Pak. j. life soc. Sci. (2024), 22(2): 6073-6087 E-ISSN: 2221-7630;P-ISSN: 1727-4915

Pakistan Journal of Life and Social Sciences

www.pjlss.edu.pk

https://doi.org/10.57239/PJLSS-2024-22.2.00455

RESEARCH ARTICLE

Correlation between Serum S100β Protein Levels and Severity of Traumatic Brain Injury as measured by the FOUR Score and Rotterdam CT Score

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ARTICLE INFO

Received: Jun 27, 2024

Accepted: Sep 21, 2024

Keywords

Traumatic Brain Injury

S100β Protein Levels

Four Score

Rotterdam CT Score

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ABSTRACT

The severity of traumatic brain injury can be anticipated through various factors, one of which is the S100β protein biomarker known for its high sensitivity and specificity. A scoring system called the Full Outline of Unresponsiveness score (FOUR score) can also be used to evaluate impaired consciousness due to brain tissue damage, especially in intubated patients, as an alternative method to forecast outcomes and mortality in individuals with traumatic brain injury. Additionally, a CT scan is still necessary to determine the seriousness of traumatic brain injury, which can be evaluated with the Rotterdam CT score. This research aims to examine the association between S100β protein levels and the severity of traumatic brain injury as determined by the FOUR score and the Rotterdam CT score. It was a cross-sectional observational study involving 31 traumatic brain injury patients at Dr. Soetomo Hospital. The participants' S100β protein levels, FOUR score, and Rotterdam CT score were documented upon their arrival at the hospital's emergency department. Statistical analysis was carried out using SPSS version 26 software with a significance level of $p < 0.05$. Among the 31 patients with traumatic brain injury, their S100β protein levels were measured, FOUR score was determined through clinical assessment, and Rotterdam CT score was assessed through radiological imaging. The S100β protein levels in the blood serum of traumatic brain injury patients ranged from 185.84 to 2738.31 (µg/L). The average FOUR score was 7.97 ± 2.6. The average Rotterdam CT score was 3.90 ± 1.60. The correlation analysis revealed a negative association between S100β protein levels and the FOUR score among traumatic brain injury patients. There was a consistent relationship between S100β protein levels and the Rotterdam CT score in individuals with traumatic brain injury. Therefore, a connection exists between S100β protein levels and both the FOUR score and the Rotterdam CT score.

INTRODUCTION

Among young adults globally, traumatic brain injury is the primary reason for both fatalities and impairments, contributing to almost half of all trauma-related deaths (Okasha et al., 2014). At present, brain injury is typically diagnosed by evaluating the patient's neurological condition and performing imaging tests like CT or MRI, as well as assessing the Glasgow Coma Scale (Adrian et al.,

2016). Traumatic brain injury is one of the problems that often causes mortality and morbidity in productive age. CDC records from 2001 to 2010 stated that around 521 - 823/100,000 people per year were hospitalised due to traumatic brain injury with a mortality of around 17 - 18/100,000 people per year (Prevention, 2015, Han et al., 2017).

In Indonesia, traumatic brain injury ranked third (11.8%) among all injuries by limb in the 2018 Basic Health Research. This type of injury is considered a major health concern worldwide, leading to high death rates, long-lasting disability and significant economic costs. (Prevention, 2015, Han et al., 2017). From several studies, it is mentioned that the outcome of traumatic brain injury can be predicted from certain parameters, one of which is with biomarkers.

S100β protein is one of the biomarkers that can be detected in brain injury patients. After brain tissue damage, an increase in S100β concentration can be measured in peripheral blood serum. This can help evaluate patients with a high risk of secondary injury, determination of repeat radiological examinations, and close monitoring (Mercier et al., 2013; Galhom et al., 2018). Another study introduced S100β protein as a highly sensitive and specific biomarker of brain injury to assess outcomes in traumatic brain injury both in the short and long term (Stefanović et al., 2017).

Brain damage that causes a decrease in consciousness can also be assessed by a score system that has been known and has been widely used, namely GCS, but this score system has limitations, namely the verbal component of patients who are in an intubated state cannot be assessed (Almojuela et al., 2019). An alternative is required to replace GCS due to its limitations. The FOUR score, which assesses brainstem reflexes, eye movements, motor responses, and breathing patterns, may provide more comprehensive information than the GCS. Each component is rated on a scale of 0-4 (Wijdicks et al., 2005, Madjid et al., 2017).

