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# Correlation between serum S100 $\beta$ protein level with neurological deficit in patients with acute intracerebral hemorrhage



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Poppy Kristina Sasmita,<sup>1,2\*</sup> Ismail Setyopranoto,<sup>3</sup> Samekto Wibowo,<sup>3</sup>  
Ahmad Hamim Sadewa<sup>4</sup>

## ABSTRACT

**Introduction:** S100 $\beta$  protein has shown its potential as biomarker of brain injury. However its efficacy is less known in intracerebral hemorrhage (ICH) cases. This study aimed to assess the relationship between S100 $\beta$  protein with neurological deficit, hematoma volume and mortality within 1 week among patients with acute ICH stroke.

**Methods:** A prospective cohort study was conducted to evaluate newly admitted ICH patients from August 2016 to December 2017. Data regarding vital sign, CT Scan, Glasgow coma scale (GCS), and Neurological deficits as ascertained with National Institute of Health Stroke Scale (NIHSS) were obtained. S100 $\beta$  protein measurement was performed from blood samples taken at the admission, 7<sup>th</sup> day of onset, and from 42 healthy controls. Spearman Rank was performed to assess correlation and ROC curve for diagnostic efficacy.

**Results:** There were 46 ICH patients with 25 men (54.3%) and 42 controls with a median age of 56 (31-76) and 34.5 (21-67) years, respectively. The most common risk factor was hypertension (78,3%). Median onset of acute ICH was 8.5 (0.5-48) hours. Median level of GCS at the admission was 14 (3-15), and the NIHSS was 11.50 (0-37). Serum S100 $\beta$  protein correlated significantly with NIHSS ( $r=0.418$ ;  $p=0.004$ ). *Area Under Curve* (AUC) of S100 $\beta$  to distinguish degree of neurological deficit was  $0.839\pm 0.103$  (95% CI, 0.638-1.000), cutoff level was 28,505 pg/mL with 80% sensitivity and 87.8% specificity ( $p=0.014$ ). Serum S100 $\beta$  protein was also significantly associated with mortality within 1 week ( $p=0.032$ ) and the hematoma volume ( $r=0.678$ ;  $p<0.001$ ).

**Conclusion:** S100 $\beta$  protein was significantly correlated with neurological deficits, hematoma volume and mortality within 1 week.

**Keywords:** S100 $\beta$  protein, stroke, intracerebral hemorrhage, NIHSS

**Cite this Article:** Sasmita, P.K., Setyopranoto, I., Wibowo, S., Sadewa, A.H. 2019. Correlation between serum S100 $\beta$  protein level with neurological deficit in patients with acute intracerebral hemorrhage. *Bali Medical Journal* 8(1): 63-68. DOI:10.15562/bmj.v8i1.1249

<sup>1</sup>Doctorate Program of Medical and Health Science, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia.

<sup>2</sup>Department of Anatomy, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Jakarta, Indonesia

<sup>3</sup>Department of Neurology, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada - Dr. Sardjito General Hospital, Yogyakarta, Indonesia

<sup>4</sup>Department of Biochemistry, Faculty of Medicine, Public Health, and Nursing Universitas Gadjah Mada, Yogyakarta, Indonesia

\*Corresponding to:

Poppy Kristina Sasmita. Department of Anatomy, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Jakarta, Indonesia. Jl. Pluit Raya no. 2, Jakarta Utara 14440  
poppyksasmita@yahoo.com

## INTRODUCTION

Stroke is a disease caused by the disruption of cerebral blood flow. Currently, stroke has been one of the major causes of mortality and disability throughout the world. In the United States, overall total stroke incidence was 3.73 per 1,000 persons per year. Incidence of ischemic stroke was 3.29 per 1,000 persons per year, whereas for hemorrhagic stroke was 0.49 per 1,000 persons per year.<sup>1</sup> In Indonesia National Health Survey (RISKESDAS) conducted by Ministry of Health in 2007, the prevalence of stroke is 8.3 per 1000 persons; it increases to 12.1 per 1000 persons in RISKESDAS 2013.<sup>2</sup> Intracerebral hemorrhage (ICH) is the second most common type of stroke.<sup>3</sup> According to the American Heart Association (AHA), the most common type of stroke is an ischemic stroke of 87%, followed by intracerebral hemorrhage by 10-15% and subarachnoid hemorrhage by 3%.<sup>4</sup> However, the mortality rate in ICH (68%) was higher compared with ischemic stroke (57%).<sup>1</sup>

