THE ROLE OF SERUM S100 LEVELS PREDICT SURVIVAL IN PATIENTS WITH ACUTE CEREBRAL INFARCTION

Hoang Trong Hanh[1], Nguyen Cuu Loi[1], Hoang Khanh[2]
(1) Hue Central Hospital, Vietnam
(2) Hue University of Medicine and Pharmacy, Vietnam

Abstract
Objectives: Study the serum S100 levels in patients with cerebral infarction in acute phase and the value of the S100 and a number of factors in survival prognosis. **Subjects and Methods:** We investigated 84 patients with cerebral infarction hospitalized in the ICU Department, Hue Central Hospital and 84 healthy controls. Quantifying serum S100 by polarized immunofluorescence assay using Cobas 6000 at Hue Central Hospital. Collecting data through medical records of cerebral infarction patients. Descriptive cross-sectional study. Data processing using medical statistics, with SPSS 19.0 software. **Results**: Median of S100 in case group was 0.341 (95%CI: 0.206 – 0.616), in control group was 0.059 (95% CI: 0.048 – 0.068). S100 cut- off point > 0.218 have the highest death prognosis value, with the sensitivity of 83.9%, specificity of 58.5%, the area under the curve (ROC) was 0.737. Glasgow Coma Scale (OR = 0.675, 95% CI: 0.463 - 0.984, p <0.05) and NIHSS (OR = 1.148, 95% CI: 1.026 - 1.283, p <0.05) are independent factors with statistical significance in mortality prognosis in patients with cerebral infarction. **Conclusions:** S100 increased in patients with cerebral infarction. S100 was not a independent factor in survival prognosis. We should combine with Glasgow coma scale and NIHSS scale to predict mortality.
Keywords: *Cerebral infarction, S100, survival prognosis.*

1. BACKGROUND

Cerebral infarction has been an urgent current issue of medicine for every nations, ethnic group, the elderly and young people, regardless of male or female, rural or urban. Cerebral infarction accounts for 80-90% of Stroke in European and American countries as well as developed countries. In Vietnam, this ratio is about 60% [3].

There is an increasing number of new and modern diagnostic methods, new highly effective medicine help for early diagnosis, timely treatment and more effective prevention, improve prognosis.

Recently the international authors have noticed a number of factors help for early diagnosis and prognosis of cerebral infarction whereas lesions had not seen on computerized tomography, among which is serum S100 protein [6], [7], [8]. In Vietnam there have been no studies on this issue, so we conducted a study: *"**The role of serum S100 levels predict survival in patients with acute cerebral infarction**"* with the following two objectives:

- *Study the serum S100 levels in patients with cerebral infarction in acute phase.*
- *The value of the S100 and a number of factors in survival prognosis.*

2. SUBJECTS AND METHODS

2.1. Subjects

We investigated 84 patients with cerebral infarction diagnosed by cranial CT scan, hospitalized in the Department of ICU, Hue Central Hospital from April 2011 to February 2014 and 84 healthy controls.

2.2. Research Methods: Descriptive cross-sectional study.

Methods of data collection: selecting 84 patients with cerebral infarction hospitalized at Hue Central Hospital. Collect data through medical records of acute cerebral infarction patients and 84 healthy controls.

- Quantifying serum S100 by polarized immunofluorescence assay using Cobas 6000 at Hue Central Hospital. Normal range serum S100: 0.046-0.105 ng/ml [13].
- Data processing using medical statistics, with SPSS 19.0 software.

3. RESULTS

3.1. Age and gender features in the patients and controls group

- Corresponding author: Hoang Trong Hanh, email: hanhci6@gmail.com
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Table 3.1. Age and gender characteristics in the patients and controls group

Group / Features		Patients (n = 84)	Controls (n = 84)	p
		n (%)	n (%)	
Gender	**Male**	46 (54.8)	50 (59.5)	> 0.05
	Female	38 (45.2)	34 (40.5)	
Age	**≤ 60**	24 (28.6)	30 (35.7)	< 0.001
	> 60	60 (71.4)	54 (64.3)	
	p	< 0.001	< 0.01	
	$\overline{X} \pm SD$	68.93 ± 13.27	66.56 ± 12.19	> 0.05

Number of male patients with cerebral infarction was 46 cases, accounted for 54.8%. The number of female patients with cerebral infarction was 38 cases, accounted for 45.2%. No differences between the patients and controls group (p> 0.05). In patients group, ratio of patient > 60 years old higher than ≤ 60 with statistical significance (**< 0.001)**.

