Relation of Serum Ferritin Level with Severity of Neurological Disability among Patients with Acute Ischemic Stroke

*Sakib AA[1], Miah MAH[2], Alam MK[3], Rashid MH[4], Mohsin M[5], Khan MM[6], Rahman MA[7], Mondal E[8], Noor RII[9], Mia E[10], Debnath S[11]

Stroke is one of the major causes of morbidity and mortality throughout the world. Research is going on to find out the factors which are associated with the severity of acute ischemic stroke. One of the factors which has gained interest in the field of research in recent time is serum ferritin. Serum ferritin is an acute phase reactant. It is recently under research as a marker of severity and prognosis of acute ischemic stroke. The aim of this study was to assess the relation of serum ferritin level with the severity of acute ischemic stroke. This cross-sectional study was conducted in the Department of Medicine in Mymensingh Medical College Hospital, Bangladesh from June 2020 to March 2023. In this study, 323 patients with acute ischemic stroke were enrolled. The severity of neurological disability was evaluated in all participants using National Institute of Health stroke scale (NIHSS) within 48 hours of onset of stroke. Blood was taken for estimation of serum ferritin levels within 48 hours of admission. In this study, mean serum ferritin level was 208.3 ± 161.1 ng/ml in patients with acute ischemic stroke. The study showed most of the participants with high serum ferritin level had severe stroke (n=57, 77.0%; p<0.001). A statistically significant correlation was found between NIHSS and serum ferritin levels in acute ischemic stroke patients (r=0.71). This study revealed that serum ferritin level is associated with severity of neurological disability among patients with acute ischemic stroke. Further studies are required to establish the role of serum ferritin as a prognostic marker of acute ischemic stroke.

Introduction

Around 80.0% of noncommunicable disease related deaths occur in low and middle-income countries (LMICs). Among noncommunicable diseases, stroke is one of the major causes of mortality and disability throughout the world[1]. Stroke is the third leading cause of mortality in Bangladesh. The prevalence of stroke in Bangladesh is 0.3%[2]. The highest stroke prevalence (14.71 per thousand) was found in the Mymensingh division[1]. Search is going on to find out the factors which can help to assess the prognosis of stroke. One of the prognostic indicators, which has gained attention in the field of research in recent times, is the level of serum ferritin[2]. Several studies were done in different countries to find out the relation of serum ferritin level and acute ischemic stroke. Many of those studies found positive correlation between serum ferritin and severity of acute ischemic stroke[3,4,5]. Very few studies in Bangladesh have explored the association of serum ferritin level with severity of acute ischemic stroke; hence, it was felt that a study on association of serum ferritin level with severity of neurological disability in acute ischemic stroke patients attending in a medical college hospital like Mymensingh Medical College Hospital should be done.

1. *Dr Abrar Al Sakib, Resident, Department of Internal Medicine, Mymensingh Medical College (MMC), Mymensingh, Bangladesh; E-mail: sheehan.mmc@gmail.com
2. Professor Dr Md Abdul Hannan Miah, Professor and Head, Department of Medicine, MMC, Mymensingh, Bangladesh
3. Dr Md Khurshed Alam, Associate Professor, Department of Medicine, MMC, Mymensingh
4. Dr Md Harun Or Rashid, Associate Professor and Head, Department of Anesthesia and Intensive Care, MMC, Mymensingh, Bangladesh
5. Dr Muhammad Mohsin, Assistant Professor, Department of Medicine, MMC, Mymensingh
6. Dr Md Mohiuddin Khan, Senior Consultant, Department of Medicine, Mymensingh Medical College Hospital (MMCH), Mymensingh, Bangladesh, Mymensingh, Bangladesh
7. Dr Md Atikur Rahman, Junior Consultant, Department of Medicine, MMCH, Mymensingh
8. Dr Ershad Mondal, Medical Officer, Department of Endocrinology, MMC, Mymensingh, Bangladesh
9. Dr Ramim Islam Ibne Noor, Resident, Internal Medicine, MMC, Mymensingh, Bangladesh
10. Dr Earshad Mia, Assistant Registrar, Department of Rheumatology, MMCH, Mymensingh
11. Dr Shurabhi Debnath, Registrar, Pediatric Neurology, MMC, Mymensingh, Bangladesh

