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Impact of Admission Anaemia on Short Term Outcome in Patients following Acute Ischemic Stroke

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Abstract:

Background: *Acute ischemic stroke causes a great amount of disability with economic and social burden. Therefore, prevention of stroke remains the most important means of reducing its morbidity and mortality. Effective prevention requires understanding the factors associated with the occurrence of ischemic stroke and the population subgroups at greatest risk. Reduced hemoglobin concentration has an adverse impact on the ischemic penumbra in patients with ischemic stroke as it causes reduced oxygen delivery to neuronal tissue and predisposes to infarct expansion.* ***Aims:*** *The purpose of this study is to evaluate the impact of admission anaemia on short term outcome in patients following acute ischemic stroke.* ***Methods:*** *This cross sectional study was carried out in the Department of Neurology, Dhaka Medical College and Hospital (DMCH), Dhaka for a period of two years from July 2020 to June 2022. Two hundred and seventy nine patients of acute ischemic stroke were selected consecutively through screening with set of inclusion and exclusion criteria. Each patient underwent CT of the head and/or MRI of brain and blood tests, including hemoglobin (Hb) concentration on the first day of hospitalization. Demographic, risk factor from all subjects were collected with a structured questionnaire. Neurological state of the patients was assessed on the first day of hospitalization by National Institute of Health Stroke Scale (NIHSS) and the functional status (disability) on the 1st and 30th day after the onset of stroke by Modified Rankin Scale (MRS). After data collection analysis was done by SPSS for Windows version 26. A p value d" 0.05 was considered statistically significant.* ***Results:*** *Anaemia was observed more among the older patients than younger patients but there was no significant difference. Poor outcome was significantly higher in Anaemic (60.8%) than non-anaemic (39.2%) patients. Age was found significantly higher in poor outcome than good outcome (63.41±14.33 years vs 57.24±13.72 years). Admission hemoglobin was significantly lower among the patients with poor outcome both in male and female. Poor outcome was found significantly higher among male (56.6%) than female (43.4%). Anemia was found significantly higher among the patients with severe stroke (46.8%). Among anaemic patients' mortality was significantly higher than non-anaemic patients (18.3% vs 8.2%). According to the Cox regression analysis, anaemia on admission was associated with short-term mortality in patients suffering from acute ischemic stroke [HR=2.52(95%CI: 1.18-5.36; p=0.016)].* ***Conclusion:*** *Anaemia is common among patients with acute ischemic stroke and is associated with severity of stroke, unfavorable outcome and higher mortality.*

Key words: *Anaemia, acute ischemic stroke, outcome.*

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Introduction:

Stroke is a common medical emergency caused by either a sudden reduction in the blood supply to the brain or rupture of intracerebral vessel resulting in hemorrhage causing focal neurological deficit. Most strokes (>99%) are arterial in origin, among them 85% are ischemic and rest 15% are hemorrhagic[1]. Stroke is rated the second leading cause of mortality and one of the biggest causes of long-term disability all over the world[2].

The World Health Organization (WHO) ranks mortality due to stroke in Bangladesh as number 84 in the world in 2011 and in 2017 the rank change to 34 in the world (World Health Rankings, 2011 and 2017). The WHO reported that the number of disability-adjusted life years (DALY) lost (per 1000 people) because of stroke was 485, while the age-standardized DALY rate (per 100000 people) for stroke was 864 [3]. A study by a group of neurologists of Dhaka Medical College Hospital, Bangladesh in 2011 showed that stroke prevalence was 3 per thousand population [4]. These numbers indicate that stroke will have a great economic burden in Bangladesh in the future. Although stroke is largely considered a consequence of hypertension and atherosclerosis, there are also other less common causes in stroke patients including cardioembolism, hematologic disorders, substance abuse, dissections, oral contraceptive use, connective tissue disorders, pregnancy, post-partum stage and migraine. However, the cause of stroke in young patients remains undetermined in about 30% of cases[5].

