Original Article

# Association Between Serum Ferritin Level As A Prognostic Factor And Outcome In Patients With Acute Ischemic Stroke

**Dr.R. Bala krishnan[1], Dr.V.R. Mohan Rao[2]**

[1]Final Year Postgraduate, Department of General Medicine, CHRI, Kelambakkam, Tamil Nadu.
[2]HOD, Department of General Medicine, CHRI, kelambakkam, Tamil Nadu.
**DOI:** 10.47750/pnr.2023.14.02.60

## Abstract

**Background:** We planned to assess the serum ferritin levels among ischemic stroke cases and to correlate it with early neurological deterioration and prognosis of acute ischaemic stroke and to find the relationship between serum ferritin and various risk factors for Stroke.

**Methods:** This study was conducted as a cross sectional observational study among patients attending outpatient and inpatient department of General medicine, Neurology and emergency with acute ischemic stroke during August 2022 – November 2022 in Chettinad medical Center Hospital in Chennai. A total of sixty patients with acute ischemic stroke were included in this study. All data was entered in excel sheet and analyzed using SPSS.

**Results:** A significant association between high levels of serum ferritin and severe and poor prognosis cases with acute ischemic stroke. Also, we noted significant rise in serum ferritin in ischemic stroke patients in correlation with high scores with NIHSS which indicates the severity. This study also reveals the poor outcome in correlation with high serum ferritin values and good outcome in correlation with low serum ferritin values, based on Modified Rankin scale. Also, diabetes mellitus and systemic hypertension, alcohol consumption and loss of consciousness were found to be associated with serum ferritin levels, in this study.

**Conclusion:** Increased serum ferritin is linked with poor outcome in AIS cases. Hence more focus to be paid on cases with high serum ferritin and all cases with AIS should be assessed for serum ferritin routinely.

**Keywords:** Acute Ischemic Stroke, NIHSS, Prognosis, Outcome.

## INTRODUCTION

Stroke is one of the most common reasons for mortality, both in developed and developing countries. Among the stroke subtypes of stroke, Ischemic stroke (IS) contributes about 75% of all stroke cases followed by hemorrhagic stroke contributes about 15% of all strokes and the remaining 10% is contributed by all other types of stroke[1]. According to definition of World Health Organization (WHO), Stroke is defined as a clinical syndrome consisting of 'rapidly developing clinical signs of focal or global disturbance of cerebral function, with duration lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin[2]. Iron is an essential element which is very essential for every human being and it acts by catalyzing many biological reactions due its dual redox nature. But iron is also able to produce free radicals and oxidative stress. In order to prevent the adverse effect that can occur due to iron, there are mechanisms that keep free iron under toxic levels[3-5]. Among them, ferritin is one of key component in the mechanisms, which acts by storing the excess iron inside the cells and thus avoiding free radicals' production from free iron.

Ferritin is the known source of iron for the synthesis of iron containing proteins such as cytochromes. In brain tissue, ferritin is localized in astrocytes and microglia[6]. Serum concentration of ferritin is known to be directly proportional to iron stores in tissues and therefore may be used to evaluate iron stores in the absence of inflammatory conditions, infectious diseases, and cancer[7]. Low serum ferritin level indicates decreased iron stores. Next to liver, iron gets stored largely in brain, where highest

rates of metabolic activity occur. Any impairment in these metabolic activities would results in occurrence of neurodegenerative disorders[8]. During, cerebral ischemia, the iron homeostasis occurs, leading to iron release in the ischemic tissue and therefore to an increased oxidative damage[9]. Some studies reported that elevated levels of serum ferritin, were associated with poor outcome after ischemic stroke[10,11] and intracerebral haemorrhage[12]. But, direct evidences of iron toxicity after experimental stroke are controversial. Hence this study was planned to assess the serum ferritin levels among ischemic stroke cases and to correlate it with early neurological deterioration and prognosis of acute ischaemic stroke and to find the relationship between serum ferritin and various risk factors for Stroke.

