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Research Article

SERUM FERRITIN LEVELS AS A PROGNOSTIC INDICATOR IN ACUTE ISCHEMIC STROKE: A COMPREHENSIVE CLINICAL STUDY

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ABSTRACT

Objective: This clinical study investigates the potential of serum ferritin levels as a prognostic indicator in acute ischemic stroke.

Methods: This cross-section study included 75 patients enrolled in our outpatient clinic, General Medicine Department, and SMS Medical College. The study enrolled all patients who had a new onset focal neurological deficit due to a stroke. A total of 75 patients (25 in each group (mild/moderate/severe) as per the National Institute of Health Stroke Scale scoring) of >14 years old, presenting in the general medicine wards were enrolled for the study. The study assesses the correlation between serum ferritin levels and various clinical parameters, including stroke severity, consciousness status, and disability outcomes.

Results: Severe group had the highest average blood ferritin level (408.48 with a standard deviation (SD) of 68.63). A significant relationship was observed between ferritin levels and loss of consciousness. In addition, the mean ferritin residue ratio (MRS) also correlated with ferritin levels, with MRS correlating to ferritin levels. A significant association between elevated serum ferritin levels and severe stroke, as well as unfavorable outcomes.

Conclusion: The findings suggest that serum ferritin could serve as a promising prognostic index in acute ischemic stroke, aiding in patient risk stratification and clinical decision-making.

Keywords: Serum ferritin, Acute ischemic stroke, Prognostic indicator, Stroke severity, Consciousness status, Disability outcomes.

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INTRODUCTION

Stroke, according to the WHO, is defined as "a rapidly progressing clinical manifestation of focal (and in some cases global) brain dysfunction that lasts more than 24 h, or without apparent signs leading to death." Clinical syndrome: Stroke has now overtaken heart disease, cancer, and diabetes as the most common, potentially fatal, preventable neurodegenerative disease. According to the Indian Council of Medical Research, diabetes and stroke caused $46 billion economic losses in India from 2006 to 2015 [1]. In medical practice, stroke and cerebral accidents (CVAs) can be categorized as follows: Ischemic strokes: Strokes that are ischemia and hemorrhage-free but do not involve bleeding around the brain. About 80% of CVA cases are caused by a lack of blood flow to the brain. The remaining 20% are caused by brain hemorrhage. When something blocks a blood vessel in the brain, a stroke is an ischemia.

Vascular inflammation and coagulation are both thought to be involved in the formation of the blood clot. These theories suggest that coagulopathy and vascular abnormalities may be associated with an increase in the likelihood of either a hematologic or ischemic stroke, as a result of interactions between these risk factors [3,4] and other risk factors [5]. Evidence from acute stroke (a condition in which prognostic factors are poor) [6] supports this hypothesis.

It is generally thought that the brain is more susceptible to hypoxic injury than other organs in the body. This is largely due to the high concentration of glutamate (a neurotransmitter) in the brain, as well as the relatively high level of metabolic activity. Hypoxic injury can also be caused by an occlusive cerebral artery, such as an embolism or an intracellular thrombus [7,8].

Lipid peroxidation, to which iron contributes, results in the activation of membrane-binding enzyme complexes, reduced membrane fluidity, cell membrane breakdown, and ultimately cell death. Therefore, tissue iron content and lipid peroxidation are thought to be related [9,10]. Ferritin is the positive acute phase iron storage protein. It is the primary protein responsible for storing iron within cells [11,12]. The main control of cellular ferritin level is the level of free iron intracellularly. Thus, ferritin provides a method to safely store the metal within the cells. Although ferritin occurs in blood in very small amounts, its function is as yet unknown. Serum ferritin has been used extensively in clinical practice, mainly as a measure of body iron stores [13-15].

Even with extensive research on the topic of stroke, predicting an acute attack may be challenging. Future prognostic biomarkers are currently being studied, such as stroke hyperglycemia, stroke infection, stroke TNFa, or interleukin, among others. Serum ferritin is one of the predictive biomarkers that have recently gained considerable clinical attention. Serum fibrillation was initially thought of as a stress-related response to stroke but is now being studied as a prognostic marker [16-18].

Serum ferritin testing helps identify high-risk individuals due to the close relationship between the early neurological decline in stroke patients and serum ferritin levels.

METHODS

This cross-section study included 75 patients enrolled in our outpatient clinic, General Medicine Department, SMS Medical College, and its associated network of hospitals. All patients provided written informed consent before enrolment in this study. This hospital-based comparative observational study is scheduled to commence in May 2020 with a full year of follow-up. A randomized, stratified sample of 25 patients (mild, moderate/severe) was selected based on their National Institute of Health Stroke Scale (NIHSS) scores.