Anaemia is associated with increased mortality, decreased physical performance and disability regardless of the underlying cause[6,22]. Low hemoglobin levels are associated with decreased oxygen carrying, inflammatory response, alterations in blood viscosity and impairment of cerebral autoregulation [7]. It has been shown that within 3 years of onset of first-ever atherosclerosis-related ischemic stroke, the mortality rate was significantly higher in patients suffering from anaemia at the time of admission [8]. Moreover, data from the Acute Stroke Registry and Analysis of Lausanne (ASTRAL) suggested that anaemia on admission predicts short- and long-term outcomes in patients with acute ischemic stroke[9].

Among the many reasons as to why successful therapeutic reperfusion of acute ischemic strokes does not always result in complete recovery, anaemia has been considered a possible factor. It is shown that anaemia is associated with increased stroke severity by interfering with the salvation of neurons in the ischemic penumbra by depleting the oxygen-carrying capacity of the blood, which could result in poor functional stroke outcomes[10]. Recent evidence according to retrospective analyses clearly informs that anaemia is a predictor of death following a stroke[9,23]. However, some prospective studies have found an uncertain relationship between anaemia and stroke outcomes when adjusted for confounders such as smoking and blood pressure[11]. Furthermore, the main focus of previous studies has been on the impact of anaemia on mortality related to stroke. Long-term functional outcomes following stroke are largely determined by the level of disability at the early stage of the disease. This has implications on stroke management particularly because the presence of anaemia in the individual patient is likely to determine the individual's prognosis after stroke. Nonetheless, data with regard to the relationship between anaemia status upon admission and short- and long-term outcome post-stroke are limited[12,13,24]. Therefore, this study was aimed to evaluate the impact of admission anaemia on short term outcome in patients following acute ischemic stroke in Dhaka Medical College Hospital (DMCH), Dhaka.

Study Procedure: This cross sectional study was carried out in the department of Neurology, Dhaka medical college and hospital, Dhaka from July 2020 to June 2022. Before doing the study, ethical clearance was taken from Ethical Review Committee of DMC. Patients of acute ischemic stroke admitted within 72 hours of onset of symptoms and age ≥18 years in Neurology and Medicine ward of DMCH were enrolled in the study through purposive sampling. Patients with recurrent ischemic stroke, hemorrhagic stroke, transient ischemic attack, venous stroke, sickle cell disease, hemoglobinopathies, polycythemia, hematological and other malignancy were excluded from the study. Patient or their legal guardian was

thoroughly informed about the objectives and procedure of the study. After getting informed written consent clinical history was taken and relevant examination was done. Demographic profile including age, sex, and risk factors were recorded. Acute ischemic stroke was diagnosed according to the WHO criteria and based on radiological images (computed tomography (CT) and/or magnetic resonance imaging (MRI) of the brain (Stroke–1989, WHO). Patient with CT or MRI proved acute ischemic stroke were assessed by the investigator. The NIHSS score was used to assess the stroke severity on first day of hospitalization and functional status was assessed on 1st day and 30th day of onset of stroke by MRS (outcome). Good outcome was defined as MRS 0-3 and poor outcome was defined as MRS 4-6. Mortality was recorded. Blood sample (3ml of venous blood) was collected by EDTA tube (Vaccum tube) for CBC, kept in fully automated Hematology analyzer (Sysmex, XE-5000, Japan). Hb was estimated by Spectrophotometric method, total count and differential count were done by florescent flow cytric method, Red blood cell and Platelet count were done by electrical impedance method. Results were found in one minute when given on fully automated hematology analyzer (Sysmex, XE-5000). PBF was also done along with CBC from the department of Haematology, DMCH. Random blood glucose, fasting lipid profile & Serum creatinine, serum electrolytes were also measured from Clinical Pathology Department, DMCH. ECG was done from cardiology department. All measurements were fulfilled the WHO criteria for precision and accuracy of measurements.

Data analysis: Data was entered, cleaned and analyzed using Statistical Package for Social Sciences (SPSS-26) software. For background variables and sociodemographic variables descriptive statistics and relative frequency were generated. Continuous variables were statistically described in terms of mean and standard deviations (± SD). For normally distributed data, means was compared using Student's t-test. For skewed data, Mann-Whitney U test/ Willcoxson sum rank test was applied for two groups. Qualitative or categorical variables was described as frequencies and proportions. Proportions was compared using chi-square or Fisher's exact test whichever was applicable. Statistical significance was defined as $p<0.05$ and confidence interval set at 95%level. All parameters that obtained the level of significance were further investigated using a multivariate binary logistic regression analysis. A survival analysis using Kaplan–Meier curve was drawn using outcomes as the dependent variable and anaemia as independent variables.

