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Association of Admission Serum Ferritin Level with 90 days Outcome in Acute Ischemic Stroke

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Abstract:

Background: *Elevated serum Ferritin level is associated with the increased risk of ischemic stroke, stroke severity, the progression of stroke status, but functional outcome is unsettled.****Objective:*** *To determine the association between admission serum ferritin level and 90 days outcome in patients with acute ischemic stroke.****Methodology:*** *This hospital-based observational study was conducted in the Department of Neurology of Dhaka Medical College Hospital from July 2018 to June 2019. Total 95patients, age e"18 years with acute ischemic stroke were selected according to the inclusion & exclusion criteria. Serum ferritin level was measured within 48 hours of stroke and the functional outcome of these patients was assessed at day 90 with the modified Rankin Scale(mRS).* ***Results:*** *The mean age was57.63 ±11.30 years with a range from 25-85 years.The mean Ferritin level was 131.50 ±51.49 found in mRS1,151.61 ±40.16 in mRS 2,177.15 ±72.46 in mRS3, 324.71±107.05 in mRS 4,426.50 ±2.12 in mRS 5, and 429.16 ±84.13 in mRS 6.The above findings indicate that the mRS score increase with the mean ferritin level. It is statistically significant (p-value <0.05). On the Receiver-operating characteristic (ROC) curve, ferritin level had an area under curve 0.946 and gave a cut off value 388 with 71.4% sensitivity and 89.3% specificity. The binary logistic regression model showed that elevated serum Ferritin had a positive impact on poor-outcome after adjusting all independent variables.* ***Conclusion:*** *Elevated serum Ferritin level on admission was significantly associated with 90 days poor outcome in patients with acute ischemic stroke.*

Keywords: *Ischemic stroke, Ferritin,mRS score.*

Introduction:

Stroke is one of the most common and devastating diseases in the world. It is the second leading cause of death and the third leading cause of disability worldwide[1]. Globally, 70% of strokes and 87% of both stroke-related deaths and disabilities occur in low- and middle-income countries[2]. Approximately 15 million new acute stroke events occur every year and approximately 55 million people have had a stroke at some time in the past[3].Ischemic stroke is one of the major causes of death and places a tremendous burden on health resources. Timely intervention can dramatically improve outcomes& reduce disability[4].

Ischemic stroke is one of the major causes of death and places a tremendous burden on health resources.About one-fifth of patients with an acute stroke die within a month of the event and at least half of those who survive are left with a physicaldisability[5]. The reported prevalence of stroke in Bangladesh is 0.3%[6].The incidence of ischemic stroke in the young is increasing with age

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in patients over 35, is higher in women than men aged 18–44 years, and has increased by 23% in one decade[7].

Despite, a lot of researches in the field of stroke, accurate prognostication of an acute attack is difficult. Several prognostic factors like site of the infarct, size of the infarct, size of the vessel involved, Glasgow coma scale, level of cerebral edema, intracranial tension have been found to be significant in ischemic stroke. One of the prognostic indicators which have gained a good clinical interest is the level of serum ferritin.Initially, it was considered only a stress response to stroke but its concentration in serum are not increase during the first 2 days with the stress reaction and acute phase response[8]. Serum ferritin in high concentrations plays an important role to intensify and progress neurological problems immediately following a stroke, including increased weakness, speech and orientation difficulties, and decreased levels of consciousness[9]. Patients with progressing stroke and high ferritin concentrations also have larger areas of brain damage[10].The short-term (90 days) functional outcome is usually measured by modified Rankin Scale (mRS) scale. The mRS score d”3 is thought to be a good outcome suggesting mild to moderate disabilities and >3 considered as a poor outcome suggesting severe disabilities[11].

Although thrombolytic and endovascular therapy has emerged as standard treatment for patients with acute ischemic stroke in window period, it cannot be executed to many of these patients due to multiple factors including time constraints, availability, high cost, and presence of contraindications to thrombolysis. Possible therapeutic potential of iron chelation therapy can be a great advancement in the field of treatment of acute ischemic stroke[12].Very few nationwide studies have discovered the role of serum ferritin for the prognosis of acute ischemic stroke; thus, the purpose of this study is to find out the association between serum ferritin levels at admission and 90 days functional outcome in patients with acute ischemic stroke.

