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Relationship of Serum S-100B Protein and Prognosis of Traumatic Brain Injury Patients: A cross-sectional study

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ABSTRACT

Introduction: Serum S100 protein is one of the biomarkers used for predicting (prognosis) the outcome of patients with traumatic brain injuries. S-100B protein helps predict moderate to severe traumatic brain injuries and evaluates patients at high risk for secondary brain injury, radiological reassessment, and strict monitoring. This study aimed to investigate the relationship between serum S100 protein and the prognosis of traumatic brain injury patients.

Methods: The present study was cross-sectional in traumatic brain injury patients. 32 patients with traumatic brain injury were included. Blood samples were drawn within 1 to 24 hours of injury.

Results: S-100B concentration for moderate brain injury (mean 0.132 ± 0.08) is higher with worse outcomes than mild brain injury (mean 0.024 ± 0.009). A significant correlation exists between S-100B concentrations and mild brain injury (-0.554; P=0.003) and moderate brain injury (-0.926; P=0.008) from GOS values.

Conclusion: The overall mean of serum S-100B concentration for patients in the moderate brain injury (MBI) category is significantly higher than those in the mild brain injury category. Lower serum S-100B concentration has a higher correlation with mild brain injury from the Glasgow Outcome Scale (GOS). Therefore, serum S-100B concentration is a reliable predictor when used for the prognosis of patients with traumatic brain injury.

Keywords: Traumatic Brain Injury; S-100B; Glasgow coma scale; Glasgow Outcome Scale.
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INTRODUCTION

Globally, brain injury is the leading cause of mortality in all countries, mainly in individuals under 40 years old.[1] In terms of a national level, the overall prevalence rate of traumatic brain injury (TBI) in Indonesia is 8.2%, with the highest and lowest prevalence rates in the South Sulawesi province (12.8%) and the Jambi province (4.5%), respectively.[2] When comparing the National Basic Health Research 2007 and the National Basic Health Research 2013, the overall prevalence rate of head injury in Indonesia shows an ascending trend from 7.5% to 8.2%.[3,4]

Signs and symptoms of traumatic brain injury vary depending upon the location of the trauma, type of trauma, and trauma severity level. Traumatic brain injury is determined from radiological examination via brain scanning using computed tomography (CT) and magnetic resonance imaging (MRI). The Glasgow Coma Scale (GCS) is the most common scale used to grade the severity level of traumatic brain injury according to cognitive behavioral outcomes.[5,6]

A brain injury can be detected by measuring biomolecular markers in the cerebrospinal fluid (CSF) and the blood directly after traumatic brain injury (TBI). These biomarkers are valuable for confirming a brain injury shortly after it takes place, and persistent biomarker levels can reveal a past TBI event. This information can help a person avoid risky behaviors that may result in a secondary head injury. Serum S-100 protein is one of the biomarkers used for predicting (prognosis) the outcome of patients with traumatic brain injuries.[5] Serum S100 protein is a calcium-binding protein in the form of S-100B with two β subunits (95%) and S100A protein with two α subunits (5%). After brain tissue impairment, an increase of S-100B concentration can be measured in peripheral blood serum.[7] S-100B protein helps predict moderate to severe traumatic brain injury and evaluates patients at high risk for secondary brain injury, radiological reassessment, and strict monitoring.[8] A low concentration of S-100B stimulates the growth of neurons and raises their survival during injury and development. In contrast, a higher concentration of S-100B tends to be toxic and evokes cell death.[9]

Regarding high morbidity and mortality rates due to traumatic brain injury cases and the significant function of S-100B protein as a biomolecular marker that relates to mortality and worse outcomes in brain injury cases, the authors of the present study intend to investigate the relationship between serum S-100B protein and the prognosis of traumatic brain injury patients.

METHODS

The present study was cross-sectional in traumatic brain injury patients at the Clinical Pathology and Medical Laboratory of Dr. Wahidin Sudirohusodo General Hospital in Makassar, Indonesia, from April to October 2020. This study was approved by the Health Research Ethics Committee of Hasanuddin University, Makassar, Indonesia, issued under registration number 431/UN4.6.4.5.31/PP36/2019. Determination of S-100B concentration was carried out at the Clinical Pathology and Medical Laboratory of Dr. Wahidin Sudirohusodo General Hospital in Makassar, Indonesia.