## METHODOLOGY

This study was conducted as a cross sectional observational study among patients attending outpatient and inpatient department of General medicine, Neurology and emergency with acute ischemic stroke during August 2022 – November 2022 in Chettinad medical Center Hospital in Chennai. All patients with new onset focal neurological deficit following ischemic stroke, presented within 24 hours of onset of stroke, patients aged more than 14 years and from both sexes, and patients with new onset stroke with past history of hypertension, diabetes mellitus, dyslipidemia, smoking, alcohol were included in this study. Patients with age more than 80 years, patients with malignancy and individuals with Connective Tissue disorders and Rheumatic heart disease, Coronary Artery diseases, prior history of transient ischemic attacks or reversible, Ischemic neurological deficit, cerebrovascular accidents, haemorrhage in CT scan and history of recent surgery and trauma were excluded from this study. A total of sixty patients with acute ischaemic stroke were included in this study. Ethical committee approval was obtained for this study from the Institutional Human Ethics Committee.

After taking the written informed consent, all the study patients were assessed for the demographic and clinical presentation by the principal investigator using a pre structured proforma. Following which the principal investigator assessed the detailed history of the participants and clinical examination was done. For assessing the biochemical parameters about 5 ml of venous blood was collected from each participant and the blood sample was sent for analysis of serum ferritin levels. Based on the history and examination the severity of stroke of each patient was categorized as mild, moderate and severe based on the National Institute of Health Stroke Scale (NIHSS) and the prognosis of each case was categorized as good prognosis and poor prognosis using the Modified Rankin Scale. NIHSS scores were grouped as mild, moderate and severe with the score 0-5, 6-20 and more than 20, respectively. Similarly Modified Rankin scale was categorized as scores between 0-2 as good prognosis and score more than 2 as poor prognosis. All the reports were entered in the same proforma where clinical presentation was entered by the principal investigator.

The data was entered in excel sheet and analyzed using SPSS (Version 17). Descriptive statistics with mean, standard deviation and proportions (%) were calculated for quantitative variables. To test the hypothesis Chi Square test and Independent sample t test were done appropriately. p value $<0.05$ was considered as statistically significant.

## RESULTS

In this study 41.7% of subjects had normal serum ferrtin levels and the rest had high levels of serum ferritin. Meanwhile serum ferritin was found to be high among 19 and 16 participants with alcohol consumption and without alcohol consumption respectively. There was association found between alcohol consumption and serum ferritin level, the p value was statistically significant. In this present study serum ferritin was found to be normal among 12 and 13 participants with diabetes mellitus and without diabetes mellitus respectively. Meanwhile serum ferritin was found to be high among 30 and 5 participants with diabetes mellitus and without diabetes mellitus respectively. There was association found between alcohol consumption and serum ferritin level and the p value was highly statistically significant. Among the sixty participants in this study 37 acute ischemic stroke participants had hypertension, among them 10 were found to have normal serum ferritin and 27 participants had high serum ferritin level. Among 23 non hypertensive participants 15 participants were found to have normal serum ferritin level and 8 participants had high serum ferritin level. The association between hypertension and serum ferritin was found to be statistically significant. However, the association was not found to be statistically not significant.

**Table 1:** Demographic parameters vs Serum ferritin levels

| Variables | Serum ferritin | | Total | P value |
|---|---|---|---|---|
| | Normal | High | | |
| **Age group** | | | | |
| < 50 years | 8 (50) | 8 (50) | 16 (100) | 0.429 |
| ≥ 50 years | 17 (38.6) | 27 (61.4) | 44 (100) | |
| **Sex** | | | | |
| Male | 18 (45) | 22 (55) | 40 (100) | 0.458 |
| Female | 7 (35) | 13 (65) | 20 (100) | |
| **Smoking habit** | | | | |
| Yes | 12 (48) | 13 (52) | 25 (100) | 0.401 |
| No | 13 (37.1) | 22 (62.85) | 35 (100) | |
| **Alcohol consumption** | | | | |
| Yes | 4 (17.3) | 19 (82.6) | 23 (100) | 0.002* |
| No | 21 (56.7) | 16 (43.2) | 37 (100) | |
| **Diabetes mellitus** | | | | |
| Present | 12 (28.5) | 30 (71.4) | 42 (100) | 0.001* |
| Absent | 13 (72.2) | 5 (27.7) | 18 (100) | |
| **Hypertension** | | | | |
| Present | 10 (27) | 27 (72.9) | 37 (100) | 0.003* |
| Absent | 15 (65.2) | 8 (34.7) | 23 (100) | |
| **Dyslipidemia** | | | | |
| Present | 7 (29.1) | 17 (70.8) | 24 (100) | 0.108 |
| Absent | 18 (50) | 18 (50) | 36 (100) | |
| Total | 25 (41.7) | 35 (58.3) | 60 (100) | |

