Relationship between Anemia and Stroke Severity- A Tertiary Care Hospital Experience

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Abstract

Objective: There is growing evidence that anemic patients suffer more severe strokes. We evaluated the relationship between anemia and stroke severity in our patient population.

Methods: This descriptive cross-sectional study was carried out over six months in Dow University Hospital which is a tertiary care hospital in Karachi. Patients admitted with acute ischemic stroke, with symptoms duration of up to 72 hours and age more than 20 and less than 80 years were recruited. Patients were divided into two categories, anemic and non-anemic. The stroke severity was classified according to the National Institute of Health Stroke Scores (NIHSS) into three categories, i.e. mild, moderate, and severe. The demographic details, NIHSS scores at admission, symptom duration, and hemoglobin concentration were entered into spreadsheets and later transferred to SPSS software for statistical analyses.

Results: A total of 104 patients were recruited after applying inclusion and exclusion criteria, out of which 55 patients were anemic. The mean age was 54.6 (±13) years. The mean hemoglobin concentration was 10 (±2) g/dl among anemic patients while in non-anemic patients it was 13.9 (±1.2) g/dl. Anemic stroke patients were more likely to have severe strokes, compared to non-anemic patients 41 (74.5%) vs 18 (36.7%), *P-value* = 0.001. The mean NIHSS was higher in anemic compared to non-anemic stroke patients 18.3 (±6.7) vs 13.5 (±6.6), *P-value <.001*, (95 % CI, 2.2, 7.3). Patients with severe anemia had higher stroke severity but did not reach statistical significance (11/13,84.6% vs 48/91, 52.7%, *P-value =.082)*.

Conclusion: Ischemic stroke patients with anemia have more severe strokes when compared to non-anemic patients. The level of hemoglobin may also be associated with stroke severity. These findings should be evaluated by more studies in stroke patients.

Keywords: Acute ischemic stroke, severity, anemia.

IRB: Approved by Institutional Review Board, Dow University of Health Sciences, Karachi. Ref# IRB-2340/DUHS/Approval/2021/724, Dated: 7th February 2022.

Citation: Huma Z, Khuda IE, Tahir SA, Zaki S, Saeed SJ, Ali A. Relationship between anemia and stroke severity- A tertiary care hospital experience [Online]. Annals of ASH & KMDC: 29(3) 256-261

Introduction

Stroke is due to disturbance in the blood supply to the brain resulting in loss of brain function [1]. The number of strokes is increasing worldwide [2]. The incidence of stroke is higher in Asia than in in Western countries [3]. Men are more prone to develop ischemic stroke than women. In about 30% of the cases, the cause remains unknown, especially in young adults. Stroke may be either due to ischemia or hemorrhage. It is the major cause of disability all over the world leading to a big financial burden on caregivers and society [4]. Stroke can lead to many disabilities including sensory, motor, language, visual, and cognitive functions. Stroke affects the quality of life and causes a burden to society and family. Risk factors leading to stroke are diabetes mellitus, dyslipidemia, hypertension, smoking, obesity, sedentary lifestyle, and increasing age.

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Date of Submission: 17th January 2024
Date of 1st Revision: 12th August 2024
Date of Acceptance: 28th August 2024

The severity of stroke on neurological examination is the most important factor, which affects functional outcomes in stroke patients. Generally, large strokes with severe initial clinical deficits have poor outcomes compared with smaller strokes. Different clinical scales measure neurological impairment, which is now being increasingly used for research studies and in clinical practice. The most commonly used scale is the National Institute of Health Stroke Scale (NIHSS). NIHSS measures neurological impairment using a 15-item scale, which includes the level of consciousness, gaze deviations, visual field analysis, facial palsy, motor arm, and leg weakness individually for all four limbs, limb ataxia, sensory loss, language assessment, dysarthria, extinction and inattention. NIHSS scores range from 0 to 42. An NIHSS score of$\leq$6 predicts a good recovery (able to live independently), while a score $\geq$16 was associated with a high probability of death or severe disability. Hence higher NIHSS scores indicate more severe strokes which are associated with higher morbidity and mortality. In third-world countries like Pakistan, it is important to know the factors that may play a role in increasing stroke severity, as more severe strokes are a major cause of disability in the community.

