ROLE OF SERUM S100B PROTEIN AND NSE CONCENTRATION IN THE DIAGNOSIS, AND PROGNOSIS OF PATIENTS WITH ACUTE CEREBRAL INFARCTION

Hoang Trong Hanh[1], Hoang Khanh[2], Nguyen Cuu Loi[1],
Le Thi Phuong Anh[1], Bui Manh Hung[1], Pham Trung Hieu[1],
Tran Thua Nguyen[1], Le Thi Dieu Phuong[1]

ABSTRACT

Objective: *1. To survey serum S100B protein and NSE concentrations in patients with acute cerebral infarction and roles of them in the early diagnosis of cerebral infarction.*

2. To access the value of serum protein S100B and NSE in survival prognosis in patients with acute cerebral infarction.

Patients and Methods: *The subject of our study are patients of 18 years or older comprised of two groups: 98 patients with acute cerebral infarction and 112 controls. Time of sample collection study: 4/2011 - 02/2014 in Hue Central Hospital. Cross-sectional descriptive study.*

Results: *Median of S100B protein concentration in case group is 0.404 ng/ml, control group is 0.058 ng/ml. Median of NSE in case group is 26.55 ng/ml, control group is 14.47 ng/ml. Median of S100B protein in male is 0.381 ng/ml, female 0.433 ng/ml. Median of NSE are 25.04 ng/ml in male and 29.91 ng/ml in female. With the cut off point > 0.115 ng/ml for S100B protein, and > 22.3 ng/ml for NSE, they are valueable in the diagnosis of cerebral infarction, with the sensitivity of 85.7% and 61.2%; specificity 100% and 100%, respectively. NSE > 25.23 ng/ml is a significant independent fators in predicting the 7- day mortality in hospitals for patients with acute cerebral infarction.*

Conclusion: *Protein S100B and NSE are significant factors in the diagnosis of acute cerebral infarction. NSE is an independent factor having prognostic significance in hospital mortality in patients with acute cerebral infarction*

Key words: *S100B protein, NSE, acute cerebral infarction, diagnosis, prognosis.*

I. INTRODUCTION

Cerebral infarction has been an current urgent medical issue for every country. Cerebral infarction can cause rapid death or sequelae burden to family and society. Despite significant advances in diagnosis and treatment, mortality rate due to cerebral infarction is still high in developed countries and very high in Vietnam [1].

In cerebral infarction, astrocytes were injured early, especially cerebral edema, damaging astrocytes, cells involved in metabolic intermediate between capillaries and nerve cells, thereby they releasing S100B protein and neuron specific enolase (NSE).

Thus, the study of serum S100B protein and NSE concentration will help early diagnosis and prognosis of cerebral infarction, especially when we haven't seen the brain injury on computerized tomography [2], [3], [6].

In Vietnam, there have not been any research on these two biomarkers, so we conducted a research project on "Role of serum S100B protein and NSE concentration in the diagnosis, and prognosis of patients with acute cerebral infarction", with the following objectives:

1. To survey serum S100B protein and NSE concentrations in patients with acute cerebral infarction and roles of them in the early diagnosis

1. Hue Central Hospital
2. Hue University of medicine and pharmacy

Corresponding author: Hoang Trong Hanh
Email: hanhquy2006@yahoo.com.vn
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of cerebral infarction.

2. To access the value of serum protein S100B and NSE in survival prognosis in patients with acute cerebral infarction.

II. MATERIALS AND METHOD

2.1. Study subjects

The subject of our study are patients of 18 years or older comprised of two groups: patients with acute cerebral infarction and control groups.

Time of sample collection study: 4/2011 - 02/2014.

2.1.1. Case group

Consisting of 98 patients with cerebral infarction in the acute phase, treated at ICU Department and cardiovascular internal medicine department, Hue Central Hospital, who agreed to participate in the study with no underlying medical problem which can affect the concentration of serum S100B protein and NSE.