Patients with ICH, who have same hematoma volume at the same location and received similar appropriate treatments, could have different

neurological deficits and different prognoses. Brain hematoma can damage cellular structure due to laceration, compression, and distortion.<sup>5</sup> Nowadays, it is believed that many damages occurred in the subacute period were due to a complex pathophysiology pathway that still needs to be proven. In recent years, several studies had been conducted on biomarkers potential to help assess patient prognosis. The levels of some biomarkers may involve in the process of inflammation, the blood-brain barrier impairment, endothelial dysfunction, and neuron toxicity that cause secondary brain injury. Although some plasma biomarkers have been found to rise in response to acute ICH, but no blood biomarkers been routinely used, up until this day for clinical prognostication.

The S100 $\beta$  protein is a member of S100 protein, an acidic protein with a molecular weight of 21 kilodaltons and consist of two subunits  $\alpha$  and  $\beta$  chain. The combination of these subunits was varied and differed among locations within the human body. The location of S100 $\beta$  protein is in the glial cell and Schwann cell.<sup>6</sup> S100 $\beta$  is primarily

Received: 2018-07-23

Accepted: 2018-09-25

Published: 2019-4-1

expressed in astrocytes and has been implicated in the regulation of cell cycle progression and differentiation.<sup>7</sup> In adults, S100 $\beta$  protein level was found to be elevated in the presence of nervous system damages. In the presence of metabolic changes such as lack of oxygen and glucose in the brain, the initial response occurring in glia is the removal of the S100 $\beta$  protein.<sup>8,9</sup> In head injury, cerebral hemorrhage, and other conditions that affecting the central nervous system that results in damage to the astroglial cellular structure can cause leakage of S100 $\beta$  protein into the extracellular matrix, cerebrospinal fluid and finally enter the bloodstream. According to Lai et al. study, S100 $\beta$  was a potential prognostic marker for the outcome of subarachnoid hemorrhage.<sup>7</sup> The S100 $\beta$  protein may be used as a prognostic biomarker as well as a target of pharmacological therapy.<sup>10</sup> S100 $\beta$  protein has been used as a marker of cell damage and severity of brain injury, but the studies mostly focused on ischemic stroke, head injury, and subarachnoid hemorrhage. Although the S100 $\beta$  protein has been shown to predict prognosis after those conditions, it is still unusual for S100 $\beta$  protein or other biomarker proteins to be used in daily practice and has not been incorporated in standard prognostication.

## MATERIAL AND METHODS

### Study subjects

A prospective study was performed in 46 consecutive patients who were hospitalized at Dr. Sardjito General Hospital, Yogyakarta, Atma Jaya Hospital, Jakarta and Mitra Keluarga Kelapa Gading Hospital, Jakarta within 48 hours after onset of ICH between August 2016 and December 2017. The patients met the following inclusion criteria: (1) ICH noted on brain computed tomography (CT) scan; (2) age  $\geq$  30 years old; (3) admission time  $\leq$  48 hours; (4) no other previous systemic diseases including malignancy, chronic heart or lung disease, liver cirrhosis; (5) give a consent to join this study. Informed consent was obtained from study participants or their families. The exclusion criteria include (1) history of head trauma; (2) history of previous stroke or TIA or subarachnoid hemorrhage. Histories of the illness, vital signs, level of consciousness assessed by *Glasgow Coma Scale* (GCS) and neurological deficits assessed by the National Institute of Health Stroke Scale (NIHSS) were obtained from all patients. To determine the reference value for S100 $\beta$  protein, measurement of S100 $\beta$  protein level in 42 healthy individuals were also performed. This study was approved by the Medical and Health Research Ethics Committee

(MHREC) Faculty of Medicine Universitas Gadjah Mada – Dr. Sardjito General Hospital.