The literature review study by Airlangga et al. (2020) at RSUD Dr Soetomo Surabaya showed that the FOUR score from various studies that have been conducted, has proven to have good validity, reliability, and suitability. The four components contained in the FOUR score provide detailed information from neurological examinations such as brainstem reflexes and eye movements. The FOUR score is simpler and provides better information, especially in intubated patients, so it is recommended to be used as an alternative in predicting patient outcomes and mortality (Airlangga, et al., 2020).

Another advantage of the FOUR score is that it can still be used in patients with acute metabolic disorders, shock, or other non-structural brain damage because it can detect changes in consciousness earlier (Wijdicks, et al., 2005, Kasprowicz et al., 2016). A study in a government hospital in Surabaya City found that FOUR score had better sensitivity and specificity (94.4% sensitivity and 96.2% specificity) than GCS (88.9% sensitivity and 91.4% specificity) to predict mortality in traumatic brain injury patients (Airlangga, et al., 2020).

The development of today's advanced medical technology makes it easier for doctors with a new scoring system, namely Rotterdam CT scoring using more examination elements and more specifically assessing the status of the basilar system and the presence or absence and degree of SAH and IVH (Maas et al., 2005). Marshall and Rotterdam scoring have been shown to be good at assessing mortality prediction after moderate and poor traumatic brain injury (Deepika et al., 2015). Rotterdam scoring system uses more variables than Marshall such as SAH which makes this scoring system better used for global traumatic brain injury (Deepika, et al., 2015). The Rotterdam scoring system uses four variables in assessing the degree and prediction of death within six months after trauma. Based on this background, the researcher aims to conduct a study on the relationship between S100β protein levels and the severity of traumatic brain injury as measured by FOUR score and Rotterdam CT Score.

The main aim of this research was to explore how S100β protein levels are linked to the severity of

traumatic brain injury, as assessed by the FOUR score and Rotterdam CT Score. Specific aims were: 1) To examine S100β protein levels in individuals with traumatic brain injury; 2) To evaluate how S100β protein levels relate to the FOUR score in traumatic brain injury patients; 3) To evaluate how S100β protein levels correlate with the Rotterdam CT score on CT scans of traumatic brain injury patients; 4) To examine the distribution of FOUR score in individuals with traumatic brain injury; and 5) To analyse the distribution of Rotterdam CT score classification on CT scans of traumatic brain injury patients.

LITERATURE REVIEW

Consciousness

Consciousness is a medical term to identify how awake and how alert a person is to their surroundings. It also describes the extent to which a person can respond to responses coming from outside. A consistent medical term describing one's level of consciousness helps in communication between healthcare providers, especially when one's level of consciousness fluctuates over time. There are various medical conditions and medications that contribute to a person's level of consciousness (Apriady et al., 2022; Mishra et al., 2022).

Traumatic Brain Injury

Traumatic brain injury (TBI) is the primary reason for fatalities and incapacity among young adults on a global scale and plays a role in around half of all trauma-related deaths. The majority of victims come from countries with lower or middle-income levels. Apart from causing death, traumatic brain injury can result in impairment, potentially ruining the prospects and lives of individuals and families, and also leading to significant expenses for hospitals and community systems in relation to the recovery and ongoing care of these people (Prevention, 2015, Airlangga, et al., 2020).

Full Outline of Unresponsiveness (FOUR) Score

A new coma assessment tool called the FOUR Score was introduced by Wijdicks and colleagues in 2005. It measures four distinct factors to gauge a patient's level of awareness, encompassing eye movement, physical reactions, brainstem reflexes, and breathing patterns. It can identify conditions like locked-in syndrome and vegetative states that may go unnoticed by the Glasgow Coma Scale. This updated assessment tool is known as the FOUR Score (Wijdicks et al., 2005).

Protein S100β

S100 is a multifunctional protein with various roles in cellular processes. S100 acts by mediating calcium binding, although Zn2+ and Cu2+ also play a role in the biological activity of these proteins. The most studied member of the S100 protein group is the S100β protein, which has neurotrophic (at physiological concentrations) or neurotoxic (at high concentrations) activities. Expression of these proteins both in serum and in immunohistochemical staining is found in various clinical disorders. The S100 protein group includes S100A1-S100A18, S100β, S100G, S100P, and S100Z (Arrais et al., 2022). S100β is abundantly found in the brain and is released by various cells like astrocytes, oligodendrocytes, and schwann cells. This protein is believed to function as a signal both inside and outside cells, potentially causing positive or negative effects on nerve cells based on its concentration. Additionally, S100 activates microglia and could be involved in the development of neurodegenerative conditions. Elevated levels of S100β are linked to conditions like astrocytoma, glioblastoma, Schwannoma, and melanoma. Apart from the brain, S100β is also produced by tissues outside the brain such as fat cells and chondrocytes, so caution is advised when using increased serum levels of S100β as an indicator of brain injury (Arrais et al., 2022).

