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Research Article

Correlation Between Cerebrospinal Fluid Glial Fibrillary Acidic Protein (GFAP) Levels and the Severity of Traumatic Brain Injury Measured by Glasgow Coma Scale and Marshall Classification

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Abstract
In comparison with other diseases that affect the human brain, Traumatic Brain Injury (TBI) has the highest incidence; it is a significant public health issue. In addition to being a critical factor in determining appropriate medical actions and predicting patients' outcomes, assessing TBI severity is imperative. Numerous recent studies indicate that biofluid-based TBI biomarker tests have promising outcomes for diagnosing TBI severity and prognosis. Therefore, this study aimed at investigating how GFAP levels in cerebrospinal fluid correlate with TBI severity determined using GCS and Marshall Classification. This research utilized an analytical observational cross-sectional design involving fifteen TBIs who underwent ICP monitor installation at healthcare centres within Surabaya's Dr Soetomo General Hospital from January to March 2024. 15 subjects tested GCS based on clinical conditions at initial hospitalization, calculated Marshall Classification based on radiological examination and protein levels of GFAP on LCS when ICP Monitor was installed. Correlation test of CSF GFAP level with GCS obtained a correlation coefficient value r = 0.939, means there is a strong correlation. CSF GFAP level and Marshall Classification shows a strong correlation (r = 0.695). There is a significant correlation between the CSF GFAP with the Glasgow Coma Scale and the Marshall Classification.

Keywords: TBI, Cerebrospinal fluid, GFAP, Glasgow Coma Scale, Marshall Classification

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INTRODUCTION

Traumatic Brain Injury (TBI) is frequently seen as the primary neurological condition, resulting in significant health consequences worldwide. TBIs form and severity may vary from mild impaired consciousness to coma and death (Galgano et al., 2017). In 2014, CDC reported 2.53 million TBI cases in emergency rooms around the world and 288,000 of those required hospitalization and 56 ,800 resulted in death (Taylor, 2017). TBI death rate at Dr. Soetomo General Hospital Surabaya from 2002 to 2013, varied from 6.2% to 11.2% (Wahyuhadi et al., 2014). Evaluating the extent of a traumatic brain injury is a crucial element in deciding on the right course of medical treatment and forecasting the patient's recovery. The Glasgow Coma Scale (GCS), head CT scans, and MRI can be used to identify and classify TBI. The GCS aids as a clinical decision-making, while the Marshall classification has demonstrated predictive value for TBI outcomes (Hukkelhoven et al., 2005; Maas et al., 2005). Glial fibrillary acidic protein

(GFAP) can be located within the astroglial cytoskeleton and is classified as an intermediate filament protein.

It functions as a biomarker in TBI patients and is secreted during damage to the central nervous system (CNS) (Žurek, 2017). GFAP is a marker for focal lesions and intracranial hemorrhage because it is linked to astroglial damage and is released following injury to the astroglial cytoskeleton (Huie et al., 2021). Reactive astrocytic response to brain trauma, particularly in the context of blood-brain barrier disruption, underlies the interest in GFAP as a TBI biomarker (Yue et al., 2020).

A literature review by Sutrisno et al. (2024) highlighted the significance of GFAP, NSE, and S100β as biomarkers in TBI conditions. Papa et al. (2015) discover that in trauma patients with mild TBI and extracranial injuries, using GFAP is a more efficient method to detect intracranial lesions than S100β. This is because it is suspected that in polytrauma cases with bone lesions, S100β is also released from bone, resulting in higher levels. Under shock conditions, notable increases in NSE and S100β are also noted. Having a proper understanding of the seriousness of traumatic brain injury is vital in deciding on suitable treatment interventions and predicting the survival rate. Some newly released investigations asserted that severity about TBI and probability of patients' survival can be determined using tests on TBI biomarkers from bio-fluids. Hence, this research examines how CSF GFAP levels are related to TBI severity measured by means of GCS score and Marshall Classification.

METHODS

This study is an observational analytic study with a cross-sectional design, as the data were obtained at a single point in time, no sequential changes observed over time. Informed consent was given by family of the patients. A total of 15 subjects of TBI patients who have had an ICP monitor placed that met the criteria between January to March 2024 at Dr. Soetomo General Hospital Surabaya were included.

Inclusion Criteria

Patients who provided informed consent to participate in the study and met the following criteria were included:

- Aged ≥18 years old
- Patients with TBI who have had an ICP monitor placed.
- Complete data and examination records

Exclusion Criteria

Exclusion criteria include the following:

- Not being able to obtain CSF during ICP monitor placement.
- Patients with a history of Alzheimer's disease, diabetes mellitus, melanoma, Down syndrome, and epilepsy.
- Incomplete data and examination records.
- TBI patients with airway, breathing, and circulation disorders.