### Laboratory evaluations

Blood samples (10 cc) were drawn from all ICH patients via antecubital vein into heparin tubes on the day of admission and on the 7<sup>th</sup> day of onset. One-time blood samples were also drawn from 42 healthy individual controls. Samples were centrifuged (1000 rpm) for 10 minutes to obtain serum and stored at  $-20^{\circ}\text{C}$  until analyzed. Serum S100 $\beta$  protein levels were determined using a Human S100 $\beta$  ELISA kit (BioVendor, *Cat.no* RD192090100R, *Lot.no* E17-092) according to the manufacturer's protocol.

### Statistical Analysis

Statistical analysis was conducted using SPSS version 21. Continuous data were presented as mean  $\pm$  standard deviations or medians (minimum-maximum), as appropriate. A parametric test was used on data with a normal distribution, and the nonparametric Mann-Whitney *U* test was used for non-normally distributed data. Correlation between two variables was tested by Spearman's rank-order correlation coefficient analysis. A Receiver Operating Characteristics (ROC) curve was generated to identify serum S100 $\beta$  protein cutoff levels that predict a neurological deficit. A *p*-value of less than 0.05 was considered statistically significant.

## RESULTS

In this study, a total of 82 subjects which consist of 46 patients diagnosed with ICH in the patient's group and 42 healthy individuals in the control group. Among patients with ICH, there were 25 (54.3%) men and 21 (45.7%) women with median age of 56 (31-76) years. The median age in healthy individuals was 34.5 (21-67) years. From all patients with ICH, 36 patients had prior hypertension history, 6 with diabetes, 7 with hyperlipidemia while in the control group, 3 individuals had prior hypertension history, no diabetes and 7 with hyperlipidemia (Table 1). There were significant differences between the two groups in the presence of hypertension and diabetes histories. The ICH patients compared to control group showed higher systolic blood pressure 180 (110-260) versus 110 (90-140) mmHg ( $p < 0.001$ ), diastolic blood pressure 100 (90-140) mmHg versus 80 (60-100) mmHg ( $p < 0.001$ ), heart rate 86 (52-139) versus 80 (68-100) beats/minutes ( $p = 0.042$ ) and respiratory rate 20 (16-44) versus 18 (16-24) respirations/minute ( $p < 0.001$ ) (Table 2). The Mann-Whitney *U* test showed that median serum

**Table 1** Characteristic data of patients and control

	Patients n= 46 (%)	Control n= 42 (%)	P-value*
Demographics			
Age (years)	56 (31-76)	34.5 (21-67)	<0.001
Sex (M)	25(54.3)	20 (47.6)	0.531
History of risk factors			
Hypertension	36 (78.3)	3 (7.1)	<0.001
Diabetes	6 (13.0)	0 (0.0)	0.016
Hyperlipidemia	7 (15.2)	7 (16.7)	0.854

\*The Mann-Whitney U test

numerical variables were presented as median (minimum-maximum)  
categorical variables were presented as counts (percentage)

**Table 2** Vital signs on admission between patients and control

	Patients n= 46 (%)	Control n= 42 (%)	P-value*
Blood pressure			
Systolic (mmHg)	180 (110-260)	110 (90-140)	<0.001
Diastolic (mmHg)	100 (65-180)	80 (60-100)	<0.001
Heart Rate (x/minute)	86 (52-139)	80 (68-100)	0.042
Respiratory rate (x/minute)	20 (16-44)	18 (16-24)	<0.001
Temperature (°C)	36.6 (36.0-39.6)	36.5 (35.7-37.0)	0.129

\*The Mann-Whitney U test

variables were presented as median (minimum-maximum)

**Table 3** Comparison of vital signs and laboratory of the survival and non-survival groups on admission

	Survival n=37	Non-survival n=9	P-value*
Blood pressure			
systolic, mmHg	180 (110-260)	180 (142-255)	0.967
diastolic, mmHg	100 (65-180)	100 (70-113)	0.163
Heart rate (beats/minute)	84 (52-108)	88 (70-139)	0.437
Respiratory rate (respirations/minute)	20 (16-28)	20 (17-44)	0.808
Body temperature (°C)	36.5 (36-37)	36.7 (36.3-39.6)	0.159
Blood hemoglobin level (g/L)	14.10 (9.50-17.2)	14.5 (7.3-15.9)	0.956
Blood white blood cell count (μ/L)	9710 (5400-18230)	9700 (4400-23500)	0.846
Blood glucose level (mg/dL)	124 (90-247)	154 (121-188)	0.027
Protein S100β (pg/mL)	21.325 (19.06-63.28)	25.86 (19.78-445.99)	0.032