Rotterdam CT Score

Computerised tomography scan (CT scan) is a radiological facility used in conjunction with a scoring

system that can assess severity and prognosis (Badjatia et al., 2008). Marshall scoring established in 1991 using the National Traumatic Coma Database is one example of a scoring system that is often used in TBI cases (Deepika et al., 2015). In accordance with the development of medical technology, the new scoring system, Rotterdam CT scoring, uses more examination elements and more specifically assesses the status of the basilar system and the presence or absence and degree of SAH and IVH (Maas Al, et al., 2005). The assessment of the severity of trauma and the likelihood of mortality within six months is based on four factors in the Rotterdam scoring system.

Research hypothesis

There is an association between S100β protein levels and the severity of traumatic brain injury as measured by FOUR score and Rotterdam CT Score.

RESEARCH METHOD

This research utilised an observational cohort approach with a cross-sectional analytical survey design to investigate the correlation between levels of S100β protein and the severity of traumatic brain injury assessed by FOUR score and Rotterdam CT Score. The investigation took place in the resuscitation area of the Emergency Department at RSUD Dr Soetomo. It spanned from January to June 2024. The research included all traumatic brain injury patients who visited RSUD Dr Soetomo's emergency room and were admitted to the resuscitation area. The participants were selected based on specific inclusion criteria using purposive sampling within a limited timeframe and number of samples. Based on the unpaired numerical comparative analysis test formula (Stefanović et al., 2017), the minimum sample size calculated was 25 patients, but rounded up to 30 patients.

Inclusion criteria

1. Moderate (GCS 13-9) and severe (GCS <9) TBI patients presenting in the emergency department.
2. Patients aged 18-65 years old.
3. Maxillofacial trauma patients without eyeball damage.
4. Musculoskeletal trauma patients who can still move their hands.

Exclusion criteria

1. The patient's family refused to be included in the study.
2. Patients with a history of Alzheimer's disease, diabetes mellitus, melanoma, Down syndrome, epilepsy, and brain stem death (MBO).
3. Hypoxic patients (Saturation < 96% with free air oxygen) after resuscitation.
4. Patients with MAP < 65 upon arrival in the emergency room 4.
5. Trauma patients more than 12 hours after the incident.

Research Variables

S100β Levels

FOUR Score

Rotterdam Score

The research instruments used for the study were data collection sheets and tools and reagents to measure S100β protein levels in blood serum. Data were collected through a special data collection sheet (LPD). Data and research results are presented in the form of tabulations, graphs / diagrams, text / writing that clarifies graphic diagrams. The data collected was then processed using computer

software (SPSS 22). Existing data is tested for normality using the Kolmogrov-Smirnov test. If the data is determined to follow a standard distribution, the Spearman correlation test is employed, whereas if the data does not follow a standard distribution, the Mann Whitney U Test is used.

RESULT AND DISCUSSION

Research Result

The focus of the research was to establish a connection between S100β protein levels and the severity of traumatic brain injury by using an observational approach and a cross-sectional analytical survey design. The study involved 31 traumatic brain injury patients who met specific criteria. Demographic characteristics were divided into general (gender, age, ethnicity) and clinical (comorbidities, trauma, MAP, HR, SpO2, temperature, Blood Pressure). The findings of the demographic characteristics were displayed in a table showing frequency, percentage, mean, and standard deviation.