*for correspondence

Methods

This cross-sectional study was carried out in the Department of Medicine of Mymensingh Medical College Hospital, Mymensingh, Bangladesh. Institutional Review Board of Mymensingh Medical College reviewed and approved the research protocol (Memo no. MMC/IRB/2021/328, Date: 13/03/2021). In this study purposive sampling method was used, and data was collected from March 2021 to January 2023. Total 886 patients who were admitted in Department of Internal Medicine ward, Mymensingh Medical College Hospital with stroke were interviewed. Patient with old ischemic stroke, venous stroke, hemorrhagic stroke, Stroke with other structural brain disorder, demyelinating disease, Patient with previous disability, trauma, Patients having known medical condition that could affect serum ferritin level, including patients with infection, malignancy, chronic inflammatory disease, haemochromatosis, hematological disorders, liver or kidney disease; those who are alcoholic or had received repeated blood or blood component transfusion; patients who is on treatment with iron currently were excluded. After exclusion a total 323 patients were included. Informed written consent was ensured before participation of all patients. On admission, patient's medical history and data from physical examination were recorded on a semi-structured questionnaire by the investigator. Clinical history and physical examination were evaluated with special attention to severity of the disease and comorbidities: age, sex, smoking habits, hyperlipidemia, arterial hypertension, diabetes mellitus, heart disease, history of cerebrovascular events. The severity of neurological disability was evaluated in patients with acute ischemic stroke using National Institute of Health (NIH) stroke scale within 48 hours of onset of stroke. Acute ischemic stroke was confirmed by neuroimaging by CT scan or MRI in the department of Radiology and imaging. Two (2) mililitre (ml) of antecubital venous blood samples for determination of serum ferritin values were taken within 48 hours of admission. Serum ferritin concentration was determined in the laboratory medicine department using IMMULITE 1000 Ferritin a solid-phase, enzyme labeled chemiluminescent immunometric assay. Ferritin level was evaluated according to severity of neurological disability. Information was recorded in pre-designed structured case record form. And after that they were transferred into the statistical software. Analysis was done by SPSS Version 26.0. Qualitative variables were summarized by percentage. Quantitative variables were summarized by mean and Standard Deviation (SD). Data were presented by tables, diagrams and graphs based on the nature of data. Pearson Correlation coefficient test was carried out to find out the relation between severity of neurological disability of acute ischemic stroke with serum ferritin level. A multiple linear regression was calculated to predict the dependent variable NIHSS score based on age, gender, presence of hypertension, diabetes mellitus, tobacco Smoking, dyslipidemia, family history of stroke, cardiac disease and the level of serum ferritin. Multiple logistic regression analysis of risk factors of moderate to severe (NIHSS $\geq$ 16) acute ischemic stroke was done. The variables were age, gender, hypertension, DM, smocking status, dyslipidemia, family history of stroke, cardiac disease and high serum ferritin.

Results

Results and observations of this study are given below in tables and figures.

Among the participants majority were aged between 51 to 70 years (52.0%), mean age ±SD was (60.70±14.49) years. Male was 62.5% and female 37.4%. Majority resided in rural area (62.2%) and 43.9% of the respondents were smoker (Table I).