Results:

Initially, 308 patients of acute ischemic stroke admitted in DMCH, fulfilling inclusion and exclusion criteria were enrolled in this study. After being discharged from the hospital, 29 patients lost to follow up. Finally, the data from 279 patients who completed follow up were included in analysis. Appropriate statistical tests were applied in analysis of results. Data was presented in table and figure as appropriate.

Fig. 1 shows the distribution of anaemic and non-anaemic patients by thirty-day outcome. Poor outcome was significantly higher in Anemic (60.8%) than non-anemic patients (39.2%) ($p<0.001$, where p value derived from Chi-Square test).

Table I shows on admission hemoglobin level of the study subjects in good and poor outcome by gender. Admission hemoglobin was significantly lower among the patients with poor outcome both in male and female.

Table II shows association of demographic parameters of the study subjects with outcome.

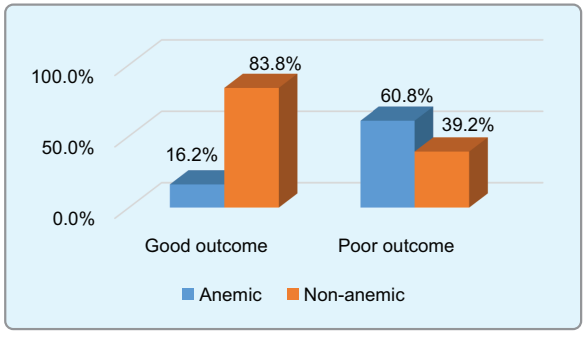

Fig.-1: *Distribution of anaemic and non-anaemic patients by thirty-day outcome (n=279)*

Table-I

On admission hemoglobin level of the study subjects in good and poor outcome by gender (n=279)

Gender	All participants (N=279)	Good outcome (n=136)	Poor outcome (n=143)	p-value
MaleMedian (IQR)	13.4 (12.1-14.2)	14.0 (13.3-14.8)	12.3 (10.8-13.5)	<0.001
FemaleMedian (IQR)	12.1 (10.0-12.7)	12.6 (12.1-13.3)	10.6 (9.8-12.2)	<0.001

Mann-Whitney U test was done

Table-II

Association of demographic parameters of the study subjects with outcome (n=279)

	All participants (N=279)	Good outcome (n=136)	Poor outcome (n=143)	p-value
Age (years)				
d”40	27 (9.7)	19 (14.0)	8 (5.6)	[a]0.020
41 - 50	42 (15.1)	24 (17.6)	18 (12.6)	
51 - 60	82 (29.4)	41 (30.1)	41 (28.7)	
61 - 70	74 (26.5)	34 (25.0)	40 (28.0)	
>70	54 (19.4)	18 (13.2)	36 (25.2)	
Mean ± SD	60.40 ± 14.35 (18 - 95)	57.24 ± 13.72 (18 - 85)	63.41 ± 14.33 (20 - 95)	[b]<0.001
Gender				
Male	176 (63.1)	95 (69.9)	81 (56.6)	[a]0.022
Female	103 (36.9)	41 (30.1)	62 (43.4)	

[a]Chi-Square and [b]Unpaired t test was done

Poor outcome was found significantly higher among the aged patients. Poor outcome was found higher among male patients (56.6%) than female patients (43.4%) and the difference was statistically significant.