Tabel 1. Distribution of Demographic characteristics

Characteristics	N (%)	Range	Mean±Sd	p value normality
General Characteristics				
Gender				
Male	20 (64,5%)	-	-	
Female	11 (35,5%)	-	-	-
Age	31 (100%)	18 - 63	40,68 ± 16,69	0,002
Clinical Characteristics				
Comorbid				
Not Available	19 (61,3%)	-	-	
Available	12 (38,7%)	-	-	-
HT	10 (32,3%)	-	-	-
DM	1(3,2%)	-	-	-
Obesity Gr 1	3 (9,7%)	-	-	-
Trauma				
KLL	27 (87,1%)	-	-	
Fall down	4 (12,9%)	-	-	-
MAP	31 (100%)	68 - 116	93,29 ± 12,73	0,232
HR	31 (100%)	69 - 116	94,61 ± 14,30	0,093
SpO2	31 (100%)	98 - 99	98,55 ± 0,51	0,000
Temperature	31 (100%)	36,2 - 36,9	36,67 ± 0,21	0,000
TD Sistol	31 (100%)	101 - 170	130,48 ± 16,85	0,335
TD Diastol	31 (100%)	50 - 90	76,26 ± 10,37	0,076

*declared normal if the p value of normality> 0.05

Based on the results of table 1, the distribution of general characteristics for gender characteristics of the 31 samples obtained for males as many as 20 (64.5%) while for females as many as 11 (35.5%). For age characteristics of the 31 samples, the age range was 18 to 63 years with a mean and standard deviation of 40.68 ± 16.69.

Based on the results of table 1, the distribution of clinical characteristics for comorbid characteristics of the 31 samples obtained who had comorbidities as many as 12 (38.7%) while there were no comorbidities as many as 19 (61.3%), based on the type of comorbidities obtained for HT comorbidities as many as 10 (32.3%), DM as many as 1 (3.2%) and for Obesity Gr 1 as many as 3 (9.7%) samples. For the characteristics of trauma from 31 samples, 27 (87.1%) were obtained for KLL trauma while 4 (12.9%) were obtained for fall trauma. For MAP characteristics for the range of values 68 to 116 with a mean and standard deviation of 93.29 ± 12.73. HR characteristics for the range of values from 67 to 116 with a mean and standard deviation of 94.61 ± 14.30. SpO2 characteristics for the range of values 98 to 99 with a mean and standard deviation of 98.55 ± 0.51. Temperature characteristics for the range of values 36.2 to 36.9 with a mean and standard deviation of 36.67 ± 0.21. Systolic BP characteristics for the range of values 101 to 170 with a mean and standard deviation of 130.48 ± 16.85. Diastolic BP characteristics for a range of values from 50 to 90 with a mean and standard deviation of 76.26 ± 10.37.

Overview of S100β Protein Levels

The significance of measuring S100β protein levels in blood serum using the ELISA method lies in the fact that the data obtained is in a ratio form. To assess whether the distribution of S100β protein level data is normal, a normality test such as the Shapiro Wilk test is necessary, especially with a sample size of 31 samples (less than 50 samples). This test helps in determining the type of statistical method to be employed for the next stage of analysis – parametric methods for normal data and non-parametric methods for non-normal data. Presented below is a summarised table showing the levels of S100β protein and the outcomes of the normality test:

Table 2. Results of descriptive analysis and normality test of S100β protein levels

	N	Range	Mean±Sd	p value Normality
Protein Levels S100β	31	0,1858 – 2,738	0,612 ± 0,647	0,000

*declared normal if the p value of normality> 0.05

Based on the results of table 2 for S100β protein levels from 31 samples in the range of 0.1858 to 2.738 with an average or mean value and standard deviation of 0.612 ± 0.647. Based on the results of the normality test using Shapiro Wilk, the p value is 0.000 where the value is <0.05, which means that the distribution of S100β protein levels is not normally distributed, so for the next S100β level test using non-parametric methods.

Rotterdam CT-Score Overview

Rotterdam CT-Score is a scoring system using CT-Scan to assess the degree of severity in patients with TBI within 4-24 hours based on damage to anatomical structures seen based on the morphology of the cisterna basalis, the presence of midline shift, epidural mass lesions, intraventricular hemorrhage or subarachnoid hemorrhage. The results of the examination using Rotterdam CT-Score are grouped into score 1, score 2, score 3, score 4, score 5, and score 6. Due to the Rotterdam CT-Score data in the form of values, it is necessary to do a normality test to see whether the Rotterdam CT-Score data distribution is normally distributed or not. The following is a descriptive table of

Rotterdam CT-Score and normality test results:

Table 3. Results of descriptive analysis and Normality Test Rotterdam CT-Score

	N	Min-Max	Median
Rotterdam CT-Score	31	1 – 6	4.00

Based on the results of table 3, the Rotterdam CT-Score value of 31 samples is at a minimum of 1 maximum of 6 with a median value of 4.00. Due to the Rotterdam CT-Score data in the form of an ordinal scale, the Rotterdam CT-Score test further uses non-parametric methods.

