PREDICTIVE VALUE OF SERUM FERRITIN, TRANSFERRIN, IRON CONCENTRATION FOR PROGNOSTIC IN PATIENTS WITH ACUTE PHASE CEREBRAL INFARCTION

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Abstract

Background: The relationship between the concentration of serum ferritin, transferrin, iron and their prognostic value for patients with cerebral infarction during the acute phase??. **Subjects and Methods:** Cross-sectional descriptive methods, 104 cases including 52 patients with cerebral infarction and 52 control subjects in Hue University Hospital. Data were processed by usual medical statistics and SPSS 15.0. **Results:** Mean age of cerebral infarction group was 64.90 ± 11.85 and 65.17 ± 11.48 in control group ($p > 0.05$). (i) In cerebral infarction group, ferritin concentration (378.4 mg/L) and iron concentration (25.2 mmol/L) were, higher than the control group ($p < 0.001$ and $p < 0.01$, respectively). There was no difference in transferrin concentration between patient group and the control group ($p > 0.05$); (ii) Ferritin concentrations had good diagnostic value with confidence interval of 95% (0.784 - 0.924), AUC was 0.862. Iron had little diagnostic value than ferritin in cerebral infarction patients with confidence interval of 95% (0.564 - 0.753), AUC was 0.664; (iii) Analysis of multivariate logistic regression showed that both ferritin and iron have used to predict cerebral infarction (Glasgow = 15), AUC was 0.768 with a sensitivity and specificity of 77.78% and 64%, respectively; (iv) Ferritin levels correlated with cerebral infarction lesion size > 2cm, higher than serum iron, with AUC was 0.91. With the choice of cut-off point ≥ 403.1, specificity was high (approximately 92%). **Conclusions:** The concentration of serum ferritin, iron was high and correlated with severity in cerebral infarction patients with acute phase.

Key words: *Serum ferritin, transferrin, iron, cerebral infarction, acute phase.*

1. BACKGROUND

Cerebral vascular accident types and cerebral infarction have occurred very popular and fairly high proportion become a matter of medical urgency for all countries in the world. Severe situation, sudden onset, high mortality rate, severe neuropsychiatric sequelae, requiring long-term care and treatment, reducing quality of life, increasing the burden on family and society are the significant concerns of this disease. There have been many advances in stroke research sincemost neuroscientists agreed that the current diagnostic field has made remarkable progress over the treatment field. The scientific studies also showed that prevention of risk factors of stroke (hypertension, diabetes, dyslipidemia, transient cerebral infarction,...) have contributed significantly to the decrease of cerebral infarction rate. Lots of topics, many works have been carried out to understand the pathogenesis of cerebral infarction, especially risk factors in order to control the development of this dangerous disease. In recent years, there has been a lot of researches in the world focused on understanding the role of serum ferritin, transferrin, iron in cerebral infarction and has made some preliminary conclusions. In Vietnam, there are not many studies in patients with cerebral infarction. From above issues, we made this subject with two objectives:

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1. To determine the concentration of serum ferritin, transferrin, iron in patients with cerebral infarction.

2. To evaluate the correlation between these factors with severity levels in patients with cerebral infarction.

2. SUBJECTS AND METHODS

2.1. Disease group

52 patients aged 18 or older, treating at the Department of Internal Medicine, Hue University Hospital with a confirmed diagnosis of cerebral infarction, including clinical symptoms combined with computerized tomography brain scan (CTScan or MRI).

We did not put on the team in the following cases:

- Paralysis after focal partial epilepsy, epilepsy or history of epilepsy.
- The other intracranial diseases, such as brain tumors, cerebral hemorrhage, transient cerebral infarction, intracranial abcess, ...
- Cerebral infarction including these conditions: cancer, systemic disease, alcoholism,...

2.2. Control group

52 normal people agreed to participate in research, had health checked and blood tests made at Hue University Hospital at the time of the study.

Age, gender was similar with the disease group.

2.3. Research methodology

We used cross-sectional descriptive methods.

2.3.1. Clinical examination methods:

Taking history, medical history, thorough clinical examination were used to select research subjects, and assesse risk factors.

Diagnosis of cerebral infarction was based on clinical and subclinical criteria.

* Clinical: Based on WHO definition of cerebral infarction in 1998.

* Subclinical: computerized tomography brain scan (CTScan)

Cerebral infarction: density of 20-40 HU units

* Phase Diagnosis: At S.Oppenheimer and V.Hachinski.