2.1.2. The control group

Consisting of 112 control subjects that are similar in age, gender, race distribution that come for a medical examination at the Department of Outpatient, Hue Central Hospital, without any medical problems affecting the concentrations of serum S100B protein and NSE and voluntarily participate in the study.

2.2. Methodology

2.2.1. Study design: cross-sectional descriptive study with comparison with control and monitoring.

2.2.2. Assessment mortality in the hospital

We evaluated the mortality rate at hospital in the first 7 day.

2.2.3. Computerized tomography of the brain

Computed tomography scanner HiSpeed Dual effect - GE (England), 2 images / rotation, produced in 2009. Carried out at the Department of Diagnostic Imaging at Hue Central Hospital.

2.2.4. S100B protein and NSE tests

- Quantification of serum S100B protein and NSE by immune electrochemical luminescence technique on the machine biochemical autoimmune Cobas 6000 (USA) at Hue Central Hospital.

2.2.5. Methods of data processing

The data analysis was processed by SPSS version 19.0.

III. RESULTS

3.1. Patients common characteristics

3.1.1. Characteristics of the case and control group

Table 3.1. The distribution of male and female between the case and control group

Study group		Case group		Control group		*p*
		n	%	n	%	
Gender	Male	56	57.1	64	57.1	> 0.05
	Female	42	42.9	48	42.9	> 0.05
	Total	98	100.0	112	100.0	
Age (year)	≤ 60	30	30.6	42	37.5	> 0.05
	> 60	68	69.4	70	62.5	
	Male	65.79±13.73		66.67±13.87		> 0.05
	Female	71.29±12.40		66.46±13.04		> 0.05
	Total	68.14±13.39		66.58±13.46		> 0.05

Comment: There are 56 male patients, accounting for 57.1%, and 42 female patients, accounting for 42.9%. There is no difference in gender between case group and control group (p>0.05). The average age in case group is 68.14±13.39. There is no statistically significant difference (p>0.05) between the age of male, female and both sex in case group and control group. In case group, min age is 32, max age is 90.

3.1.2. Lesion volume on Computed tomography in case group

Table 3.2. Lesion volume on Computed tomography in case group

Lesion volume (cm^3)	n	%
≤30	49	50.0
>30	49	50.0
Average ($\overline{X}$ + SD)	98.09 ± 138.15	
Median (95%CI)	31.01 (17.85 – 56.92)	

Comment: There are 49 patients with lesion volume ≤30cm^3 and 49 patients with lesion volume >30cm^3, accounting for 50.0%.

3.2. Characteristics of serum S100B protein and nse in patients with acute cerebral infarction and in survival prognosis value

3.2.1. The concentration of serum S100B protein and NSE in case group and control group

Table 3.3. The concentration of serum S100B protein and NSE in case group and control group

Parameter		Case group (n=98)	Control group (n=112)	p	$\overline{X}$+ 2SD Control group
S100B protein (ng/ml)	$\overline{X}$ + SD	1.450 ± 2.588	0.059 ± 0.026		0.111
	Median (95%CI)	0.404 (0.263 – 0.689)	0.058 (0.049 – 0.066)	< 0.001	
NSE (ng/ml)	$\overline{X}$ + SD	37.44 ± 33.39	14.93 ± 3.41		21.75
	Median (95%CI)	26.55 (22.49 – 33.02)	14.47 (13.75 – 15.20)	< 0.001	

Comment: The median of S100B protein and NSE of case group is higher than that of control group and it had statistically significant difference (p<0.001).

The cutoff point in healthy person is 0.111ng/ml for serum S100B protein and 21.75 ng/ml for serum NSE.