*Significant

Among acute ischemic stroke participants with loss of consciousness 2 participant were found with normal serum ferritin and 11 participants had high serum ferritin level. Among participants without loss of consciousness 23 participants had normal serum ferritin level and 24 participants had high serum ferritin levels. There was association found between loss of consciousness and serum ferritin level and it was found to be statistically significant. Among participants with speech disturbance (46) 19 participants had normal serum ferritin level and 27 participants had high serum ferritin level. Among participants (14) who do not had speech disturbance 6 participants had normal serum ferritin level and 8 participants had high serum ferritin level. There was no association found between speech disturbance and serum ferritin in this study. Facial nerve involvement was present among 49 participants and in whom 19 had normal serum ferritin level and 30 participants had high serum ferritin level. Among 11 participants who had no facial nerve involvement 6 participants were found with normal serum ferritin and 5 participants were found to have high serum ferritin level. There was no association found between facial nerve involvement and serum ferritin in this study and the p value was found to be statistically insignificant.

National Institute of Health Stroke Scale (NIHSS) score was moderate among 36 study participants in whom 23 participants had normal serum ferritin levels and 13 participants had high serum ferritin level. Among 24 severe National Institute of Health Stroke Scale (NIHSS) patients 2 were found to have normal serum ferritin value and 22 had high serum ferritin value. The association between National Institute of Health Stroke Scale (NIHSS) score and serum ferritin was found to be highly statistically significant.

Serum ferritin was normal among 16 and 9 participants with good and poor Modified Rankins Scale respectively and serum ferritin was found to be high among 8 and 27 participants with good and poor Modified Rankins Scale respectively, in this study. There was high statistical significant association found between Modified Rankins Scale and serum ferritin.

**Table 2:** Clinical profile vs Serum ferritin levels

| Variables | Serum ferritin | | Total | P value |
|---|---|---|---|---|
| | Normal | High | | |
| **Loss of Consciousness** | | | | |
| Present | 2 (15.3) | 11 (84.6) | 13 (100) | 0.0298* |
| Absent | 23 (48.9) | 24 (51) | 47 (100) | |
| **Speech disturbance** | | | | |
| Present | 19 (41.3) | 27 (58.7) | 46 (100) | 0.917 |
| Absent | 06 (42.9) | 08 (57.1) | 14 (100) | |
| **Facial nerve involvement** | | | | |
| Present | 19 (38.8) | 30 (61.2) | 49 (100) | 0.337 |
| Absent | 06 (54.5) | 05 (45.5) | 11 (100) | |
| **NIHSS** | | | | |
| Moderate | 23 (63.8) | 13 (36.1) | 36 (100) | 0.000* |
| Severe | 2 (8.3) | 22 (91.6) | 24 (100) | |
| **MRS** | | | | |
| Good | 16 (66.6) | 8 (33.3) | 24 (100) | 0.001* |
| Poor | 9 (25) | 27 (75) | 36 (100) | |
| Total | 25 (41.7) | 35 (58.3) | 60 (100) | |

*Significant

In this current study the mean NIHSS score among participants with normal serum ferritin was found to be 12.5±4.82 and among 35 participants with high serum ferritin value the NIHSS score was found to be 16.3±7.34. The mean difference in NIHS score for serum ferritin was found to be statistically significant. In this study the mean MRS among participants with normal serum ferritin (25) was found to be 3.1 ±1.3 and among 35 participants with high serum ferritin value the mean MRS was found to be 3.9 ±1.5. The mean difference in MRS for serum ferritin was found to be statistically significant. The mean serum ferritin among participants with moderate NIHSS score was 175.92±75.32 and among severe NIHSS score participants the mean serum ferritin was found to be 228.16±81.48. The mean serum ferritin for NIHSS score for was found to be statistically significant. In this study among acute ischemic stroke participants with good MRS the mean serum ferritin was found to be 121.45±67.41 and among poor MRS participants the mean serum ferritin was 247.84±80.64. The mean serum ferritin based on MRS was found to be highly statistically significant.