Acute phase: ≤ 1 week; subacute phase: 2-4 weeks; chronic phase: > 4 weeks

2.3.2. Functional exploration methods:

Computerized tomography brain scan, ECG, chest X ray, carotid Doppler ultrasound, echocardiography.

2.3.3. Laboratory test methods:

Quantify ferritin, transferrin, iron, blood counts, blood sugar, and lipid profile at presentation.

- Management of data on SPSS 15.0 program.

3. RESULTS

3.1. Age distribution between patients and control group

Table 3.1. Age distribution between patients and control group

Group / Age	Patient group (n=52) ($\overline{X}$ ± SD)	Control group (n=52) ($\overline{X}$ ± SD)	p
Mean age	64.90 ± 11.85	65.17 ± 11.48	> 0.05
Minimum Age	44	44	
Maximum Age	89	86	

The above table showed the average age of cerebral infarction group was 64.90 ± 11.85 and 65.17 ± 11.48 in control group, and there was no similarities between the 2 groups, p > 0.05.

3.2. Comparing levels of serum ferritin, transferrin and Fe in patient group and control group

Table 3.2. Comparing levels of serum ferritin, transferrin and Fe in patient group and control group

Parameters		Cerebral infarction	Control Group	p
Ferritin (mg/L)	Average	378.4 (198.89)	164.76 (55.21)	< 0.001
	Median	319.4 (106.7 – 784.5)	153.9 (87.14 – 289.24)	
Fe (mmol/L)	Average	25.2 (14.9)	15.1 (5.3)	< 0.01
	Median	18.3 (7.3 – 58.3)	14.4 (5.9 – 39.9)	
Transferrin (g/L)	Average	2.6 (0.6)	2.4 (0.4)	> 0.05
	Median	2.5 (1.6 – 4.4)	2.5 (1.5 – 4.4)	

The average concentration of ferritin, Fe in patient group were higher than in the control group with $p < 0.001$ and $p < 0.01$, respectively. There was no significant difference of average concentration of transferrin in the disease group and the control group, $p > 0.05$.

3.3. Value of the area under the ROC curve (AUC) of ferritin, Fe levels in patients with cerebral infarction

Table 3.3. The area under the ROC curve of ferritin, Fe levels in patients with cerebral infarction

	The area under the ROC curve (AUC)	Standard error	CI 95 %
Ferritin (mg/L)	0.862	0.036	0.784 – 0.924
Fe (mmol/L)	0.664	0.055	0.564 – 0.753

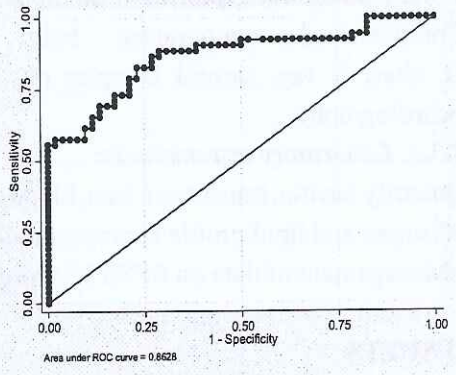

Chart 3.1. ROC curve of Ferritin in acute cerebral infarction

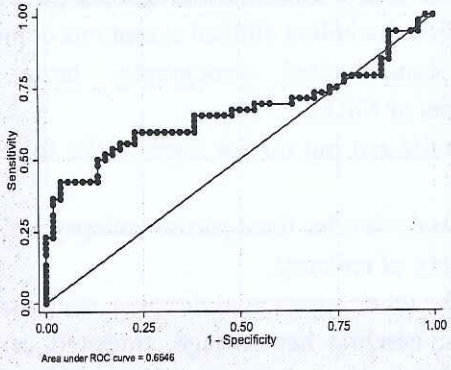

Chart 3.2. ROC curve of Fe in acute cerebral infarction

The results in table and chart above showed that ferritin has good diagnostic value with confidence interval of 95% (0.784 - 0.924), the AUC was 0.862. Fe level has little diagnostic value than ferritin level in cerebral infarction patients with confidence interval of 95% (0.564 - 0.753), the AUC was 0.664.

