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Original Research Article

Evaluation of serum ferritin as a prognostic marker in acute ischemic stroke: a prospective observational study

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ABSTRACT

Background: Stroke is an important health problem causing of morbidity and mortality globally. Serum ferritin has gained clinical significance as a prognostic factor that can aggravate the cytotoxicity of brain ischemia. The present study investigated the prognostic significance of serum ferritin levels with the severity of stroke using NIHSS scale.
Methods: It was a prospective observational study conducted on 60 patients with acute ischemic stroke admitted in the general medicine department of a tertiary care teaching hospital. Serum ferritin levels were assessed on all participants using the instrument "immulite". National institute of health stroke scale scoring was applied at the time of admission and on the seventh day to assess the impairment caused by a stroke. IBM SPSS version 22 was used for statistical analysis.
Results: The mean serum ferritin levels at admission in patients with severe stroke, moderate stroke and mild and less stroke were 337.41±58.76, 285.56±49.37, and 197.91±111.01 ng/mL, respectively. The mean serum ferritin levels at admission were 178.76±114.70 ng/mL and 341.91±62.292 ng/mL in subjects who did not deteriorate and those who deteriorated, respectively. Whereas the mean serum ferritin levels on the sixth day were 198.34±106.88 and 348.10±57.34 ng/mL in subjects who did not deteriorate and those who deteriorated, respectively.
Conclusions: Serum ferritin has a significant positive correlation with the severity of acute ischemic stroke severity on admission ($p<0.001$) and negative correlation with the severity of acute ischemic stroke severity on seventh day of admission ($p<0.001$). Thus, serum ferritin can be used as a prognostic marker in acute ischemic stroke.

Keywords: Ferritin, Prognostic marker, Acute ischemic stroke, Prognostic factor, Brain ischemia

INTRODUCTION

Acute ischemic stroke (IS) is defined as a sudden loss of brain function resulting from severe interference in the flow of blood and oxygen in cerebral arteries. IS has a heterogeneous aetiology caused by modifiable and non-modifiable risk factors. Genetic factors, age and gender are the non-modifiable risk factors. Hypertension, diabetes mellitus (T2DM), dyslipidemia, and smoking are modifiable risk factors.[1] Reports have demonstrated the increased burden of IS worldwide in the last 25 years, especially in developing countries.[2]

After acute myocardial infarction and malignancy, ischemic stroke is the third leading cause of death and disability. As per Indian council medical research (ICMR) reports, stroke and diabetes together brings the estimated national economic loss of approximately 46 billion dollars in India between 2006 to 2015. India's growth of gross domestic product (GDP) is estimated to fall by 1%.[3]

Ferritin (Ft) is intracellular iron storage protein located within the body cells.[4] Serum Ft has been used widely in clinical medicine chiefly as an indicator of body iron stores. It is an acute-phase reactant involved in cellular defence against oxidative stress and inflammation along

with transferrin. Iron also plays a role in ischemic stroke by activating platelets via a protein kinase-C mechanism. Another proposed mechanism of ferritin in ischemic vascular disease, is through reperfusion injury. After the event of ischemic stroke, reperfusion causes marked increase in oxygen-radical production as well as a release of iron ions, causing further tissue damage and cellular death.[5,6]

Recent animal experiments have suggested that iron overload contributes to the vascular diseases development by promoting thrombosis after arterial injury.[7] High serum ferittin on admission of acute stroke patients (within 24 to 48 hours after stroke onset) had poor prognosis implicating that increase in body iron stores before stroke onset can aggravate the brain ischemia cytotoxicity. It also acts as a risk factor for ischemic episodes by enhancing atherogenesis.[8] There are only limited studies in India to assess the serum ferritin levels on stroke prognosis. Hence, the present study investigated the prognostic significance of serum ferritin levels with the severity of ischemic stroke.

METHODS

Current study was a prospective observational study conducted on 60 patients with acute ischemic stroke admitted in the general medicine department of a tertiary care teaching hospital. The study was conducted from May 2019 to June 2020 after obtaining approval from institutional ethics committee.

Inclusion criteria

Both male and female subjects with age ≥18 years were included in the study. Subjects with onset of acute ischemic stroke symptoms presented within 48 hours were diagnosed based on clinical examination and neuro-imaging (computed tomography/magnetic resonance imaging brain).