Four Score overview

Four Score is a scale of a patient's level of consciousness. This coma scale involves the assessment of the following four components, each on a scale with a maximum score of four: eye response, motor response, brainstem reflexes and breathing. In the Four Score measurement consists of scores from 0 to 16, the maximum score is 16 points and the minimum score is 0 points. Because the Four Score data is in the form of values, it is necessary to do a normality test to see whether the Four Score data distribution is normally distributed or not. The following table illustrates the Four Score.

Table 4. Descriptive analysis results and Four Score Normality Test

	N	Min-Max	Median
Four Score	31	4 – 14	7.00

Based on the results of table 4 for the Four Score value of 31 samples, the minimum is 4 maximum 14 with a median value of 7.00. Because the Four Score data is in the form of an ordinal scale, the next Four Score test uses non-parametric methods.

Characteristic Test with Rotterdam CT Score

General and clinical characteristics will be tested against the Rotterdam CT-Score to ensure that characteristics are not a confounding factor in the size of the Rotterdam CT-Score. The following table shows the descriptive results and the test of characteristics with Rotterdam CT-Score:

Table 5. Description and Test of Characteristics with Rotterdam CT-Score

Characteristics	N = 31	Rotterdam CT Score Mean±Sd	p value
General Characteristics			
Gender			
Male	20	4,15 ± 1,72	0,221[a]
Female	11	3,45 ± 1,29	
Age	31	3,90 ± 1,60	0,355[b]
Clinical Characteristics			
Comorbid			
Not Available	19	4,26 ± 1,59	0,106[a]
Available	12	3,33 ± 1,50	
Trauma			

KLL	27	4,04 ± 1,51	0,228[a]
Fall down	4	3,00 ± 2,16	

*a is using Mann Whitney test, b is using Spearman test

* declared to be confounded if the p value <0.05

Based on the results of table 5 analysis of the test of general characteristics with Rotterdam CT-Score, the p value for gender p=0.221, age p=0.355 and ethnicity p=0.395 where the value is> 0.05 which means that there is no relationship between general characteristics and Rotterdam CT-Score where it can be concluded that general characteristics are not declared as confounders in Rotterdam CT-Score which means that the general characteristics of gender, age, and ethnicity have no connection or relationship with the size of Rotterdam CT-Score.

Based on the results of table 5 analysis of clinical characteristics test with Rotterdam CT-Score, the p value for comorbid p=0.106, trauma p=0.228, MAP p=0.342, HR p=0.873, SpO2 p=0.237, Temperature p=0.596, BP systole p=0.235, BP diastole p=0.479 where the value > 0, 05 which means that there is no relationship between clinical characteristics and Rotterdam CT-Score where it can be concluded that clinical characteristics are not declared as confounders in Rotterdam CT-Score which means that comorbid clinical characteristics, trauma, MAP, HR, SpO2, Temperature and Blood pressure have no association or relationship with the size of Rotterdam CT-Score.

Characteristic Test with Four Score

General and clinical characteristics will be tested against the Four Score to ensure that the characteristics are not a confounding factor in the size of the Four Score. The following table shows the descriptive results and tests of characteristics with Four Score:

Table 6. Description and Characteristic Test with Four Score

Characteristic	N = 31	Four ScoreMean±Sd	p value
General Characteristics			
Gender			
Male	20	7,75 ± 2,65	0,558[a]
Female	11	8,36 ± 2,69	
Age	31	7,79 ± 2,64	0,543[b]
Clinical Characteristics			
Comorbid			
Not Available	19	7,74 ± 2,68	0,696[a]
Available	12	8,33 ± 2,64	
Trauma			
KLL	27	7,96 ± 2,65	0,952[a]
Fall Down	4	8,00 ± 2,94	

*a is using Mann Whitney test, b is using Spearman test

* declared to be confounded if the p value <0.05

Based on the results of table 6 analysis of the test of general characteristics with Four Score, the p

value for gender p=0.558, age p=0.543 and ethnicity p=0.121 where the value is> 0.05 which means that there is no relationship between general characteristics and Four Score where it can be concluded that general characteristics are not declared as confounders in Four Score which means that the general characteristics of gender, age, and ethnicity have no relationship or relationship with the size of Four Score.