\*The Mann-Whitney U test

Values were presented as median (minimum-maximum)

S100β protein levels were significantly higher in the patient group compared to the control group ((22.70 (19.06-445.99) versus 16.3 (15.58-23.79) pg/mL,  $p < 0.001$ )).

The median onset of stroke was 8.5 (0.5-48) hours. The median GCS was 14 (3-15), and NIHSS score was 11.50 (0-37) in the ICH patient. On head CT Scan, the median hematoma volume was estimated 11.21 (0.3-95.0) ml. There were 33 (84.6%) patients with edema, 13 (33%) with intraventricular hemorrhage and 7 (17.9%) with midline shift.

Blood glucose level was significantly lower in the survival group than in the non-survival group ( $p = 0.027$ ). The Mann-Whitney U test revealed that serum S100β protein level was significantly higher in the non-survival group than in the survival group, 25.86 (19.78-445.99) versus 21.325 (19.06-63.28) pg/mL,  $p = 0.032$  (Table 3). Based on the results of the CT scans between survival and non-survival groups, there were statistically significant differences in the hematoma volume ( $p = 0.006$ ), the presence of edema ( $p < 0.001$ ) and presence of intraventricular hemorrhage ( $p < 0.001$ ) (Table 4).

### The relationship between serum S100β protein levels and neurological deficit (NIHSS score)

Spearman's rank-order correlation coefficient analysis revealed that there was a significant positive correlation between serum S100β protein levels and NIHSS ( $r = 0.418$ ;  $p = 0.004$ ). The area under the curve (AUC) of serum protein S100β was  $0.839 \pm 0.103$  (95% CI 0.638-1.000), with cut off level was 28.505 pg/mL to distinguish the degree of stroke severity with 80% sensitivity and specificity of 87.8% ( $p = 0.014$ ). When the relationship between serum S100β protein levels and mortality was evaluated, it was shown that serum S100β protein levels were significantly associated with mortality within 1 week after the onset ( $p = 0.032$ ).

### The relationship between GCS score, hematoma volume, and serum S100β protein levels

Spearman's rank-order correlation coefficient analysis revealed that there was a significant negative correlation between serum S100β protein levels and GCS on admission ( $r = -0.376$ ;  $p = 0.010$ ) and a significant positive correlation between serum S100β protein levels with hematoma volume ( $r = 0.678$ ;  $p = 0.000$ ).

### Changes in serum S100β protein levels

In this study, there were 28 patients with ICH whose blood samples were taken twice. The median level of S100β protein on admission to hospital was 22.70 (19.31-96.74) pg/mL and on day 7 of onset was 21.24 (19.27-141.83) pg/mL. Serial median protein S100β serum changes in 28 patients were

