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High Serum S100B Protein Levels As A Predictor Of Cognitive Function Disorders In Moderate Traumatic Brain Injury Patients

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ABSTRACT

Objective: To prove high serum S100B protein levels as a predictor of impaired cognitive function in patients with moderate traumatic brain injury. ***Method:*** A prospective cohort analytic observational study. The subjects are patients with a moderate degree of TBI with inclusion criteria: onset of TBI 24 hours, age 17-40 years old, and the exclusion criteria were the presence of impaired cognitive function pre-traumatic brain injury (Short IQCODE) 3), depression and multiple trauma. Patients/families/guardians who agreed to the informed consent were checked for S100B levels at <24 hours, then matched with the Montreal Cognitive Assessment version Indonesia (MoCA-INA) questionnaire on day 14 after TBI. This study's data analysis consisted of univariate and bivariate analysis using Chi-Square. The significance level is stated with p <0.05, 95% confidence interval (CI) assisted by the IBM SPSS version 23. ***Results:*** There were 43 research subjects; 23 in the high S100B group and 20 in the S100B group were not high. The mean age is 28 years, with a ratio of 4:1 for men and females. Most of the years, education ≥12 years. The incidence of cognitive dysfunction in patients with moderate traumatic brain injury in the high serum S100B group was 76.19%, while in the non-high serum S100B group was 23.80%, with RR = 6.85, with 95% CI between 1.78-26 .36, and p-value = 0.005. ***Conclusion:*** High serum S100B protein levels as a predictor of cognitive function disorders were statistically significant in moderate traumatic brain injury patients with a risk of 6.85 times.

Keywords: traumatic brain injury; S100 B protein levels; impaired cognitive function

INTRODUCTION

Traumatic Brain Injury (TBI) is a complex injury that can cause brain damage, impaired brain function, and even cause death as a result of a blow or jolt to the head. This condition can cause a very important public health problem. Traumatic brain injury not only causes high mortality but can also cause complications after injury, such as infection, injury-related dementia, hemiplegia, and depression. These complications can have an impact on the economic burden of society as well as the quality of life of individuals and families[1,2]

Traumatic brain injury is known as a "silent epidemic" condition based on congressional reports on TBI in the United States. This congress estimates that approximately two million people with TBI in the United States visit emergency departments yearly. About 40% of TBI cases result in acute injury deaths in the United States[3].

Traumatic brain injury is estimated to be around 200,000 victims requiring inpatient treatment, and approximately 1.74 million people who experience moderate TBI cannot carry out daily activities.[4]. The risk of TBI in the United States is more experienced at the age of 15 - 30 years. Studies in other countries, such as Korea, based on the "2009 Trauma Statistics Centers for Disease Control and Prevention (CDC) found that around 160,000 people experience TBI in South Korea annually.[5]. Data in Indonesia shows that the percentage of head injury cases is 11.9%, with the highest rate occurring in the Gorontalo area, which is 17.9%. While cases in other areas, such as Maluku, are above 10%.[6]

Traumatic brain injury is a heterogeneous condition and can occur in various ways, leading to complex pathogenesis pathways (i.e., cerebral hemorrhage, edema, and ischemia).

Traumatic brain injuries can be classified according to the mechanism of injury (e.g., motor vehicle accidents, falls, and assaults). Meanwhile, based on the clinical severity, it can be assessed using the Glasgow Coma Scale (GCS) instrument or by the characteristics of structural damage.[2,7,8]. Several risk factors are associated with the development and recovery of TBI, such as age, race, and gender, and the above conditions are factors that cannot be modified.

Research conducted by Slavoca et al. in 2020 examined the S100B protein biomarker and Neuron-specific Enolase at four hours and seventy-two hours post-traumatic. This study found no correlation between S100B protein and neurocognitive outcome, suggesting that this biomarker may have a better predictive value between 12 and 24 hours.[9]. Several studies have been conducted to find the relationship between S100B protein biomarkers and TBI outcomes, including cognitive function and depression. The results of previous studies showed that the time for taking S100B protein levels was four hours and seventy-two hours post-traumatic[7,10,11]. Some studies have not found a relationship between S100B protein levels and cognitive function. This is presumably due to the sampling time; besides that, most of the previous studies took special populations with mild brain injury. Therefore, researchers would like to propose a study of high serum S100B protein levels to predict decreased cognitive function in moderate-grade traumatic brain injury patients with an onset of fewer than 24 hours at Prof. Dr. IGNG Ngoerah Hospital.