Population and Samples

The correct number of samples was determined using the Cochran formula, coming to 32 patients. Outcomes of patients after traumatic brain injury (TBI) were conducted from the results of anamnestic reactions and physical checks of intracranial lesions by CT scan examinations. The inclusion criteria of the samples were patients who were 18-65 years old and had intracerebral hemorrhage with edema cerebri. The exclusion criteria were patients with multiple traumas, GCS<3, subdural hematomas and subarachnoid hematomas, a history of hypotension, trauma of more than 24 hours, undergoing mannitol/diuretic therapy, diffuse axonal injury, or were pregnant or breastfeeding.

Glasgow Outcome Scale (GOS)

The Glasgow Outcome Scale (GOS) was used for the prognosis of traumatic brain injury outcomes put into 5 categories: good recovery (score 5), moderate disability (score 4), severe disability (score 3), persistent vegetative state (score 2), and death (score 1).

Criteria of Traumatic Brain Injury (TBI)

Criteria of traumatic brain injury (TBI) were classified into 3 categories based on the scoring system of the Glasgow Coma Scale (GCS): mild brain injury (GCS of score > 12), moderate brain injury (GCS of score 9-12), and severe brain injury (GCS of score < 9).

S-100B measurements

Patients with traumatic brain injury were identified with head CT scans using computed tomography SOMATOM scope (Siemens Healthineers AG, Erlangen, Germany). Sampling of serum S-100B was carried out by taking patients' blood from the vena mediana cubiti using a 5 ml suction syringe after making the area aseptic or sterile with 70% alcohol. Blood samples were then put into calibrated tubes (vacutainer), kept at room temperature, and centrifuged. Serum proteins were kept under -20°C until all samples were ready for analysis. Concentrations of serum S-100B were measured using the ELISA Human S-100B (BioVendor-Laboratorní Medicína a.s. Brno, Czech Republic) with no. Catalog RD19209100R (10). Absorbance readings were obtained using a microplate reader, model 680 (Bio-Rad Laboratories Inc., Ca, USA) at a wavelength of 450 nm with microplate manager software version 5.2.1 (Bio-Rad Laboratories Inc, Ca, USA). Serum S-100B concentrations were measured in ng/L.

Analysis of the Data

Serum S-100B concentrations were expressed as mean±standard deviation. The Kolmogorov-Smirnov statistical test determined whether the observed variables were normally or nonnormally distributed from the sampled data. Correlations between S-100B concentration and the prognosis of the traumatic brain injury patients were analyzed using Spearman's correlation test and the chi-square test, in which a p-value of less than 0.05 was considered significant. Figures were presented using a Box plot. All data were processed using the SPSS™, version 17.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

The study included 32 patients suffering from traumatic brain injuries: 25 males (78.1%) and 7 females (21.9%). The mean value of patients was 30.6 ± 8.9 years (Table 1).

Table 2 indicates the minimum and maximum values of GOS and serum S-100B, with the minimum and maximum values of GOS at 2 and 5, respectively. A higher value GOS leads to better outcomes, whereas a lower value GOS results in a worse outcome. Serum S-100B concentrations with the minimum value (0.0126) and the maximum value (0.283) indicate an increasing level of S-100B concentration.

As shown in Table 3, stratification of GOS for the study subjects (n = 32) appears to negatively correlate with the level of serum S-100B concentration, in which a higher level of serum S-100B results in lower patient outcome (lower

Table 1. Description of baseline data of the study cohort

Variable	Mean Value ± SD
Age (mean ± SD) in years	30.6 ± 8.9
Gender n(%)	
Male	25 (78.1)
Female	7 (21.9)
S-100B (mean ± SD) µg/L	0.044 ± 0.05
GOS	4.5 ± 0.8

SD, standard deviation

Table 2. Variations of serum S-100B concentrations in patients suffering from traumatic brain injuries within the mild and moderate categories (n = 24)

Variable	Measured Values		
	Minimum	Maximum	Mean ± SD
Glasgow Outcome Scale (GOS)	2	5	4.5 ± 0.8
S-100B serum (µg/L)	0.0126	0.283	0.044 ± 0.05
Mild brain injury	0.01	0.05	0.024 ± 0.009
Moderate brain injury	0.06	0.28	0.132 ± 0.08