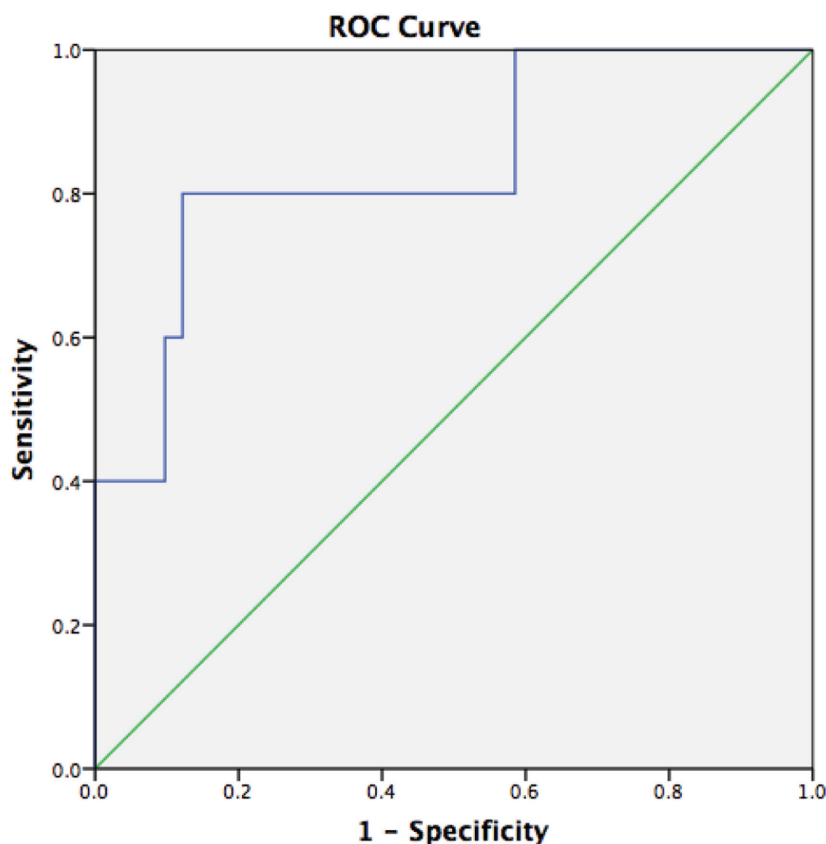
**Table 4 Radiological findings of the survival and non-survival groups on admission**

	Survival n=37(%)	Non-survival n=9(%)	P-value*
Hematoma volume (ml)	9.75 (0.3-70.0)	61.43 (9.0-95.0)	0.006*
Presence of			
Edema	29(78.4)	9 (100)	< 0.001**
Intraventricular hemorrhage	6 (16.2)	3 (33.3)	< 0.001**
Midline shift	10 (27.0)	6 (66.7)	0.039**

\* Mann-Whitney test, \*\* Chi-Square test  
numerical variables were presented as median (minimum-maximum)  
categorical variables were presented as counts (percentage)

**Table 5 Changes in serum S100 $\beta$  protein levels**

	Protein S100 $\beta$ (pg/mL)
Control (n=42)	16.3 (15.58-23.79)
ICH Patients (n=28)	
<48 Hours	22.70 (19.31-96.74)
7 <sup>th</sup> day of onset	21.24 (19.27-141.83)



**Figure 1** Receiver operating characteristics curve of the serum S100 protein measurement on admission for the neurological deficit. A cut off level of admission S100 protein of 28.505 pg/mL predicts neurological deficits (NIHSS) with 80% sensitivity and 87.8% specificity. AUC=0.839 (95% CI, 0.638-1.000; p=0.014)

taken at <48 hours and at the 7th day of onset was as shown in Table 5. Based on the Mann-Whitney *U* test, the median level of S100 $\beta$  protein on day 7 of onset was significantly different with control (<0.001). With Spearman's rank-order correlation coefficient analysis, serum S100 $\beta$  protein level on day 7 of onset was significantly correlated with NIHSS score ( $r=0.613$ ;  $p=0.001$ ).

## DISCUSSION

S100 $\beta$  protein can be detected at a very low amount in the blood of normal individuals. Neither gender nor age affects S100 $\beta$  protein, but the race influences it.<sup>11,12</sup> S100 $\beta$  protein levels in healthy individuals ranged from 0.02 to 0.15  $\mu\text{g} / \text{L}$  (i.e. 20-150 pg / mL) depending upon the race.<sup>13</sup> A study conducted by Selçuk et al. found that S100 $\beta$  protein was not affected by age and sex, and risk factors like hypertension, diabetes mellitus and dyslipidemia.<sup>14</sup> In this study, the median S100 $\beta$  protein level of healthy individuals was 16.3 (15.58-23.79) pg/mL. The levels of S100 $\beta$  protein in this study were higher than a study conducted by Alatas in Turkey and lower than study in China and Korea. According to Alatas et al., the mean S100 $\beta$  protein level was  $0.08 \pm 0.03 \mu\text{g}/\text{L}$ , while a study in China by Hu et al. was  $52.3 \pm 14.5 \text{ pg}/\text{mL}$  and by Li et al. was  $0.59 \pm 0.07 \text{ pg}/\text{mL}$ .<sup>15,16,17</sup> According to study Yoon et al. in Korea, median levels for healthy individuals, were 0.05 (0.036-0.066)  $\mu\text{g}/\text{L}$ .<sup>18</sup>