Table I: Socio-demographic characteristics of respondents (n=323)

Variables	Frequency (n)	Percent (%)
Age groups (years)		
31-50	99	30.7
51-70	168	52.0

71-90	51	15.8
>90	05	01.5
Mean age ±SD (years)	60.70±14.49	
Gender		
Male	202	62.5
Female	121	37.4
Occupation		
Service holder	83	25.7
House wife	90	27.9
Farmer	62	19.2
Businessman	55	17.0
Day laborer	31	9.6
Retired person	02	0.6
Residence		
Urban	118	36.5
Rural	201	62.2
Suburban	04	01.2
Level of education		
No formal education	100	31.0
Primary	67	20.7
SSC	52	16.1
HSC	47	14.6
Graduate and above	57	17.6
Smoking status		
Smoker	142	43.9
Nonsmoker	181	56.0

Regarding risk factors 165(51.0%) 0f the participants were hypertensive, 94(29.1%) of the respondents were diabetic, 99(30.7%) respondents had dyslipidemia, 83(25.7%) respondents had family history and 83(25.7%) respondents had cardiac disease.
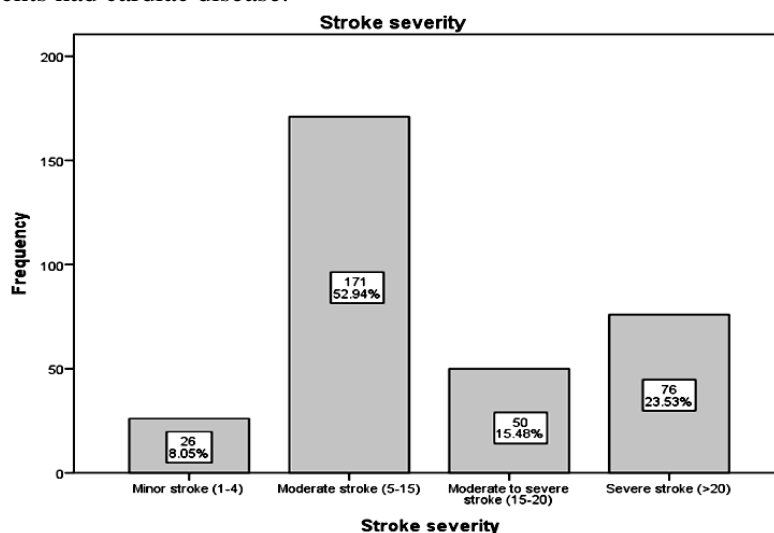

Figure 1: Distribution of respondents by severity of stroke (n=323)
Most of the respondent (52.94%, n=171) had moderate stroke (Figure 1).

Table II: Prevalence of family history, cardiac disease, high serum ferritin and dyslipidemia in different levels of severity of stroke

Variable	All	Minor stroke (1-4) (n=26)	Moderate stroke (5-15) (n=171)	Moderate to severe stroke (15-20) (n=50)	Severe stroke (>20) (n=76)	p value (Chi-square test)
	n (%)	n (%)	n (%)	n (%)	n (%)	
Family history	83(100.0)	08(9.6)	39(47.0)	15(18.1)	21(25.3)	0.630
Cardiac disease	83(100.0)	13(15.7)	40(48.2)	19(22.9)	11(13.3)	0.001
High serum ferritin	74(100.0)	00(00.0)	10(13.5)	07(09.5)	57(77.0)	0.001
High total cholesterol	45(100.0)	03(06.7)	16(35.6)	11(24.4)	15(33.3)	0.047
Low HDL cholesterol	35(100.0)	06(17.1)	19(54.3)	06(17.1)	04(11.4)	0.087
High LDL cholesterol	38(100.0)	04(10.5)	21(55.3)	09(23.7)	04(10.5)	0.149
High triglycerides	20(100.0)	03(15.0)	10(50.0)	04(20.0)	03(15.0)	0.521
Any lipid abnormality	99(100.0)	11(11.1)	49(49.5)	24(24.2)	15(15.2)	0.004

NIHSS Categories (spanning header over All/Minor/Moderate/Moderate to severe/Severe columns)

This Table II shows cardiac disease; level of ferritin, cholesterol and dyslipidemia are significantly related to the severity of acute ischemic stroke as per NIHSS categories. Most of the participants with high serum ferritin level had severe stroke (n=57, 77.0%).