Procedure

Families of patients who met the inclusion criteria were first provided with an explanation of the study's purpose. The study began by obtaining informed consent from the families. Patient characteristics such as age, gender, comorbidities, trauma mechanism, and type of trauma were recorded through *heteroanamnesis*. Upon arrival at the emergency department, GCS was evaluated and a physical examination was conducted. Patients with GCS 3–8 performed a primary survey in order to stabilize Airway, Breathing, Circulation, Disability, and Exposure, including endotracheal intubation and fluid administration, if necessary (Christin et al., 2023).

Compromised components were treated for patients with GCS 9–12, and the patient was stabilized. Patients with GCS 13–15 had their primary survey examined in order to keep their status stable. Head CT scans were performed and evaluated using the Marshall Classification. Cerebrospinal fluid (CSF) samples for GFAP analysis were collected during intracranial pressure monitor insertion in the operating room, with a volume of 3 ml. Samples were then analyzed using a Human ELISA Kit (Elabscience Biotechnology) using spectrophotometer with a wavelength of 450 nm. Results were recorded in ng/mL. The GFAP levels in the CSF were then correlated with the severity of TBI based on the GCS and Marshall Classification.

Statistical Analysis

Data collected was analyzed with SPSS 26. Results of the analyzed data will be presented in tables. Normality tests were conducted using the Shapiro-Wilk test. Pearson correlation was applied to normally distributed data, while Spearman correlation was used for non-normally distributed data.

RESULTS

Demographic Data

Table 1. Characteristics of research subject

Characteristics	N (%)	*Range*	*Mean*±SD
General Characteristics			
Sex			
Male	14 (93.3%)	-	-
Female	1 (6.7%)	-	-
Age (year)	15 (100%)	19 - 72	44.47 ± 16.61
Clinical Characteristics			
Comorbidity			
Yes	3 (20.0%)	-	-
No	12 (80.0%)	-	-
Trauma			
Vehicle Accident	11 (73.3%)	-	-

Fall	4 (26.4%)	-	-
MAP	15 (100%)	75 – 122	96.00 ± 13.17
HR	15 (100%)	64 – 120	92.67 ± 17.37
SpO2	15 (100%)	96 - 99	98.33 ± 0.82
Temperature	15 (100%)	36,3 - 36,9	36.67 ± 0.19
SBP	15 (100%)	104 – 161	133.93 ± 18.04
DBP	15 (100%)	61 – 104	77.20 ± 12.83

Table 2. Concentration of CFS GFAP

	N	*Range*	*Mean*±SD	*P value*
CSF GFAP Concentration	15	0.818 – 2.205	1.549 ± 0.295	0.111

Table 3. GCS score

	N	*Range*	*Mean*±SD	*p value*
GCS	15	4 - 8	6.33 ± 1.05	0.048

Table 4. Marshall Classification

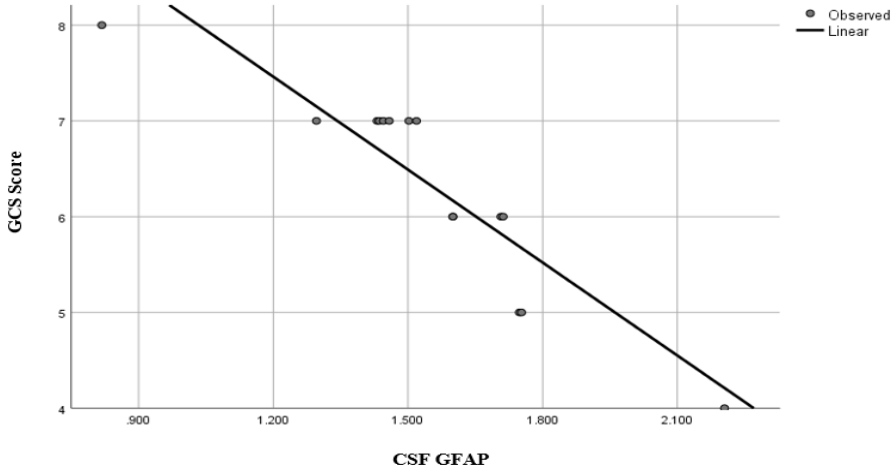
Marshall Classification	N (%)
Category I	0 (0%)
Category II	0 (0%)
Category III	0 (0%)
Category IV	0 (0%)
Category V	12 (80,0%)
Category VI	3 (20,0%)

Table 1 provides further details on the subject's characteristics including general and clinical characteristics of all study participants (n = 15). There is no statistically significant difference seen in the age, BMI, or vital sign data between the two groups. Concentration of CSF GFAP found in the subjects was shown in table 2 in ng/mL. Table 3 provides GCS score data found in 15 research subjects and table 4 shown most of the subjects is classified as category V of Marshall classification.