SD, standard deviation

Table 3. Stratification of the study subjects according to serum S-100B concentrations

Variable	S-100B Concentration		P*
	N	Spearman's Correlation	
Glasgow Outcome Scale (GOS)	32	-0.790	0.000

*Mann-Whitney; SD, standard deviation

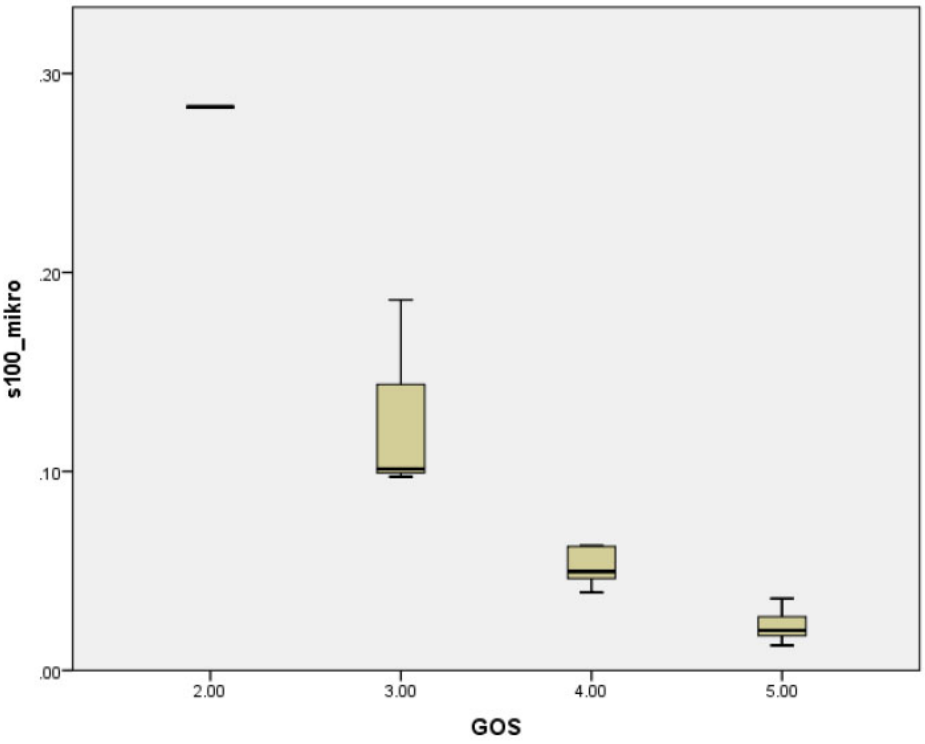

Figure 1. Boxplot of S110 values for each category of GOS.

Table 4. Correlations between serum S-100B concentration and Glasgow Outcome Scale (GOS) value

Variable	S-100B Concentration		P*
	N	Spearman's Correlation	
Mild brain injury	6	-0.554	0.003
Moderate brain injury	26	-0.926	0.008

value of GOS), with strong correlation of the study variable (Figure 1).

Table 4 shows a significant correlation of S-100B concentrations and mild brain injury and moderate brain injury from GOS values. Samples (n = 6) of moderate brain injury indicate negative and high-level correlations, as do those of mild brain injury (n = 26). The two tables show that the overall S-100B concentration for moderate brain injury is higher with worse outcome compared to that of mild brain injury (Figure 2).

DISCUSSION

The Scandinavian consensus published in 2013 in treating traumatic brain injury recommended S-100B protein for diagnostic assessments using CT scans. A cranial CT scan is only used for patients suffering from brain injury with serum S-100B concentrations of > 0.1 µg/L.[11] There is a significant correlation between S-100B and worse outcomes in patients with severe brain injury. However, the data of various studies about the association between S-100B and cases of traumatic brain injury (TBI) are inconsistent.[11,12]

The blood-brain barrier integrity in patients with traumatic brain injury is disrupted due to the production of reactive oxygen species (ROS) and its derivatives after traumatic brain injury. Production of ROS in traumatic brain injury may lead to ischemic injury in the endothelial cells of the blood-brain barrier.[8] In addition, the blood-brain barrier worsens due to the conjugation of superoxide and nitric oxide to form peroxynitrite, a cytotoxic and proinflammatory molecule. Stimulation of inflammation is also a mediator of blood-brain barrier dysfunction in intracranial lesions. In addition, astrocytes produce inflammatory signals that exacerbate oxidative stress in the central nervous system during traumatic brain injury.[8,9]