Exclusion criteria

Subjects who presented with symptoms of acute ischemic stroke after 48 hours were excluded. Subjects with recent infection, malignancy, anemia, or liver failure and those who had received blood/blood component transfusion in the previous 7 days were excluded from the study.

Once subjects got admitted, written informed consent was obtained from patient or attenders. Complete relevant medical history, neurological examination, routine blood and CT scan were recorded in a standardized proforma. CT scan was taken to exclude the haemorrhagic stroke. Furthermore, serum ferritin laboratory investigations were assessed on all subjects using the instrument "immulite" based on the principle of "chemiluminescence". National institute of health stroke scale (NIHSS) scoring was applied at the time of admission and on the seventh day to assess the impairment caused by a stroke. NIHSS is composed of 11 components, which scores a specific ability between 0 and 4. Cranial nerve/visual disturbances, level of consciousness, motor weakness and language were the four important parameters. Total scores ranges from 0-42 with higher values representing more severe infarcts.[9] In this study, patients with a score of 1-4 were considered as mild, score 5-15 were considered as moderate, score >15 were considered as severe category. On the seventh day of admission, the stroke severity was re-assessed clinically using NIHSS and serum ferritin levels were again measured in all the subjects. The NIHSS scores at admission and on the seventh day were then compared and the patients were categorized into two groups; "not deteriorated" group (patients in whom, over the course of 7 days, the NIHSS scores decreased or remained the same) and "deteriorated" group (patients in whom the NIHSS score increased). The mean admission-day and seventh day serum ferritin levels were determined in each of these groups, and the comparison between the two groups ("not deteriorated" and "deteriorated") was then made using the Student's t-test. For normally distributed Quantitative parameters the mean values were compared between study groups using independent sample t-test (2 groups) and ANOVA test (>2 groups). $p<0.05$ was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.

RESULTS

A total 60 patients were included into the final analysis. The mean serum ferritin at admission was 247.50±123.3 ng/ml in the study population. The mean NIHSS score was 9.42±3.89 in the study population. The mean serum ferritin on seventh day was 206.34±113.28 ng/ml in the study population. The mean NIHSS score on seventh day was 9.42±3.09 in the study population (Table 1).

The mean serum ferritin at admission within upto 50 years was 257.83±120.53 ng/ml, it was 260.92±117.83 ng/ml in 51 to70 years, and 220.65±138.47 ng/ml in 70 years and above, and it was not statistically significant (p=0.555). The mean serum ferritin at seventh day up to 50 years was 266.25±103.72 ng/ml, 279.18±107.34 ng/ml in 51 to 70 years and 223.63±128.65 ng/ml in 70 years and above, and was statistically not significant (p=0.278).

The mean NIHSS score at admission up to 50 years was 8.16±1.81, 9.41±2.32 in 51 to 70 years and it was 7.98±1.52 in 70 years and above, and was statistically not significant (p=0.07).The mean NIHSS scores at seventh day within up to 50 years was 8.02±2.02, it was 9.13±3.51 in 51 to 70 years and it was 8.29±2.64 in 70 years and above, and was statistically not significant (p=0.473). There were no statistically significant gender differences in serum ferritin and NIHSS score levels on admission and on the seventh day (Table 2).

Table 1: Serum ferritin and NIHSS scale score at admission and on the tenth day (n=60).

Parameters	Summary statistics (range)	Confidence interval	
		Lower	Upper
Serum ferritin at admission (ng/ml)	247.50±123.3 (67 to 465)	216.30	278.69
NIHSS at admission	9.42±3.89 (5 to 27)	8.44	104.0
Serum ferritin on seventh day (ng/ml)	206.34±113.28 (97 to 462)	231.68	289.0
NIHSS on seventh day	9.42±3.09 (6 to 31)	8.64	10.20

Table 2: Comparison of outcome parameters across the age group and gender (n=60).