Anemia is the most common disorder of the blood worldwide. According to WHO, anemia is defined as hemoglobin concentration less than 13 g/dl in men and less than 12 g/dl in women [5]. Approximately one-fourth of the world's population is affected by it. It is a common and major health problem in the elderly with its prevalence increasing with advanced age [6]. It is common in developing countries of Africa and South Asia and according to WHO, Pakistan is one of them[7]. It could be because of poor dietary intake due to poverty [8]. Blood loss, inadequate production, and increased breakdown of RBCs may also contribute [9]. Iron deficiency anemia is the most common cause of anemia. There are ways of classification of anemia. Anemia is classified according to mean corpuscular volume (MCV) into microcytic, normocytic, and macrocytic anemia. The causes of microcytic anemia are iron deficiency anemia, thalassemia, zinc deficiency, and lead toxicity. Causes of normocytic anemia are renal diseases and mixed deficiency. Macrocytic anemia may be megaloblastic or non-megaloblastic. Vitamin B12 deficiency, folate deficiency, and DNA synthesis inhibitors cause megaloblastic anemia. Aplastic anemia, liver diseases, hypothyroidism, and myelodysplasia cause non-megaloblastic macrocytic anemia.

It is also important to note that both stroke and anemia are major health problems in Pakistan [10]. There is growing evidence that anemia may be associated with more severe strokes. Hence, the objective of this study was to assess the relationship between anemia and stroke severity in Pakistani stroke patients. The rationale of this study is to validate the relationship between anemia and stroke severity. Such studies may provide groundwork for future studies examining innovative therapies in stroke.

Methodology

This study was conducted in Dow University Hospital Karachi. This was a descriptive cross-sectional study. The sample size was 104 [6] which was calculated by using pass version 11, chi-square test for association of anemia with the severity of the stroke, 99% confidence interval 95% power of the test, and effect size of 0.446 with 2 degrees of freedom. The effect size was calculated using a cross table between anemia and stroke severity.

Consecutive patients with acute ischemic stroke, with symptoms duration of up to 72 hours and age between 20 and 80 years admitted over six months (1st July 2022, until 31st Dec 2022), were evaluated. Acute ischemic stroke was diagnosed when there was a sudden onset, persistent neurological deficit, and the brain imaging was consistent with cerebral ischemic changes in an arterial distribution, corresponding to the clinical deficit. The brain imaging criteria for acute ischemic stroke was Computed Tomography of the brain showing hypodense areas (early ischemic changes) and absence of hemorrhage. Magnetic Resonance Imaging shows an intense lesion on Diffusion-Weighted Imaging,

Apparent Diffusion Coefficient showing hypo intensity, with Fluid Inversion Recovery images showing hyperintensity in the same areas). Patients with cognitive impairment, those more than 80 years old, Transient Ischemic Attack (TIA), those who did not fulfill the diagnostic criteria including brain imaging criteria mentioned above, and stroke mimics were excluded. The patients were then recruited, after getting informed consent. Their demographic details, NIHSS scores at admission, symptom duration, and hemoglobin concentration were entered in spreadsheets. The data thus entered was transferred to SPSS software and statistical analyses were performed. Patients were divided into two categories, anemic and non-anemic. The Stroke severity according to NIHSS was divided into three categories. Mild for NIHSS of <6, moderate for NIHSS of 6 to 15, and severe for NIHSS of >15. For nominal data like gender, age categories, anemia, and arterial territory involved, the Chi-square test was applied. For numerical data including, hemoglobin concentration, NIHSS scores, and age, means were compared using independent samples T-test. A *P*-value of less than 0.05 was considered statistically significant.