Table 4 shows that S-100B protein has a valuable prognostic role after traumatic brain injury and the findings in our study are similar to other similar studies. Another study found that S-100B is a potential biomolecular marker used to predict outcomes after traumatic brain injury (TBI) in adult subjects with severe TBI from multivariate logistic regression, as confirmed CSF S-100B profiles in predicting Glasgow Outcome Scale (GOS), as Disability Rating Scale (DRS) scores, and mean and peak serum S-100B as acute mortality predictors after severe TBI.[13] This is also attested by a previous study showing that S100 protein and NSE levels are valuable diagnostic and prognostic tools after severe TBI, to be used as potential therapy with the main outcome of GOS.[14]

In our present study there are significantly different values of GOS in patients with higher serum S-100B concentrations [P = 0.00]. Higher serum S-100B leads to worse outcomes in brain injury patients. The mean value of serum S-100B was 0.044 ± 0.05 µg/L. The overall mean value of mild brain injury (0.024 ± 0.09 µg/L) was lower compared to the overall mean value of moderate brain injury (0.132 ± 0.08 µg/L). Therefore, patients in the category of mild brain injury reach a more favorable outcome (better prognosis) compared to those in the category of moderate brain injury. Our finding is consistent with another study that serum S-100B concentrations of patients in the moderate brain injury

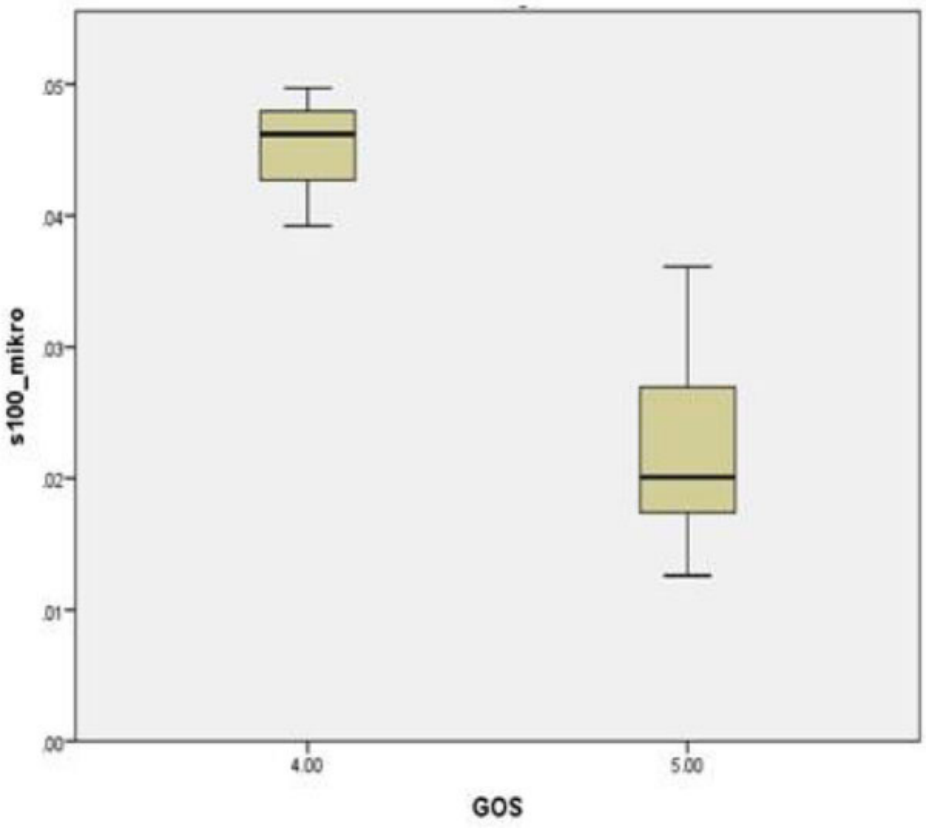

Figure 2. Boxplot of S110 values for each category of GOS in traumatic brain injury.

category on admission were significantly higher than those of the lower category.[15]

