Original Article

Hemoglobin level is associated with severe stroke among stroke patients in Saudi Arabia

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ABSTRACT

Objectives: The purpose of this study was to examine the association between abnormal hemoglobin (Hb) level and stroke severity (as assessed by the National Institutes of Health Stroke Scale [NIHSS]). The study further aimed to describe the demographic and clinical characteristics of stroke patients in the middle region of Saudi Arabia.

Methodology: We performed a retrospective review of all medical records of the stroke patients who were treated at a major hospital in Qassim province between 2016 and 2018. Reviewed data ($n = 400$) included demographics, Hb level on admission, type of stroke (ischemic vs. hemorrhagic), stroke risk factors, and NIHSS scores. Analysis of variance (ANOVA) test was used to assess the univariate association between NIHSS and Hb level. Regression statistics were utilized to examine the effect of abnormal Hb level on NIHSS scores while controlling for the other study variables. Data were analyzed using Statistical Package for the Social Sciences.

Results: Sixty-nine percent of the patients were men. More young women than men (≤ 39 years) had a stroke. Ischemic stroke is considerably more common than hemorrhagic stroke (a ratio of 12.7:1). ANOVA test showed that the mean score of NIHSS was significantly lower among patients with a normal Hb level. Regression showed that NIHSS scores were significantly associated with abnormal Hb level, in terms of low and high level.

Conclusions: This study demonstrated further evidence of the association between abnormal Hb level NIHSS. Thus, our results emphasize the predictive importance of Hb level on identifying individuals who might be at higher risk of worse neurological outcomes after stroke. Physicians need to be cognizant of the negative effect of abnormal Hb level on the outcomes of stroke patients.

Keywords: Abnormal hemoglobin levels, Saudi Arabia, severity, stroke

Introduction

Stroke is rated the second leading cause of mortality and one of the biggest causes of long-term disability all over the world.[1] Stroke is a common health problem in Saudi Arabia (SA). In 2014, a study found that the incidence of stroke in SA was 30 cases per 100,000 people per year.[2] A more recent study in 2018 reported a higher incidence of stroke among Saudis (57.64 cases per 100,000 people per year).[3] Similar to the case in the U.S,[4] there is a similarity in the regional variation of stroke rates in SA. A study by Alahmari and Paul in 2016 found that Al-Qassim region was among the top regions in SA in the prevalence of stroke along with Qunfudhah, Al Hassa, and Jazan regions.[5]

Stroke is defined as the rapid loss of brain function due to a disturbance in the blood supply to the brain.[6] A stroke happens when a part of the brain has an insufficient or interrupted blood supply and decreased oxygenation and nutrition to brain tissue.[7] Ischemic and hemorrhagic strokes are believed to have opposite mechanisms. Ischemic stroke, which is comparatively more common than hemorrhagic stroke, is characterized by limitation of blood supply to the brain, whereas hemorrhagic is described by the presence of too much blood within the closed cranial cavity tissue.[6,7]

Multiple risk factors, with various magnitudes, have been identified to be associated with increased risk of acute stroke, including age, gender, hypertension, diabetes mellitus, dyslipidemia, obesity, cardiovascular disease, smoking, and previous stroke.[8] On the other hand, additional coexisting conditions may increase stroke severity, resulting in worse outcomes in terms of both mortality and disabilities. Among

these conditions are the accompanying abnormal (low or high) hemoglobin (Hb) levels. Hb has a direct relation with blood supply and the delivery of oxygen to the central nervous system.[9] A substantial body of research revealed that low Hb level on admission (i.e., anemia) among stroke patients was associated with more severe stroke.[9-17] Furthermore, a pilot study on the association between baseline Hb at the time of stroke and discharge destination showed that midrange levels were associated with a better discharge outcome.[18] Contrasting the low-Hb level, the effect of high Hb-level on stroke severity has been less frequently addressed in the scientific literature.[9-17] Yet, most available studies revealed that high Hb level on admission among stroke patients was also associated with more severe stroke.[11,12,16,17]

The economic burden of stroke on health-care systems is high. According to the latest report by the center for disease control and prevention care for stroke, in the U.S, stroke survivors were estimated to cost 18.8 billion dollars in a single year in addition to 15.5 billion dollars as a result of premature mortality and loss of productivity.[4] There are no clear data on the economic burden of stroke in SA; nevertheless, the burden is expected to be high, especially while rehabilitation therapy is included in the public insurance system.

