ORIGINAL ARTICLE

Serum ferritin level as a severity marker in patients with ischemic stroke using modified Rankin scale

Santhosh B T[1], Anuja Kadagud[1], Anand P. Ambali[2]*

[1]Department of Medicine, [2]Department of Geriatric Medicine, BLDE (DU), Shri B M Patil Medical College Hospital and Research Centre, Vijayapura- 586103 (Karnataka) India

Abstract

Background: Stroke is an acute vascular event that leads to increased mortality and morbidity and has a poor quality of life due to the disability it produces. The high serum ferritin levels in patients with stroke are a risk factor for poor outcomes, suggesting that increased body iron stores before the onset of a stroke may aggravate the cytotoxicity of brain ischemia. *Aim and Objectives:* To know the association between serum ferritin levels and ischemic stroke severity using the modified Rankin Scale (mRS). *Material and Methods:* In a cross-sectional study, we assessed serum ferritin and correlated it to stroke severity using the mRS in patients admitted with history, clinical features and radiological evidence for ischemic stroke. *Results:* In our study, the majority (26.5%) were between 70 to 79 years of age. The oldest patient was a 97-year-old male, and we had male predominance (54.4%). The most common stroke territory was the middle cerebral artery territory (58%). The mRS was applied to assess stroke severity in all the patients presenting within 24 hours of the onset of symptoms and correlated with serum ferritin level. The results were plotted using a scatter diagram, which showed ferritin was in an increasing trend as the mRS grading was increasing, which signifies the higher the ferritin, more the severity of the stroke with a significant p-value. *Conclusion:* The present study illustrated that the higher the serum ferritin level, more severe was the disability of stroke. It was concluded that evaluating serum ferritin levels in patients presenting with ischemic stroke at admission will help predict the severity.

Keywords: Ischemic stroke, mRS, Serum ferritin, and severity marker

Introduction

According to the World Health Organization (WHO), stroke is "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting for more than 24 hours or leading to death, with no apparent cause, other than that of vascular origin." [1].

A study by Khurana *et al*. (2021) showed that the prevalence rate of stroke for India's urban and rural population in India varied from 44.54 to 150 per 1,00,000 population [2]. The 30-day case fatality rate of stroke ranged from 41.08% to 42.06% in the urban population and 18% to 46.3% in the rural population. Hypoxic acidosis or oxidative stress leads to the accumulation of Reactive Oxygen Species (ROS), the release of ferritin from cells, which is free iron, which will catalyze the preformed radicals like hydrogen peroxide (H_2O_2) and superoxide ($O_2^{\bullet-}$) into a highly reactive toxic hydroxyl radical (•OH) which aggravates the damage. Dixon in 2012, suggested the concept of ferroptosis, a non-apoptotic, iron-dependent form of cell death characterized by the accumulation of lipid ROS. Ferroptosis differs from necrosis, apoptosis, and

autophagy in cell morphology and function. High serum ferritin levels on admission in patients with acute stroke helps to predict a lousy prognosis, suggesting that increased body iron stores before stroke onset can aggravate the cytotoxicity of brain ischemia [3].

The modified Rankin Scale (mRS) has become the most commonly used scale for measuring dependence in the daily activities of people or the degree of disability who have suffered neurological deficits due to stroke or other causes. It's been widely accepted and used for measuring clinical outcomes in stroke [4]. It is graded from 0 to 6 based on the patients' activity post-stroke. With this background, our study intended to know the association between serum ferritin levels and ischemic stroke severity using the mRS.

Material and Methods

Our study was a hospital-based cross-sectional study that included 68 patients above the age of eighteen years, admitted with history, clinical findings, and radiological evidence for ischemic stroke and presented within 24 hours of onset of symptoms in BLDE (DU) Shri B M Patil Medical College Hospital and Research Centre, Vijayapura, after getting approval from the Institutional Ethics Committee.

Exclusion criteria: Patients who had a history of recent infections like pneumonia, urinary tract infection, malignancy, anemia, current parenteral iron supplementation, and history of stroke and hemorrhagic stroke in the recent past were excluded. Data were analyzed using SPSS 21.0 statistical software (SPSS Inc, Chicago, Illinois, USA). Descriptive analysis and Spearman's coefficient were applied, and results were plotted in a scatter graph.