Table III: Mean (SD) of serum ferritin and lipids among patients with acute ischaemic stroke (n=323)

Variable	All	Minor stroke (1-4)	Moderate stroke (5-15)	Moderate to severe stroke (15-20)	Severe stroke (>20)	p value (ANOVA test)
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Serum ferritin level (ng/ml)	208.3±161.1	97.0±66.2	138.2±77.2	217.0±110.0	398.4±190.7	0.001
Total cholesterol (mg/dl)	171.0±74.4	147.3±62.5	155.7±47.0	176.9±52.8	209.6±115.6	0.001
HDL cholesterol (mg/dl)	45.2±12.4	45.5±12.8	47.0±13.0	47.5±13.4	39.3±8.0	0.001
LDL cholesterol (mg/dl)	87.1±51.4	68.30±70.89	83.36±45.10	93.74±53.24	97.6±54.0	0.042
Triglycerides(mg/dl)	101.5±45.1	108.5±40.4	99.8±46.0	102.9±48.4	102.1±42.6	0.817

This Table III shows, mean level of serum ferritin was 208.3±161.1, mean level of total cholesterol was 171.0±74.4, mean level of HDL cholesterol was 45.2±12.4, mean level of LDL cholesterol was 87.1±51.4 and mean level of triglycerides was 101.5±45.1. Mean level of serum ferritin, total cholesterol and LDL cholesterol were significantly higher with increasing level of severity of stroke.
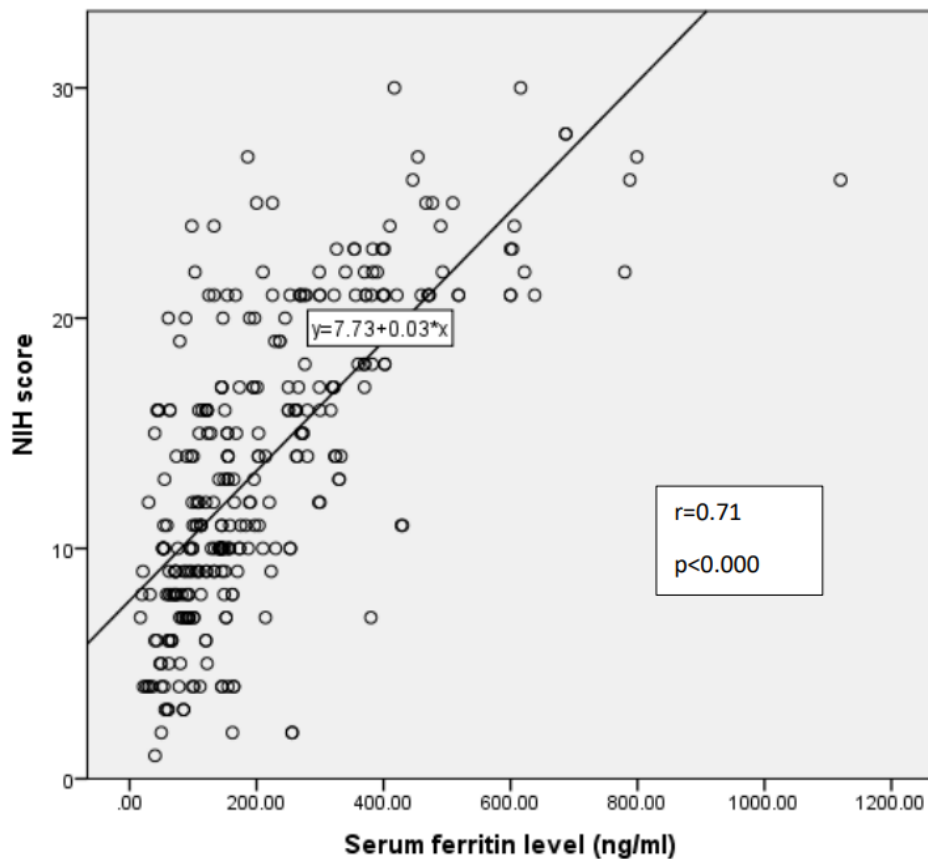
*Pearson correlation test was done

Figure 2: Scatter diagram showing correlation between serum ferritin level (ng/ml) and NIH score of the patients with acute ischemic stroke (r=0.71, p<0.001).
Figure 2 shows serum ferritin level had a positive correlation with NIH stroke score (r=1 0.71, p<0.001). That means NIH stroke score increases along with the increase of serum ferritin level.