Results

In total, 104 patients were recruited. They were more than 20 years of age having ischemic stroke and presented within 72 hours of symptom onset. The mean age was 54.6 (±13) years. There were 44 (42.3%) females and 60 (57.7%) males. When divided among different age categories, there were 17 (16.3%), patients with ages less than 40 years, 39 (37.5%) were between 40 and 60 years, and 48 (46.2%) were 60 and above. There were 82 (78.8%) patients with anterior circulation infarction, while the rest had posterior circulation ischemic strokes. The median duration of symptoms was 10 (min-max range of 1-72) hours, with a mean of 17.7 (±19.5) hours. There were 20 (19%) patients who came within 3 hours, 43 (41%) came within the first 6 hours (23 between 3 to 6 hours), and 88 (85%) patients came within 24 hours (45 between 6 to 24 hours). The mean hemoglobin concentration for the whole sample was 11.8(± 2.6) g/dl. The mean NIHSS score for all the patients was 16.1 (±7). There were 10 (9.6%) patients with minor stroke, 35 (33.7%) had moderate strokes, while the rest 59 (56.7%) had severe strokes. Anemia as defined by WHO was found in 55 (52.9%) patients. In patients with anemia, the mean hemoglobin concentration was 10 (±2) gm/dl while in non-anemic patients it was 13.9 (±1.2) g/dl. There was no difference between males and females and mean age among anemic and non-anemic patients (Table 1). The mean NIHSS in anemic patients was 18.3 (± 6.7), while that in non-anemic patients, was 13.5 (±6.6), (*P-value* < *.001*, CI; 2.2, 7.4) as shown in table 1.

Anemic patients with severe strokes were 41 (74.5%), while there were only 3 (5.4%) and 11 (20%) patients who had mild and moderate strokes in this group respectively (*P*<.001) as shown in Table 2. In the non-anemic category, there were 8 (16.3%), 23 (47%), and 18 (36.7%) patients with mild, moderate and severe strokes respectively (Table 2). When the stroke severity was analyzed in different age categories, no significant associations were observed (table 2). Patients with hemoglobin of less than 8 gm/dl had more severe strokes 11/13 (84.6%) vs those above 8 gm/dl, 48/91 (52.7%), however, this difference could not achieve statistical significance (table 2). No significance in stroke severity was found when patients were divided according to their age, sex, and vascular territory involved (table 2).

Table 1. Differences between Anemic and Non-anemic Stroke Patients

	Anemic (55)n(%)	Non- anemic (49)n(%)	P-value	95% CI
Age	55.3 ± 14	53.8 ± 11.7	0.55	-3.5, 6.5
Sex				
Female (44)	23 (52.3)	21 (47.7)		
Male (60)	32 (53.3)	28 (46.7)	0.536	-
Territory				
Anterior circulation (82)	42 (51.2)	40 (48.8)		
Posterior circulation (22)	13 (59)	9 (41)	0.340	-
Hb (mean)	10 ± 2 g/dL	13.9 ± 1.2 g/Dl	<0.0001	-4.5, -3.2
NIHSS (mean)	18.3 ± 6.7	13.5 ± 6.6	<0.0001	2.2, 7.3

Table 2. Differences between Different Categories of Stroke Severity

	Minor stroke N=10n(%)	Moderate stroke N=35n(%)	Severe stroke N=59n(%)	P-value
Sex				
Females (44)	4 (9)	15 (34)	25 (57)	
Males (60)	7 (11.7)	19 (31.7)	34 (56.6)	0.903
Anemic (55)	3 (5)	11 (20)	41 (74.5)	
Non- anemic (49)	8 (16.3)	23 (47)	18 (36.7)	0.001
Hb level	0.082			
Above 8 (91)	10 (10.9)	33 (36.3)	48 (52.7)	
8 and less (13)	1 (7.6)	1 (7.6)	11 (84.6)	0.082
Age category				
20 to 39 (17)	3 (17.6)	3 (17.6)	11 (64.7)	
40 to 59 (39)	3 (7.6)	14 (35.8)	22 (56.4)	
60 and above (48)	4 (8.3)	18 (37.5)	26 (54.2)	0.528
Territory/circulation				
Anterior (82)	9 (11)	26 (31.7)	47 (57.3)	
Posterior (22)	2 (9)	8 (36.3)	12 (54.5)	0.906