METHOD

This study used a prospective cohort analytic observational study design to determine high serum S100B protein levels as a predictor of impaired cognitive function in patients with moderate degrees of traumatic brain injury.

The research will be conducted in the emergency department, treatment room, and outpatient room for SMF Neurosurgery and SMF Neurology at Prof. Dr. IGNG Ngoerah Hospital from March 2022 to June 2022. Inclusion criteria included the following: 1) Moderate traumatic brain injury; 2) Brain injury onset ≤ 24 hours; 3) Age 17 - 40 years; 4) Patients can use spoken and written Indonesian well; 5) Patients who come in a conscious condition are willing to participate in the study after receiving an explanation of the aims and objectives and completing research procedures by signing an informed consent; 6) For patients who come unconscious, the guardian/witness of the patient, after receiving an explanation of the full intent, purpose, and procedure of the study, can sign an informed consent; 7) Has high and not high S100B protein levels The exclusion criteria are as follows: 1). There is a pre-traumatic brain injury cognitive function disorder, namely if the value of the Short Form of the Informant Questionnaire on Cognitive Decline in 41 the Elderly; 2) There is depression; 3) Presence of multiple trauma (kidney and liver); 4) Patient confirmed COVID-19; 5) Loss of consciousness on the day.

The research data will be analyzed statistically with the help of Windows SPSS version 20. Data analysis was carried out in two stages: descriptive and analytic statistics. The descriptive statistics stage describes the basic characteristics of the research subjects. The statistical analytic stage was carried out by comparing the incidence of cognitive impairment after moderate TBI between two groups, called the risk or relative risk (RR). The difference in proportions between the two groups was assessed by testing the hypothesis of comparing two unpaired groups, namely bivariate analysis using the Chi-Square. This is done because it uses independent variables and dependent variables on a nominal scale. So the level of significance is expressed by $p < 0.05$ with a 95% confidence interval.

RESULTS

The study involved 52 moderate TBI subjects who met the inclusion criteria; as many as 9 people (17.30%) of the 52 subjects were declared dropouts because it coincided with the Idul Fitri holiday so there were subjects who left the Bali area, lived far outside the city. There were patients on On the 14th day, there was a decreased consciousness. The basic characteristics of the research subjects are listed in Table 1.

TABLE 1: Basic Characteristics of Research Subjects.

Demographic Profile	S100B High 23 Subjects; n(%)		S100B is not tall 20 Subjects); n(%)		p-value*
Gender					
Man	19	(82,42)	17	(85,76)	0.764
Woman	4	(20.00)	3	(15.00)	
Age (years)					
Early adulthood (18-34)	13	(56,52)	14	(70.00)	0.780
Late Adults (35-45)	10	(43,47)	6	(30.00)	
Average age ± SD	29.78±8.63		28.05±8.08		
Education					
< 12 years	8	(34,78)	7	(35.00)	0.377
≥ 12 years	15	(65,21)	13	(65.00)	
Causes of TBI					
Traffic accident	18	(78.2)	17	(85.00)	
Fall	3	(13.04)	2	(10.00)	0.439
Violence	2	(8,69)	1	(5.00)	
NPRS headaches					
No Pain (0)	10	(43,47)	9	(45.00)	0.778
Light (1-3)	13	(56,52)	11	(55.00)	
MoCA-Ina					
Cognitive impairment	7	(30,43)	15	(75.00)	0.007
No Cognitive Impairment	16	(69,56)	5	(25.00)	
Mean MoCA-INA ± SD	23.91±2.52		26.55±2.04		
Mean S100B ± SD (ng/L)	**162.49±149.85**		**33.02±7.75**		

TBI: traumatic brain injury; NRS: numeric rating scale; MoCA-Ina: Montreal cognitive assessment- Indonesian version; SKG: Glasgow coma scale, ICH: Intracerebral hemorrhagic; SAH: subarachnoid hemorrhage; EDH: epidural hemorrhage; SDH: subdural hemorrhage.

In Table 2, the cognitive domain of the MoCA-Ina instrument was described for the high S100B and low S100B groups.

TABLE 2: Characteristics of the MoCA-Ina Instrument Domain against S100B.