Method:

This prospective longitudinal study was carried out in the department of Neurology of Dhaka Medical College Hospital from July 2018 to June 2019. Patients were enrolled from the department of Neurology and department of Medicine in DMCH. Following admission, patients with acute ischemic stroke were sorted out according to inclusion & exclusion criteria. All of the study population were counseled regarding the aim, objective & usefulness of the study. Written informed consent was collected from each patient and interviews were taken by the researcher himself with a semi-structured questionnaire. In the case of unconscious patient’s data were collected from the attendants of the patients. History regarding demographic profile (age, sex); risk factors (hypertension, diabetes mellitus, dyslipidemia, smoking habit &obesity) and clinical presentation were noted on the questionnaire. The time from symptom recognition to admission was recorded. Under proper aseptic precautions 2 ml venous blood sample was collected & sent for estimation of serum ferritin to the laboratory of the Department of Clinical Pathology, DMCH. The serum ferritin was measured by electrochemiluminescence immunoassay by using the Dimension EXL-200/ Maglumi 2000 analyzer. The value of serum ferritin was considered for further analysis. The functional outcome of the patients was assessed with the Modified Rankin Scale (mRS) score at day 90. The personal contact number of each patient was collected during the interview. Subjects with incomplete data were excluded before the final analysis.

Results:

It was observed that one third (32.6%) of patients belonged to age 51-60 years. The mean age was57.63 ±11.30 years with a range from 25-85 years. It was observed that male was higher (55.8%) than female (44.2%).

It was found that hypertension (75.8%) was the more common risk factor followed by diabetes (47.4%), dyslipidemia (45.3%), smoking (39.8%) and obesity (16.8%).

The mean serum ferritin level was 246.44±134.12 (ng/ml)with a range from 86 to 548 (ng/ml).

Table I showed that the mean Ferritin level were 131.50 ±51.49 found in mRS 1,151.61 ±40.16 in mRS 2,177.15 ±72.46 in mRS 3, 324.71±107.05 in mRS 4,426.50 ±2.12 in mRS 5 and 429.16 ±84.13 in mRS 6.The above findings indicated that mRS score increased with the mean Ferritin level. It was statistically significant(p-value<0.05)

Table II shows the distribution of study patients by mRS and serum Ferritin in groups. All patients were divided into two groups according to serum Ferritin level.Patients having ferritin level d"388 ng/ml was considered as group I and Ferritin level >388 ng/ml was considered as groupII.Regarding the association between the mRS score with the Ferritin level, the mean mRS was 2.80±1.02 in Group I and 5.32±0.99 in Group II. The mean mRS score was significantly (p<.05) higher in patients with Ferritin level >388 ng/ml. mRS score belonged to 4-6, in 15.71% in group I and 96% in group II.

Table III shows the independent variables with their impact on the outcome variable which was measured by the mRS score. mRS score d"3 was considered a good outcome and score >3 was considered a bad outcome[11]. This model showed that the Ferritin level acts independently to the outcome variable (mRS score). One-unit increment of serum ferritin caused to increase in the bad outcome (mRS score >3) by 1.02 times. Age, Gender Hypertension, Diabetes Dyslipidemia, Smoking and obesity were failed to show a statistically significant relationship to poor outcome in this model.

Figure 2: shows the Receiver-operating characteristic (ROC) curve of the Ferritin level.ROC curve Ferritin level had an area under curve 0.912. The receiver-operating characteristic (ROC) curve was constructed by using the Ferritin level, which gave a cut off value of 388 with 75% sensitivity and 89.3% specificity for prediction of prognosis.

Table-I

Distribution of study patients by mRS score with Ferritin level (n=95).

mRS score		Ferritin level	
	n	Mean ± SD	Min-Max
1	4	131.50 ±51.49	96-208
2	23	151.61 ±40.16	86-229
3	33	177.15 ±72.46	86-408
4	14	324.71±107.05	135-430
5	2	426.50 ±2.12	425-428
6	19	429.16 ±84.13	195-548
P-value		0.000^{S}	

s=significant
p-value was reached from the ANOVA test.