Discussion

Our study has shown that stroke patients with anemia are more likely to have severe strokes with higher National Institute of Health Stroke Scale (NIHSS) scores. Furthermore, we also found a trend in our sample that those with more severe anemia also seem to have more severe strokes, however, this association could not reach statistical significance. Interestingly we also found out that stroke severity had no relationship with the vascular territory, age category, and gender. The only characteristic, among those measured in this study that had a significant relationship with stroke severity is the presence of anemia. A higher NIHSS score or stroke severity is a bad prognostic factor and is known to be associated with worse outcomes and increased mortality[11,12]. Hence our study adds to the growing evidence that anemia hurts stroke patients in terms of stroke severity and outcome, as described below.

Anemia is detrimental in various studies on ischemic stroke. It has been regarded as a predictor of mortality and severity of stroke and also as a potential cardiovascular risk factor. There are many potential mechanisms by which anemia can negatively impact stroke severity and outcome. Anemia results in decreased oxygen-carrying capacity of the blood, which might be the reason for the increased severity of stroke resulting in poor functional stroke outcomes[13,14,15]. In addition, there may be a direct effect of anemia on functional disability[16]. Reduced hemoglobin concentration hurts the ischemic penumbra in patients with ischemic stroke by causing decreased delivery of oxygen to neuronal tissue resulting in expansion of infarct. Increased secretion of erythropoietin secondary to anemia can result in reactive thrombocytosis hence hypercoagulable state[17]. Recent studies show that anemia is a predictor of death after stroke [18].

There have been many clinical studies that have shown the adverse effect of anemia/low hemoglobin concentration on ischemic stroke. Tanne et al, showed that anemia in stroke patients predicted poor functional outcomes, as assessed by Barthel's index. They also showed that the risk of death increased at both extremes of hemoglobin concentration [19]. Chang et al. measured stroke severity and disability by various scales (including NIHSS, Modified Rankin Scale (MRS), and Barthel's Index), and found that in the South Asian population in early acute ischemic stroke, anemia is an independent factor of poor functional disability[15]. Lasek et al. showed that NIHSS within 24 hours of stroke and the site of cerebral ischemia are independent determinants of poor prognosis in anemic patients in short-term follow-up. They also reported that mild anemia did not have a significant impact on the neurological condition in acute stroke but hurt functional status in subacute stroke[20]. Few

studies have also shown that anemia can cause increased mortality and stroke recurrence. Chang JY et al showed that hemoglobin concentration influenced stroke recurrence and other vascular events[21].

A meta-analysis of 13 cohort studies by Li et al, published in 2016, found that in patients with stroke, the mortality rate is increased if they are anemic [18]. Barlas et al. analyzed data from a cohort of 8013 stroke patients consecutively admitted over 11 years (January 2003 to May 2015) using a UK Regional Stroke Register. They reported strong evidence which suggested that anemic patients have increased mortality with stroke[22].

Interestingly anemia has been shown to hurt the outcome of stroke patients also receiving reperfusion therapies (intravenous alteplase and mechanical thrombectomy). Cerebral collaterals and penumbra are negatively affected by anemia. Alterberger et al. have shown that anemia on admission causes poor outcomes and increases mortality strongly and independently in stroke patients treated with intravenous thrombolysis[23]. According to Akpinar et al, poor functional outcome is noted only in moderate to severe anemic patients. In acute stroke patients treated with mechanical thrombectomy, the negative impact of moderate to severe anemia should be kept in mind by clinicians in the clinical course of illness[16].