3.4. Limit cut-off value of ferritin, transferrin and Fe concentration in patient group

Table 3.4. Limit cut-off value of ferritin concentration, transferrin and Fe in patient group

Parameter	Area	Cut point	Sensitivity	Specificity	p	CI 95%
Ferritin (mg/L)	0.8628	≥ 164.4	69.23	82.69	0.8636	0.78-0.92
Transferrin (g/L)	0.5501	≥ 2.33	46.15	50	0.6204	0.44-0.64
Fe (mmol/L)	0.6646	≥ 16.8	44.23	85.54	0.4688	0.56-0.75

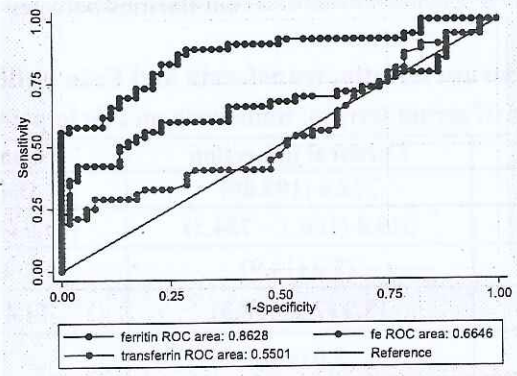

Chart 3.3. ROC curve of the concentration of ferritin, transferrin, Fe in patients with cerebral infarction

The results showed that ferritin has the best diagnostic value compare to serum transferrin and Fe, with the largest area (0.86).

Table 3.5. Diagnostic value of serum ferritin, Fe and transferrin in patients with cerebral infarction

Parameter	AUC	Log	Cut point	Sensitivity	Specificity	Increase (n %)
Ferritin (µg/L)	0.86	-45.0	**≥ 164.4**	**90.38%**	61.54%	46 (88.46)
Transferrin (g/L)	0.55	-70.73	≥ 2.33	59.62%	36,54%	30 (57.69)
Fe (µmol/L)	0.66	-61.9	≥ 16.8	59.62%	76.92%	30 (57.69)

Ferritin concentrations had the best diagnostic value with the largest log. With the choice of cut points of ferritin ≥ 164.4, the sensitivity was approximately 91%.

3.5. The correlation between the concentration of serum ferritin and Fe with lesion size on CT Scan and Glasgow

3.5.1. Limit cut-off value of serum ferritin and Fe in assessing the prognosis of severity level in patients with cerebral infarction (Glasgow score 15 and under 15)

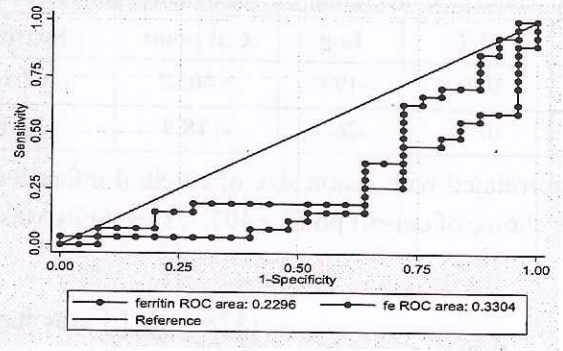

Chart 3.4. ROC curve of serum ferritin and Fe in prognosis patients with Glasgow score 15 (Glasgow score 15 at administration and under 15)

Table 3.6. The model of multivariate logistic regression between Glasgow classification and ferritin, Fe

Glassgow=15	coefficient	Standard error	p	CI 95%	Sensitivity	Specificity
Ferritin	-0.008	0.003	0.01	-0.014;-0.001	77.78%	64.00%
Fe	0.036	0.039	0.35	-0.041;0.114		
Block point	2.185	0.749	0.004	0.717;3.654		

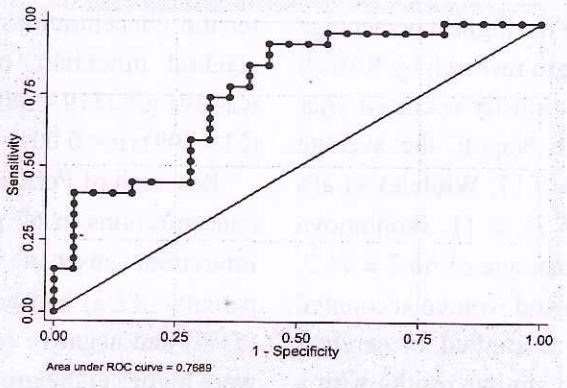

Chart 3.5. ROC curve of Fe and ferritin combination in prognosis (Glasgow score = 15)

The results in graph and table above showed that both ferritin and Fe used to predict patients with Glasgow score = 15, AUC was 0.768, sensitivity and specificity was 77.78% and 64%, respectively.

