

Relationship Between Cerebrospinal Fluid S100B Levels with Glasgow Coma Scale and Rotterdam CT Score in Traumatic Brain Injury Patients

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ABSTRACT

Background: Traumatic brain injury (TBI) stands as one of the foremost reasons for mortality and incapacitation in young adults on a global scale, accounting for nearly half of all injury-related deaths. The severity of TBI can be assessed using various biomarkers, with the S100B protein being one of them. While many studies have explored the correlation between serum protein levels and various aspects such as neuroimaging findings, clinical scores, and neuropsychological evaluations, there is a notable lack of research examining the correlation with cerebrospinal fluid (CSF) levels. **Methods:** The research design of this study was prospective and observational, employing analytic methods for analysis. Fifteen TBI patients who met the inclusion and exclusion criteria and were fitted with ICP monitors comprised the study sample. GCS data used is post-resuscitation GCS. Data on S100B protein levels were taken from the examination of CSF samples taken when the ICP monitor was installed. Rotterdam CT score variables was taken from the last CT scan performed before the patient was fitted with an ICP monitor. The statistical analysis was conducted utilizing the SPSS version 26 software. **Results:** Demographic characteristics for this study tended to be more male (73.3%), with ages ranging from 18 to 65 years, and a mean age of 34.60 ± 16.22 years. The majority of injury mechanisms were traffic accidents (80%), and the most common lesion type was ICH. The mean CSF S 100B value of the 15 samples was 2753.689 pg/ml. The results of the relationship test between S 100B CSF and GCS using the Spearman test obtained a p-value of less than 0.05, indicating a meaningful correlation between S 100B CSF and GCS, with a correlation coefficient or r value of -0.684. The results of the S100B CSF relationship test with Rotterdam CT Score obtained a p-value <0.05, with a correlation coefficient or r value of 0.827. **Conclusion:** Increased levels of S100B in cerebrospinal fluid are associated with decreased GCS and increased Rotterdam CT score in traumatic brain injury patients.

Keywords: S100B, Traumatic Brain Injury, Glasgow Coma Scale, Rotterdam CT score.

INTRODUCTION

Traumatic Brain Injury (TBI) stands as one of the foremost reasons for mortality and incapacitation in young adults on a global scale, accounting for nearly half of all injury-related deaths. Most victims hail from low- and middle-income countries. Besides fatalities, traumatic brain injuries can also result in disabilities, compromising the future of individuals and their families. Additionally, they impose significant financial burdens on hospitals and communities for the rehabilitation and long-term care of the affected patients.¹⁻³

Based on the World Health Organization (WHO) data from 2019, traffic accidents ranked as the seventh most common cause of mortality in low-income countries and the tenth in middle-income countries. Traffic accidents claim approximately 1.3 million lives each year and can result in trauma.⁴ Traumatic Brain Injury (TBI) significantly contributes to morbidity and mortality rates in Indonesia. In 2018, the Ministry of Health of the Republic of Indonesia reported an incidence rate of 189.68 per 100,000 population for Traumatic Brain Injury (TBI) in Indonesia. Meanwhile, data from patients with brain injuries admitted to RSUD Dr. Soetomo from January 2002 to December 2013 indicated mortality rates ranging from 6.2% to 11.2% across all severity levels of head injuries.⁵

Diagnosis and classification of Traumatic Brain Injury (TBI) involve various methods including neurological examinations, assessment using the Glasgow Coma Scale (GCS), and imaging techniques such as head CT scans and MRI. Several significant limitations accompany the use of the Glasgow Coma Scale (GCS) as a diagnostic tool. Objective information about the extent and location of damage is provided by employing neuroimaging techniques. Assessing the severity of traumatic brain injuries is a crucial step in determining appropriate medical interventions and predicting patient outcomes. Recent studies suggest that biofluid-based tests for TBI biomarkers have the potential to evaluate the severity of TBI and predict patient outcomes.^{6,7}

The severity of TBI can be assessed using various biomarkers, with the S100B protein being one of them. S100B is a calcium-binding protein that originates from astrocytes within the central nervous system and is subsequently released into the bloodstream. The majority of current research focuses on establishing correlations between serum protein levels and various factors such as neuroimaging results, clinical scores, and neuropsychological assessments. Nevertheless, there is limited research investigating the correlation between serum protein levels and cerebrospinal fluid (CSF) levels.⁸ Elevated levels of serum S100B have been linked to fatal outcomes and the severity of brain damage determined through neuroimaging assessments.⁹⁻¹¹

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Most studies have focused on the relationship between serum protein levels and findings from neuroimaging, clinical scores, and neuropsychological evaluations. However, there has been limited investigation into the correlation with cerebrospinal fluid (CSF) levels. This study aims to examine the association between S100B levels in cerebrospinal fluid and the Glasgow Coma Scale (GCS) and Rotterdam CT scores in patients with traumatic brain injury who have undergone intracranial pressure (ICP) monitoring.