Based on the results of table 6 analysis of clinical characteristics test with Four Score obtained p value for comorbid p=0.696, trauma p=0.952, MAP p=0.771, HR p=0.709, SpO2 p=0.479, Temperature p=0.172, BP systole p=0.693, BP diastole p=0.301 where the value > 0,05 which means that there is no relationship between clinical characteristics and Four Score where it can be concluded that clinical characteristics are not declared as confounders in Four Score which means comorbid clinical characteristics, trauma, MAP, HR, SpO2, Temperature and Blood pressure have no relationship or relationship with the size of Four Score.

Analysis of the Relationship Test of S100β Protein Level with Four Score

The Spearman examination was utilised to analyse the connection between S100β protein levels and Four Score as both datasets were deemed deviant in the normality assessment. Here is a chart illustrating the results of this evaluation on the relationship.

Table 7. Test of relationship between S100β protein levels and Four Score

	N	r	p value	Description
S100β Protein Level with Four Score	31	-0,663	0,000	Strong positive association

*stated to be associated if the p value <0.05

Table 7 displays the test results of the correlation between S100β protein levels and Four Score using the Spearman test. The p value obtained is 0.000, indicating a significant relationship between the two variables. The correlation coefficient is -0.663, suggesting an inverse relationship - as S100β protein levels increase, Four Score decreases, and vice versa. The strength of this relationship is determined to be 66.3%, categorising it as a strong connection.

Analysis of the Relationship Test of S100β Protein Level with Rotterdam CT Score

Test the relationship between S100ß protein levels and Rotterdam CT-Score using the Spearman test because both S100ß protein levels and Rotterdam CT-Score data were declared abnormal during the data normality test. The following table shows the results of the relationship test between S100ß protein levels and Rotterdam CT-Score:

Table 8. Test of association of S100β protein levels with Rotterdam CT-Score

	N	r	p value	Description
S100β Protein Level with Rotterdam CT Score	31	0,418	0,019	Moderate positive association

*stated to be associated if the p value <0.05

According to the findings presented in table 8 regarding the correlation between S100β protein levels and Rotterdam CT-Score tested using the Spearman test, the p value is 0.019, indicating a statistically significant association. The positive correlation coefficient of 0.418 suggests that there is a direct relationship between S100β protein levels and Rotterdam CT-Score, with higher levels of S100β corresponding to higher Rotterdam CT-Scores and vice versa. This correlation coefficient also indicates that the strength of the relationship between the two variables is moderate, at 41.8%.

DISCUSSION

Characteristics of Research Subjects

This study involved 31 patients with TBI who came to the emergency room and entered the resuscitation room at RSUD Dr Soetomo. The proportion of subjects with male gender was more dominant than female with a mean age of 40.68 ± 16.69 years. In all TBI accidents reported by the CDC, males represented 78.8% and females represented 21.2% and with a higher TBI rate in males (959 per 100,000) compared to females (811 per 100,000) (Prevention, 2015).

Systematic review and meta-analysis studies on the epidemiology of TBI suggest that the incidence of TBI is twice as high in men as in women (Dewan et al., 2018). The reported prevalence of TBI in the general population is 16.7% in men and 8.5% in women (Biegon, 2021). The high incidence in men may be due to men being more dominant in carrying out high-risk activities, occupational risks, and violence-related injuries when compared to women (Coronado et al., 2011). Indirectly, the data on the general characteristics of the subjects of this study, which include the proportion of gender and type of trauma, are in line with the epidemiological data of TBI in Indonesia. Traffic accidents (KLL) were the most common cause in this study, accounting for 87.1% of TBI cases.

S100β Protein Level, FOUR Score, and Rotterdam CT Score values

S100β protein levels (μg/L)), Rotterdam CT Score, and Four Score were sampled and analysed because they were the variables observed in this study. The value of S100β protein levels in blood serum increased in TBI patients was 0.1858 - 2.738 (μg/L) in this study. This is in accordance with research by Stefanovic et al., (2017) which states that there are variations in S100β protein levels in TBI patients with positive and negative outcomes. The study revealed that a rise in S100β levels greater than 0.695 μg/L within the initial 6 hours indicated a bleak prognosis. Different thresholds are determined based on when the blood sample is taken, with the most accurate delineation achieved through an examination of S100β protein levels 24 hours after the injury, yielding an AUC of 0.788 (95%CI 0.704-0.873) with a threshold of 0.258 μg/L (Stefanovic et al., 2017). A meta-analysis concluded that there is a contrast in S100β protein levels among TBI patients who survive and those who do not. The average S100β protein level predicting short-term mortality in the initial 24 hours was 0.328 ± 0.198 μg/L, while it was 0.399 ± 0.19 μg/L beyond one month (Golden et al., 2018).