Results

Age and sex wise distribution of study population: The mean age observed in our study was 62.82 ± 15.07 years. We categorized age into 30 – 39 years, 40 – 49 years, 50 – 59 years, 60 – 69 years, 70 – 79 years, and 80+ years which constituted 3 (4.4%), 10 (14.7%), 12 (17.6%), 17 (25.0%), 18 (26.5%) and 8 (11.8%), respectively. The majority (26.5%) were between 70 - 79 years. The youngest was a 30-year-old female, while the oldest was a 97-year-old male. Male predominance was (54.4%), while females constituted (45.6%) (Table 1).

Table 1: Age and sex wise distribution of study population

Age (years)	Male	Female	N (%)
30 - 39	01	02	03 (4.4)
40 - 49	08	02	10 (14.7)
50 - 59	06	06	12 (17.6)
60 - 69	10	07	17 (25.0)
70 - 79	11	07	18 (26.5)
80+	01	07	08 (11.8)
Total	37	31	68 (100)

The territory of stroke: In this study, the most common territory of stroke was in the Middle Cerebral Artery (MCA) territory (85%) followed by Anterior Cerebral Artery (ACA) territory (5.9%), Posterior Cerebral Artery (PCA) territory (4.4%), more than one territory (1.5%) and Posterior Inferior Cerebellar Artery (PICA) (1.5%) (Table 2).

Table 2: Territories wise distribution of stroke

Type	N (%)
MCA Territory	58 (85)
ACA Territory	04 (5.9)
PCA Territory	03 (4.4)
>1 Territory	02 (2.9)
PICA	01 (1.5)

Comorbidities: In our study, the comorbidities in single or combinations of two or more were present and the most common comorbidity was found to be hypertension (54.4%) followed by diabetes (38.2%), ischemic heart disease (11.7%), chronic obstructive pulmonary disease (5.8%), osteoarthritis (4.4%), bronchial asthma and epilepsy (2.9% each), and human immunodeficiency virus and rheumatic heart disease (1.5 % each) (Table 3).

Table 3: Comorbidities

Type	N (%)
Hypertension	37 (54.4)
Diabetes	26 (38.2)
Ischemic heart disease	8 (11.7)
Chronic obstructive lung disease	4 (5.8)
Osteoarthritis	3 (4.4)
Bronchial Asthma	2 (2.9)
Epilepsy	2 (2.9)
Human immune deficiency	1 (1.5)
Rheumatic heart disease	1 (1.5)

Serum ferritin and modified Rankin Scale

In our study, the mRS was used to assess stroke severity in all patients. The severity of disability and serum ferritin levels were correlated. The mRS was graded from 1 to 5, following which 11.7% of patients had mRS - 1, 32.4% had mRS - 2, 29.4% had mRS - 3, 10.3% had mRS - 4 and 16.2% had mRS - 5. Average serum ferritin found in patients under mRS - 1 was 90.9 ± 77.5 ng/dl, mRS - 2 was 112.3 ± 107.1 ng/dl, mRS - 3 was 173.1 ± 114.2 ng/dl, mRS - 4 was 292.9 ± 133.9 ng/dl, and mRS - 5 was 595.3 ± 392.2 ng/dl. (Table 4).

Table 4: Correlation between serum ferritin and modified Rankin scale

mRS	N (%)	Ferritin (ng/dl) Mean ± SD	*p*
1	8 (11.7)	90.9 ± 77.5	0.0001*
2	22 (32.4)	112.3 ±107.1	
3	20 (29.4)	173.1 ± 114.2	
4	7 (10.3)	292.9 ± 133.9	
5	11 (16.2)	595.3 ± 392.2	

** Statistically significant*

Results were plotted using a scatter diagram, which showed ferritin was in an increasing trend with the increase in mRS grading. Our study signified that higher the ferritin levels, higher was the severity of stroke (Figure 1).