METHODS

Study Design and Setting

The research methodology employed in this study is analytical observational, utilizing a prospective study design. It was conducted from October to December 2023 at the Emergency Department (ED) of Dr. Soetomo Hospital in Surabaya. The research sample consists of Traumatic Brain Injury (TBI) patients who underwent intracranial pressure (ICP) monitor placement, meeting the inclusion and exclusion criteria. Based on the formula, the sample size was determined to be 15 patients.

Glasgow Coma Scale (GCS) data used in the study represent post-resuscitation GCS scores. Information regarding the S100B protein levels was extracted from cerebrospinal fluid (CSF) samples collected during the ICP monitor placement. The Rotterdam CT score variable was derived from the latest CT scan conducted before the ICP monitor placement procedure for each patient.

Patients meeting the following criteria were included in the study: age 18 years or older, diagnosed with Traumatic Brain Injury (TBI) and undergoing intracranial pressure (ICP) monitor placement; having complete data and examinations; and consenting to be research subjects. Exclusion criteria were: Inability to collect cerebrospinal fluid (CSF) samples through ICP monitor placement; patients with a history of Alzheimer's disease, diabetes mellitus, melanoma, Down syndrome, and epilepsy; lacking complete data and examinations.

Statistical Analysis

Sample characteristics data are presented descriptively in the form of frequency values, percentages, range, mean, and standard deviation. The statistical analysis was conducted utilizing SPSS v. 26. The available data underwent a normality test using the Shapiro-Wilk test. If normal distribution was observed, the Pearson correlation statistical test was employed. When the data did not conform to a normal distribution, the Spearman correlation test was employed.

RESULTS

Subject Characteristics

The subjects in this study were characterized based on general and clinical characteristics. General characteristics examined included gender, age, and ethnicity. Clinical characteristics considered encompassed injury mechanism and lesion type. The table presenting the results of demographic characteristics is provided in the form of frequency, percentage, and mean ± standard deviation, as shown in Table 1.

According to the data presented in Table 1, the distribution of demographic characteristics for the general characteristic of gender among the 15 samples revealed that there were 11 males (73.3%), while females accounted for 4 (26.7%). Based on this frequency, it can be concluded that the samples in this study tend to have more males than females. For the general characteristic of ethnicity, out of the 15 samples, 14 (93.3%) were Javanese, and 1 (6.7%) were Batak. According to this frequency, the predominant ethnicity in the samples is Javanese.

Table 1. Distribution of Demographic Characteristics.

Characteristics	N (%)	Range	Mean ± SD
General Characteristics			
Gender			
Man	11 (73.3%)	-	-
Woman	4 (26.7%)	-	-
Ethnic group			
Java	14 (93.3%)	-	-
Batak	1 (6.7%)	-	-
Age	15 (100%)	18 - 65	34.60 ± 16.22
Clinical Characteristics			
Injury Mechanisms			
Traffic Accident (TA)	12 (80%)	-	-
Falling From a Height	3 (20%)	-	-
Lesion Type			
Fr Skull	9 (60%)	-	-
Subdural Hematoma (SDH)	9 (60%)	-	-
Traumatic Subarachnoid Hemorrhage (tSAH)	9 (60%)	-	-
Intracerebral Hemorrhage (ICH)	11 (73.3%)	-	-
Intraventricular Hemorrhage (IVH)	4 (26.7%)	-	-
Epidural Hematoma (EDH)	4 (26.7%)	-	-

Table 2. Descriptive S100B CSF and Normality Test.

	N	Range	Mean±SD	Normality p value
S100B CSF	15	790,257 – 4,726.078	2,753.689 ± 1,124.290	0.906*

*declared normal if the p-value is normal > 0.05

Regarding the general characteristic of age, among the 15 samples, the age ranged from 18 to 65 years, with a mean age of 34.60 years and a standard deviation of 16.22 years.