Another study showed a decrease in S100β levels to less than 2 μg/L after 120 hours post-trauma showed a good outcome (assessed by GOS) but a decrease in S100β protein levels at 4-6 hours post TBI had a better prognosis (Dharmajaya et al., 2017). An in vitro study showed that astrocytes during trauma or metabolic stress will release S100β protein rapidly into the extravascular 15 seconds after the lesion is formed. High levels of S100β protein in serum in TBI patients are suspected due to a disrupted BBB that causes protein leakage. The Four Score value of TBI patients in this study was in the range of 4 to 14 with a mean value of 7.97 ± 2.64, and a p value of 0.021. This is in accordance with the theory that higher FOUR score values result in better outcomes. High mortality risk (71%) in total FOUR score 0-7, moderate risk (20%) in total score 8-14 and low risk (0.8%) in total score 15-16. A study in a government hospital in Surabaya city found that FOUR score had better sensitivity and specificity (94.4% sensitivity and 96.2% specificity) than GCS (88.9% sensitivity and 91.4% specificity) to predict mortality in traumatic brain injury patients.

The Rotterdam CT-Score value of TBI patients in this study was in the range of 1 to 6 with a mean or mean value and standard deviation of 3.90 ± 1.60, and a p value of 0.009. This is in accordance with the study The final score is 1 to 6. with the Rotterdam scoring system can assess the prediction of mortality of TBI patients within six months post-trauma (Mishra et al., 2022). In accordance with the development of medical technology, the new scoring system, namely Rotterdam CT scoring, uses more examination elements and more specifically assesses the status of the basilar system and the

presence or absence and degree of SAH and IVH (Maas Al, et al., 2005). The Rotterdam scoring system uses four variables to assess the degree and predicted mortality within six months of trauma. The Rotterdam CT Score was found to be good in assessing predicted mortality after moderate and severe TBI as it uses more variables making it a better scoring system to use.

Relationship between S100β Protein Level and FOUR Score

In TBI patients, there is a negative relationship between S100β protein levels and Four Score values, with a strength of -0.663. The test results show a correlation coefficient of -0.663, indicating a negative relationship between S100β protein levels and Four Score. These findings suggest that higher levels of S100β protein are associated with lower Four Score and a strong relationship between the two variables. This aligns with previous studies suggesting that a low total FOUR score is linked to mortality and disability. The likelihood of death is higher with the lowest total FOUR score compared to the lowest total GCS score (Hamzah et al., 2020; Nair et al., 2017). Research conducted in Canada has found that the FOUR score and GCS can predict outcomes and mortality in patients with traumatic brain injury and critical illness. The FOUR score is particularly useful in predicting outcomes in patients with reduced consciousness levels and has good reliability when used by both doctors and nurses (Almojuela et al., 2019).

The literature review study by Airlangga, et al. (2020) concluded that the FOUR score from various studies that have been conducted, has proven to have good validity, reliability, and suitability. The four components contained in the FOUR score provide detailed information from neurological examinations such as brainstem reflexes and eye movements. The FOUR score is simpler and provides better information, especially in intubated patients, so it is recommended to be used as an alternative in predicting outcomes and mortality in patients with traumatic brain injury (Airlangga, et al., 2020). Other researchers from Indonesia also concluded that prognostic prediction in patients admitted to paediatric intensive care units using FOUR score is better than using. The sensitivity, specificity, positive and negative predictive values were 93%, 86%, 88%, and 92%, and the positive likelihood ratio was 6.6 (Dewi et al., 2016). Several other researchers have demonstrated that the FOUR score has an equal or even greater predictive value for mortality compared to the Glasgow Coma Scale (GCS). The area under the receiver operating characteristic curve (AUC ROC) was found to be 0.788 for the FOUR score (with a 95% confidence interval of 0.722-0.844) and 0.735 for GCS (with a 95% confidence interval of 0.655-0.797) in predicting in-hospital mortality, with a statistically significant p-value of 0.0001. Additionally, a different study revealed an odds ratio of 0.67 for the FOUR score (with a 95% confidence interval of 0.53-0.84) compared to an odds ratio of 0.68 for GCS (with a 95% confidence interval of 0.56-0.83) in predicting in-hospital mortality, with a p-value less than 0.001 (Stead et al., 2009).