3.2.2. Diagnostic value of serum S100B protein and NSE in cerebral infarction

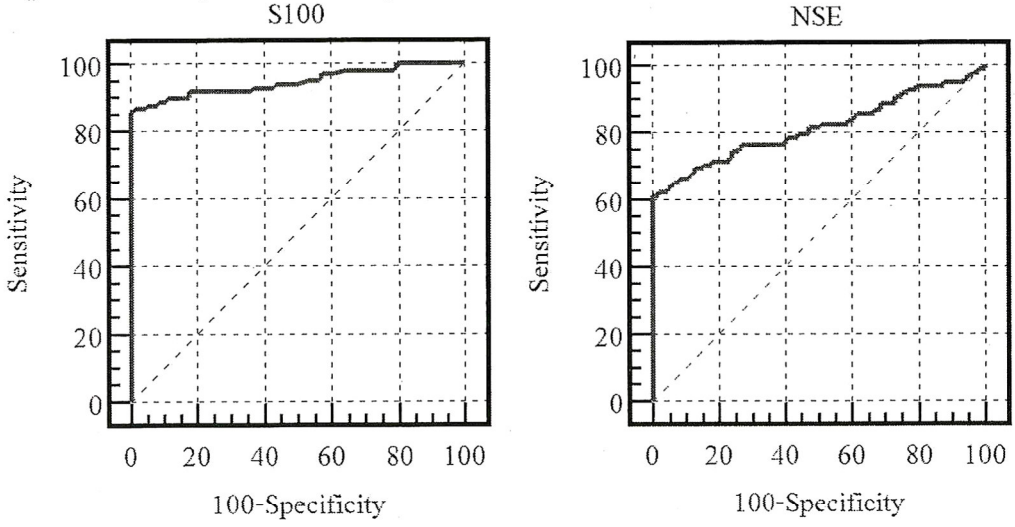

Figure 3.1. và Figure 3.2. Diagnosis acute cerebral infarction by S100B protein and NSE (case group and control group)

Comment: At cut off point of S100B protein > 0.115 has highest diagnosic value with sensitivity 85.7 (95%CI: 77.2- 92.0), specificity 100.0 (95%CI: 96.7- 100.0), the area under ROC curve is 0.946 (95%CI: 0.912 – 0.980). At cut off point of NSE >22.3 has highest diagnosic value with sensitivity 61.22 (95%CI: 50.8- 70.9) specificity 100.0 (95%CI: 96.7-100.0), the area under ROC curve is 0.814 (95%CI: 0.751 – 0.877).

Table 3.4. Diagnosis of cerebral infarction by combining serum S100B protein and NSE

Parameter \ Study group	Case group		Control group	
	n	%	n	%
Increasing S100B protein and NSE	57	58.2	1	0.9
No increasing S100B protein and/or NSE	41	41.8	111	99.1
p	<0.001			
Increasing S100B protein and/or NSE	89	90.8	7	6.2
No increasing S100B protein and NSE	9	9.2	105	93.8
p	<0.001			

Comment: When increasing in serum S100B protein and NSE, cerebral infartion diagnosis sensitivity is 58.16%, specificity is 99.11%. When increasing serum S100B protein and/or NSE, sensitivity is 90.82%, specificity is 93.75%.

Table 3.5. Comparison of diagnosing cerebral infarction by serum S100B protein, NSE with computerized tomography for the first time

Parameter \ Result		Positive		Negative	
		n	%	n	%
S100B protein (ng/ml)	Increase (> 0.111)	77	85.6	8	100.0
	Normal (≤ 0.111)	13	14.4	0	0.0
NSE (ng/ml)	Increase (>21.75)	55	61.1	6	75.0
	Normal (≤ 21.75)	35	38.9	2	25.0

Comment: In negative group on the first time CTscan, 100% of patients had increased serum S100B protein and 75% had increased serum NSE.

3.2.3. Characteristics of hospital mortality in patients with cerebral infarction

3.2.3.1. Hospital mortality of patients with cerebral infarction by gender

Table 3.6. Hospital mortality in patients with cerebral infarction by gender

Mortality \ Gender	Male		Female		General		p
	n	%	n	%	n	%	
Mortality in 7 days	10	17.9	10	23.8	20	20.4	>0.05

Comment: There is no statistically significant difference in mortality by gender (p>0.05). General mortality in 7 days is 20.4%.