Based on the results in Table 1, the distribution of demographic characteristics for the clinical characteristic of injury mechanisms among the 15 samples showed that 12 (80%) were due to traffic accidents, while 3 (20%) resulted from falls from a height. Based on this frequency, it can be concluded that the samples in this study predominantly experienced injury mechanisms from traffic accidents compared to falls from a height. For the clinical characteristic of lesion types in skull fractures, out of the 15 samples, there were 9 (60%) skull fractures, 9 (60%) Subdural Hematomas (SDH), 9 (60%) Traumatic Subarachnoid Hemorrhages (tSAH), 11 (73.3%) Intracerebral Hemorrhages (ICH), 4 (26.7%) Intraventricular Hemorrhages (IVH), and 4 (26.7%) Epidural Hematomas (EDH). Based on this frequency, the most prevalent lesion type is ICH.

Descriptive and Normality Test of S100B CSF

The S100B CSF data is measured in the form of values or ratios in pg/ml units. Since the S100B CSF data is in value form, a normality test is necessary to determine whether the distribution of the S100B CSF data is normal or not. The normality test used is the Shapiro-Wilk test due to the limited sample size of 15. The normality test serves to decide the subsequent test; if the data is deemed normal, parametric methods will be used for further analysis, while if it is not normal, non-parametric methods will be employed. Table 2 displays the descriptive statistics for S100B CSF, while the results of the normality test are illustrated in Figure 1.

From the findings in Table 2, the S100B CSF values of the 15 samples fall within the range of 790.257 pg/ml to 4,726.078 pg/ml, with an average and standard deviation of 2,753.689 ± 1,124.290 pg/ml. The

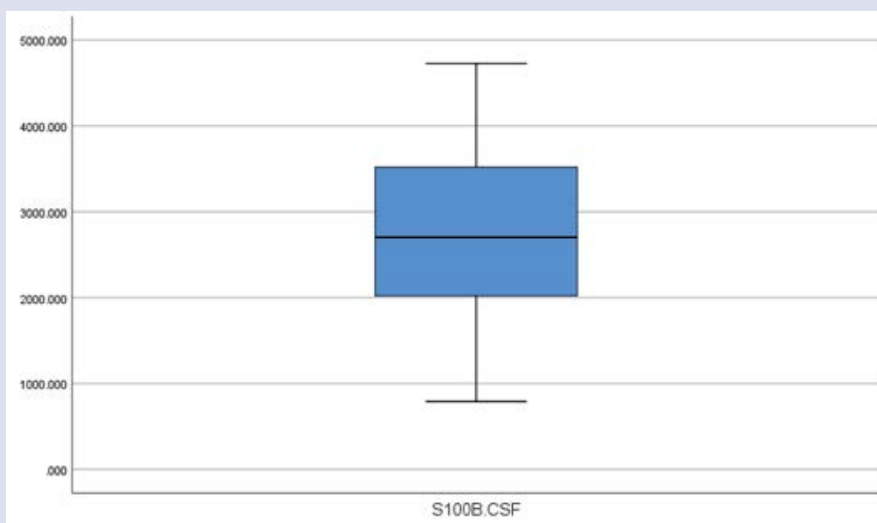


Figure 1. Overview of the distribution of S100B CSF data.

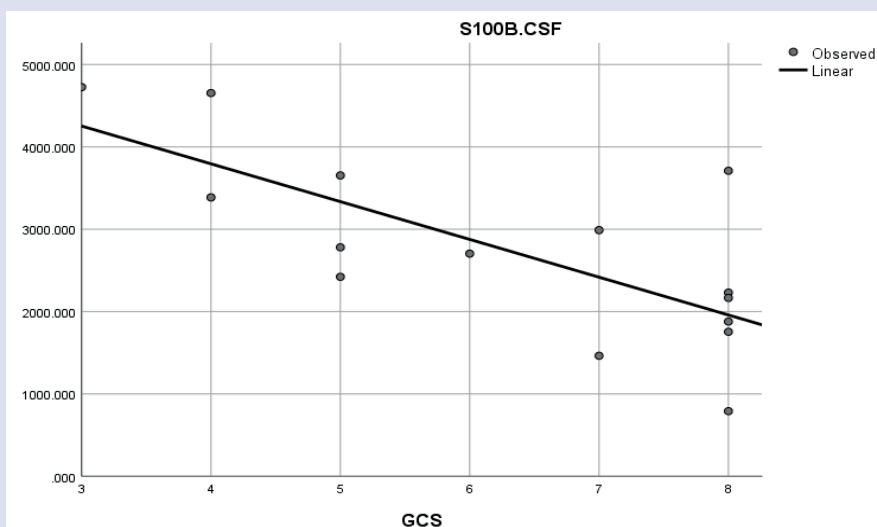


Figure 2. Scatter plot of S100B CSF with GC.