3.5.2. Limit cut-off point of serum Fe and ferritin concentration with lesion size on cranial CT (less than 2 cm and above)

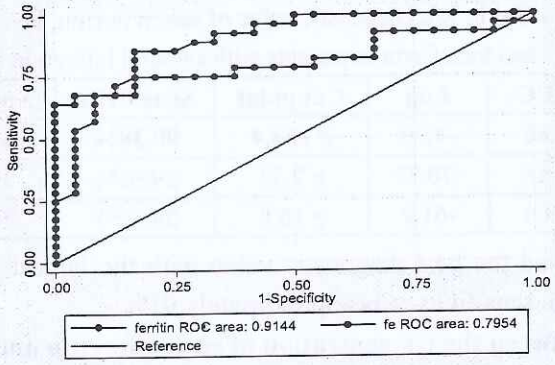

Chart 3.6. ROC curve of serum ferritin and Fe by lesion size on cranial CT Scan

Table 3.7. Limit cut-off point of serum Fe and ferritin concentration with lesion size on cranial CT (less than 2 cm and above)

Parameter	AUC	Log	Cut point	Sensitivity	Specificity
Ferritin (µg/L)	0.91	-19.6	**≥ 403.1**	67.86%	**91.67%**
Fe (µmol/L)	0.79	-26.3	**≥ 18.9**	75.00%	**83.33%**

Ferritin concentrations correlated with lesion size of cerebral infarction > 2cm, higher than serum Fe, AUC was 0.91. With the choice of cut-off point ≥ 403.1, specificity was high (approximately 92%).

4. DISCUSSIONS

We studied 104 cases including 52 cerebral infarction patients and 52 control subjects: the average age was 64.90 ± 11.85 in the patient group and 65.17 ± 11.48 in control group, no significant difference with p > 0.05. This result was consistent with epidemiological studies cerebral vascular accident by many authors in the country and the world. Hoang Khanh, Le Van Thanh found age of the patient group was 65-74 According to Tran Van Tuan et al, prevalence increases with age, the age group over 60 accounted for the highest percentage was 76.75%, and according to research by Russell (1983) in the United States mostly occurred after age 55. In the study of Di Napoli, the average age of patients was 73.01 ± 9.17. Whiteley et al's study results mean age of 72 ± 11. Ikonomova K. et al also resulted in mean age of 66.7 ± 11.2, males accounted for 67.5% and women accounted for 32.5%. Mozosa I. et al studied in cerebral infarction patients also had similar results with a mean age of 65 ± 18.

The result of our study found that the average concentration of ferritin in the patient group (378.4 µg/L) was higher than the control group (164.76 µg/L) with p < 0.001; serum average concentrations of Fe in cerebral infarction patients was 25.2 µmol/L and 15.1 µmol/L in the control group with p < 0.01. Compared to some of the world's research, the results found in this study tended to support the view that increasing serum ferritin, Fe will increase risk of cerebral infarction, contributing to the prevention and treatment cerebral infarction during the acute phase. According to the study of Dávalos A et al, plasma ferritin concentrations in 100 patients with acute cerebral infarction, mean ferritin concentration was 391 g/L (119 - 500), control group was 148 g/L (21 - 399) (p < 0.001).

Research of Fernandez - Real JM et al, ferritin concentrations in 67 patients with acute cerebral infarction, onset < 24 hours, resulting in 33 patients (49%) had good results, and 34 patients (51%) had negative results. Serum ferritin values were higher in the group of bad results (218 ± 156 µg/L compared to 133 ±125 µg/L, p = 0.004).

Along with above studies, Roest M et al studied 63 patients with cerebral infarction, they

found that patients with high serum ferritin concentration (> 200 μg/L) had the risk of stroke 2 times compare to group having normal or lower serum ferritin levels (HR: 2.5, 95% CI: 1.16 - 5.37).

The study of B Chakraborty et al on 100 patients, the results also showed that ferritin concentrations was ≥ 370 μg/L, much higher than the control group ($p < 0.0001$).

The results of our study and several studies around the world showed that the increase of serum ferritin, Fe was the threat against the risk of cerebral infarction. Research related to the severity and stroke prognosis has demonstrated that serum ferritin, Fe was an important predictor of mortality and neurological damage.