The study enrolled all patients who had a new onset focal neurological deficit due to a stroke. Patients who arrived within 48 h after the onset of the stroke were excluded from the study. Patients with bleeding-related characteristics, such as recent surgery or trauma, tumors in the central nervous system, cancer, transient ischemic attacks, reversible ischemic neurological impairment (RIA), or CVAs were also excluded from the study.

Blood samples were taken to measure serum ferritin levels. Baseline clinical data were collected based on demographics, medications, and biochemistry. Each registered patient had their personal and family medical records as well as a complete medical history. The Institution's Ethics Committee gave permission to conduct the study.

Statistical analysis

The data were analyzed and statistical analysis was performed using SPSS -PC-20 (SPSS Version 20) software (SPSS, Inc., Chicago, IL, USA). The data were presented as a mean and SD for continuous variables (normal distribution) and as a frequency for the categorical variables (range). The means were compared between the two samples using the Student's t-test (Student's t) for the continuous variables and x2 analysis (x2) for the categorical variable. The level of significance was p=0.05 for all statistical analysis.

RESULTS

In total, 75 patients were enrolled (25 patients in each group based on NIHSS score (mild, moderate/severe). Table 1 shows the age and gender distribution of patients in the study population. Maximum patients (40%) were observed in all three study groups. Mean ages observed in the mild, moderate, and severe groups were 51.96/18.79/17.89/49.24/20. 13 years. Maximum patients (72/68/68) in the mild, medium, and severe study groups were 72/68/68 males, suggesting a male-to-male predominance. Chi-square statistical analyses revealed an insignificant (p<0.05) age-to-gender association between the three study groups (Table 1).

Table 2 shows the study population by serum ferritin level, with the severe group having the highest average blood ferritin level (408.48 with SD of 68.63). An analysis of variance (ANOVA) statistical analysis revealed a statistically significant relationship between the three study groups, with p=0.05 (Table 2).

Table 3 shows the distribution of the study population by degree of loss of consciousness. Patients in the mild study group were up to 60% conscious, up to 56% semi-conscious in the moderate study group, and up to 76% unconscious in the severe study group. Chi-square statistical analysis showed a statistically significant relationship between the three study groups in terms of loss of consciousness (p=0.05) (Table 3).

Table 4 shows the proportion of patients in the study population based on MRS score. The MRS score in the mild group was 100% below 3. The MRS score was 100% above 3 in the moderate group and 100% above 3 in the severe group. Chi-square statistical analysis showed a significant statistical relationship between MRS scores in each of the study groups. The p-value for each study group was 0.05 (Table 4).

Patients who were conscious, semi-conscious, and unconscious demonstrated a correlation between ferritin and consciousness levels, as indicated by mean ferritin levels in Table 5. The ANOVA statistical analysis revealed a statistically significant relationship between ferritin levels and loss of consciousness (p=0.05). In addition, the mean ferritin residue ratio (MRS) was also correlated with ferritin levels, with MRS correlating to ferritin levels using a single sample t-test statistical analysis (Table 5).

DISCUSSION

The results of a stroke may vary depending on the location and extent of brain damage. The degree of RIA after a stroke can be evaluated through the use of scales such as the Glasgow coma scale, the NIHSS, and the Canadian stroke scale [19].

While the reliability of risk variables such as blood pressure, smoking, diabetes, and dyslipidemia is not yet fully established, there is still considerable debate and research into the adequacy of prognostic indicators and the ability to predict the occurrence of strokes. Recently, there has been an increase in interest in strokes. Some studies suggest that ferritin may affect the prognosis of ischemic stroke and contribute to ischemia. In this study, the majority of patients (100%) in the mild group had mild (1–4) score, the majority (70%) in the moderate group had intermediate (5–15) score and the majority (80%) in the severe group had severe (>15) score mic episodes due to increasing atherogenesis [16].

Patients in this study ranged in age from 41 to 50 years old, with a maximum patient prevalence of 18.67%. The mean age of the mild and moderate groups was 51.96 and 51.79 years, respectively, while the mean age of the severe and severe groups was 51.4 and 49.13 years, respectively, with a maximum of 40% of patients in each group. About

Table 1: Distribution of study population according to age group

Age group	Group mild		Group moderate		Group severe		p-value
	Frequency	%	Frequency	%	Frequency	%	
<20	2	8	2	8	5	20	0.079
20–30	2	8	2	8	0	0	
31–40	3	12	2	8	3	12.0	
41–50	5	20	5	20	4	16	
51–60	3	12	4	16	3	12	
>60	10	40	10	40	10	40	
Total	25	100.0	25	100.0	25	100.0	
Mean	51.9600	18.79379	51.4000	17.89786	49.2400	20.12726	
Gender							
Female	7	28.0	8	32.0	8	32.0	1.09
Male	18	72.0	17	68.0	17	68.0	