Acute ICH is a severe condition with a poor prognosis. After hematoma, the neurological function deteriorates rapidly over a short period of time. The hematoma activates astrocytes to secrete the S100 $\beta$  protein which then leads to vasogenic edema that negatively affects the neurological deficits or patient mortality. S100 $\beta$  protein is a biomarker for severity of brain damage and has been shown in acute ischemic stroke and traumatic brain injury. In many clinical trials of the traumatic brain injury, the S100 $\beta$  protein was increased and associated with the extension of primary brain injury, the presence of secondary brain injury and a poor prognosis.<sup>19</sup>

In this study, serum S100 $\beta$  protein were significantly correlated with NIHSS ( $r=0.418$ ;  $p=0.004$ ), with AUC =  $0.839 \pm 0.103$  (95% CI 0.638-1.000). Serum S100 $\beta$  protein was also correlated with patient mortality within 1 week ( $p=0.032$ ). The results of this study are supported by several studies. In the study of Brea et al. involving 44 patients with acute ICH also found a correlation between serum S100 $\beta$  protein levels and NIHSS ( $r=0.607$ ;  $p<0.0001$ ).<sup>20</sup> Similar results were also obtained in a study conducted by Alatas et al. serum S100 $\beta$  protein levels were positively correlated with

NIHSS score ( $r=0.397$ ;  $p<0.05$ ).<sup>15</sup> Cut off for S100 $\beta$  protein in this study to distinguish stroke severity degree with 80% sensitivity and specificity 87.8% was 28.505 pg/mL ( $p=0.014$ ). Cut off levels in this study were lower than in other studies. The previous study by James et al. also had a similar result that S100 $\beta$  protein may become an independent and strong predictor of neurological outcome.<sup>21</sup>

According to Hu et al. S100 $\beta$  protein with cut off level of 192.5 pg/mL, predict the mortality within 1 week with a sensitivity 93.8% and a specificity 70.4% ( $p<0.001$ ).<sup>16</sup> According to Delgado et al. S100 $\beta$  protein levels at hospital admission of >118 pg/mL, may predict early neurological deterioration with a sensitivity of 92% and a specificity of 70%.<sup>22</sup> In the study of Huang et al. cut off levels of S100 $\beta$  protein in plasma of 173.8 pg/mL had a sensitivity 80.0% and specificity 69.6% to predict mortality in 1 week.<sup>23</sup> A study conducted by Dilek et al predicted the mortality of patients with ICH by measuring serum S100 $\beta$  protein. The cutoff value of serum the S100 $\beta$  on the day of admittance for ICU to predict mortality was 50.9 pg/mL (AUC = 0.776, 95% CI=0.6700.882) with 73% sensitivity and 73% specificity.<sup>24</sup>

In a study conducted by Alatas et al. serum S100 $\beta$  protein levels were negatively correlated with GCS score ( $r=0.467$ ;  $p<0.01$ ).<sup>15</sup> According to research by Huang et al. there was a significant correlation between GCS scores with plasma S100 $\beta$  levels in patients with ICH ( $r=-0.451$ ;  $p=0.004$ ).<sup>23</sup> While research conducted by James et al. it was found that the S100 $\beta$  protein was not correlated with the initial GCS score ( $r^2=0.32$ ).<sup>21</sup> According to research by Hu et al. GCS score at hospital admission, day 1 and 2 was negatively correlated with plasma S100 $\beta$  protein levels ( $r=0.588$ ;  $p=0.000$ ,  $r=0.457$ ;  $p=0.000$ ,  $r=0.399$ ;  $p=0.001$  respectively) but unrelated on day 3, day 5 and day 7 ( $r=-0.185$ ;  $p=0.155$ ,  $r=-0.168$ ;  $p=0.208$ ,  $r=-0.147$ ;  $p=0.289$  respectively).<sup>16</sup> In this study, S100 $\beta$  protein content significantly shown a negative correlation with baseline GCS score ( $r=-0.376$ ;  $p=0.010$ ). This finding was similar to that of Alatas et al., Huang et al. and Hu et al. but different from the results of research conducted by James et al.