## DISCUSSION

In this study among 16 participants below 50 years of age, 8 participants were found to have normal serum ferritin level and 8 had high serum ferritin values. Likewise, above the age of 50 years among 44 participants 17 were found to have normal serum ferritin levels and 27 had high serum ferritin value. The mean serum ferritin was found to be 241.9 ± 120.16µg/lit among the study participants. The association between age group and serum ferritin in this study was found to be statistically not significant. In this study among 40 male participants 18 participants had normal serum ferritin and 55 participants had high serum ferritin levels whereas among 20 female participants 7 were found to have normal serum ferritin level and 13 participants had high serum ferritin levels. There was no association found between Gender and serum ferritin level and the p value was statistically insignificant. Similar to this study, there was no significant correlation between serum ferritin and age reported by Milman M et al[13], in their study.

### Smoking and Alcohol Consumption

Among 25 participants with smoking habits 12 were found to have normal serum ferritin level and 13 participants were found with high serum ferritin value. Among 35 participants without smoking habit 13 participants had normal serum ferritin and 22 participants had high serum ferritin level. In this study there was no association found between smoking and serum ferritin and the p value was statistically not significant. In this current study serum ferritin was found to be normal among 4 and 21 participants with alcohol consumption and without alcohol consumption respectively. Meanwhile serum ferritin was found to be high among 19 and 16 participants with alcohol consumption and without alcohol consumption respectively. There was association found between alcohol consumption and serum ferritin level, the p value was statistically significant. Similarly, there is no significant correlation between serum ferritin and smoking reported in the study conducted by Salonen et al[14].

### Diabetes

In this present study serum ferritin was found to be normal among 12 and 13 participants with diabetes mellitus and without diabetes mellitus respectively. Meanwhile serum ferritin was found to be high among 30 and 5 participants with diabetes mellitus and without diabetes mellitus respectively. There was association found between alcohol consumption and serum ferritin level and the p value was highly statistically significant. This was supported by studies conducted by Fernandez et al[15], Thomas et al[16], Kim et al[17] and Eshed et al[18].

### Hypertension

Among the sixty participants in this study 37 acute ischemic stroke participants had hypertension, among them 10 were found to have normal serum ferritin and 27 participants had high serum ferritin level. Among 23 non hypertensive participants 15 participants were found to have normal serum ferritin level and 8 participants had high serum ferritin level. The association between hypertension and serum ferritin was found to be statistically significant. These findings were consistent with the findings reported in the studies conducted by Wrede et al[19], Piperno et al[20], where they reported association between hypertension and high serum ferritin levels.

### Ferritin Levels Vs NIHSS and MRS

National Institute of Health Stroke Scale score was moderate among 36 study participants in whom 23 participants had normal serum ferritin levels and 13 participants had high serum ferritin level. Among 24 severe National Institute of Health Stroke Scale patients 2 were found to have normal serum ferritin value and 22 had high serum ferritin value. The association between National Institute of Health Stroke Scale score and serum ferritin was found to be highly statistically significant. Serum ferritin was normal among 16 and 9 participants with good and poor MRS respectively and serum ferritin was found to be high among 8 and 27 participants with good and poor MRS respectively, in this study. There was high statistical significant association found between MRS and serum ferritin. In this current study the mean NIHSS score among participants with normal serum ferritin was found to be 12.5±4.82 and among 35 participants with high serum ferritin value the NIHSS was found to be 16.3±7.34. The difference in mean NIHS score and serum ferritin levels was found to be statistically significant. In this study the mean MRS among participants with normal serum ferritin was found to be 3.1 ±1.3 and among 35 participants with high serum ferritin value the mean MRS was found to be 3.9 ±1.5. The difference in mean MRS among participants with normal and high serum ferritin levels was found to be statistically significant. The mean serum ferritin among participants with moderate National Institute of Health Stroke Scale score was 175.92±75.32 and among severe National Institute of Health Stroke Scale score participants the mean serum ferritin was found to be 228.16±81.48. The mean difference in serum ferritin levels among participants with moderate and severe scores of NIHSS was found to be statistically significant.