While realizing the fact that anemia is an important health problem in a third-world country like Pakistan, whereas stroke is also a major cause of disability and death, the relationship between these two ailments needs to be addressed. More studies are needed to confirm their relationship. It might also be interesting to look for potential beneficial effects of anemia correction on the outcome, especially in the context of hyperacute stroke reperfusion and management.

Our study has its limitations. We did not assess the cause of anemia, so it may be difficult to postulate the underlying pathophysiology. Our sample size was also small; hence the generalizability of our findings needs to be verified on a larger sample.

Conclusion

Anemia seems to be an important factor that hurts stroke severity. It may also be considered while determining prognosis. More studies are needed to verify the effect of anemia on ischemic stroke and the role of its correction in the outcome of stroke patients.

Conflict Of Interest: None

Disclaimer: None

Source of Funding: None

References

1. Rathore R, Butt NF, Iqbal A, Latif H, Azeem M, Abbas M. Association of Iron Deficiency Anemia with Stroke Severity in Patients with Acute Ischemic Stroke. J Med Heal Sci 2021;15(11):3004-6 [DOI: https://doi.org/10.58397/ashkmdc.v 28i2. 674].
2. Meschia JF, Brott T. Ischaemic stroke. Eur J neurol 2018;25(1):35-40. [DOI: https://doi.org/10.1111/ene.13409].
3. Venketasubramanian N, Yoon BW, Pandian J, Navarro JC. Stroke epidemiology in South, East, and South-East Asia: a review. J Stroke 2017; 19(3):286-294. [DOI: 10.5853/jos.2017.00234].
4. Huma Z, Nawaz Z, Tahir SA, Mobin A, Kashif SM, Khuda IE. Frequency of Iron Deficiency Anemia in Ischemic Stroke. Annals ASH & KMDC 2023; 28(2):88-95. [DOI: https://doi.org/10.58397/ashkmdc.v28i2.674].
5. Rabbani A, Dad SA, Ayub A, Adeel B, Azam M, Masood A. Association between Platelet and Iron Parameters in Patients with Iron Deficiency Anemia. Pakistan Journal of Medical & Health Sciences 2022;16(02):1002. [DOI: 10.53350/pjmhs 221621002].
6. Khan MF, Shamael I, Zaman Q, Mahmood A, Siddiqui M. Association of anemia with stroke severity in acute ischemic stroke patients. Cureus 2018;10(6). [DOI: 10.7759/cureus.2870].
7. Habib MA, Raynes-Greenow C, Soofi SB, Ali N, Nausheen S, Ahmed I, Bhutta ZA, Black KI. Prevalence and determinants of iron deficiency anemia among non-pregnant women of reproductive age in Pakistan. Asia Pac J Clin Nutr 2018;27(1):195-203. [DOI:10.6133/apjcn.042017.14].
8. Zahid M, Zubair T, Sadaf R, Rahman F. Prevalence Of Iron Deficiency Anaemia In Females Presenting To Medical OPD Of Bacha Khan Medical Complex Shahmansoor, Swabi. KJMS 2018;11(1) :61. Available from: https://kjms.com.pk/old/sites/default/files/KJMS-13.pdf. Accessed on 24th August 2024.

9. Heo J, Youk TM, Seo KD. Anemia Is a Risk Factor for the Development of Ischemic Stroke and Post-Stroke Mortality. J Clin Med 2021;10(12);2556-67. [DOI: 10.3390/jcm10122556].

10. Soofi S, Khan GN, Sadiq K, Ariff S, Habib A, Kureishy S, et al. Prevalence and possible factors associated with anemia, and vitamin B 12 and folate deficiencies in women of reproductive age in Pakistan: analysis of national-level secondary survey data. BMJ open 2017;7(12):e018007. [DOI: https://doi.org/10.1136/bmjopen-2017-018007].