This study aimed to examine the association between abnormal Hb level and stroke severity (National Institutes of Health Stroke Scale [NIHSS] scores) and among Saudi stroke patients. The study further aimed to describe the demographic and clinical characteristics of stroke patients in the middle region of SA.

Methodology

This is a retrospective review of the medical records of stroke patients (n=400), who were treated at King Fahad Specialist Hospital (KFSH) in Al-Qassim region from 2016 to 2018. Patients younger than 18 years of age were excluded from the study. This exclusion criterion was applied owing to the extremely low number of cases among this age group ($n = 2$). Accordingly, the total number of studied stroke cases was 398.

Ethical approval to review the KFSH records was obtained from the Qassim Region Research Ethics Committee.

The reviewed data included two demographic variables: gender and age. The variable of age was further categorized into four groups (18–39 years=1; 40–59 years=2; 60–79 years=3; 80 years or more=4). In addition, the type of stoke was determined (ischemic=1, hemorrhagic=2). Hb level on admission in grams per deciliter (g/dL) was measured as a continuous variable and later converted to three categorical variables in accordance with Mayo Clinic's (low ≤12 g/dl for females and <13.5 g/dL for males; normal=12–15.5 g/dL for females and 13.5–17.5 g/dl for males; and high ≥5.5 g/dL for females and > 17.5 g/dL for males).[19] The severity of stroke was assessed using the NIHSS,[20] which ranges from 1 to 42, with higher scores signifying more severe adverse effects.

Statistical analysis

The reviewed data were coded and entered into an excel spreadsheet for initial editing, and then exported to Statistical Package for the Social Sciences (SPSS) version 20 (IBM SPSS, Inc Chicago IL, USA) for statistical analysis. Proper descriptive statistics, based on the type of variables (continuous/categorical), was employed to provide an overall picture of the stroke patients. Gender differences were assessed using independent samples *t*-test for continuous variables and Chi-square test (χ^2) for categorical variables. General linear model analysis of variance (ANOVA) was used to assess the Univariate association between Hb level (low, normal, and high) and stroke severity (NIHSS scores). Multiple regression analysis was performed to identify the influence of Hb level on stroke severity. Before analysis, all categorical variables were coded into dummy variables. For example, a risk factor was coded (1) when it was present, and coded (0) when it was absent (reference group). Age, dummy-coded gender, and dummy-coded stroke risk factors were entered in the first step as controlled variables, whereas the Hb level was entered in the second step. A P=0.05 was considered statistically significant.

Results

Demographic and clinical characteristics of stroke patients

Approximately two-thirds of the patients (69.1%) were males (male to female ratio was 2.2:1). The mean age of the stroke patients was 60.1 years and the most dominant age group was 60–79 years. The mean Hb level was 13.2 g/dL. Furthermore, around one-third of the patients (33.2%) had anemia on admission, whereas 2.5% had above normal Hb level. The mean NIHSS total score was 8.8 (SD = 6.1). Our results showed that ischemic stroke is much more common than hemorrhagic one (a ratio of 12.7:1).

Concerning gender differences in characteristics of stroke patients, there were only two significant differences revealed. First, younger females (39 years of age or younger) and older males (80 years of age or older) were more likely to experience stroke events than their counterparts. Second, males were more likely to be smokers than females. Table 1 summarizes the demographic and clinical characteristics of stroke patients in addition to gender differences.