3.2.3.2. Value of protein S100B and NSE in prognosis mortality

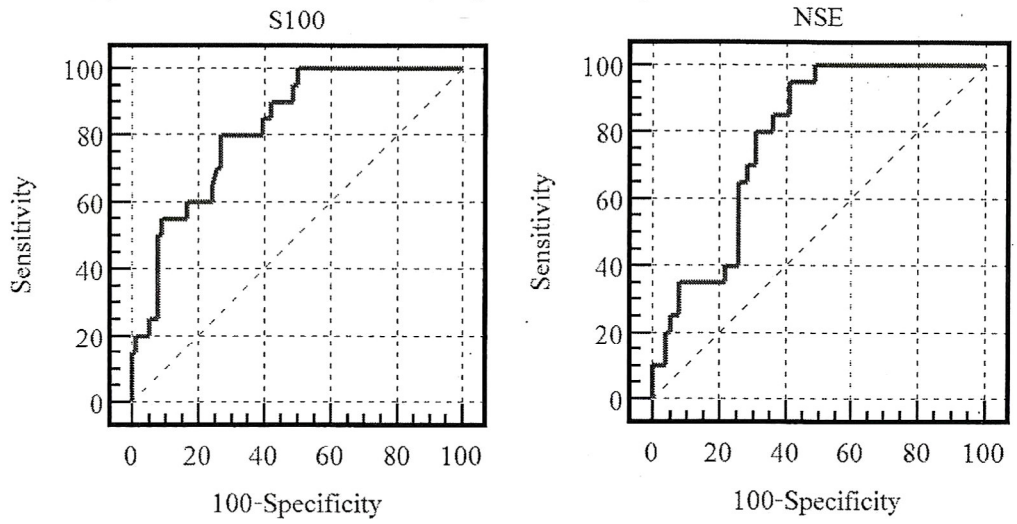

Figure 3.3. và Figure 3.4. Determining the risk of death in hospital with S100B protein and NSE after 7 days

Comment: At cut off point of S100B protein > 0.749 ng/ml and NSE > 25.23 ng/ml has highest diagnosic value with sensitivity 80.0 (95%CI: 56.3- 94.1) and 95.0 (95%CI: 75.1-99.2), specificity 73.1 (95%CI: 61.8 – 82.5) and 59.0 (95%CI: 47.3-70.0), the area under ROC curve is 0.823 (95%CI: 0.733 – 0.913) and 0.783 (95%CI: 0.690 – 0.875).

3.2.3.3. The probability of survival in patients with cerebral infarction in 7 days

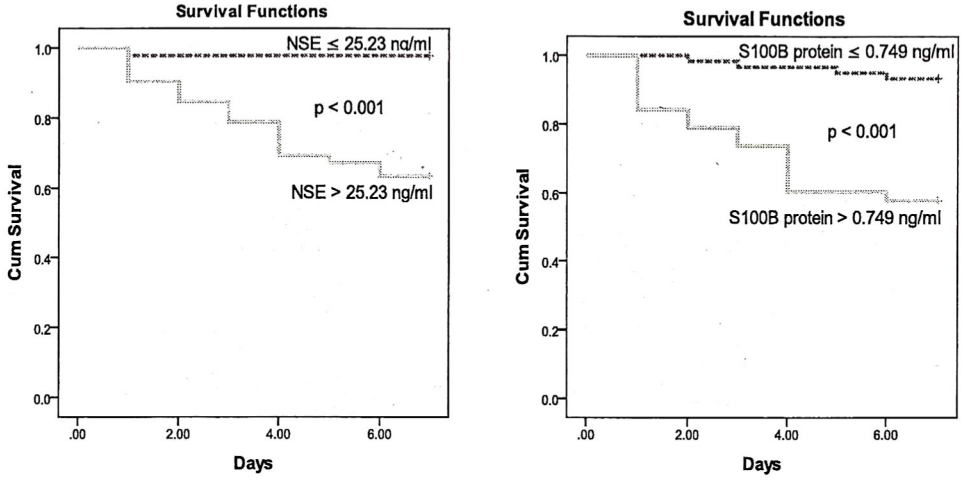

Figure 3.5. và Figure 3.6. The probability of survival in patients with cerebral infarction by S100B protein and NSE in 7 days