Variable	S100B High		S100B is not tall	
	23 Subjects n(%)		20 Subjects n(%)	
Visuospatial/executive				
Disturbed	13	(56,52)	7	(35.00)
Not disturbed	10	(43,47)	13	(65.00)
Naming				
Disturbed	3	(13.04)	1	(5.00)
Not disturbed	20	(86.95)	19	(95.00)
Attention				
Disturbed	14	(60,86)	7	(35.00)
Not disturbed	9	(39,14)	13	(65.00)
Language				
Disturbed	14	(60,86)	4	(20.00)
Not disturbed	9	(39,14)	16	(80.00)
Abstraction				
Disturbed	12	(52,17)	7	(30.00)
Not disturbed	11	(47,83)	13	(70.00)
Delay Memory				
Disturbed	23	(100)	20	(100)
Not disturbed		-		-
Orientation				
Disturbed	10	(43,47)	6	(30.00)
Not disturbed	13	(56,52)	14	(70.00)

MoCA-Ina: Indonesian version of Montreal cognitive assessment.

Data on serum S100B values were obtained with a range of 18.67 to 601.60 ng/L, with a median of 51.11. Furthermore, the statistical method of the Receiver Operating Characteristic (ROC) procedure was carried out and assessed the Area Under the Curve (AUC) to determine S100B as a predictor of impaired cognitive function. The ROC curve (Figure 1) shows that the S100B has a fairly good diagnostic as the curve is above the 50% line.

The AUC value obtained from the ROC method was 71.8% (95% CI 0.559–0.877, p= 0.015). Statistically, the AUC value shows sufficient diagnostic power. The results of the ROC coordinates showed that the cut-off value of S100B 50 ng/L used in this study had a sensitivity of 81.0% and a specificity of 86.4%.

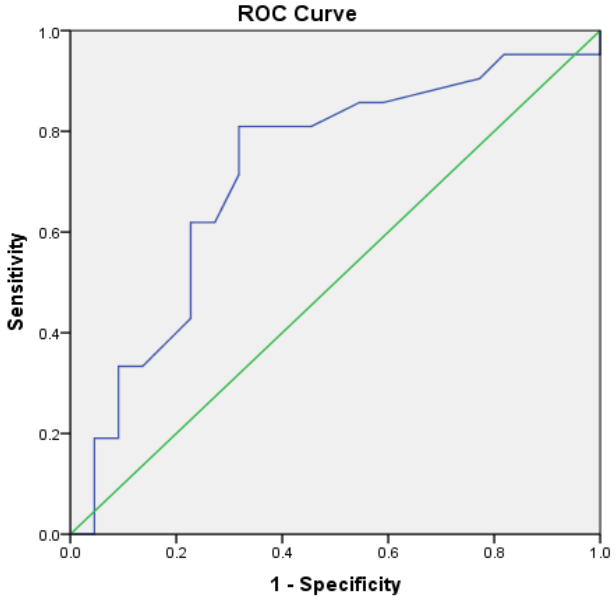

FIGURE 1: The results of the S100B ROC procedure on cognitive function with an AUC value of 71.8%.

Protein content high serum S100B as a predictor of impaired cognitive function in patients with moderate-grade traumatic brain injury was assessed using bivariate analysis. The hypothesis test used is Chi-square.

The relative risk (RR) value is obtained with a 95% confidence interval (CI). The significance of this study was determined at the probability value of p <0.05. The results of the analysis are presented in Table 3.

TABLE 3: S100B Bivariate Analysis with Impaired Cognitive Function.

Variable		Cognitive Function		RR	CI 95%	p-value
		Disturbed	Not disturbed			
S100B rate	Tall	16 (76,19)	7 (31,81)	6.85	1.78-26.36	0.005
	Not high	5 (23.80)	15 (68,18)			

The incidence of cognitive dysfunction in patients with moderate traumatic brain injury in the high serum S100B group was 76.19%, while in the low serum S100B group, it was 23.80%. This shows that there is a difference in the incidence of cognitive dysfunction in patients with moderate degrees of traumatic brain injury between the high and low serum S100B groups with RR = 6.85, 95% CI between 1.56-16.76, and p = 0.005, which means the risk of experiencing cognitive dysfunction in patients with a moderate degree of traumatic brain injury in subjects with high serum S100B was 6.85 times compared to subjects with low serum S100B, this result was statistically significant.