Association between Hb level and stroke severity

Table 2 shows the result of ANOVA test and Tukey's *post hoc* test in NIHSS scores according to Hb level (low, normal, and high). The results revealed that the mean score of NIHSS was significantly lower among patients with normal Hb levels,

Table 1: Characteristics of the stroke patients according to their gender

Characteristics	Total sample (*n*=348)	Gender		*P*-value*
		Male (*n*=275)	Female (*n*=123)	
Mean (SD)**				
Age in years	60.9 (15.1)	62.2 (14.3)	58.0 (16.2)	0.02
NIHSS scores	8.8 (6.1)	8.6 (6.2)	9.3 (5.6)	0.29
Percentages***				
Age in years (categories)				
≤39 years	29 (7.3)	14 (5.1)	15 (12.2)	0.03
40–59 years	145 (36.4%)	99 (36.0)	46 (37.4)	
60–79 years	176 (44.2)	124 (45.1%)	52 (42.3)	
≥80 years	48 (12.0)	38 (13.8)	10 (8.1)	
Hb level (categories)				
Low	132 (33.2)	90 (32.7)	42 (34.1)	0.82
Normal	256 (64.3)	178 (64.7)	78 (63.4)	
High	10 (2.5)	7 (2.5)	3 (2.4)	
Type of stroke				
Ischemic	369 (92.7)	252 (91.6)	117 (95.1)	0.22
Hemorrhagic	29 (7.3)	23 (8.4)	6 (4.9)	
Proportion of patients with the risk factor				
Hypertension	294 (73.9)	209 (76.0)	85 (69.1)	0.148
DM	227 (57.0)	164 (59.6)	63 (51.2)	0.117
Dyslipidemia	61 (15.3)	47 (17.1)	14 (11.4)	0.144
Obesity	169 (42.5)	114 (41.5)	55 (44.7)	0.543
CVD	128 (32.2%)	90 (32.7)	38 (30.9)	0.718
Smoking	77 (19.3)	67 (24.4)	10 (8.1)	0.000
Previous stroke	120 (30.2)	91 (33.1)	29 (23.6)	0.056

*Significant differences are shown in bold font. **Gender differences assessed using independent samples *t*-test. **Gender differences assessed using the Chi-square test (χ²). CVD: Cardiovascular disease

Table 2: Univariate association between Hb level and stroke severity

Hb level	Mean NIHSS scores (SD)	F-value	*P*-value
		10.39	<0.001
Low (*n*=132)	10.31 (6.65)		
Normal (*n*=258)	7.91 (5.22)		
High (*n* = 9)	13.78 (11.51)		

in other words, abnormally low and high Hb levels were associated with more severe stroke.

Table 3 summarizes the bivariate association of NIHSS scores with Hb level while controlling for the other variables. The results showed that NIHSS scores were significantly associated with abnormal Hb level in terms of low and high levels with a predictive value of 10%.

Discussion

In accordance with previous data from SA,[2] Saudi men have more strokes than women (men-to women

ration=2.2/1). Remarkably, the opposite trend arises from U.S studies.[21] According to Bushnel *et al.*, more American women are experiencing strokes than men as female life expectancy at birth is higher than that of males.[21]

Concerning the age of onset, the mean age of our population was 60.9 years, which is far younger than the average age of presentation in the U.S population with the average age being 69.3 years.[22] This variation may be partly attributed to the differences in life expectancy between the two countries.