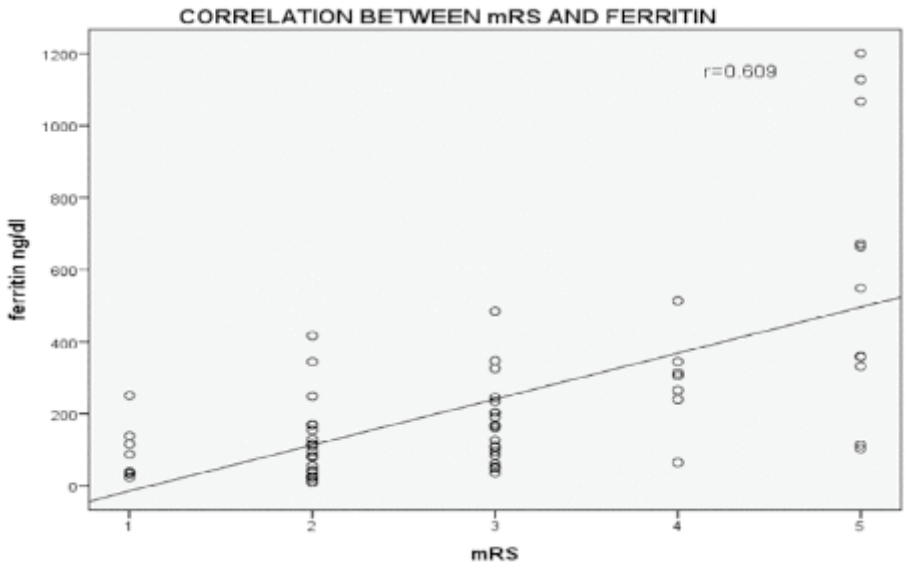

Figure 1: Correlation between mRS and ferritin

The correlation between serum ferritin and mRS had $p < 0.0001$, which is statistically significant and Spearman's correlation coefficient was **r=0.609,** which signifies a moderate correlation.

Discussion

Stroke is considered a significant health issue for every individual and society. Ischemic stroke is the third leading cause of death after acute myocardial infarction and malignancy and is also one of the leading causes of disability. Initially, serum ferritin was considered only a stress response to stroke, but now, serum ferritin is under research as a prognostic indicator in stroke. The possible mechanisms of ferritin as a risk factor are due to the release of ferritin from the cell, which is free iron and will catalyze the preformed radicals like hydrogen peroxide (H_2O_2) and superoxide ($O_2^{\bullet-}$) into a highly reactive toxic hydroxyl radical (•OH) [5].

Dixon, in 2012 [6], suggested the concept of Ferroptosis, a non-apoptotic, iron-dependent form of cell death characterized by the accumulation of lipid ROS, distinct from necrosis, apoptosis, and autophagy in cell morphology and function. Ferroptosis is distinguished from other types of cell death by the visible shrinking of mitochondria, increased membrane density, and reduced mitochondrial cristae [7].

In our study, the majority were male (54.4%), similar to the studies by Egovindarajulu *et al*. (2016), with a male predominance of 63.33% [8] and Garg *et al*. (2020) which had 56% males [9]. In comparison, Erdemoglu *et al*. (2002) had a female predominance of 58.8% [10]. The mean age observed was 62.82 ± 15.07 years, and the majority were between 70-79 years of age, which is similar to a study by Garg *et al*. (2020) where 28% were aged more than 70 years [9]. In our study, the most common territory involved was MCA (85%), similar to Ng *et al*. (2007) which had MCA involvement at 51%, PCA at 7% and ACA at 5%, [11] while more than one territory at 9%

whereas Assarzadegan *et al*. (2015) found MCA involvement in 48.5%, PCA in 20.5% and ACA 5.2% of patients [12].

Our study observed that the comorbidities were in single or combinations of two or more. The most common comorbidity encountered was hypertension (54.4%), [13] similar to a survey conducted by Ranjan U *et al.* (2023), where hypertension was the comorbidity in 68% and diabetes in 56%. At the same time, Egovindarajulu *et al*. (2016) found diabetes in 73.3%, followed by hypertension in 65.0 % of patients [8]. In our study, serum ferritin levels were correlated to the severity of stroke using the mRS scale, and a higher serum ferritin level was significantly associated with severe disability ($p<0.0001$). Studies done by Egovindarajulu *et al*. (2016), Garg *et al*. (2020), Erdemoglu *et al*.(2002), Ranjan U *et al.* (2023), Koul *et al*.(2017), and Narayan *et al.* (2018) showed a similar positive correlation. [8-10, 13-15].