3.2. Risk factors and clinical scales characteristics of the patients group

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Characteristics	n (%)
Smoking	13 (15.5)
Drinking	13 (15.5)
Hypertension	39 (46.4)
Deaths	31 (36.9)
Glasgow coma scale	10.29 ± 2.85
NIHSS scale	20.17 ± 10.21

The proportion of smokers was 15.5%, drinking was 15.5%, hypertension was 46.4%, mortality was 36.9%.

3.3. The serum S100 levels in patients and controls group

Table 3.3. The serum S100 levels in patients and controls group

Group / S100 (ng/ml)	Patients (n=84)	Controls (n=84)	p
$\overline{X} \pm SD$	1.537 ± 2.769	0.062 ± 0.029	
Median (95%CI)	0.341 (0.206 – 0.616)	0.059 (0.048 – 0.068)	< 0.001

The S100 median in patients group is higher than the controls group with statistical significance (p <0.001).

3.4. Some characteristics between the death and survival group

Table 3.4. Some characteristics between the death and survival group

Goups / Parameters	Deaths (n = 31)	Alive (n = 53)	p
S100 median (95%CI)	0.890 (0.384 – 2.740)	0.203 (0.159 – 0.330)	**< 0.001**
Glasgow	8.06 ± 1.91	11.58 ± 2.49	**< 0.001**
NIHSS	28.48 ± 6.59	15.30 ± 8.72	**< 0.001**

There are differences with statistical significance between alive group and dead group in S100 concentrations, NIHSS scale, Glasgow (p <0.01).

3.5. S100 cut- off point in mortality risk prognosis

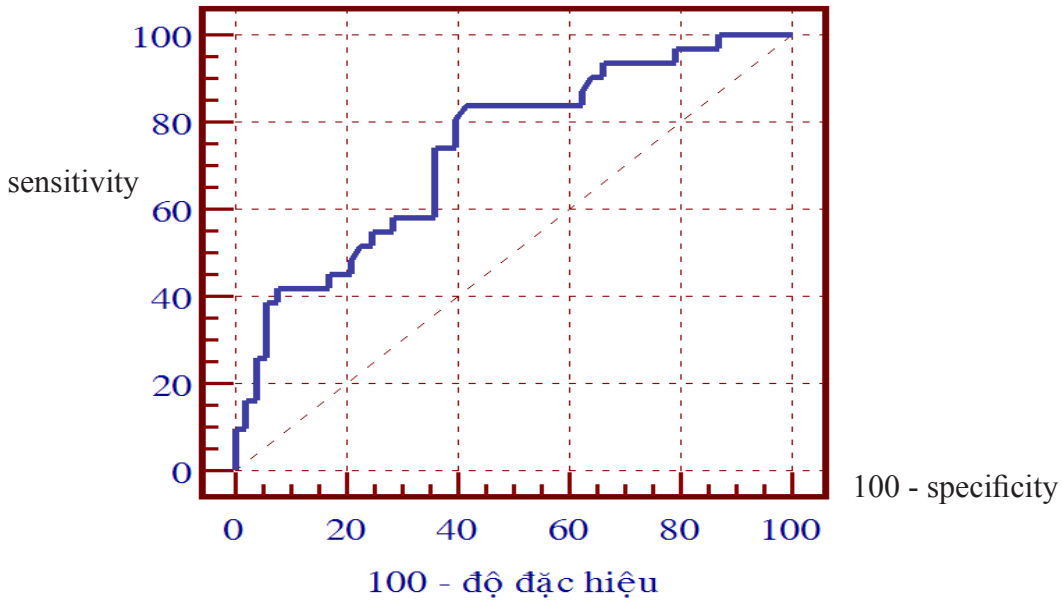

Chart 3.1. Determining mortality risk using S100

S100 cut- off point > 0.218 have the highest prognosis value of death, with the sensitivity of 83.9 (95% CI: 66.3 to 94.5), specificity of 58.5 (95% CI: 44.1 to 71.9), the area under the curve (ROC) was 0.737.

