100β were measured upon patient arrival at the hospital. We divided the patients into the severe TBI group (with a Traumatic Coma Data Bank classification of ≥III), the non-severe TBI group (non-TBI group [absence of abnormality on the computed tomography scan and extracranial injury], and the mild to moderate TBI group [TCDB classification I and II]). We compared biomarker levels between the two groups and then evaluated the accuracy of predicting severe TBI using a receiver operating characteristic curve.

Results: A total of 41 patients had severe TBI, and 138 had non-severe TBI. Mean GFAP levels were significantly higher in the severe TBI group (median, 6600 pg/mL; interquartile range [IQR], 651–15,548 pg/mL) than in the non-severe TBI group (median, 149 pg/mL; IQR, 0–695 pg/mL) (p < 0.0001). In contrast, there was no significant difference in S100β levels between the severe TBI group (median, 64 pg/mL; IQR, 0–536 pg/mL) and non-severe TBI group (median, 117 pg/mL; IQR, 0–405 pg/mL) (p = 0.637). The area under the receiver operating characteristic curve was 0.810 (p < 0.0001) for GFAP and 0.476 (p = 0.908) for S100β. For the GFAP, the optimal cutoff value for detecting severe TBI was 947 pg/mL (sensitivity, 75.6%; specificity, 78.3%).

Conclusions: In patients with severe multiple trauma, the GFAP level at hospital arrival could predict severe TBI, whereas the S100β level was not a useful predictor.

1. Introduction

Traumatic brain injury (TBI) is the most common cause of death by trauma worldwide (Fleminger and Ponsford, 2005; Zink, 2001). TBI-induced death usually occurs 24–72 h after admission (Acosta et al., 1998).

Previous studies have reported that biomarkers can predict TBI severity in patients undergoing head computed tomography (CT). Recently, some observational studies showed that the glial fibrillary acidic protein (GFAP) level is a useful predictor of TBI in patients with mild or moderate isolated TBI (Bazarian et al., 2018; Welch et al., 2016; Diaz-Arrastia et al., 2014; Kou et al., 2013). GFAP level has been one of the outcome predictors for patients with TBI (Takala et al., 2016; Lei et al., 2015). Meanwhile, the most well-studied biomarker is S100β. The American College of Emergency Physicians recommended that in patients with mild TBI, without significant extracranial injuries, and a serum soluble protein-100β (S100β) level <0.1 µg/L measured within 4 h of injury, consideration can be given to not performing a CT scan (Level C) (Jagoda et al., 2008). This indicates that S100β is a useful biomarker for ruling out any intracranial injury that can be detected by a CT scan. Moreover, head CT scanning has some potential adverse effects, such as radiation exposure, unnecessary emergency department
resource use, and cost (Sharp et al., 2017; Brenner and Hall, 2007).

Early decompressive craniectomy can improve abnormal intracranial pressure and cerebral perfusion pressure time (Allen et al., 2018). Thus, it is helpful in patients with TBI. Moreover, a shorter time between emergency department admissions to neurosurgical intervention is associated with a significantly higher rate of patient survival (Matsushima et al., 2015; Qiu et al., 2009). Therefore, early diagnosis and determination of the proper treatment strategy are crucial for patients with severe TBI. However, previous studies on GFAP and S100β levels were conducted in patients with isolated mild or moderate TBI and to detect any abnormal signs in the CT scan. Furthermore, there are only a few investigations about the relationship between GFAP and S100β levels in patients with multiple trauma (Papa et al., 2014; Honda et al., 2010).

Therefore, this study aimed to clarify whether GFAP and S100β levels can predict severe TBI in patients with severe multiple trauma.

2. Materials and methods

This is a retrospective observational study conducted at Fukuoka University Hospital, a 915-bed academic center with a 34-bed intensive care unit. It is an emergency and critical care center that is equivalent to a Level I trauma center. Our center provides patient care in accordance with the Japan Advanced Trauma Evaluation and Care (JATEC™) guidelines. The study protocol was approved by the Institutional Review Board of Fukuoka University Hospital (no. 15-10-09). The need for informed consent was waived, given the retrospective nature of the study and anonymous presentation of data. In our hospital, informed consent was obtained from the patients when extra blood samples were collected and stored for research purposes. Our study measured GFAP and S100β levels retrospectively using the frozen serum samples.