Comment: The probability of survival in patients with cerebral infarction in non-elevated S100B protein group is higher than that of elevated S100B protein group with statistically significant difference (p<0.001). The probability of survival in patients with cerebral infarction in non-elevated NSE group is higher than elevated NSE group with statistically significant difference (p<0.001).

3.2.3.4. Factors associated with mortality in cerebral infarction

From the results of the Kaplan Meier analysis, we take the parameters of S100B protein, NSE, Glasgow Coma Scale, NIHSS, lesion volume and age in the regression analysis of binary logic to determine factors that really have prognostic significance in mortality in patients with cerebral infarction in 7 days.

Table 3.7. Factors associated with mortality in cerebral infarction in 7 days as a results of binary logistic regression

Independent factors	B	OR	95% CI của OR	P
S100B protein > 0.749 ng / ml	1.073	2.924	0.561 – 15.231	> 0.05
NSE > 25.23 ng / ml	3.533	34.233	2.732 – 428.908	**< 0.01**
Glasgow score < 10	0.329	1.389	0.111 – 17.316	> 0.05
NIHSS score > 22	3.223	25.105	2.173 – 290.055	**< 0.05**
Lesion volume > 110 cm^3	2.696	14.828	2.302 – 95.514	**< 0.01**
Age > 81	0.868	2.382	0.487 – 11.661	> 0.05
Constant	-8.961			
Statistically evaluate model Hosmer và Lemeshow test: $\chi^2 = 3.541$, df = 8, p = 0.896.				

Comment: The results of statistical evaluation of binary logistic regression model showed that NSE> 25.23 ng / ml, NIHSS> 22, the volume of lesions> 110 cm^3 are independent factors that have statistically significance in 7- day prognosis mortality in cerebral infarction.

IV. DISCUSSION

4.1. General charateristics

4.1.1. Distribution of age, gender in case group and control group

Table 3.1 shows that there were 56 male patients, accounting for 57.1% case, 42 female patients, accounting for 42.9%.

Foerch C. et al reseached on 39 patient with acute middle cerebral artery infarction in German in 2005 showed: average age of patient was 69.1± 11.5, female accounted for 35.9%[2]. Sun Y.'s reseach showed that male patient accounted for 53.7% [10].

4.1.2. Lesion volume on CTscan in case group

Table 3.2 shows that 50% of patients have lesion volume ≤30cm^3.The average lesion volume area was 98.09 ± 138.15 cm^3.

Herrmann M. et al's reseach showed that average lesion volume is 34.2 ± 72.2 cm^3[4]. Zaheer S. et al studied on 75 patients with acute cerebral infarction in India showed that average lesion volume is 53.88 ± 42.92 cm^3[13]. Lesion volume in our study is higher than above probably because our patient was in ICU with high mortality risk so the lesion volume is larger.

4.2. Charateristic of S100B protein and NSE in patients with acute cerebral infarction and their value in survival prognosis

4.2.1. Concentration of S100B protein in case group

Results from table 3.3 show that median of S100B protein in case group is 0.404, it is higher than control group (0.058), there is a statistically significant difference (p<0.001).

Wiesnn M. Et al study on more than 200 healthy volunteers showed that the median of serum S100B protein is 0.052ng/ml [12]. This result is similar to that of our control group. Average concentration of serum S100B protein in our control group is 0.059 ± 0.026 ng/ml, above the limitation ($\overline{X}$+ 2SD) is 0.111ng/ml.