Other factors such as gender, age, and level of education also play a role in causing impaired cognitive function. The relationship of other factors as a cause of cognitive dysfunction was analyzed using the Chi-square test. The results of the analysis are presented in Table 4.

TABLE 4: Bivariate Analysis of Other Variables with Impaired Cognitive Function.

Variable	Cognitive Function		RR	CI 95%	p-value
	Disturbed n=22	Not disturbed n=21			
Gender					
Man	20 (90,91)	16 (76,19)	3,12	0.53-18.28	0.406
Woman	2 (9.09)	5 (23.80)			
Age (years)					
Early adulthood (18-34)	14 (63,63)	13 (61.90)	1.07	0.31-3.71	0.907
Late Adults (35-45)	8 (36,36)	8 (38.09)			
Education					
< 12 years	7 (31,81)	8 (38.09)	0.75	0.21-2.66	0.666
≥ 12 years	15 (68,18)	13 (61.90)			

DISCUSSION

In the study results, the majority of subjects were male82,42%, with the ratio of men: to women being 4:1; this is to the incidence of TBI in Indonesia and abroad. There are more men than women, with an incidence of up to 2 times the percentage difference than women[12]. This incident proves that the large number of activities that cause TBI in men is due to high mobility in men as a result of work demands, social life, which requires most men to do activities outside the home by using vehicles, and low awareness when driving to maintain road safety[13].

The early adult age group in this study was more than the late adult age group, with a ratio of 1.3. This is by research conducted by Kusuma et al. with the age group 18-29 years as the largest group at 38.8%, followed by the age group ≥50 years as much as 32.9%, and finally, the age group 30-49 years as much as 28.2%[14]This study groups the ages into 2, namely early adulthood (age 18-35 years) and late maturity (age 36-45 years) which refers to the age distribution according to the 2013 Riskesdas.[15] The results of this study are also consistent with the proportion of traumatic brain injuries based on the 2013 Basic Health Research, which showed head injuries mainly occurred in the productive age group (ages 15-44 years). The risk of TBI in the United States is also greater at the age of 15-30 years[16]. The results of research from Corrigan et al., in line with this study, which evaluated the prevalence of traumatic brain injury throughout life, showed that the percentage of events was almost similar in the two age groups above.[17]

In this study, more education levels were obtained at the age of ≥12 years compared to <12 years with a ratio of 1.8: 1; this is due to regulations from the region in Bali which require a minimum education of up to high school/equivalent by local rules in the Area of the provincial government of Bali Which regulated in Law Number 23 of 2014 concerning education in the Bali region. In this study, subjects with education <12 years will get additional data points by conducting the MoCA-Ina examination. This aims to increase the sensitivity and specificity of the MoCA-Ina examination[18]. Rambe et al., through their research, show the value of MoCAIna is highly dependent on the number of years of education[19]

The results in research on the causes of TBI are traffic accidents; this is by previous research and data in the world that the most common causes of head trauma injuries are traffic accidents compared to falls or violence and have become the first-order reasons in the last 4 decades both in developing and developed countries[13]

In this study, the highest light pain intensity was 55.81% different from the research from Rapport et al., who got a moderate degree of headache more than a mild degree. This could be due to the research by Rapport et al. evaluating pain intensity across all degrees of TBI, including mild, moderate, and severe TBI. In this study, patients also endeavored to experience mild pain because it would affect the examination of the questionnaire, which was carried out if the pain intensity increased and made the patient uncomfortable.[20]

This study showed that the incidence of cognitive dysfunction in patients with moderate degrees of traumatic brain injury in the high S100B group was higher than in the low S100B group. This shows a difference in the incidence of impaired cognitive function in patients with moderate degrees of traumatic brain injury between the

S100B group is not high. The S100B group is high, with the risk of experiencing cognitive function disorders in patients with moderate degrees of traumatic brain injury in subjects with high S100B 6.85 times compared to subjects with S100B not high (RR=6.85).