Table-II

Distribution of study patients by mRS and serum Ferritin in groups (n=95).

mRS score	Ferritin level				P-value
	Group I n =70	(≤388ng/ml) %	Group II n =25	(>388ng/ml) %	
0-3	59	84.29	1	04	
4-6	11	15.71	24	96	
Mean±SD	2.80±1.02		5.32±0.99		0.000^{s}
Range (Min-Max)	86-408		105-548		

s=significant
p-value was reached from an independent t-test.

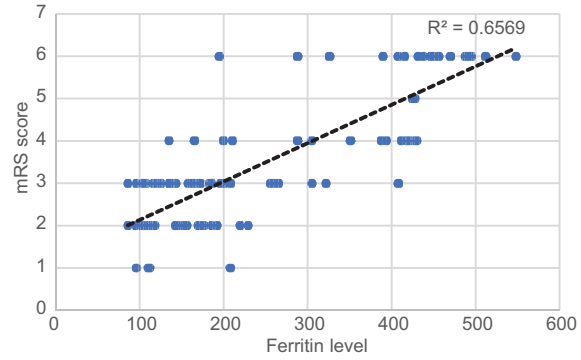

Fig.-1: *A scattered diagram showing positive correlation (r=0.810, p=0.000) between Ferritin level and mRS score.*

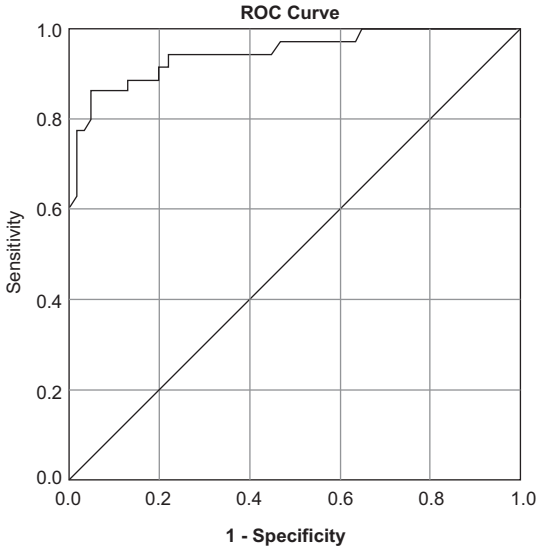

Fig.-2: *Receiver-operating characteristic (ROC) curve of Ferritin level.*

Table-III

Independent variables impact onthe outcome variable (Binary logistic regression model).

Variables	Odds ratio	p-value
Hypertension	0.37	0.448^{ns}
Diabetes	0.18	0.117^{ns}
Dyslipidaemia	2.97	0.278^{ns}
Smoking	1.24	0.898^{ns}
Obesity	3.31	0.451^{ns}
NIHSS score	1.32	0.057^{ns}
Ferritin level	1.02	0.000^{s}

ns=not significant, s=significant,
p values are obtained from the binary logistic regression model.

Discussion:

In this present study, it was observed that one third (32.6%) of patients belonged to age 51-60 years. The mean age was 57.63 ±11.30 years with a range from 25-85 years. A closely related study found that the age ranged from 22-90 years and the age group with the maximum number of patients was 61-70 which was higher than the current study[13]. In another study, Egovindarajulu et al found that 23.33% of patients were in the age group of d" 50 years and 76.67% of patients were in the age group of > 50 years which was consistent with the current study[14,15-17]. On the other hand, another study found that the mean age having an ischemic stroke was 65.9 years which is higher than the present study[15]. The higher mean age and age range maybe due to geographical variations, racial, ethnic differences, and genetic causes that may have a significant influence on patients with ischemic stroke in their study subjects.

There were many studies showed that stroke had various recognized modifiable and non-modifiable risk factors[12-15]. Non-modifiable risk factors include age, gender, ethnicity, heredity, and race. Modifiable risk factors include, but are not limited to hypertension, diabetes mellitus, hyper-cholesterolemia, atrial fibrillation, smoking, and alcoholism. Regarding the risk factor in this present study, it was observed that hypertension (75.8%) was the more common risk factor followed by diabetes (47.4%), dyslipidemia (45.3%), smoking (39.8%) and obesity (16.8%). One study also observed that hypertension was the more common risk factor in their study, which was similar in the current study[15].