2.1. Study population

We included patients aged ≥18 years, with an Injury Severity Score (ISS) (Baker et al., 1974) of ≥16, who were admitted to our center between April 2013 and December 2015. The exclusion criteria were a lack of extra blood samples, cardiopulmonary arrest on hospital arrival, absence of head CT scan on arrival, and burns. We divided the patients into the severe TBI group and the non-severe TBI group. Severe TBI was defined as having a Traumatic Coma Data Bank (TCDB) classification of ≥III. The TCDB classification is based on the Marshall classification (Lawrence et al., 1991). Furthermore, non-severe TBI included non-TBI (absence of CT scan abnormality and extracranial injury) and mild to moderate TBI (TCDB classification I and II). CT scans were evaluated by one or two neurosurgery physicians and an emergency physician. The inclusion and exclusion criteria are shown in Fig. 1.

2.2. Data collection

We collected data on age, sex, mechanism of injury, the time between injury and biomarker measurement, Glasgow Coma Scale (GCS) on arrival, TCDB classification, vital signs on arrival, Abbreviated Injury Scale (AIS), ISS, probability of survival (Ps) based on the Trauma Injury Severity Score (Boyd et al., 1987), rate of performing craniotomy within 24 h, 24-h mortality rate, 28-day mortality rate, and GFAP and S100β levels on admission.

2.3. Biomarker assays

Blood samples were taken immediately upon arrival. The blood was centrifuged at 1400 g for 15 min, and the serum was stored at −70 °C. The frozen serum was allowed to melt to become liquid at room temperature before GFAP and S100β testing. GFAP and S100β levels were measured using the following enzyme-linked immunosorbent assays (ELISAs): Human GFAP ELISA and Human S100β ELISA (BioVendor, Brno, Czech Republic), respectively. Standard curves for S100β and GFAP levels are shown in Supplementary Fig. 1.

2.4. Accuracy of detecting severe TBI

We evaluated the accuracy of detecting severe TBI by using receiver operating characteristic (ROC) curves. Furthermore, we calculated the areas under the curve (AUCs) to evaluate the accuracy of GFAP and S100β levels for detecting severe TBI.

2.5. AIS score and biomarker levels

To determine which sites of injury were associated with an elevation in biomarker levels, we evaluated the relationship between AIS score

![Fig. 1. Inclusion and exclusion criteria of the study. ISS, Injury Severity Score; TBI, traumatic brain injury.](image-url)
Injury Score; ISS, Injury Severity Score; Ps, probability of survival, GFAP; glial fibrillary acidic protein.

2.6. Statistical analysis

All variables were expressed as medians and interquartile ranges (i.e., 1st–3rd quartiles) or numbers (percentages). Intergroup comparisons were performed using the Mann-Whitney U test for continuous variables and the chi-squared test for categorical variables. ROC curves of variables with statistical significance by logistic regression analysis were constructed to predict severe TBI. Cutoff values were defined based on the Youden index. To investigate the relationship between AIS score and biomarker levels, we performed multiple regression analysis that included GFAP and S100β levels as objective variables and AIS scores for head/neck, face, chest, abdomen, extremity/pelvic, and external injuries as explanatory variables. All statistical analyses were performed with JMP® version 14 (SAS Institute, Cary, NC, USA). The level of significance was set at \( p < 0.05 \).

3. Results

3.1. Patients and characteristics

The non-severe TBI group comprised 138 patients, and the severe TBI group had 41 patients. The characteristics of both groups are shown in Table 1. Patients with severe TBI had significantly higher age, severity of TBI based on TCDB classification, head/neck AIS score, ISS, rate of massive transfusion, and GFAP levels on admission, in contrast to a significantly lower GCS score on admission, AIS score (thorax, abdomen, extremity/pelvic, and external) and Ps. Furthermore, there was no significant difference in time from injury to admission between the non-severe TBI and the severe TBI group. The GFAP level in the severe TBI group was significantly higher than that in the non-severe TBI group, whereas there was no significant difference in S100β levels between both groups.