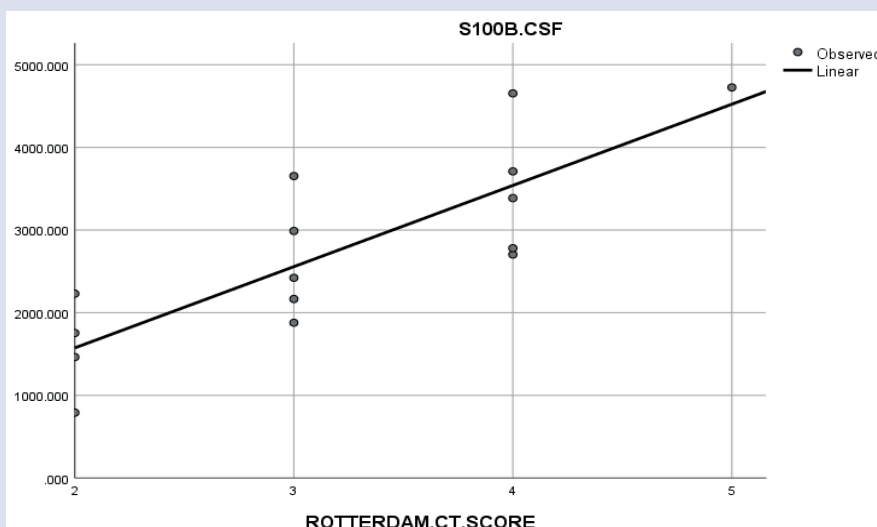


Figure 3. Scatter plot of S100B CSF with Rotterdam CT Score.

Table 3. Test the Relationship between S100B CSF and GCS.

	N	r	p-value	Information
S100B CSF with GCS value	15	-0.684	0.005*	Negatively Associated

*stated to be related if the p-value < 0.05

Table 4. Correlation Test of S100B CSF with Rotterdam CT Score.

	N	r	p-value	Information
S100B CSF with Rotterdam CT Score	15	0.827	<0.001*	Positively Associated

*stated to be associated if the p-value is < 0.05

normality test results employing the Shapiro-Wilk test indicated a p-value of 0.906, where this value > 0.05 implies that the distribution of S100B CSF values is considered normal. Consequently, for subsequent S100B CSF tests, parametric methods will be utilized.

Test Analysis of The Relationship Between S100B CSF and GCS

The Spearman correlation test was employed to assess the relationship between S100B CSF and GCS in the analysis. Table 3 displays the results of the relationship test between S100B CSF and GCS, while Figure 2 provides a graphical representation of the correlation:

The findings presented in Table 3 indicate that the Spearman correlation test conducted to assess the relationship between S100B CSF and GCS yielded a p-value of 0.005. Given that this value is less than 0.05, it signifies a statistically meaningful relationship between S100B CSF and GCS. The correlation coefficient or r value obtained from the test is -0.684, and since this value is negative, it suggests an inverse relationship between S100B CSF and GCS. This implies that when S100B CSF is high, GCS is low, and vice versa. The correlation coefficient or r value also indicates the strength of the relationship between S100B CSF and GCS. In this instance, the correlation coefficient of -0.684 denotes a strong relationship between the two variables.

Correlation Test Analysis of S100B CSF with Rotterdam CT Score GC

The analysis examined the relationship between S100B CSF and Rotterdam CT Score using the Spearman correlation test. Table 4 displays the relationship test results between S100B CSF and Rotterdam CT Score, while Figure 3 illustrates the graphical representation.

Based on the findings in Table 4, the Spearman correlation test between S100B CSF and Rotterdam CT Score resulted in a p-value of < 0.001, indicating a meaningful relationship between the two variables. The correlation coefficient (r) was 0.827, suggesting a positive correlation. This means that when S100B CSF levels are high, Rotterdam CT Scores are also high, and vice versa. The correlation strength of 0.827 denotes a very strong relationship between S100B CSF and Rotterdam CT Score.

DISCUSSION

Subject Characteristics

The study sample consisted of 73.3% males, with an average age of 34.6 years. It is noteworthy that there is a gender difference in the occurrence of TBI, with males more frequently experiencing TBI than females. According to epidemiological data, males have a 40% higher likelihood of experiencing TBI compared to females in the general adult population. According to a study, the prevalence of TBI in the general population is 16.7% among males and 8.5% among females. Additionally, research found that 67.3% of the mild TBI group consisted of males.