But when we study transferrin concentration, we found that there was no difference between the two groups. This result was different from studies of Domenico L et al. That study showed that transferrin had a strong relationship to assess clinical status, it inversely correlated with lesion size of cerebral infarction. This research also showed that transferrin may play a protective role in the early stages of stroke, can interfere with the oxidation and limit the expansion of the damage. Our study was limited in determining the concentrations of transferrin in relation to cerebral infarction because of small sample size. So, the near future studies are needed to confirm these data in a larger sample and better define the biological mechanisms. It is necessary to examine the prognostic value and reliability of transferrin to predict clinical progression in the acute phase of stroke.

Studying correlations between concentrations of serum ferritin, transferrin and Fe with the severity of cerebral infarction by Glasgow scale and lesion size of cerebral infarction showed a positive correlation between ferritin levels with lesion size of cerebral infarction ($r = 0.8055$, $p < 0.001$). Ferritin concentrations correlated with lesion size of cerebral infarction > 2 cm, at the same cut-off point the sensitivity and specificity was highest compared with the serum Fe and transferrin. With the choice of ferritin cut-off point ≥ 403.1, the specificity was high (approximately 92%).

According to the research results, we found that ferritin and Fe did not have good prognostic value in the severity of disease with admission Glasgow score of 15. This can be explained by the characteristics of the study group that patients hospitalized with conscious state, Glasgow score was not lower than 13. But when using a combination of both ferritin and Fe to predict patients with Glasgow score = 15, there were more positive values, the AUC was 0.76 with a sensitivity and specificity of 78 % and 64 %, respectively.

Other previous studies also confirmed the role of serum ferritin and Fe in cerebral infarction. In our study, logistic regression equation of ferritin AUC was 0.8628, the sensitivity was 69.23%, a specificity of 82.69%. Similar to Fe, the AUC was 0.664, sensitivity was 44.23%, and specificity was 86.54%.

Thus, we can see both ferritin and Fe have good specificity. This means that the high concentration of serum ferritin and Fe will lead to high risk of cerebral infarction, > 80%. But not any acute cerebral infarction patients had high ferritin and Fe level, which represented in the sensitivity of Fe and ferritin. Moreover, we also understand the factors leading to cerebral infarction was very diverse, not only Fe and ferritin. Analysis of this issue showed that Fe and ferritin were also valuable not only for prevention but also for diagnosis of cerebral infarction.

Our study was consistent with researches in the world, in recent years there have been many studies on the world discovered the role of the concentration of serum ferritin, transferrin, Fe in the risk of acute cerebral infarction, as well as contribute to the diagnosis, early treatment and prognosis of the disease:

Research of Stankiewicza JM and SD Brassa in Neurology Harvard Medical School, U.S. showed that Fe balance disorder caused acute of cerebral infarction. In recent years, significant evidence has highlighted the role of Fe in neurotoxicity in of cerebral infarction patients. Understanding this issue may provide new therapeutic targets to improve outcomes of stroke patients.

Research Millerot - Serrurot E. et al (France) found an increase in levels of serum ferritin, Fe in patients with cerebral infarction patients ($p < 0.001$) and offer early treatment to prevent the absorption of Fe (chelation therapy) by putting restrictions on supplement and used 2,2'-dipyridyl.

Research of M. Millan et al on 134 cerebral infarction patients treated by rtPA, ferritin concentrations, Fe, IL-6, glutamate also noticed. The high ferritin concentrations was associated to the severity of cerebral infarction patients, studies have also identified correlation between ferritin

and glutamate ($r = 0.59$, $p < 0.001$), between ferritin and IL - 6 ($r = 0.55$, $p < 0.001$).

Research of Emre U. (Turkey) on the role of acute phase reactants in 43 acute cerebral infarction patients and 37 control subjects, ferritin concentration results, CRP, fibrinogen,... in acute cerebral infarction patients was higher than that in the control group ($p < 0.01$).

The most recent study of Dubyk MD (Canada) on 94 patients with acute cerebral infarction and transient stroke, concentrations of ferritin, transferrin, Fe also demonstrated that higher levels of ferritin related to the severity of disease ($p < 0.001$).

5. CONCLUSIONS

There was an increase in the concentration of serum ferritin, iron in patients with acute cerebral infarction. There was a correlation between the concentration of ferritin, iron with the severity of the disease according to the size of cerebral infarction and Glasgow scale.

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