Table 2: According to serum ferritin level

Parameters	Group mild		Group moderate		Group severe		Analysis of variance statistical analysis	
	Mean	SD	Mean	SD	Mean	SD	F-statistic	p-value
Serum Ferritin	155.2	102.17	305.84	66.08	408.48	68.63	32.541	0.022*

SD: Standard deviation, *p<0.05 is significant

Table 3: According to loss of consciousness

Loss of consciousness	Group mild		Group moderate		Group severe	
	Frequency	%	Frequency	%	Frequency	%
Conscious	15	60.0	1	4.0	0	0
Semi-conscious	10	40.0	14	56.0	6	24.0
Unconscious	0	0	10	40.0	19	76.0
Total	25	100.0	25	100.0	25	100.0
p-value	0.001*					

*p<0.05 is significant

Table 4: According to MRS score

MRS score	Group mild		Group moderate		Group severe	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
<3	25	100.0	0	0	0	0
≥3	0	0	25	100.0	25	100.0
Total	25	100.0	25	100.0	25	100.0
p-value	0.011*					

*p<0.05 is significant

Table 5: Correlation between ferritin and consciousness levels

Loss of consciousness	Mean ferritin		p-value
	Mean	SD	
Conscious	87.5625	60.76728	0.023*
Semi-conscious	277.4667	35.92687	
Unconscious	414.2414	53.14311	
MRS			
<3	155.2000	102.17999	0.003*
≥3	357.1600	84.46358	

*p<0.05 is significant

37% of the patients were female, and 69% were male, indicating a male-to-female ratio of 72%, 68%, and 68%, respectively. Similar to our findings, Mahur *et al*. study [20] showed a male predominance with a mean age of the patients of 63.40 years.

Serum FIT is primarily used in clinical medicine to evaluate the body's iron reserves. In addition, iron plays a role in the development of ischemic stroke through the activation of platelets through the Protein kinase C mechanism. In acute stroke patients with elevated serum ferritin, poor prognosis was observed when admitted within 24–48 h of the onset of the stroke. This suggests that an elevation of body iron reserves before the stroke may have contributed to the exacerbation of brain ischemic cytotoxicity. Furthermore, increased iron levels may increase the risk of ischemia events due to an increase in atherogenesis [21].

Serum ferritin has not been extensively studied in India. Hence, the present study focused on the relationship between serum ferritin and the prognosis of ischemic stroke severity. In this study, average serum ferritin concentrations increased with stroke severity. Age was not statistically related to ferritin ($p<0.05$). Hypertension and ferritin were statistically related ($p=0.05$).

Blood ferritin at admission in patients with severe stroke, moderate stroke, mild stroke, and less severe stroke was 337.41, 285.56, and 197.91 nl/mL in patients who did not worsen, and 178.76 nL/mL, 285.56 mmoL/moL, and 341.91 mmoL/moL in participants who did worsen.

In our study, there was a statistically significant association between the levels of ferritin in the blood of the participants in the three study groups ($p<0.05$). Furthermore, based on the findings of Thanicachalam *et al*. [21], there is a significant positive relationship between the level of ferritin present in the blood and the degree of acute ischemic stroke severity at admission. As a result, ferritin may serve as a prognostic factor in acute ischemic strokes.

The correlation between serum ferritin levels and NIHSS scores was statistically significant ($p=0.000$) in a study by Gupta *et al*., published in the Journal of Neurology [22]. The modified Rankin score as well as the NIHSS, which is used to evaluate the severity of the stroke, was also highly correlated with serum ferritin concentrations in a study by Koul, published in the journal of neuropsychopharmacology [23]. In other words, the degree of stroke at admission is correlated to serum ferritin concentration on the day of admission.

One possible explanation is that high levels of ferritin in the serum indicate higher levels of iron storage in the brain. Cerebrovascular ischemia causes more iron to be discharged from injured brain cells during a CVA. More iron leads to more oxidative stress. When more iron is discharged into the area surrounding the damaged tissue, more free hydroxy radicals are produced. This increases the risk of further tissue damage during cerebral ischemia. Another possible explanation is that damaged brain cells released more glutamate during ischemia, which further damages the tissue. Both of these mechanisms lead to further tissue injury during ischemia [24,25].

CONCLUSION

According to our analysis, men predominate. The severe group had the highest mean blood ferritin levels, which were strongly related to all three research groups. According to the research, serum ferritin may be a useful prognostic indicator for acute ischemic stroke patients, helping with patient risk classification and clinical judgment.

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AUTHORS' CONTRIBUTION

All the authors have contributed equally.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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