In this study among acute ischemic stroke participants with good MRS the mean serum ferritin levels was found to be 121.45±67.41 and among poor MRS participants the mean serum ferritin was 247.84±80.64. The mean difference in serum ferritin levels based on the prognostic predictor score, MRS was found to be highly statistically significant, in this study. There were several studies favoring this fact include Davalos et al[11], Fernandez et al[15] and Thakur et al[21]. Studies related to severity and prognosis of stroke demonstrated that serum ferritin was a significant predictor of mortality and neurologic deterioration[11,22]. Also there were several studies investigating the relationship between stroke subtypes, post stroke mortality and serum ferritin level. Some studies found a meaningful relationship between serum ferritin and stroke severity and mortality[23] and some did not[24,25].

In addition, some results of some studies suggest an important relation between increased iron stores and neurologic worsening within the early acute phase of ischemic stroke. Plasma ferritin more than 275 ng/mL measured within the first 24 hours of the onset of symptoms increased risk of subsequent progressing stroke, independent of other important predictors of neurologic worsening identified in recent clinical studies[11,26].

## CONCLUSION

From the present study we conclude that there was a significant association between high levels of serum ferritin and severe and poor prognosis cases with acute ischemic stroke. This study demonstrates the significant rise in serum ferritin in ischemic stroke patients in correlation with high scores with NIHSS which indicates the severity. This study also reveals the poor outcome in correlation with high serum ferritin values and good outcome in correlation with low serum ferritin values, based on Modified Rankin scale. Also, diabetes mellitus and systemic hypertension, alcohol consumption and loss of consciousness were found to be associated with serum ferritin levels, in this study. There is no statistically significant relationship between serum ferritin and gender, age, smoking and facial nerve involvement were reported in this study. Further multicenter large-scale studies involving population from different ethnicity and food habits can be conducted to find the in depth of the association in various populations.