Table IV: Multiple linear regression model of factors influencing severity of neurological disability in acute ischemic stroke (n=323)

Model	Beta	Std. Error	p value
Age	0.107	0.017	0.001
Gender	-0.314	0.655	0.632
Hypertension	0.360	0.305	0.238
Diabetes Mellitus	0.427	0.582	0.464
Tobacco Smoking	0.831	0.639	0.194
Dyslipidemia	0.219	0.678	0.747
Family history of stroke	-0.896	0.677	0.187
Cardiac disease	0.667	0.705	0.345
Serum ferritin level	0.027	0.002	0.001
*Dependent Variable: NIHSS score of patient			

NIHSS score based on age, gender, presence of hypertension, diabetes mellitus, tobacco Smoking, dyslipidemia, family history of stroke, cardiac disease and the level of serum ferritin. A significant

regression equation was found (p<0.001), with an r^2 of 0.565. Among the independent variables age and serum ferritin were found as significant predictors of NIHSS score of the respondents.

Table V: Multiple logistic regression analysis of risk factors of moderate to severe (NIHSS ≥16) acute ischemic stroke

Variables	Odd ratio ((95% Confidence interval)	p value
Age>50	4.07 (2.02-8.19)	0.001
Male gender	3.81 (1.68-8.63)	0.001
Hypertension	0.72 (0.34-1.54)	0.408
DM	1.02 (0.51-2.05)	0.942
Smoking	0.45 (0.21-0.96)	0.040
Dyslipidemia	1.59 (0.73-3.46)	0.243
Family history	1.25 (0.57-2.75)	0.564
Cardiac disease	0.48 (0.20-1.16)	0.104
Ferritin >365ng/ml in men and >148ng/ml in women	1.57 (1.11-2.23)	0.001

A multiple logistic regression was calculated to predict the of moderate to severe (NIHSS ≥16) acute ischemic stroke based on age, male gender, presence of hypertension, diabetes mellitus, Smoking, dyslipidemia, family history of stroke, cardiac disease and the high level of serum ferritin. Among the independent variables age >50, male gender and high ferritin level were found as significant predictors of moderate to severe (NIHSS ≥16) acute ischemic stroke.

Discussion
In this study majority of the respondents were aged between 51 to 70 years. A nationwide study in Bangladesh also found nearly similar age group of strokes[1]. In this study about two third of the respondents were male and approximately one third were female. Many researchers found nearly similar findings in their study[6,7,8]. Here, majority of respondents came from rural area. These findings support some others studies[1,6]. This also can be explained by the place of the study, as this study was conducted in MMCH where majority of the patients come from rural area. This study shows majority of respondents were housewife and service holder by occupation. But, most of the similar studies did not asses the occupations of the participants. In risk factor assessment, 51.08% were hypertensive, 43.96% of patients were smoker, 29.1% were diabetic, 30.7% had dyslipidemia, 25.7% had family history of stroke and 25.7% had cardiac disease. Mondal et al., also found nearly similar risk factors in stroke[1]. In this study mean serum ferritin level was 208.3±161.1ng/ml. Another study found nearly similar mean serum ferritin level in patients of acute ischemic stroke[3]. Patient were divided into minor stroke (1-4), moderate stroke (5-15), moderate to severe stroke (16-20), severe stroke (>20) group according to NIHSS. Most of the participants with high serum ferritin level had severe stroke as per NIHSS. An important finding of this study was mean serum ferritin levels were significantly higher with increasing level of severity of stroke. Shivakumar et al. 2022 in their study also found mean serum ferritin levels were significantly higher with increasing level of severity of stroke[7]. In this study, significant correlation between serum ferritin level (ng/ml) and NIH stroke score of the patients with acute ischemic stroke was found. Chakraborty et al.[4] and Shivakumar et al.[7] also found significant correlation between serum ferritin and NIHSS score in acute ischemic stroke patients. However, Ozkan et al. found no significant correlation between ferritin level and NIHSS[9]. A multiple linear regression was calculated to predict the dependent variable NIHSS score based on age, gender, presence of hypertension, diabetes mellitus, tobacco smoking, dyslipidemia, family history of stroke, cardiac disease and the level of