Based on the injury mechanisms, out of a total of 15 samples, 80% experienced traffic accidents (TA) compared to falls from a height.

TBI poses a substantial public health concern in both developed and developing countries. The primary causes of TBI vary depending on the country and region. In developing countries, TA is the leading cause of TBI, accounting for nearly 60% of all cases, with falls from a height constituting only 10%. Conversely, in developed countries, falls from a height are the most common cause of TBI, especially in older adults and children, followed by motor vehicle accidents and acts of violence. Other causes of TBI include sports injuries, gunshot wounds, and explosive blasts.

The etiology of traumatic brain injury can be attributed to any event causing impact or violence to the head. The highest causes of traumatic brain injury are traffic accidents at 45%, followed by falls from a height at 34%, firearm-related injuries at 16%, and physical violence at 5%.¹²

Analysis of the Relationship Between S100B CSF Levels and GCS

In this study, S100B CSF data was measured in pg/ml units, ranging from 790,257 pg/ml to 4,726.078 pg/ml among 15 samples, with an average and standard deviation of $2,753.689 \pm 1,124.290$ pg/ml. Among the 15 samples, the Glasgow Coma Scale (GCS) values spanned from 3 to 8, with an average of 6.27. The analysis employed the Spearman correlation test to assess the relationship between increased S100B levels in CSF and the severity of TBI, as evaluated by GCS.

The Spearman correlation test results between S100B CSF and GCS yielded a p-value of 0.005, where this value is < 0.05, indicating a meaningful and meaningful relationship between S100B CSF and GCS. The correlation coefficient (r) obtained was -0.684, suggesting a negative correlation. This implies that when S100B CSF levels are high, GCS is low, and vice versa. The study found that as the severity of traumatic brain injury increases, the S100B levels also rise.

The protein S100B is a member of the multigene family known as low molecular weight calcium-binding S100 proteins, which typically range in size from 9 to 13 kD. It is predominantly found in glial cells of the central nervous system, particularly astrocytes. The biological half-life of S100B is approximately 2 hours.¹³ Sampling S100B later (12-36 hours after trauma) has shown better prognostic value compared to earlier sampling.¹⁴ S100B, a calcium-binding protein primarily found in astroglial cells, is released into the extracellular space following brain trauma and ischemic injuries when astroglial cells are activated.

Several studies have linked increased levels of S100B protein with the severity of injuries, increased mortality, and poor clinical outcomes. Additionally, there exists a positive correlation between S100B protein levels and intracranial pressure, along with cranial CT findings subsequent to TBI.^{15,16}

S100B levels in cerebrospinal fluid (CSF) shortly following TBI are usually much higher than S100B levels in the serum. Studies suggest that S100B demonstrates adequate sensitivity in detecting and evaluating diverse traumatic intracranial lesions, such as epidural hematomas, subdural hematomas, cerebral contusions, and traumatic subarachnoid hemorrhages. Increased levels of S100B in cerebrospinal fluid (CSF) following severe brain injury could indicate ongoing structural damage and cellular demise.

Normal values of S100B in serum (50 ± 10 pg/ml) are approximately 10% of the concentration in CSF (660 ± 80 pg/ml). The normal serum S100B level is around 50 pg/ml. Previous research indicates that these concentrations may rise to nearly 5,000 pg/ml following severe Traumatic Brain Injury (TBI). The observed rise in serum S100B levels within 24 hours after severe TBI is highly correlated with mortality prognosis. Similarly, S100B is beneficial in predicting whether patients will regain consciousness within 3-6 months post-injury or remain unconscious. In patients with favorable outcomes, the average peak

serum S100B values range from 200 to 1,500 pg/ml, whereas in those with poor outcomes, they range between 1,100 and 4,900 pg/ml. The threshold for predicting unfavorable outcomes typically falls within the range of 2,000 to 2,500 pg/ml.¹⁷

Patients with positive CT findings have higher serum S100B protein levels compared to those with negative CT findings. A low positive correlation exists between serum S100B protein levels and Rotterdam CT score. To conclude, the severity of acute TBI and early patient prognosis can be evaluated using serum S100B protein levels, GCS score, and Rotterdam CT score as indicators. The combination of these three indicators is better at predicting prognosis than individual indicators. More investigation is necessary to delve into the guiding value of serum S100B protein in selecting clinical imaging examinations.¹⁸ Serum S100B protein, GCS score, and Rotterdam CT score are closely related indicators to the severity of trauma and poor early prognosis. Serum S100B protein has the best predictive effect in forecasting prognosis compared to GCS and CT scores.