In the case of TBI, the S100B protein can be secreted into the systemic circulation along with the blood-brain barrier. In the early phase of TBI, the S100B protein is secreted as a TBI compensator with the effect of a neurotropic agent that has a neuromodulating action and supports memory and thought processes. In the final phase, marked by a very high inflammatory process and disrupted blood-brain barrier, the S100B protein acts as a neuron destroyer. This results from the stimulation of proinflammatory cytokines and free radical activity, often found in neurodegenerative disorders' pathophysiology.[21]

A moderate degree of traumatic brain injury characterized by impaired short-term memory and attention occurs in approximately 75 - 85% of TBI sufferers in the general or military population. The consequences of TBI can be short-term and long-term cognitive deficits. Deficits usually occur in attention, learning, memory, and higher executive functions[22,23]

Damage to the blood-brain barrier will have an impact, namely a decrease in cognitive function. Previous studies have also shown that the hippocampus is an important cognitive area of the brain. At micromolar concentrations of S100B protein, it can cause an increase in extracellular glutamate, which binds to NMDA receptors so that calcium enters the intracellular, causing mitochondrial dysfunction and causing apoptosis in hippocampal astrocytes. Changes in synaptic plasticity can lead to a decrease in LTP and an increase in long-term depression (LTD), the two main mechanisms underlying learning and memory processes.[24].

Research Linking Moderate Brain Injury to Cognitive Impairment Using S100B Research conducted by Boussard et al. 2005 conducted a study on S100B protein and cognitive impairment after moderate traumatic brain injury. This study found that S100B protein and S100A1B protein concentrations were above the limit of 31% and 48%, respectively.[25]. Research conducted by Slavoaca et al. in 2020 which examined the S100B protein biomarker and Neuron-specific Enolase at four hours and seventy-two hours post-traumatic did not find S100B protein levels as a predictor of cognitive dysfunction, presumably due to insufficient time to take it. S100B upgrade[26].

S100B in patients with type 2 DM showed that the results of S100B increased cognitive impairment in type 2 DM patients, namely 7.5 times with p = 0.000 with results in mild cognitive impairment with an average of 52 ± 2.7 and patients Moderate-severe cognitive 87±15 ng/L with the most significant results experiencing attentional disorders with p 0.000, delayed memory p 0.061, and visuospatial disorders with p 0.039[24]. The S100B study on cognitive impairment in patients with impaired kidney function was also found to be significant, with results increasing by 40%. In 13 subjects with cognitive impairment, it was found with an average43.0 ± 17.2 ng/L.

Other factors that play a role in cognitive dysfunction include gender, age, and level of education. Regarding gender, the highest number of cases of TBI was found in males. The results of the statistical analysis showed that there was no significant relationship between gender and cognitive dysfunction. Similar results were obtained in research conducted by[27]that there was no difference in cognitive impairment in women and men. The same is true of a study conducted by[28]In moderate TBI with 207 male and 27 female subjects aged 19-60 years; it was found that there was no difference in cognitive impairment in the two groups, the most important role being part of the brain structure that was injured.

The age variable found that the incidence of cognitive dysfunction in early adulthood was higher than in late adulthood. Statistical tests did not show a significant relationship between age and cognitive dysfunction. In research conducted by Miotto et al., (2010)using a comprehensive protocol (PN01) neuropsychological test found 12 patients with moderate TBI with a mean age of 39.75 ± 2.56 years in all patients found significant episodic memory disturbances, including immediate and delayed verbal memory, verbal recognition, immediate and delayed visual memory, naming, verbal fluency, and information processing speed.

Gauthier's study showed a statistical difference between age and impaired cognitive function obtained from the Boston Naming Test, Chapman-Cook-Speed of Reading test, and the letter-category verbal fluency test. Still, there was no significant difference in the Boston Diagnostic Aphasia examination. This may be due to the cognitive function tests performed by Gauthier et al. using a cognitive function examination tool that assesses certain domains. In contrast, this study uses MoCA-Ina, which evaluates the domain as a whole.[30]

This research has several strengths. This prospective cohort study can assess the temporal relationship between risk factors and effects well. This study used strict inclusion criteria, including the absence of cognitive impairment before the onset of traumatic brain injury. This study used the MoCA-Ina instrument to assess overall cognitive function with high specificity and sensitivity values. The weakness of this study is that the follow-up time was only carried out once, so it was not possible to see trends in cognitive function disorders and when cognitive function improvements began to occur after the onset of traumatic brain injury.

CONCLUSION

Based on the results of this study, it was concluded that high serum S100B levels were a predictor of impaired cognitive function in patients with moderate degrees of traumatic brain injury. High serum S100B levels increase the incidence of cognitive dysfunction by six-point eighty-five times.

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