S-100B protein is a useful screening tool for the treatment of head injury, as indicated by 6 patients with moderate brain injury and 44 patients with low/mild brain injury (0.75 µg/L interval: 0.66 – 6.5 µg/L vs. 0.29 µg/L interval: 0.14 – 0.76 µg/L).[16] Their study is consistent with our findings that S-100B protein on admission is a valuable tool for distinguishing patients with moderate or mild brain injury. Serum S-100B for patients in the category of moderate brain injury is higher compared to those of low brain injury due to the damage of glial cells and astrocytes. In addition, impairments of the blood-brain barrier of patients with moderate brain injury are higher compared to those with low brain injury. This was proven by the CT scan examinations that showed most patients in the category of moderate brain injury had an intracranial hemorrhage and skull fracture, compared to those with low to mild brain injury.

Age is an indicator that affects a lower concentration of S-100B, which is associated with patients who have an increased S-100B level and a good prognosis (outcome) and have significantly lower serum S-100B concentration on admission (0.96 ± 5.5 µg/L).[11] This finding is consistent with our present study, although with a lower mean value of S-100B. In addition, lower serum S-100B concentration (below 2 µg/L) results in significantly better GOS during follow-up (4 ± 1.8) within a limited range of prediction (outcome) in the long-term with a 75% sensitivity and an 82% specificity within 6 hours from the onset of severe head injury.[17] This is in line with our study that low serum S-100B concentration (below 2 µg/L) with a mean value of GOS (4.5 ± 0.8) resulted in a better prognosis (outcome) of the traumatic brain injury cases.

As shown in our present study, there was a significant correlation between serum S-100B concentration and the Glasgow Outcome Scale (GOS) for each patient in the categories of mild and moderate brain injury, in which patients with mild brain injury had a higher correlation with serum S-100B concentration (P = 0.008) compared to those with moderate brain injury (P = 0.003). Our study is compatible with the study of Galhom et al. (2013) that serum S-100B protein was a significant predictor for long-term outcomes in patients with mild to moderate traumatic brain injuries, and half of all 15 investigated patients in the category of moderate head injury had higher initial mean serum S-100B (2.43 µg/L) compared to those in the category mild head injury (0.95 µg/L), indicating a significant difference ($p<0.01$) between the two groups.[12]

A previous study compared S-100B values for patients with minor and major head injuries and proved that all patients with a minor head injury had nonpathological values (although its mean value was 0.35 µg/L) and were discharged from the hospital with better outcomes.[18] This is also in line with a study by Galhom et al., in which they serially studied 104 head injury patients on admission at emergency installation units, excluding multiple traumas and suspected alcohol intoxication. In the study, 78% of the patients with no initial symptoms completely recovered within 6 months. All patients with no initial symptoms and an S-100B concentration (<0.3 µg/L) recovered from their head injury. They concluded that the increase of serum S-100B concentration was significantly correlated with the outcome of patients with a mild head injury.[12]

There are several limitations associated with our present study. First, the study samples may not be representative, resulting in over-prediction. Second, the time interval between measurements of serum S-100B concentrations and determination of GOS from the onset of post-traumatic brain injury was not observed, which might indicate variations in S-100B concentrations. Finally, the study design did not proportionally involve male and female patients, which might result in bias for drawing a robust generalization.

Concerning its strong predictive value for TBI patients' outcome (prognosis), conducting advanced studies to determine serum S-100B concentration is suggested. These studies should consider representative populations with suitable population numbers in the control group

to achieve a more reliable level of specificity value from data analysis. Moreover, classifying patient populations into specific age groups needs to be considered to reduce study bias appropriately.

CONCLUSIONS

The overall mean of serum S-100B concentration for patients in moderate brain injury (MBI) category is significantly higher than those of mild brain injury. Lower serum S-100B concentration has a higher correlation with mild brain injury from the Glasgow Outcome Scale (GOS). Therefore, serum S-100B concentration is a reliable predictor to be used for the prognosis of patients with traumatic brain injury.

CONFLICT OF INTEREST

All authors declared that there is no conflict of interest regarding this article.

ETHICS APPROVAL

This study had been ethically approved by Health Research Ethics Committee of Hasanuddin University, Makassar, Indonesia, issued under registration number 431/UN4.6.4.5.31/PP36/2019.

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AUTHOR CONTRIBUTION

All authors contributed equally.

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