3.2. Accuracy of predicting severe TBI

The AUC for GFAP as a predictor of severe TBI was 0.810 (95% confidence interval [CI], 0.712–0.881; \( p < 0.001 \)), whereas that for S100β was 0.476 (95% CI, 0.377–0.577; \( p = 0.908 \)). The optimal cutoff value for GFAP measurement was 947 pg/mL (sensitivity, 75.6%; specificity, 78.3% (Table 2)). The ROC curves for both GFAP and S100β are shown in Fig. 2.

3.3. AIS score and biomarker levels

The results of the multiple regression analysis are shown in Table 3. The head/neck AIS score was an independent factor for the elevation in GFAP levels in the multiple regression analysis (coefficient 1605.852 95% CI; 1048.487–2163.217, \( p < 0.001 \)). In contrast, AIS scores not only for the head/neck (coefficient 45.756 95% CI; 9.078–82.435, \( p = 0.015 \)) but also for the thorax (coefficient 56.808 95% CI; 24.804–88.812, \( p = 0.001 \)) and extremity/pelvic (coefficient 120.070, 95% CI; 76.780–163.361, \( p < 0.001 \)) injuries were independent factors for the elevation in S100β levels.

4. Discussion

This study revealed that the GFAP level could predict severe TBI with high accuracy in patients with severe multiple trauma, whereas the S100β level did not show any significant difference. Furthermore, an elevation in the GFAP level was associated with only head/neck AIS score, and as the GFAP level increased, TBI severity increased. Recent meta-analyses show that S100β levels are a more suitable screening tool than GFAP for the detection of TBI in mild to moderate (Amo et al., 2022) and moderate to severe (Monello et al., 2021) patients with TBI in the emergency room. In contrast, a cohort shows that GFAP levels have higher accuracy for predicting non-severe and severe TBI (ICU and general ward), but this is not the case for S100β (Czete et al., 2020). This recent evidence indicates that S100β levels can help informed decision-making in emergency care, possibly reducing resource use, but not in a hospital setting such as the ICU. Furthermore, we analyzed the comparison in the biomarker levels among TBI severities, shown in Supplementary Fig. 2. Elevation in GFAP levels was significantly associated with an increase in TBI severity. However, there was no significant difference in S100β levels and TBI severity.

In this study, a TCDB classification of >III was considered the cutoff point of severe TBI. Corral et al. (2012) reported that TCDB classifications of III, IV, and VI are one of the independent predictors of death (odds ratio [OR], 3.69; 95% CI, 1.43–9.51). In a large cohort study (Maas et al., 2007), TCDB CT classification was strongly related to outcome, with a worse outcome for patients with diffuse injuries in CT class III (OR, 2.50; 95% CI, 2.09–3.0) or CT class IV (OR, 3.03; 95% CI, 2.12–4.35). Moreover, our study showed that all patients who underwent craniotomy were included in the severe TBI group, and this group had a significantly higher mortality rate than the non-severe TBI group (Table 2). These findings suggest that using a TCDB classification of >III in predicting TBI severity is clinically acceptable.

In this study, even with multiple trauma, GFAP levels showed a high AUC value for predicting severe TBI (Table 2). Pelinka et al. (2004a) reported that GFAP levels were not elevated in patients having multiple trauma without TBI. Papa et al. (2014) also reported that even if
extracranial fractures were present, the GFAP level could predict trauma severity/pelvic AIS scores were independent predictors for the elevation in GFAP levels (Table 3). Particularly, the extremity/pelvic AIS score coefficient was relatively high compared with the AIS scores of other parts. Papa et al. (2014) reported that S100β levels were significantly higher in patients with fractures than in those without fractures (p < 0.001), regardless of whether moderate TBI was present or not. Unden et al. (2005) also reported that S100β levels were elevated in 29% (16/55) of patients with acute fractures without apparent cerebral injury. These findings suggest that the S100β level is not a useful predictor of TBI or TBI severity in patients with multiple trauma.