The increase in S100β levels in TBI patients in this study is also in accordance with the research of Stefanovic et al, (2017) which found that an increase in S100β levels > 0.695 μg / L in the first 6 hours has a poor prognosis. There is evidence that S100β protein can be used as a biochemical marker of brain cell damage, as measured by a simple blood test. Elevated serum levels of the protein are thought to predict intracranial pathology. S100β concentration correlates well with the extent of brain damage such as in cerebral haemorrhage, capitis trauma, vascular damage, and stroke after cardiac surgery. Recent studies have also shown that elevated S100β in the blood may correlate with the extent of brain damage after cerebral haemorrhage and severe brain injury (Dharmajaya et al., 2017).

This shows that S100β protein levels can be used as a predictor of mortality equivalent to the results of the Four score. Of the 31 subjects in this study obtained varied results for the Four score. ranging from a range of 4-14 with a mean of 7.97 ± 2.64 SD. This is in accordance with previous research that obtained the sensitivity and specificity values of the FOUR score at the cut-off point of value 9 were 93% and 86%. This result is in accordance with previous research which determines the cut-off point

of the FOUR score in determining the prognosis of death in the hospital is 9 (Hamzah et al., 2020). The results of the general and clinical characteristics test in this study were also declared not as confounders in the Four Score, which means that there is no association or relationship with the size of the Four Score with a p value> 0.05.

Relationship between S100β Protein Level and Rotterdam CT Score

There is a unidirectional relationship between S100β protein levels and Rotterdam CT-Score in TBI patients with a relationship strength of 0.418. The results of the relationship test between S100β protein levels and Rotterdam CT-Score obtained a p value of 0.019 where the value is <0.05 which means that there is a significant or meaningful relationship between S100β protein levels and Rotterdam CT-Score. These results indicate that higher levels of S100β protein correlate with higher Rotterdam CT-Score and have an r value that shows the relationship between the two variables in the moderate relationship category. This is in accordance with previous research conducted by Mata-Mbemba et al. (2014) on 245 adult patients with mild to severe TBI, stating that the Rotterdam CT-Score score is positively associated with statistically significant mortality. Death from TBI occurred in patients with higher Rotterdam CT Score (Deepika et al. (2015) Mata-Mbemba et al., 2014). This suggests that S100β protein levels can be used as a predictor of mortality equivalent to the Rotterdam CT-Score results. The 31 subjects in this study obtained varied results for Rotterdam CT-Score ranging from 1-6 with a mean of 3.90 ± 1.60 SD.

From the test of clinical characteristics of patients with RCS, it was found that the distribution of p value >0.05 showed a statistically insignificant relationship so that it could be said that clinical characteristics were not a confounder of Rotterdam CT-Score results. Radiographic evaluation is important in the initial stratification of injury severity and to monitor acute changes. Rotterdam CT-Score has been widely used in research as a patient with TBI or as an independent predictor of patient outcome (Huang et al., 2012). The Rotterdam CT Score was found to be good in assessing mortality prediction after moderate and severe TBI as it uses more variables making it a better score system to use.

CONCLUSION

This research highlights several limitations, including the need for studies with a larger sample size to improve accuracy. Additionally, the age and presence of undiagnosed or known central nervous system degenerative diseases in patients may influence S100β protein levels. Another limitation is the lack of serial examinations of S100β protein levels and evaluations during clinical improvements or worsening, which could provide more comprehensive insights into patient outcomes. Despite these limitations, the study found that S100β protein levels in blood serum ranged from 0.1858 to 2.738 µg/L in patients with traumatic brain injury (TBI). The research also identified an inverse relationship between S100β protein levels and Four Score values, and a positive correlation between S100β protein levels and Rotterdam CT-Score in TBI patients.

Based on these findings, it is recommended that S100β protein levels be used as a prognostic tool to identify at-risk patients, allowing for timely and appropriate therapy. Future research should involve larger sample sizes from multiple healthcare centers to confirm these results. Additionally, serial evaluations of S100β protein levels before and after interventions, as well as periodic assessments of Four Score values, are necessary to track patient progress. Including data on comorbidities, trauma history, and the specifics of head trauma will further enhance the accuracy of the findings by addressing potential confounding factors affecting S100β protein levels.

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