11. Krishnamoorthy S, Sylaja PN, Sreedharan SE, Singh G, Damayanthi D, Gopala S, et al. Biomarkers predict hemorrhagic transformation and stroke severity after acute ischemic stroke. J Stroke Cerebrovasc Dis 2023;32(1):106875. [DOI: https://doi.org/10.1016/j.j stroke cerebrovasdis. 20 22.106875].

12. Leventis I, Perlepe K, Sagris D, Sirimarco G, Strambo D, Georgiopoulos G, et al. Characteristics and outcomes of embolic stroke of undetermined source according to stroke severity. Int J Stroke 2020;15(8):866-71. [DOI: https://doi.org/10.1177/1747493020909546].

13. Choi E, Sanchez-Rotunno M, Gonzales N. Ischemic stroke related to severe iron deficiency anemia in adults may benefit from blood transfusion (PO1.232), PO1 cerebrovascular disease I.-Neurology 2013:80(7):P01.232. [DOI: https://doi.org/10.1212/WNL.80.7_supplement.P01.232].

14. Zhang Q, Shan K S, O'Sullivan C, Nace T. Iron Deficiency Anemia: An Unexpected Cause of an Acute Occipital Lobe Stroke in an Otherwise Healthy Young Woman. Cureus 2020;12(4):e7852. [DOI: 10.7759/cureus.7852].

15. Chang T, Weeratunga P, Vithanage T, Wijewickrama P, Kularathne S, Fernando S, et al. Anemia as a predictor of functional disability in the early stage of ischemic stroke in a South Asian population. Ann Indian Acad Neurol 2020;23(4):515-21. [DOI: 10.4103/aian.AIAN _357 _19].

16. Akpinar CK, Gurkas E, Aytac E. Moderate to severe anemia is associated with poor functional outcome in acute stroke patients treated with mechanical thrombectomy. Interv Neurol 2018;7(1-2):12-8. [DOI: 10.1159/000480642].

17. Kaiafa G, Savopoulos C, Kanellos I, Mylonas KS, Tsikalakis G, Tegos T, et al. Anemia and stroke: Where do we stand? Acta Neurol Scand 2017;135(6):596-602. [DOI: 10.1111/ane.12657].

18. Li Z, Zhou T, Li Y, Chen P, Chen L. Anemia increases the mortality risk in patients with stroke: a meta-analysis of cohort studies. Sci rep 2016;6(1):26636. [DOI: 10.1038/srep26636].

19. Tanne D, Molshatzki N, Merzeliak O, Tsabari R, Toashi M, Schwammenthal Y. Anemia status, hemoglobin concentration and outcome after acute stroke: a cohort study. BMC neurol 2010;1-7. [DOI: 10.1186/1471-2377-10-22].

20. Lasek-Bal A, Holecki M, Stêposz A, Du³awa J. The impact of anemia on the course and short-term prognosis in patients with first-ever ischemic stroke. Neurol Neurochir Pol 2015;49(2):107-12. [DOI: 10.1016/j.pjnns.2015.03.001].

21. Chang JY, Lee JS, Kim BJ, Kim JT, Lee J, Cha JK, et al. Influence of hemoglobin concentration on stroke recurrence and composite vascular events. Stroke 2020;1(4):1309-12. [DOI: 10.1161/STROKEAHA.119.028058].

22. Barlas RS, Honney K, Loke YK, McCall SJ, Bettencourt Silva JH, Clark AB, et al. Impact of hemoglobin levels and anemia on mortality in acute stroke: analysis of UK regional registry data, systematic review, and meta analysis. J Am Heart Assoc 2016;5(8):e003019. [DOI: 10.1161/JAHA.115.003019].

23. Altersberger VL, Kellert L, Al Sultan AS, Martinez-Majander N, Hametner C, Eskandari A, et al. Effect of hemoglobin levels on outcome in intravenous thrombolysis-treated stroke patients. Eur Stroke J 2020 (2):138-47. [DOI: 10.1177/2396987319889468].