This study has some limitations. First, it is a retrospective study with a small sample. Second, we evaluated biomarker levels at only one point in time. Third, we did not describe long-term outcomes in these patients. Fourth, there was some difference in time between injury and biomarker measurement, such as within 60 min or the others (Table 1). However, the diagnostic accuracy of using GFAP levels in predicting TBI in our study was similar to that (during the first 2 hospital days) of other studies in patients with multiple trauma. S100β genes are expressed not only in the brain but also in other tissues, including muscle, skin, and adipose tissue and those of the reproductive, gastrointestinal, respiratory, and urinary system (Zimmer et al., 1995). Moreover, our multiple regression analysis showed that not only head/neck but also thorax and extremity/pelvic AIS scores were independent predictors for the elevation in S100β levels (Table 3). Particularly, the extremity/pelvic AIS score coefficient was relatively high compared with the AIS scores of other parts.

GFAP, glial fibrillary acidic protein; AUC, area under the curve; CI, confidence interval; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value.

Table 3

| Biomarker | Variable          | coefficient | 95%CI      | p value |
|-----------|-------------------|-------------|------------|---------|
|           | lower             | upper       |            |         |
| S100β (pg/mL) | head/neck         | 45.756      | 9.078      | 82.435  | 0.015   |
|           | face              | 32.874      | −32.014    | 97.762  | 0.319   |
|           | thorax            | 56.808      | 24.804     | 88.812  | 0.001   |
|           | abdomen           | 43.351      | −1.226     | 87.927  | 0.057   |
|           | extremity/pelvic  | 120.070     | 76.780     | 163.361 | <.0001  |
| GFAP (pg/mL)  | head/neck         | 1605.852    | 1048.487   | 2163.217| <.0001  |
|           | face              | −415.898    | −1401.923  | 570.127 | 0.406   |
|           | thorax            | 155.066     | −331.262   | 641.955 | 0.530   |
|           | abdomen           | 158.590     | −518.783   | 835.962 | 0.645   |
|           | extremity/pelvic  | 510.959     | −146.878   | 1168.797| 0.127   |
|           | external          | 1334.422    | −78.059    | 2746.902| 0.064   |

GFAP, Gial fibrillary acidic protein; CI, confidence interval; ISS, Injury Severity Score; TBI, traumatic brain injury.

Fig. 2. ROC curves. The GFAP level as predictor demonstrated a high AUC value, while S100β levels did not. Solid black and solid gray lines indicate GFAP and S100β levels, respectively. ROC, receiver operating characteristic; GFAP, glial fibrillary acidic protein; AUC, area under the curve; CI, confidence interval; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value.

Table 2

Accuracy of detecting severe traumatic brain injury.

|               | AUC   | 95% CI      | p value | Optimal cut-off value | Se (%) | Sp (%) | PPV (%) | NPV (%) |
|---------------|-------|-------------|---------|-----------------------|--------|--------|---------|---------|
| GFAP          | 0.810 | 0.712–0.881 | <0.0001 | 947 pg/mL             | 75.6   | 78.3   | 50.8    | 91.5    |
| S100β         | 0.476 | 0.377–0.577 | 0.908   | 485 pg/mL             | 26.8   | 79.7   | 28.2    | 78.6    |

GFAP, Gial fibrillary acidic protein; AUC, area under the curve; CI, confidence interval; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value.

extracranial fractures were present, the GFAP level could predict traumatic intracranial lesions on CT scans in trauma patients with mild TBI (AUC, 0.93) but not with S100β levels (AUC, 0.75). Moreover, Honda et al. (2010) showed that the GFAP level was a highly specific biomarker for TBI (AUC, 0.983) compared with the S100β level (AUC, 0.658) on admission; their study included patients with multiple trauma with a median ISS of 26 for TBI and 21 for non-severe TBI. Furthermore, Lumpkins et al. (2008) demonstrated that GFAP levels highly predicted for CT-documented TBI in patients with multiple trauma. These results support that of our study. On the other hand, a study reported that GFAP mRNA or protein expression in human tissue was observed in the brain but not in other tissues (Yang and Wang, 2015). Therefore, GFAP can detect severe TBI with high specificity in patients with severe multiple trauma. In studies by Pelinka et al., 2004a, 2004b, GFAP levels increased as the TCD classification of severity increased. Such findings are also consistent with our results. Therefore, the GFAP level not only detects TBI on the CT scan but also reflects TBI severity.