Table 5. Correlation between CSF GFAP level and GCS score

	N	r	*p value*
CSF GFAP Level and GCS	**15**	**-0,939**	**0,000**

Figure 1. Scatter plot of CSF GFAP Level and GCS Score

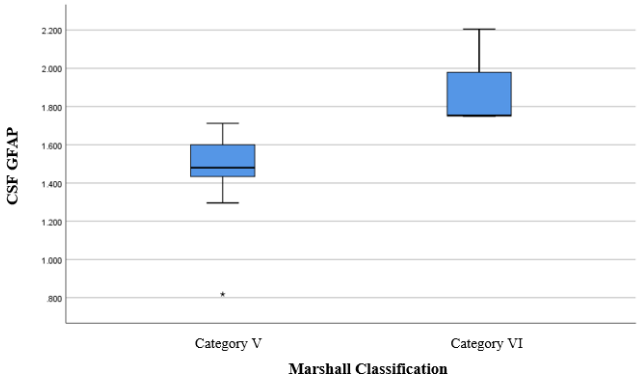


The Spearman correlation analysis shown by table 5 revealed a major inverse within CSF GFAP levels and GCS ($p < 0.05$). The correlation coefficient was -0.939, indicating a very strong negative correlation. This suggests that higher CSF GFAP levels are strongly associated with lower GCS scores.

Table 6. Correlation between CSF GFAP level and Marshall Classification

Marshall Classification	**N**	**CSF GFAP Level**		**r**	***p value***
		Range	***Mean±SD***		
Category V	12	0,818 – 1,712	1,460 ± 0,235		
Category VI	3	1,748 – 2,205	1,902 ± 0,262	0,695	0,004

Figure 2. Box plot of CSF GFAP Level and Marshall Classification



The Marshall Classification and CSF GFAP levels had a significant positive correlation, according to the Spearman correlation analysis ($p < 0.05$). Strong correlation was indicated by the r=0.695. This implies that there is a correlation between higher Marshall Classification grades and greater CSF GFAP levels.

DISCUSSION

GFAP, an astroglial protein, is a crucial biomarker for traumatic brain injury (TBI) and is specific to the CNS. Its levels increase significantly in the blood following astrocyte damage from neurodegenerative disorders, stroke, and TBI (Herrmann et al., 2000; Lumpkins et al., 2008; Middeldorp & Hol, 2011; Vos et al., 2010). Typically, GFAP levels in CSF and blood are low (0.03–0.07 ng/mL), but rise notably after injury (Di Pietro et al., 2015; Diaz-Arrastia et al., 2014; Missler et al., 1999). In our study, CSF GFAP levels ranged from 0.818 to 2.205 ng/mL (mean 1.549 ng/mL). The levels reported by Neselius et al, who observed a range of 0.070 to 1.020 ng/mL in boxers with minor CNS injuries is lower than levels found in our study (Neselius et al., 2012). Our focus on severe TBI is probably the cause of the discrepancy. Sun et al., documented the effectiveness of GFAP in distinguishing multiple sclerosis (MS) from controls (Sun et al., 2021). In children with severe TBI, Fraser et al. found high CSF GFAP levels (15.5 ± 6.1 ng/mL, which decreased over 7 days (Fraser et al., 2011). Lei et al. (2015) reported serum GFAP levels of 1.924 ng/mL in severe TBI patients versus 0.058 ng/mL in controls ($p < 0.001$), while Pitra et al. found 2.48 ng/mL (Dian Ayu Hamama Pitra et al., 2021). The Glasgow Coma Scale (GCS) measure consciousness levels in circumstances of acute medical and trauma (Jain & Iverson, 2020). According to Pavlovic et al, TBI severity is categorized as mild (GCS 13-15), moderate (GCS 9-12), or severe (GCS 3-8) (Pavlovic et al., 2019). In our study, the GCS score of our study subjects ranged from 4 to 8, with a mean of 6.33 ± 1.05, indicating severe TBI. Basak et al. (2022) reported 40.5% of severe TBI cases were found, which aligns. However, Okidi et al. (2020) and Tegegne et al. (2023) found different distributions, with Okidi et al, reporting a broader range of GCS scores and Tegegne et al, showing a predominance of mild TBI. Discrepancies may stem from our study's focus on severe TBI patients with ICP monitoring, as recommended for GCS <9 and abnormal CT scans or specific conditions (Bratton et al., 2007). Lower GCS scores are associated with higher mortality (Assele et al., 2021; Bratton et al., 2007; Owattanapanich et al., 2018; Tegegne et al., 2023; van Leeuwen et al., 2012). Overall, there is a consistent inverse correlation between GCS and TBI mortality. According to our study, 20% of patients were classified as class VI and 80% of patients as Marshall class V, suggesting severe TBI. This differs from Mondello et al. (2011) who discovered that 44% of injuries were diffuse and 56% had focal lesions. Elkbuli et al. (2021) observed 52.8% of patients with Marshall class less than IV, while Mohammadifard et al. (2018) recorded the majority of patients in class II. A higher Marshall score is associated with a higher death rate. According to Elkbuli et al. (2021) patients with severe TBI who had Marshall scores ≥ IV had a considerably greater fatality rate (68%) than those who had scores < IV (16%) ($P < 0.05$). Higher Marshall scores were also strongly correlated with higher mortality, according to Kumoro et al. (2019).