serum ferritin. Among the independent variables age and serum ferritin were found as significant predictors of NIHSS score of the respondents. A multiple logistic regression was also calculated. Here, among the independent variables age >50, male gender and high ferritin level were found as significant predictors of moderate to severe (NIHSS ≥16) acute ischemic stroke. In this study serum ferritin levels were measured after the occurrence of stroke. So, it was not ascertained whether ferritin levels were already elevated prior to stroke or higher ferritin levels resulted from a stress response to stroke itself.

Conclusion

Higher values of serum ferritin were associated with higher severity of acute ischemic stroke. Significant association between serum ferritin level and NIH stroke score of the patients with acute ischemic stroke was found.

Recommendation

Further studies with serial measurement of serum ferritin along with NIHSS are needed to establish serum ferritin's role in prognostication of acute ischemic stroke.

Limitations

A limitation of the study was though the normal serum ferritin level differ between premenopausal and postmenopausal state in female, in this study normal serum ferritin level was considered same in both groups. Another limitation was as purposive sampling method was used in this study there might be chance of bias. To assess severity of stroke NIHSS score was used. NIHSS score is time-dependent in predicting acute ischemic stroke severity and prognosis with increasing predictive value over time. But as the study design does not permit, serial measurement of NIHSS score along with serum ferritin were not possible.

References

1. Mondal MB, Hasan AH, Khan N, Mohammad QD. Prevalence and risk factors of stroke in Bangladesh: A nationwide population-based survey. Eneurological Sci. 2022;28:100414.
2. Islam MN, Moniruzzaman M, Khalil MI, Basri R, Alam MK, Loo KW, Gan SH. Burden of stroke in Bangladesh. International Journal of Stroke. 2013;8(3):211-3.
3. 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. Annals of African Medicine. 2020;19(2):95.
4. Chakraborty B, Vishnoi G, Goswami B, Gowda SH, Chowdhury D, Agarwal S. Lipoprotein (a), ferritin and albumin in acute phase reaction predicts severity and mortality of acute ischemic stroke in North Indian Patients. Journal of Stroke and Cerebrovascular Diseases. 2013;22(7):e159-67.
5. Narayan M, Singh SK. Study of association between serum ferritin and prognosis of patients in acute ischemic and haemorrhagic stroke. IOSR Journal of Dental and Medical Sciences. 2018;17:46-56.
6. Gopinathan R, Gopalakrishna D, Beegum S, Iype T. Serum Ferritin Levels in Acute Ischemic Stroke Patients-A Cross Sectional Study from Thiruvananthapuram, Kerala.
7. Shivakumar H, Durairaj A, Madhu G, Nirmala AC. A cross sectional study of correlation of serum ferritin levels with NIHSS scoring scale in patients of acute ischemic stroke. Panacea Journal of Medical Sciences. 2023;12(1):123-7.
8. Helmy MA, Khodair RM, El-Azab MH, Butros MK. Serum Level of Ferritin and Fibrinogen as Prognostic Indicator for Acute Ischemic Stroke. Benha Medical Journal. 2021;38(2):559-68.
9. Kusvuran Ozkan A, Umit Yemisci O, Nur Saracgil Cosar S, Oztop P, Turhan N. Can high-sensitivity C-reactive protein and ferritin predict functional outcome in acute ischemic stroke? A prospective study. Topics in Stroke Rehabilitation. 2013;20(6):528-36.