Multiple trauma management guidelines such as JATEC™ and Advanced Trauma Life Support (ATLS®) recommend the ABCDE (airway, breathing, circulation, dysfunction of the central nervous system or disability, and exposure) approach and not the CT scan on initial assessment. Therefore, a definite, timely diagnosis of severe TBI is possible after the initial assessment. Having immediate results on GFAP levels may enable quick decision-making on performing procedures for severe TBI, such as decompressive craniectomy, hyperosmolar therapy, prophylactic hypothermia, and intracranial pressure monitoring (Carney et al., 2017). This early decision-making with timely procedures may improve survival and neurological outcome.

In our study, S100β was not a useful predictor for severe TBI in patients with severe multiple trauma. S100β genes are expressed not only in the brain but also in other tissues, including muscle, skin, and adipose tissue and those of the reproductive, gastrointestinal, respiratory, and urinary system (Zimmer et al., 1995). Moreover, our multiple regression analysis showed that not only head/neck but also thorax and extremity/pelvic AIS scores were independent predictors for the elevation in S100β levels (Table 3). Particularly, the extremity/pelvic AIS score coefficient was relatively high compared with the AIS scores of other parts. Papa et al. (2014) reported that S100β levels were significantly higher in patients with fractures than in those without fractures (p < 0.001), regardless of whether moderate TBI was present or not. Unden et al. (2005) also reported that S100β levels were elevated in 29% (16/55) of patients with acute fractures without apparent cerebral injury. These findings suggest that the S100β level is not a useful predictor of TBI or TBI severity in patients with multiple trauma.

This study has some limitations. First, it is a retrospective study with a small sample. Second, we evaluated biomarker levels at only one point in time. Third, we did not describe long-term outcomes in these patients. Fourth, there was some difference in time between injury and biomarker measurement, such as within 60 min or the others (Table 1). However, the diagnostic accuracy of using GFAP levels in predicting TBI in our study was similar to that (during the first 2 hospital days) of other studies in patients with multiple trauma (Lumpkins et al., 2008). Furthermore, we have analyzed GFAP expression adjusted by age, time of blood removal, and severe-TBI or not. In addition, GFAP expression and severe-TBI were also significantly correlated (Supplementary Table 1). Thus, the difference in time between the injury and biomarker measurement may not affect the AUC value. Forth, the number of trauma and their location could not be added as covariates in the multiple regression analysis since the sample size was small. Lastly, as far as we know, there is no point of care test (POCT) system for the GFAP measurement system. Therefore, we need to consider developing the...
POCT for GFAP measurement.

5. Conclusions

The GFAP levels on hospital arrival could predict severe TBI in patients with severe multiple trauma, whereas S100β levels did not show any significance. Having immediate results of GFAP measurement could contribute to quick decision-making on performing procedures for severe TBI. Further large prospective studies and the development of a kit for rapid measurement of serum GFAP levels are needed.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Yoshikiko Nakamura: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision. Taisuke Kitamura: Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Supervision. Yasumasa Kawano: Formal analysis, Investigation, Resources. Kota Hoshino: Formal analysis, Investigation, Resources. Yuhe Irie: Formal analysis, Investigation, Resources. Kentaro Muranishi: Investigation, Resources. Mitsutoshi Iwaasa: Investigation, Resources, Funding acquisition: None. Hironao Ishikura: Conceptualization, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank Ms. Kanae Misumi of the Department of Emergency and Critical Care Medicine, Faculty of Medicine, Fukuoka University, for assisting in data coding, and LSU Medienere Corporation for measuring the GFAP and S100β levels.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.crmeur.2022.100047.

Abbreviations

GFAP (glial fibrillary acidic protein)
S100β (soluble protein-100β)
TBI (traumatic brain injury)
TCDB (Traumatic Coma Data Bank)
IQR (interquartile range)
CT (computed tomography)
JATEC (Japan Advanced Trauma Evaluation and Care)
ISS (Injury Severity Score)
GCS (Glasgow Coma Scale)
AIS (Abbreviated Injury Scale)
Ps (probability of survival)
ELISAs (enzyme-linked immunosorbent assays)
ROC (receiver operating characteristic)
AUC (areas under the curve)
CI (confidence interval)
OR (odds ratio)
ATLS (Advanced Trauma Life Support)

(PCT) point of care test

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