Table III shows the association of the risk factors of acute ischemic stroke with outcome. Hypertension was found significantly higher among the patients with poor outcome (71.3%) than good outcome (57.4%). Diabetes mellitus was also

Table-III

Association of the risk factors of acute ischemic stroke with outcome (n=279)

	All participants (N=279)	Good outcome (n=136)	Poor outcome (n=143)	p-value
Hypertension	180 (64.5)	78 (57.4)	102 (71.3)	[a]0.015
Diabetes mellitus	78 (28.0)	30 (22.1)	48 (33.6)	[a]0.032
Dyslipidemia	98 (35.1)	46 (33.8)	52 (36.4)	[a]0.657
History of IHD	40 (14.3)	22 (16.2)	18 (12.6)	[a]0.393
Smoking history				
Non-smoker	142 (50.9)	65 (47.8)	78 (54.5)	[a]0.342
Smoker(Current+Ex)	137 (49.1)	71 (52.2)	66 (45.5)	
Alcohol consumption	12 (4.3)	6 (4.4)	5 (4.2)	[b]0.929
Family history of stroke	75 (26.9)	40 (29.4)	35 (24.5)	[a]0.353
AF	12 (4.3)	5 (3.7)	7 (4.9)	[b]0.616
CKD	19 (6.8)	6 (4.4)	13 (9.1)	[b]0.121

[a]Chi-Square and [b]Fisher’s Exact test was done

significantly higher among the patients with poor outcome (33.6%) than good outcome (22.1%). There was no significant association of outcome with dyslipidemia, history of IHD, smoking, alcohol consumption, family history of stroke, AF and CKD.

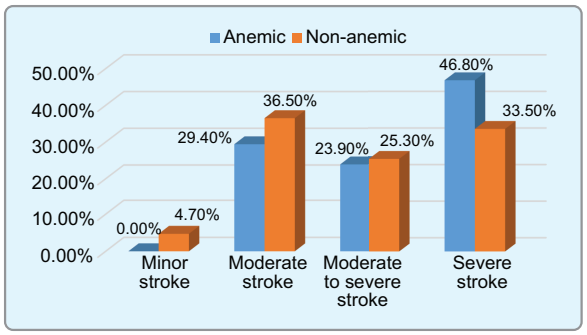

Fig.-2: *Association of admission anemia with severity (NIHSS) of stroke (n=279)*

Fig. 2 indicates the association of admission anemia with severity of stroke. Anemia was found significantly higher among the patients with severe stroke (46.8%) [p=0.027, where p value derived from Chi-Square test].

Table IV shows the association between low admission hemoglobin with disability at day thirty. Severe disability was significantly higher in anaemic (8.2%) than non anaemic patients and Moderately severe disability was found significantly higher in anaemic (53.2%) than non anaemic patients. Death was higher in anaemic patients (18.3%) than non-anaemic patients (8.2%).

Table V shows association of admission anemia with mortality. Mortality was significantly higher in anemic patients (18.3%) than non-anemic patients (8.2%).

In table VI-Binary logistic regression was performed to assess the impact of several factors on the short-term poor outcome of the acute ischemic stroke patients. The model contained six independent variables (Age, gender, anemia, hypertension, diabetes mellitus and NIHSS). Anaemia and NIHSS were found statistically significant.

Table-IV

Association between low admission hemoglobin with disability (MRS) at day thirty (n=279)

MRS (0-6)	All participants (N=279)	Anemic (n=109)	Non- anemic (n=170)	p-value
0 - No symptoms	0	0	0	
1 -No significant disability	20 (7.2)	3 (2.8)	17 (10.0)	0.042
2 -Slight disability	22 (7.9)	8 (7.3)	14 (8.2)	1.000
3 -Moderate disability	93 (33.3)	11 (10.1)	82 (48.2)	<0.001
4 -Moderately severe disability	97 (34.8)	58 (53.2)	39 (22.9)	<0.001
5 -Severe disability	13 (4.7)	9 (8.2)	4(2.3)	0.046
6 –Death	34 (12.2)	20 (18.3)	14 (8.2)	0.019

Chi-Square test was done

Table-V

Association of admission anemia with mortality at day thirty (n=279)

Mortality	All participants (N=279)	Anemic (n=109)	Non- anemic (n=170)	p-value
Yes	34 (12.2)	20 (18.3)	14 (8.2)	0.012
No	245 (87.8)	89 (81.7)	156 (91.8)	

Chi-Square test was done

Table-VI

Binary logistic regression of factors associated with the poor outcome of acute ischemic stroke patients at day thirty (n=279)