Our findings align with Matoha et al. (2016) who reported a significant correlation between Marshall classification and GCS score ($X^2 = 32.359$, $P < 0.001$). Higher Marshall classifications in our study reflect the severe TBI focus, consistent with literature showing more severe CT abnormalities and lower GCS scores in higher Marshall classes (Farshchian et al., 2012; Matoha et al., 2016). Previous studies have documented elevated levels of GFAP or GFAP breakdown protein (GFAP-BDP) in CSF and serum following mild, moderate, or severe brain injury in adults (Czeiter et al., 2012; Lee et al., 2015; McMahon et al., 2015; Okonkwo et al., 2013; Welch et al., 2016). Our findings demonstrate a significant inverse correlation between CSF GFAP levels and GCS ($r=-0.939$, $p<0.05$), indicating that higher GFAP levels correspond to lower

GCS scores. This strong inverse correlation aligns with previous research showing GFAP levels correlate with injury severity defined by GCS (Chandra et al., 2024; Czeiter et al., 2020; Diaz-Arrastia et al., 2014; Okonkwo et al., 2013). Additionally, serum GFAP-BDP measurements within the first 24 hours post-injury can differentiate injury severity assessed by GCS scores, with significantly higher levels associated with lower GCS (ANOVA, Sidak pairwise $p<0.01$). GFAP-BDP's ability to distinguish between mild and moderate-severe injuries, measured by AUC, is 0.87 (95% CI, 0.81–0.93), and its discriminative ability for mild-moderate versus severe injuries is 0.84 (95% CI, 0.77–0.91) (Okonkwo et al., 2013).

This study reinforces GFAP's potential as a biomarker for assessing brain injury severity. Mondello et al. (2011) found notable variations in the average of GFAP levels among all groups, which were 0.56 ± 0.12 ng/mL for diffuse injuries I–II, 1 ± 0.2 ng/mL for diffuse injuries III–IV, and 2.95 ± 0.48 ng/mL for focal lesions within 24 hours post-injury. GFAP levels in adult TBI patients also correlate positively with the severity of CT findings based on the Marshall Classification (Pelinka et al., 2004; Vos et al., 2010). Research conducted on pediatric populations reveals that although GFAP may not always be able to discriminate between positive and negative CT scans, it is considerably raised in TBI with positive scans when compared to controls (Mondello et al., 2011; Papa et al., 2015). We found a significant correlation ($r=0.695$) between CSF GFAP levels and the Marshall Classification, being the first study to do so. Specifically, we found that GFAP levels were greater in Marshall Class VI than in Class V. This validates earlier studies showing that GFAP levels can represent the severity of an injury. Differences in GFAP levels between diffuse and focal injuries may be attributed to the greater resilience of astrocytes compared to neurons. In the CNS, astrocytes outnumber neurons and are therefore less vulnerable to excitotoxicity and ischemia injury. According to Chen & Swanson (2003) focal lesions result in extensive necrosis in both glial and neuronal cells, which raises GFAP levels. Reactive astrogliosis also adds to the heightened GFAP levels.

CONCUSION

This study demonstrates that individuals with severe TBI, shows a significant inverse correlation between CSF GFAP levels and GCS scores. Higher GFAP levels are associated with lower GCS scores. Marshall classification was used to measure severity of traumatic brain injury in this study and a major relationship between GFAP levels in CSF (cerebrospinal fluid) and degree of damage to the brain as defined by Marshall was also shown, where GFAP concentrations were higher in Marshall class VI than in class V. These findings highlight the potential of GFAP as a reliable biomarker for assessing TBI severity and prognosis. Future research should focus on comparing CSF and serum GFAP to show which one will be more reliable.

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