Parameters	Outcome			
	Serum ferritin at admission	**Serum ferritin at seventh day**	**NIHSS score at admission**	**NIHSS score at seventh day**
Age group (years)				
≤50 (N=12)	257.83±120.53	266.25±103.72	8.16±1.81	8.02±2.02
51-70 (N=32)	260.92±117.83	279.18±107.34	9.41±2.32	9.13±3.51
>70 (N=16)	220.65±138.47	223.63±128.65	7.98±1.52	8.29±2.64
P value	0.555	0.278	0.07	0.473
Gender				
Male (N=35)	260.32±126.81	277.21±119.35	8.52±2.82	8.46±3.73
Female (N=25)	236.33±121.02	245.42±107.64	7.96±2.72	8.85±2.45
P value	0.464	0.286	0.442	0.627

Table 3: Correlation between the serum ferritin and NIHSS at different time periods in the study population (n=60).

Parameters	Pearson correlation	Type of correlation	P value
Serum ferritin vs. NIHSS score at admission	0.681	Positive	<0.001
Serum ferritin vs. NIHSS score at seventh day	-0.99	Negative	<0.001
Admission serum ferritin vs. NIHSS score at seventh day	-0.92	Negative	<0.001

Table 4: Comparison of age and serum ferritin values across the different level of strokes (NIHSS) (n=60).

Parameters	Stoke status (NIHSS)			P value
	Mild	**Moderate**	**Severe**	
Age group (years)				
≤50 (n=12) (%)	4 (33.3)	5 (41.7)	3 (25)	0.622
51-70 (n=32) (%)	13 (40.6)	14 (43.8)	5 (15.6)	
>70 (n=16) (%)	3 (18.8)	9 (56.2)	4 (25)	
Serum ferritin at admission (ng/ml)	197.29±113.75	285.56±49.37	337.41±58.76	0.001
Serum ferritin on seventh day (ng/ml)	159.91±111.01	197.45±51.76	290.95±51.05	0.001

There was a moderate positive correlation between serum ferritin and NIHSS score at admission (R value; 0.681, p<0.001). There was a very strong negative correlation between serum ferritin and NIHSS score at seventh day (R value; -0.99, p<0.001).

There was a very strong negative correlation between admission serum ferritin and NIHSS score at seventh day (R value; -0.92, p<0.001) (Table 3). Among participants below 50 years age group, most of them had 5 (41.7%) had moderate stroke among 51 to 70 years age group, 14 (43.8%) people had moderate stroke. The difference in the proportion of NIHSS score across age group was statistically not significant (p=0.622). The mean serum ferritin at admission was 197.91±111.01 ng/ml in mild stroke, 285.56±49.37 ng/ml in moderate stroke and 337.41±58.76 ng/ml in severe stroke.

The mean difference of serum ferritin at admission was statistically significant (p=0.001). The mean serum ferritin on seventh day was 159.91±111.01 ng/ml in mild stroke, 197.45±51.76 ng/ml in moderate stroke and 290.95±51.05 ng/ml in severe stroke. The mean difference of serum ferritin on seventh day was statistically significant (p=0.001) (Table 4).

Table 5: Comparison of age and outcome parameters between the NIHSS scale changes from day 0 to seventh day (n=60).

Parameter	NIHSS changes		Chi square/ T value	P value
	Deteriorated (n=26)	Not-deteriorated (n=34)		
Age group (years)				
≤50 (n=16) (%)	7 (43.75)	9 (56.25)		
51-70 (n=31) (%)	14 (45.16)	17 (54.83)	0.17	0.92*
>70 (n=13) (%)	5 (38.46)	8 (61.53)		
Serum ferritin at admission (ng/ml)	341.91±62.29	179.76±114.70	7.05	<0.001†
Serum ferritin on seventh day (ng/ml)	248.10±57.34	132.34±106.88	6.93	<0.001†
Stroke status				
Mild (n=20) (%)	6 (30)	14 (70)		
Moderate (n=28) (%)	16 (57.14)	12 (42.85)	4.12	0.13†
Severe (n=12) (%)	4 (33.3)	8 (66.6)		

* Chi square test, † Independent sample test.

Among deteriorated and not deteriorated groups the difference in proportion across age groups was statistically not significant (p=0.92). Serum ferritin at admission and on seventh day was more in deteriorated group and it was statistically significant (Table 5).