Research by Böhmer et al. revealed an elevation in S100B levels in cerebrospinal fluid (CSF) in patients with severe traumatic brain injury (TBI) compared to control individuals. The increase in S100B levels in CSF is associated with primary brain injury resulting from severe TBI. Additionally, this study indicates that an early rise in CSF S100B levels can predict patients who will experience brain death more rapidly than those who survive. However, CSF NSE levels are more accurate in predicting brain death due to severe TBI compared to S100B.⁹ The results of this study demonstrate a meaningful relationship between S100B values in CSF and GCS as parameters describing the level of intracranial structural damage and the severity of brain injury. These findings support existing theories and state that CSF S100B levels and GCS can be utilized to determine the degree of severity of traumatic brain injuries.

Analysis of the Relationship between S100B Levels in CSF and the Rotterdam CT Score

The Rotterdam CT score, measured as values or ratios, ranged from 2 to 5 in the 15 samples, with a mean and standard deviation of 3.20 ± 0.941 . The Spearman correlation test revealed a p-value of < 0.001 , indicating a meaningful relationship between S100B CSF and Rotterdam CT Score. The correlation coefficient (r) was found to be 0.827, signifying a positive correlation. This implies that when S100B CSF is high, the Rotterdam CT Score is also high, and vice versa.

The Rotterdam CT score is an assessment system used to evaluate the severity of traumatic brain injury (TBI) based on CT scan results. First published in 2005, this scoring system has proven beneficial in predicting early mortality and TBI patient prognosis. The Rotterdam scoring system uses four variables to assess the degree and predict mortality within six months after trauma. The Basal Cistern variable is assessed in three categories: normal with a score of 0, compressed with a score of 1, and absent with a score of 2. The Midline Shift variable is assessed based on the presence or absence of midline shift, with a score of 0 for midline shift less than 5mm and a score of 1 for midline shift greater than 5 mm. The Epidural Mass Lesion variable is assessed for its presence, with a score of 0 for absence and 1 for the presence of an epidural mass lesion. The SAH/IVH variable is assessed based on its presence, with a score of 1 for presence and 0 for absence. Finally, the scores are summed up, resulting in a final score ranging from 1 to 6. The Rotterdam scoring system can predict the mortality of TBI patients within six months post-trauma.¹⁹⁻²¹

The findings of this study demonstrate a meaningful correlation between S100B levels in CSF and the Rotterdam CT score as parameters in depicting the extent of intracranial structural damage and the severity of traumatic brain injury (TBI).²² Moreover, the combined use

of S100B levels, GCS, and the Rotterdam CT score complements each other's deficiencies, considering their high correlation.

The assessment of S100B levels can be incorporated into routine examinations for TBI patients as a biomarker for intracranial damage, while the Rotterdam CT score serves as an additional interpretation of radiological readings. Therefore, the examination of S100B levels, GCS, and the Rotterdam CT score provides practical benefits in portraying the severity of TBI patients, enhancing the quality of patient care.

LIMITATIONS OF THE STUDY

This study has several limitations, including: 1. The study was conducted at a single healthcare facility with a small sample size, which may restrict the applicability of the findings to a broader scale of TBI occurrences. 2. The study did not involve the periodic evaluation of S100B levels and GCS values in the subsequent days, which may hinder the depiction of S100B prognosis values in TBI patients.

CONCLUSION

Based on the statistical analysis and discussion outcomes, the following conclusions can be inferred from this investigation: (1) Elevated levels of S100B in cerebrospinal fluid are associated with a decrease in the Glasgow Coma Scale (GCS) score ($r = -0.684$) in TBI patients with ICP monitoring. (2) Increased levels of S100B in cerebrospinal fluid are correlated with an elevation in the Rotterdam CT score ($r = 0.827$) in TBI patients with ICP monitoring.

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ETHICAL CLEARANCE

This study has obtained approval from the Research Ethics Committee of Dr. Soetomo Surabaya Regional General Hospital with the ethical clearance letter number: 0755/KEPK/VII/2023.

CONFLICTS OF INTEREST

There is no conflict of interest for this study.

AUTHORS CONTRIBUTION

All authors contributed to data analysis, writing, and revising the manuscript, and jointly accepted responsibility for all aspects of this study.

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