3.6. Factors associated with mortality evolution of cerebral infarction

Table 3.5. Factors associated with mortality evolution of cerebral according to the results of binary logistic regression analysis

Independent variables	B	OR	95% CI of OR	*p*
Age	0.040	1.040	0.986 – 1.098	> 0.05
S100	0.193	1.213	0.955 – 1.541	> 0.05
Glasgow	- 0.393	0.675	0.463 – 0.984	**< 0.05**
NIHSS	0,138	1.148	1.026 – 1.283	**< 0.05**
Constants	- 3.073			
Model statistical Evaluation: Hosmer and Lemeshow test: $\chi^2 = 9.433$, df = 8, p = 0.307. Overall prediction accuracy: 85.7% The area under the curve ROC = 0.920 (p < 0.001).				

NIHSS and Glasgow coma scale are independent factors with statistical significance in mortality prognosis in patients with cerebral infarction.

4. DISCUSSION

4.1. Age and gender characteristics in the patients and controls group

Results in Table 3.1 showed that: male patients with cerebral infarction was 46 study (54.8%). Female patients with cerebral infarction was 38 (45.2%). No differences between patients and controls group (p> 0.05). In the patients group, the proportion of patients > 60 years of age (71.4%) is higher than the group of patients ≤60 years of age (28.6%) with statistical significance (p <0.001).

International and domestic studies also had similar results as our study: age group of > 65 years and men is more than women. Study of Nguyen Duc Hoang in Hue (2007) showed that the age of stroke patients was 62.35 ± 13.02, male accounted for 60.19%, female is 39.81% [1]. Findings of Foerch C. et al on 39 patients with middle cerebral artery infarction in Germany in 2005 showed that the average age of the patients is 69.1 ± 11.5, women is accounted for 35.9% [6]. In another study of Foerch C. on 275 patients with cerebral infarction in 2007, the average age is 69 ± 13, female proportion is 46% [7].

4.2. Risk factors and clinical scales characeteristics of the patients group

Results in Table 3.2 show that: the proportion of smokers was 15.5%, drinking was 15.5%, hypertension was 46.4%, and the mortality rate

was 36.9%. The average score of Glasgow coma scale was 10.29 ± of 2.85, of NIHSS scale was 20.17 ± 10.21.

International and domestic studies has the same results as our studies relating to the risk factors of cerebral infarction. The study of Nguyen Van Khach (2012) on 181 patients with cerebral infarction at Cu Chi hospital showed that: the most common risk factors are hypertension (71.8%), hyperlipidemia (21%), and diabetes (13.3%) [2]. Study of Nguyen Duc Hoang in Hue (2007) showed that hypertension rate is 83.33% [1]. With international studies, findings of Foerch C. et al on 39 patients with middle cerebral artery infarction in Germany in 2005 showed that: hypertension rate was 71.8% [6]. Study of Oryńska M.K. et al showed that among patients with cerebral infarction, 75% with hypertension, 48% with hyperlipidemia, and 25.3% with diabetes [12]. In the study of Brea D. (2009) on 224 patients with cerebral infarction, 52.2% has a history of hypertension, diabetes in 17.3%, 23.3% with dyslipidemia [5].

Study of Weimar C. on 1307 patients with acute cerebral infarction showed that after 100 days, mortality rates was 10.7% [15]. Study of Ogawa A. on two groups of patients with cerebral infarction in UK and Japan showed that, mortality rate in English group after 90 days was 5.3%, in Japan was 3.5%, the difference between the two groups is not statistically significant (p> 0.05) [11].

4.3. The serum S100 levels in patients and controls group

Results in Table 3.3 showed that the S100 median in patients group (0.341 (from 0.206 to 0.616)) is higher than the controls group (0.059 (0.048 to 0.068)) with statistical significance (p <0.001).

Study of Orynska M.K. et al showed that S100B concentration in patients with cerebral infarction is higher than the controls group with statistical significance (0.85 ± 1.74 versus 0.10 ± 0.03 ng/ml) [12]. Study of Martens P. (1998) showed that the median concentrations of S100 in study group is 0.78 ng/ml is higher than the controls group 0.19 ng / ml (p <0.00029) [10]. The results of both groups of study and controls in these studies is higher than our study. In the study of Jauch E.C. vs al (2006) on 359 patients with cerebral infarction, S100B median concentrations (ng/ml) at admission, 2 hours after admission and 24 hours after admission was 0.021 (95% CI: 0.0 to 0.309), 0.022 (95% CI: 0.0 - 0.255), 0.034 (95% CI: 0.0 - 0.762), respectively [8]. Thus, S100 tends to increase over time after admission. S100 will increase and reach peak concentration for a few days after cerebral infarction.