	B	SE	p-value	OR	95% CI for OR	
					Lower	Upper
Age	.018	.012	.135	1.018	.994	1.042
Gender (Male)	.519	.330	.116	1.680	.879	3.211
Anemia	2.626	.362	.000	3.423	1.794	5.083
Hypertension	.250	.356	.483	1.284	.639	2.580
Diabetes mellitus	.000	.367	.999	2.150	.487	3.054
NIHSS	.161	.029	.000	1.575	1.109	1.844

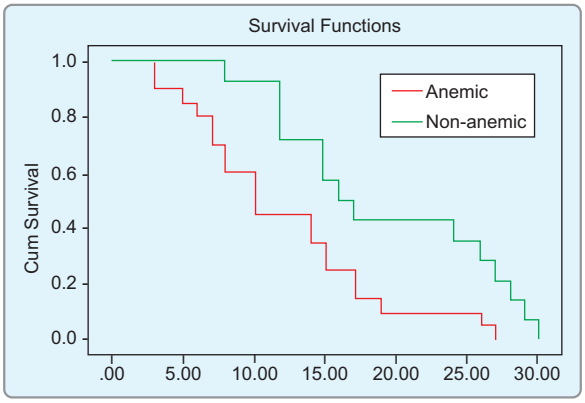

Fig.-3: *Kaplan-Meier survival Curve by anemia*

According to *log rank test* there was significant difference between the two survival curves of anaemic and non anaemic patients (p = 0.013). Cox regression implies that anemia on admission was associated with short-term mortality in patients suffering from acute ischemic stroke [HR=2.52(95%CI: 1.18-5.36; p=0.016)].

Discussion:

The global anaemia prevalence is estimated to be 32.9%, South Asia is one of the regions with the highest burden. Its overall prevalence in females is higher in most regions[14]. Anemia is a major problem faced by middle income countries like Bangladesh. This study was done to find out the impact of admission anaemia on short term outcome in patients following acute ischemic stroke.

Initially, 308 patients with acute ischemic stroke were included in this study. After being discharged from the hospital, 29 individuals were dropped out. Finally, the data from 279 patients were analyzed.

In our study, on admission hemoglobin level in case of male in all patients were 13.4 (12.1-14.2); in good outcome group hemoglobin was 14 (13.3-14.8), in poor outcome group hemoglobin was 12.3 (10.8-13.5) and the result was statistically significant. On admission hemoglobin level in case of female in all patients were 12.1 (10.0-12.7); in good outcome group hemoglobin was 14 (12.1-13.3), in poor outcome group hemoglobin was 10.6 (9.8-12.2) and the result was statistically significant.

In this study, anaemia was observed more among the older patients than the younger but the difference was not statistically significant[9]. found anemia more among the aged stroke patients and anaemia was observed significantly higher among smoker than non-smoker. No significant relationship was found between anemia and the subjects' gender similar to this study[15]. In their study they found anemia among the aged population. In this study, age was found significantly higher among the acute ischemic patients with poor outcome than good outcome [63.41 ± 14.33 years vs 57.24 ± 13.72 years; p=0.020]. Poor outcome was found higher among male patients (56.6%) than female patients (43.4%) and the difference was statistically significant in this study.

In our study, there was no association of poor outcome with dyslipidemia, history of IHD, alcohol onsumption, family history of stroke, AF and CKD. Hypertension and diabetes mellitus was found significantly higher mong the patients with poor

outcome than good outcome. Poor outcome was found higher among nonsmoker but the difference was not statistically significant.