DISCUSSION

An ischemic stroke occurs due to cessation of blood flow due to extracranial or intracranial thrombosis, embolism, and hypoperfusion. Previous studies have suggested that high iron levels contributed to the vascular disease development by promoting thrombosis after arterial injury. In the present study high serum ferritin levels were observed at admission and positive correlation is reported between serum ferritin and NIHSS score at admission. It indicates poor prognosis in acute stroke patients, aggravating the brain ischemia cytotoxicity. Thus, it has been suggested that high serum ferritin influences the prognosis of ischemic stroke and also acts as a risk factor for ischemic episodes by enhancing atherogenesis.[10,11]

The present study was carried out on 60 patients (35 males and 25 females) with acute ischemic stroke admitted within 48 hours of onset of symptoms. The mean serum ferritin levels at admission and on the seventh day were 247.50±123.3 and 206.34±113.28 ng/ml, respectively. In a similar study by Garg et al the mean serum ferritin levels at admission and on the seventh day were 245.50±121.36 and 259.58±112.25 ng/ml, respectively.[12] The age and gender related variations in the serum ferritin levels and CSS scores at admission and on the seventh day were not statistically significant. Egovindarajulu et al in their study also noted that there was no significant difference in the serum ferritin levels between the two age groups (≤50 years and >50 years) (*p*=0.918).[13]

In current study statistically significantly positive correlation (R value; 0.681, p<0.001), between serum ferritin levels and NIHSS scores at admission, and a significantly negative correlation (R value; -0.99, p<0.001) between serum ferritin levels and NIHSS scores on the seventh day were reported.

The mean serum ferritin in the group with severe stroke on admission was significantly higher than in the group with mild and moderate stroke on admission and on seventh day (p=0.001). Whereas in a study done by Garg et al a statistically significantly negative correlation was observed between serum ferritin levels and NIHSS scores both at admitted and on seventh day of admission.[12] Egovindrajulu et al in their study observed positive correlation between serum ferritin and NIHSS scores (p=0.000).[14]

In another study by Koul et al revealed that there was a significant correlation between the serum ferritin values and NIHSS (p<0.001) and modified Rankin score (p<0.001), both of which are used to evaluate the stroke severity.[13] Therefore, it is suggested that the admission-day serum ferritin correlates with the severity of stroke on admission.

In the present study, 34 participants condition was deteriorated while 26 participants condition was not deteriorated. The mean admission-day serum ferritin in deteriorated patients (341.91±62.292 ng/ml) was significantly higher compared with participants who did not deteriorate (179.76±114.702 ng/ml) (p<0.001).

The mean serum ferritin level on the seventh day was also significantly higher in deteriorated patients (248.10±57.346 ng/ml) as compared to those who did not deteriorate (132.34±106.88 ng/ml) (p<0.001).

Current study was in line with Pankaj et al study, where the mean admission day serum ferritin in the deteriorated group (458.7 ng/ml) was significantly greater compared to the clinically improved group (87.01 ng/ml) among acute ischemic stroke patients.[14] Similarly, Narayan et al observed that mean serum ferritin in was significantly higher in deteriorated patients was (463.91 ng/ml), compared to improved patients (96.44 ng/ml).[15]

The proposed mechanism behind this is that higher serum ferritin levels indicate higher iron stores in the brain. When brain ischemia occurs during cerebrovascular accident, injured brain cells release more iron. When more iron is released into the local environment of the injured tissue, there is more oxidative stress through generation of free hydroxyl radicals. This results in tissue injury aggravation during ischemia. Another mechanism is that the injured brain cells during ischemia, release more glutamate; the released glutamate further causes tissue injury.[16,17]

The key limitation of the present study is that it is a single-centre study with a smaller sample size. Further multicentre long-term studies are required with respect to treatment modalities to control high serum ferritin levels in ischemic stroke patients.

CONCLUSION

The present study reveals a significant correlation of serum ferritin with the severity of acute ischemic stroke, depicting elevated admission serum ferritin levels with poor IS outcomes. Patients with high serum ferritin levels at admission tend to clinically deteriorate compared with those of lower serum ferritin levels. Hence, this study suggests that serum ferritin can be used as a possible prognostic index for acute ischemic stroke.

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