4.4. Some characteristics between the death and survival group

Results in Table 3.4 showed that there is a difference with statistical significance between the alive group and the dead group in the concentration of S100 (0.890, 95% CI: 0.384 - 2.740) and (0.203, 95% CI: 0.159 - 0.330), Glasgow Coma Scale (8.06 ± 1.91) and (11.58 ± 2.49) and NIHSS scale (28.48 ± 6.59) and (15.30 ± 8.72) (p <0.01).

According to Üstündag M. et al, when studying 90 patients with cerebral infarction in Turkey, 2008 – 2009, in the alive group, the S100 concentration was 0.30 ± 0.28 ng/ml, the differences were statistically significant (p = 0.003) [14]. This result is similar to our result. Lázaro et al (2013) studied 254 patients with cerebral infarction and follow-up 2 years later. The results showed that when comparing groups of dead patients (n = 20) and alive patients (n = 234), there is a difference in diastolic blood pressure (81 ± 18, 91 ± 17, p <0.05), coma on admission (25% and 6%, p <0.01), Barthel scale (77 ± 32, 94 ± 15, p <0.01) with statistical significance [9].

4.5. S100 Cut- off point in mortality risk prognosis

Findings in Figure 3.1 show that: S100 with a cut- off point of 0.218 has the highest prognostic value of death, with the sensitivity of 83.9 (95% CI: 66.3 - 94.5), a specificity of 58.5 (95% CI: 44.1- 71.9), the area under the curve (ROC) was 0.737.

P. Martens chosen the S100 cut- off point of 0.7 ng/ml in determining mortality risk. According to these authors, mortality risk in the group with S100 > 0.7 ng/ml is 31 times higher than the group with S100 ≤ 0.7 ng / ml [10].

4.6. Factors associated with mortality evolution of cerebral infarction

The results of binary logistic regression analysis in table 3.5 showed that difference between the prognostic value of mortality is significant (Hosmer and Lemeshow test with p > 0.05), overall prediction accuracy is 85.7%, the reliability of the model is excellent (area under the curve ROC is greater than the threshold of 0.90, p <0.001). Glasgow Coma Scale (OR = 0.675, 95% CI: 0.463 - 0.984, p <0.05) and NIHSS (OR = 1.148, 95% CI: 1.026 - 1.283, p <0.05) are independent factors with statistical significance

in mortality prognosis in patients with cerebral infarction. S100 has no statistical significance in death prognosis ((OR = 1.213, 95% CI: 0.955 - 1.541, p> 0.05).

Many international and domestic studies in patients with acute cerebral infarction also mentions factors associated with mortality evolution of cerebral infarction. The study of Phan Viet Nga, Nguyen Thi Thanh Nhan (2012) on 86 cerebral infarction patients with metabolic syndrome showed that: Glasgow Coma Scale score ≤ 9 are predictors of death (OR = 55.5, p <0.001) [4]. In the study of Ustundag M. et al on 90 patients with cerebral infarction in Turkey from 2008 to 2009, the S100 is an independent prognosis factor of mortality (OR = 19.7, p = 0.004) [14]. The study of Nguyen Van Khach (2012) on 181 patients with cerebral infarction at Cu Chi hospital showed that: Glasgow ≤ 8 and NIHSS ≥ 12 are independent risk factors of progressive worsening of patients with cerebral infarction [2].

5. CONCLUSIONS

The median of S100 in patient group was 0.341 (95%CI: 0.206 – 0.616), in control group was 0.059 (95%CI: 0.048 – 0.068). S100 cut- off point > 0.218 have the highest prognosis value of death, with the sensitivity of 83.9%, specificity of 58.5%, the area under the curve (ROC) was 0.737.

Glasgow Coma Scale (OR = 0.675, 95% CI: 0.463 - 0.984, p <0.05) and NIHSS (OR = 1.148, 95% CI:1.026 - 1.283, p <0.05) were independent factors with statistical significance in mortality prognosis in patients with cerebral infarction. S100 has no statistical significance in death prognosis (OR = 1.213, 95% CI: 0.955 - 1.541, p> 0.05).

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