Studied data of 982 consecutive patients with first-ever ischemic stroke and reported that patients with anemia on admission (defined as a Hb < 12 g/dl in women and Hb < 13 g/dl in men) had increased mortality within the first 3 years after stroke when compared with patients with normal Hb[8]. Analyzing retrospective data of 890 patients with a first-ever ischemic or hemorrhagic stroke[16], observed that anemia on admission (defined as a Hb < 12 g/dl in women and Hb < 13 g/dl in men) was independently associated with higher mortality within the first year after stroke. Found an association between anemia on admission (defined as a Hb < 12 g/dl in women and <13 13 g/dl in men) and increased mortality at 1 month and 1 year among 859 ischemic or hemorrhagic stroke patients[17]. Studied data of 217 patients with acute ischemic stroke and reported that poor outcome (defined as a modified Rankin Scale score from 3 to 6) and mortality at 3 months after stroke were associated with low Hb and further decreasing Hb within the first 5 days following stroke[18]. Analyzing retrospective data of 1306 patients with acute ischemic stroke[13] recently reported that anemia on admission (defined as an admission hematocrit value <30%) was associated with in-hospital mortality or discharge to hospice among patients with less severe stroke (defined as and admission NIHSS< 10), but not in the subgroup of patients with more severe stroke.

Moreover, on admission anemia is widely suggested to be related with poor functional outcome and even with increased mortality [8,19]. Recently studied about short- and long-term clinical effects of anemia in AIS patients and revealed that anemic stroke patients had an increased mortality rate[9]. In addition, when the stroke patients are assessed on the 7th day, 3rd month, and 12th month after the onset of stroke, good functional outcome was reported to be more prevalent among non-anemic patients in the same study. Kellert et al.[18] (n = 217) reported worse clinical outcome and increased mortality rates at the third-month assessment in anemic AIS patients. Similarly, in two different studies conducted on larger patient populations[16] (n = 890) and[[17] (n = 859) demonstrated an increased first-year mortality rate in anemic ischemic and hemorrhagic stroke patients compared with non-anemic stroke patients. In addition, a pooled analysis of 13 cohort studies revealed a 39% increased mortality rate in anemic stroke patients compared with non-anemic ones based on some subgroup analyses. However, in contrast, a small number of clinical studies did not find any significant relation between anemia and mortality rate in stroke patients[13,24]. In most of the clinical studies on ischemic stroke patients, anemia is widely defined as Hb levels below 12 g/dL for women and below 13 g/dL for men and anemia is reported to be related with poor clinical outcome and mortality based on this definition.

In the study of Akpinar et al. (2018)[10] they made the comparisons between three anemic subgroups and eventually they found a significant difference in terms of poor clinical outcome and mortality only in the severely anemic subgroup (Hb during performing mechanical thrombectomy. In this study, poor outcome was significantly higher in Anemic patients than non-anemic patients [60.8% vs 39.2%; p=<0.001].

In this study, anemia was found significantly higher among the patients with severe stroke [20]. Also found similar findings, in their study anemia was significantly higher in severe stroke patients. In this study, among anaemic patients severity of disability was found more than non-anaemic patients. Mortality was significantly higher in anaemic than non-anemic patients [18.3% vs 8.2%; p=0.012].On admission, severe disability was higher (77.9%) in anemic patients followed by moderately severe disability (11.0%). Death was higher (18.3%) in anaemic than non anaemic (8.2%).

To assess the impact of several factors on the short-term poor outcome of the stroke patients, Binary logistic regression was performed in this study. The model contained six independent variables (Age, gender, anemia, hypertension, diabetes mellitus and NIHSS). Here anaemia was one of the most important predictor of short-term poor outcome with an odds ratio of 3.423. In the study of Fabjan et al. (2019)[21] according to the Cox

regression analysis, anemia on admission was associated with long-term mortality in patients suffering from acute ischemic stroke [hazard ratio (HR) = 2.448, (95% CI 1.773–3.490; p < 0.001)]. Anemia also remained a strong predictor of mortality.In this study there is significant difference between the two curves according to *log rank test* (p= 0.012). According to the Cox regression analysis, anemia at admission was associated with short-term mortality in patients suffering from acute ischemic stroke [HR=2.52(95%CI: 1.18-5.36; p=0.016)].

Conclusion:
Anaemia is common in acute ischemic stroke patients and an important determinant of poor functional outcome. Admission anaemia is associated with severity of stroke, poor functional outcome and higher mortality. Health care providers should be more meticulous in the early identification and treatment of anaemia.

Ethical consideration: Ethical permission was taken from Ethical Review Committee (ERC) of DMCH. Written informed consent was taken from the patients or their legal guardian. Data taken from the patients were regarded as confidential.

Conflict of interests: None

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