This current study showed that the mean serum ferritin level was 229.15±131.52 with a range from 86 to 548 (ng/ml). A study found that the maximum and minimum mean values of serum ferritin in the study are 462.12 ng/ml and 26.48 ng/ml with an average mean of 241.39 ng/ml which is almost similar to this study[14].

In the current study, the mean mRS score was 3.46 ± 1.50 with a range from 1-6. A similar study found that the maximum and minimum mean values for the mRS scoring system in their study were 6 and 1, with an average mean of 3.42 [14].

According to the association between mRS score with Ferritin level, it was observed that the mean Ferritin level were 131.50 ±51.49 found in mRS 1,151.61 ±40.16 in mRS 2,177.15 ±72.46 in mRS 3, 324.71±107.05 in mRS 4,426.50 ±2.12 in mRS 5, and 429.16 ±84.13 in mRS 6.The above findings indicate that the mRS score increase with the mean Ferritin level. It is statistically significant (p-value <0.05). One closely resembled study was observed that the mean serum ferritin level of the group of patients improved was 85.01ng/ml and those deteriorated was 458.70 ng/ml. t-test to compare means of serum ferritin of improved and deteriorated groups[12].

Patients with mRS<3predicted to have an independent life after stroke obtained by Sung et al[17]. The investigators define mRS ≥3 as moderate to severe acute ischemic stroke. In this present study, all patients were divided into two groups according to serum ferritin level. Patients having Ferritin level ≤388ng/ml was considered as group 1 and ferritin level >388 ng/ml was considered as group 2. Regarding the association between the mRS score with the Ferritin level, the mean mRS was 2.80±1.02 in Group I and 5.32±0.99 in Group II. The mean mRS score was significantly (p<.05) higher in patients with Ferritin level >388 ng/ml. mRS score belonged to 4-6 in 15.71% in group I and 96% in group II.

The present study also found a positive correlation between serum ferritin level and mRS score with r=0.810, p=0.000 between ferritin level and mRS score.

In this present study, it was observed that in the Receiver-operator characteristic (ROC) curve Ferritin level had an area under curve 0.946.ROC curve was constructed by using the Ferritin level, which gave a cut off value of 388 with 71.4% sensitivity and 89.3% specificity for prediction of prognosis. Choi et al. study report that higher ferritin level was associated with an unfavorable functional outcome compared with those in patients with a favorable outcome[12].

Binary logistic regression analysis showed the independent variables with their impact on the outcome variable (which was measured by mRS score). mRS score ≤3 was considered a good outcome and score >3 was considered as bad outcome[18]. This model showed that the Ferritin level acts independently to the outcome variable (mRS score). One-unit increment of serum ferritin level from the baseline value (≤388) caused to increase in the bad outcome (mRS score >3) by 1.02 times following ischemic stroke. Age, Gender Hypertension, Diabetes Dyslipidemia, Smoking, and obesity were failed to show a statistically significant relationship to poor outcome in this model. Choi et al, the study showed that in the Binary logistic regression analysis model, serum ferritin levels at baseline higher than 164.1 ng/ml had an OR of 4.993 (95% CI: 2.180–11.437) for poor outcome after adjusting for all the potential factors[15]. The result was a higher significant valuethan the present study. It may due to the higher cut-off level in our study.

Conclusion:

This study has conducted to determine the association between admission serum Ferritin level and 90 days outcome in patients with acute ischemic stroke. Acute ischemic stroke is more common in 51-60 years and above and male predominant. Hypertension, DM and hyperlipidemia are a more common risk factor in acute ischemic stroke and anterior circulation stroke is more common in this study. Age, sex, risk factors are not significantly associated with 90 days outcome in patients with acute ischemic stroke. mRS score and Ferritin level are significantly correlated. The mean mRS is significantly higher in patients with elevated Ferritin level(ng/ml). Ferritin level is a sensitive and specific predictive marker for 90 days outcome in acute ischemic stroke.

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