4.2.2. Concentration of NSE in case group

Table 3.3 show that median of NSE in case group is 26.55 (95%CI: 22.49 – 33.02), it is higher than control group's (14.47) (95%CI: 13.75 – 15.20), statistically significant difference (p<0.001).

Martens P. (1998) showed that median of NSE in case group was 21.2 ng/ml, it is higher than control group's 15.2 ng/ml (p<0.001) [7]. Oryńska M.K. et al's reseach showed that NSE in case group was higher

than that of control group; there was a statistically significant difference.

Research of Oryńska M.K. et al showed that NSE concentration in cerebral infarction patients higher than that of control group and had statistically significance [9](36.9 ± 24.0 compared to 14.3 ± 9.7 ng/ml). This result was similar to result of our study.

Average concentration of NSE in control group is 14.93 ± 3.41 ng/ml, above the limitation ($\overline{X}$+ 2SD) which is 21.75 ng/ml.

4.2.3. Proportion of increasing S100B and NSE in control group

4.2.3.1. Proportion of increasing S100B in control group

In Table 3.5, with the cut off level of serum S100B protein > 0.111ng/ml, the proportion of increasing serum S100B protein in case group is 86.7%, control group is 5.4% with sesitivity is 86.73%, specificivity is 94.64%.

In Orynska's research, with the cut off level of serum S100B protein > 0.15ng/ml, S100B protein in cerebral infartion case group increase by 61.8%.

4.2.3.2. Proportion of increasing NSE in study group

With cut off level of NSE is 21.75ng/ml, proportion of increasing NSE in case group is 62.2%, in control study is 1.8%, sensitivity is 62.24%, specificity is 98.21%.

In the study of Orynska M. K. et al, proportion of increasing NSE in Cerebral infartion group was 93.5%. In this study, NSE's cut off is >12.5ng/ml[9].

Hill's study (2000) showed that in hospitalizational time, the proportion of increasing NSE in acute cerebral infartion patients is 89%[5]. This result is similar to that of Orynska M.K.'s study [9].

Table 3.6 show that in the negative group in the first time of CT Scanner, 100% patients show an increase in S100B protein and 75% increase in NSE. So, for the patients who have cerebral infartion in early stage with normal CT Scanner, their concentration of S100B protein and NSE have been increasing. It confirm the roles of these two biomakers for early diagnosis of cerebral infarction.

4.2.4. Value of serum S100B protein and NSE in prognosing the mortality in hospital

4.2.4.1. Mortality in hospital of control group

Mortality in hospital of cerebral infarction in our study at 7th day is 20.4%.

Weimar C. research on 1307 cerebral infarction patients showed that after 100 days, mortality is 10.7% [11]. Ogawa A. research on two cerebral infarction group in England and Japan showed that mortality after 90 days in English patients is 5.3%, Japanese patients is 3.5% [8].

4.2.4.2. Value of serum S100B protein and NSE in pronogsis of mortal risks

After 7 days, the concentration of NSE > 25.23ng/ml, NIHSS greater than 22 points, lesion volume > 110 cm^3 are independent factors in prognosing the mortality in patients with cerebral infartion. S100B protein is not significant in mortal pronogsis at this time.

V. CONCLUSION

Median of S100B protein concentration in case group is 0.404 ng/ml, control group is 0.058 ng/ml. Median of NSE in case group is 26.55 ng/ml, control group is 14.47 ng/ml. Median of S100B protein in male is 0.381 ng/ml and female is 0.433 ng/ml. Median of NSE is 25.04 ng/ml in male and 29.91 ng/ml in female.

With the cut off point of > 0.115 ng/ml for S100B protein and > 22.3 ng/ml for NSE, it has value in diagnosis of cerebral infarction, with the sensitivity of 85.7% and 61.2%; specificity 100% and 100%, respectively.

NSE > 25.23 ng/ml is independent fator in predicting the motality during 7 days in cerebral infarction. S100B protein is not an independent factor that can significantly predict the 7- day mortality in hospital.

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