## REFERENCES


1. de Leciñana, M.A., Egido, J.A., Fernandez, C., Martinez-Vila, E., Santos, S., Morales, A., Casado, I. Risk of ischemic stroke and lifetime estrogen exposure. Neurology, 2007; 68(1): 33-38.
2. Mackay J, Mensah G.A. The atlas of heart disease and stroke. World Health Organization; 2004.
3. Eisenstein R.S. Iron regulatory proteins and the molecular control of mammalian iron metabolism. Annual review of nutrition. 2000; 20(1): 627-62.
4. Moos, T., Nielsen, T.R., Skjørringe, T., Morgan, E.H. Iron trafficking inside the brain. Journal of neurochemistry, 2007; 103(5): 1730-1740.
5. Mackenzie, E.L., Iwasaki, K., Tsuji, Y. Intracellular iron transport and storage: from molecular mechanisms to health implications. Antioxidants & redox signaling, 2008; 10(6): 997-1030.
6. Connor, J.R., Menzies, S.L., Martin, S.S., Mufson, E.J. Cellular distribution of transferrin, ferritin, and iron in normal and aged human brains. Journal of neuroscience research, 1990; 27(4): 595-611.
7. Herbert, V., Jayatilleke, E., Shaw, S., Rosman, A.S., Giardina, P., Grady, R.W., Gunter, E.W. Serum ferritin iron, a new test, measures human body iron stores unconfounded by inflammation. Stem cells, 1997; 15(4): 291-296.
8. Berg, D., Youdim, M.B. Role of iron in neurodegenerative disorders. Topics in Magnetic Resonance Imaging, 2006; 17(1): 5-17.
9. Jomova, K., Vondrakova, D., Lawson, M., Valko, M. Metals, oxidative stress and neurodegenerative disorders. Molecular and cellular biochemistry, 2010; 345(1): 91-104.
10. Davalos, A., Fernandez-Real, J.M., Ricart, W., Soler, S., Molins, A., Planas, E., Genis, D. Iron-related damage in acute ischemic stroke. Stroke, 1994; 25(8): 1543-1546.
11. Millan, M., Sobrino, T., Castellanos, M., Nombela, F., Arenillas, J.F., Riva, E., Dávalos, A. Increased body iron stores are associated with poor outcome after thrombolytic treatment in acute stroke. Stroke, 2007; 38(1): 90-95.
12. Mehdiratta, M., Kumar, S., Hackney, D., Schlaug, G., Selim, M. Association between serum ferritin level and perihematoma edema volume in patients with spontaneous intracerebral hemorrhage. Stroke, 2008; 39(4): 1165-1170.
13. Milman, N. Serum ferritin in Danes: studies of iron status from infancy to old age, during blood donation and pregnancy. International journal of hematology, 1996; 63(2): 103-135.
14. Salonen, J.T., Nyyssönen, K., Korpela, H., Tuomilehto, J., Seppänen, R., Salonen, R. High stored iron levels are associated with excess risk of myocardial infarction in eastern Finnish men. Circulation, 1992; 86(3): 803-811.
15. Fernández-Real, J.M., Peñarroja, G., Castro, A., García-Bragado, F., López-Bermejo, A., Ricart, W. Bloodletting in high-ferritin type 2 diabetes: effects on vascular reactivity. Diabetes care, 2002; 25(12): 2249-2255.
16. Thomas, M.C., MacIsaac, R.J., Tsalamandris, C., Jerums, G. Elevated iron indices in patients with diabetes. Diabetic medicine, 2004; 21(7): 798-802.
17. Kim, N.H., Oh, J.H., Choi, K.M., Kim, Y.H., Baik, S.H., Choi, D.S., Kim, S.J. Serum ferritin in healthy subjects and type 2 diabetic patients. Yonsei medical journal, 2000; 41(3): 387-392.
18. Eshed, I., Elis, A., Lishner, M. Plasma ferritin and type 2 diabetes mellitus: a critical review. Endocrine research, 2001; 27(1-2): 91-97.
19. Wrede, C.E., Buettner, R., Bollheimer, L.C., Scholmerich, J., Palitzsch, K.D., Hellerbrand, C. Association between serum ferritin and the insulin resistance syndrome in a representative population. European journal of endocrinology, 2006; 154(2): 333-340.
20. Piperno, A., Trombini, P., Gelosa, M., Mauri, V., Pecci, V., Vergani, A., Mancia, G. Increased serum ferritin is common in men with essential hypertension. Journal of hypertension, 2002; 20(8): 1513-1518.
21. Thakur, J.S., Paika, R., Singh, S. Burden of noncommunicable diseases and implementation challenges of National NCD Programmes in India. Medical Journal Armed Forces India, 2020; 76(3): 261-267.
22. Erdemoglu, A.K., Ozbakir, S. Serum ferritin levels and early prognosis of stroke. European Journal of Neurology, 2002; 9(6): 633-637.
23. Etgen, T., Baum, H., Sander, K., Sander, D. Cardiac troponins and N-terminal pro-brain natriuretic peptide in acute ischemic stroke do not relate to clinical prognosis. Stroke, 2005; 36(2): 270-275.
24. Christensen, H., Boysen, G., Johannesen, H.H., Christensen, E., Bendtzen, K. Deteriorating ischaemic stroke: cytokines, soluble cytokine receptors, ferritin, systemic blood pressure, body temperature, blood glucose, diabetes, stroke severity, and CT infarction-volume as predictors of deteriorating ischaemic stroke. Journal of the neurological sciences, 2002; 201(1-2): 1-7.
25. van der, D.L., Grobbee, D.E., Roest, M., Marx, J.J., Voorbij, H.A., van der Schouw, Y.T. Serum ferritin is a risk factor for stroke in postmenopausal women. Stroke, 2005; 36(8): 1637-1641.
26. Toni, D., Fiorelli, M., Gentile, M., Bastianello, S., Sacchetti, M.L., Argentino, C., Fieschi, C. Progressing neurological deficit secondary to acute ischemic stroke: a study on predictability, pathogenesis, and prognosis. Archives of neurology, 1995; 52(7): 670-675.