The relation of serum ferritin levels to assess the severity of infections and its outcome especially in patients with COVID-19 [16] has been studied extensively, while it is less studied in patients with vascular events. This study has made an attempt to suggest serum ferritin as a severity marker in patients with stroke at time of admission. The use of serial levels of serum ferritin levels on prognosis needs further studies.

Conclusion

The severity of stroke is directly proportional to high serum ferritin levels. Assessment of serum ferritin at admission will help us predict the severity and disability that may occur irrespective of age group. Ferroptosis that leads to cell death also leads to higher serum ferritin levels. So, this study proposes serum ferritin level as a risk and prognostic marker in all patients who are at risk of stroke. Further, whether or not iron chelation therapy in patients with high serum ferritin levels improves overall outcomes needs to be studied.

References

1. Hatano S. Experience from a multicentre stroke register: a preliminary report. *Bull World Health Organ* 1976; 54(5):541-553.
2. Khurana S, Gourie-Devi M, Sharma S, Kushwaha S. Burden of stroke in India during 1960 to 2018: A systematic review and meta-analysis of community based surveys. *Neurology India* 2021; 69(3):547.
3. Davalos A, Fernandez-Real JM, Ricart W, Soler S, Molins A, Planas E, *et al*. Iron-related damage in acute ischemic stroke. *Stroke* 1994; 25(8):1543-1546.
4. Saver JL, Filip B, Hamilton S, Yanes A, Craig S, Cho M, Conwit R, Starkman S. Improving the reliability of stroke disability grading in clinical trials and clinical practice: the Rankin Focused Assessment (RFA). *Stroke* 2010;41(5):992-995.
5. Reif DW. Ferritin as a source of iron for oxidative damage. *Free Radic Biol Med* 1992; 12: 417-427.
6. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, *et al*. Ferroptosis: an iron-dependent form of nonapoptotic cell death. *Cell* 2012;149(5):1060-1072.
7. Li J, Cao F, Yin HL, Huang ZJ, Lin ZT, Mao N, Sun B, Wang G. Ferroptosis: past, present and future. *Cell Death Dis* 2020;11(2):1-3
8. Egovindarajulu K, Maaran AT, Prathiba P, Saiprashanth PR. A study on prognostic significance of serum ferritin in patients with acute ischemic stroke. *IOSR J Dental Med Sci* 2016; 15(10):31-39.
9. Garg R, Aravind S, Kaur S, Chawla SP, Aggarwal S, Goyal G. Role of serum ferritin as a prognostic marker in acute ischemic stroke: A preliminary observation. *Ann Afr Med* 2020; 19(2):95.

10. Erdemoglu AK, Ozbakir S. Serum ferritin levels and early prognosis of stroke. *Eur J Neurology* 2002; 9(6): 633-637.
11. Ng YS, Stein J, Ning M, Black-Schaffer RM. Comparison of clinical characteristics and functional outcomes of ischemic stroke in different vascular territories. *Stroke* 2007;38(8):2309-2314.
12. Assarzadegan F, Tabesh H, Shoghli A, Yazdi MG, Tabesh H, Daneshpajooh P, *et al*. Relation of stroke risk factors with specific stroke subtypes and territories. *Iranian J Public Health* 2015; 44(10):1387.
13. Ranjan U,Panneerselvam K. Association of serum ferritin in patients with acute ischemic stroke in tertiary care hospital. *Int J Adv Med* 2023;10:518-22.
14. Koul RK, Yaseen Y, Amreen S, Shah PA, Hakeem MM. Role of serum ferritin in determining the severity and prognosis of stroke: A hospital based study. *Int J Sci Stud* 2017;6(7):142-145.
15. Narayan M, Singh SK. Study of association between serum ferritin and prognosis of patients in acute ischemic and hemorrhagic stroke. *IOSR J Dental Med Sci* 2018; 17:46-56.
16. Patil VC, Kasireddy SR, Gada HN, Patil HV. Laboratory parameters in patients with moderate and severe COVID-19 in 2020 and 2021: A comparative study. *J Krishna Inst Med Sci Univ* 2021; 10(4):64-73.

Author for Correspondence:
Dr. Anand P. Ambali, Department of Geriatric Medicine, BLDE (DU), Shri B M Patil Medical College Hospital and Research Centre, Vijayapura-586103 Karnataka
Email: anand.ambali@bldedu.ac.in Cell:9845821477

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