In an intracerebral hemorrhage, the hematoma will activate astrocytes to secrete the S100 $\beta$  protein. There is a study linking S100 $\beta$  protein levels with hematoma volume, for example, a study conducted by Alatas et al. the results of serum S100 $\beta$  protein levels were positively correlated with hematoma volume ( $r=0.564$ ;  $p<0.001$ ).<sup>15</sup> According to Huang et al. there was a significant correlation between hematoma volume with the S100 $\beta$  level in plasma ( $r=0.380$ ;  $p=0.019$ ) and cerebrospinal fluid ( $r=0.468$ ;  $p=0.003$ ) among

patients with intracerebral hemorrhage.<sup>23</sup> A study conducted by James et al. obtained results that the S100 $\beta$  protein content correlated with hematoma volume ( $r=0.48$ ;  $p=0.01$ ).<sup>21</sup> According to Hu et al. volume of bleeding at the time of admission, day 1 and 2 was positively correlated with plasma S100 $\beta$  protein levels ( $r=0.568$ ,  $p<0.0001$ ,  $r=0.455$ ;  $p<0.0001$ ,  $r=0.363$ ;  $p=0.002$ , respectively) but no correlation was found on day 3, day 5 and day 7 ( $r=0.157$ ;  $p=0.228$ ,  $r=0.034$ ;  $p=0.803$ ,  $r=0.099$ ;  $p=0.474$ , respectively).<sup>16</sup> The results of the study by Yoon et al. there was a positive correlation between volume of hematoma and serum S100 $\beta$  protein level at hospital admission ( $r=0.663$ ;  $p=0.001$ ) and on day 3 ( $r=0.609$ ;  $p=0.021$ ), but no correlation was shown on day 7.<sup>18</sup> According to research by Delgado et al. there was a positive correlation between the volume of hematoma at admission and plasma S100 $\beta$  protein levels ( $r=0.45$ ;  $p<0.0001$ ) and between perihematomal edema and plasma S100 $\beta$  protein levels ( $r=0.27$ ;  $p=0.033$ ). However, the median level of baseline S100 $\beta$  protein was not associated with the possibility of further bleeding or perihematomal edema expansion.<sup>22</sup> A similar result was also shown by Brea et al. with serum S100 $\beta$  protein levels correlated with intracerebral hematoma within the first 24 h ( $r=0.607$ ;  $p<0.0001$ ).<sup>20</sup> A somewhat different study was conducted by Li et al. in patients with intracerebral hemorrhage grouped by hematoma volume, i.e., mild bleeding (<20 cc), moderate bleeding (20-40 cc) and severe bleeding (>40 cc). According to this study, the larger hematoma volume was accompanied by a larger serum S100 $\beta$  protein ( $1.03\pm 0.12$ ,  $1.79\pm 0.20$ ,  $2.85\pm 0.30$  pg/mL).<sup>17</sup> In Junttila et al. S100 $\beta$  protein concentration in serum at baseline was associated with hematoma volume ( $\rho=0.50$ ;  $p<0.001$ ).<sup>25</sup> In this study, the results were similar to the aforementioned studies, that serum S100 $\beta$  protein levels at baseline correlated with hematoma volume ( $r=0.678$ ;  $p<0.001$ ).

Given the result of our study and supported with many previous finding, we think that S100 $\beta$  protein level is an important marker for predicting neurological function and mortality within 1 week because of the relationship between S100 $\beta$  protein levels and NIHSS, GCS, and hematoma volume.

## CONCLUSION

In this study, high levels of serum S100 $\beta$  protein were present in patients with ICH. It also shows a significant correlation with neurological deficits, mortality within 1 week and hematoma volume. These findings suggest that serum S100 $\beta$  protein has potential prognostic utility for acute ICH.

## ACKNOWLEDGMENTS

We are grateful to the patients and their families who participated during the entire period of our data collection.

## DISCLOSURE

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

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