Concerning the type of stroke, our results revealed a bigger difference in the ratio between ischemic and hemorrhagic stroke (12.7/1) compared to two local studies in the early nineties with ratios of 3.2/1 and 6.7/1.[23,24] The arising dominance of ischemic stroke over the hemorrhagic one might be attributed to the socioeconomic changes which SA has been witnessing for the past few decades. These changes have resulted in alteration in lifestyles, including lack of exercise and an unhealthy diet, which led to the high prevalence of obesity, hypertension, and diabetes.[25] The notation that half of the stroke-related deaths are attributable to poor management of the controllable risk factors[26]

Table 3: Multiple linear regression analysis of Hb level on stroke severity

Variable	Adjusted model		
	Beta (*)	SE (**)	*P*-value***
Adjusted model			
Age	−0.031	0.021	0.551
Gender-Male	−0.051	0.664	0.319
Hypertension- Present	−0.005	0.734	0.931
DM- Present	0.056	0.658	0.302
Dyslipidemia- Present	0.137	0.858	**0.007**
Obesity- Present	−0.016	0.610	0.748
CVD- Present	0.050	0.649	0.318
Smoking- Present	0.069	0.773	0.169
Previous stroke- Present	−0.046	0.674	0.336
Hb level			
Low	0.167	0.642	**0.001**
High	0.160	2.02	**0.001**
Total R²	0.10		

*Standardized coefficient. **Standard error. ***Bold font indicates statistical significance.
DM: Diabetes mellitus, CVD: Cardiovascular disease

highlights the need to better management strategies of stroke risk factors.

Our results showed that women were more likely than men to have a stroke in the age group of 39 years or younger. This finding is inconsistent with data from U.S,[21] which reported that men have strokes at younger ages compared to women. Further national research is needed to explain why these differences occur. In general, there are variations in the rates of stroke by both age group and gender by age group. Therefore, it is recommended to collect data based on age-specific rates by gender to facilitate the interpretation of stroke trends in the targeted population.[22]

The results of this study demonstrate evidence of the association between Hb level and stroke severity. Patients with abnormal Hb levels at the time of admission (low and high) were more likely to experience more severe strokes, whereas patients with midrange Hb levels were less likely to experience severe strokes. The adverse effects of low-Hb level (anemia) on stroke severity have been addressed in multiple previous studies. Milionis *et al.*[15] found that anemia on presentation was a significant predictor of adverse outcomes among stroke patients. Moreover, higher mortality rates were reported among stroke patients with anemia on admission.[11-13,16] Contrasting the low-Hb level, the effect of high Hb-level on stroke severity has not been adequately addressed in the scientific literature. Among available studies, Furlan *et al.* concluded that a high Hb level on admission was associated with more morbidity and mortality, in addition to a longer hospital stay.[12] Moreover, a recent systematic review and meta-analysis analysis of UK regional registry data revealed an association between mortality and abnormally high Hb on presentation and among stroke patients.[11] Consistent with our hypothesis, three previous

studies reported a nonlinear association between stroke severity and Hb level.[12,16,17] Naess *et al.* in their recent study explored a U-shaped association between stroke severity and Hb level, which were evident in the Lowess smoother curves.[17] In addition, Tanne *et al.* found that the risk of mortality in stroke patients increases at both extremes of Hb levels.[16] The results of the study of Furlan *et al.* also indicated nonlinearity in the influence of abnormal Hb level in mortality in stroke patients (according to the resulted Kaplan-Meier curves).[12]

As the study has significantly demonstrated that abnormal Hb level is linked to a poorer outcome for stroke patients, it is imperative to identify subjects at high risk and optimize the management. At present, there is insufficient evidence to provide strong recommendations regarding which Hb level to be targeted, and which transfusion strategy to use (indication vs. contraindication). A randomized trial is needed to confirm the benefit and safety of any therapy before we consider it. For stroke patients with high Hb level, if the etiology is hyperviscosity, then hemodilution with venesection may be the safest acute treatment.

There were limitations to our study. We had only one baseline measurement of Hb level. Therefore, we were not able to determine whether long-term changes in Hb level were associated with stroke risk. Furthermore, we did not categorize anemia according to its types. Moreover, we did not collect data on stroke "non-survivors" from the included population. Such data could have provided further comparisons on the patient's characteristics, especially the accompanying Hb level. Nevertheless, our study has a major strength, namely being the first study in SA, and maybe in the Middle East, to address the relationship between Hb level and NIHSS.

Conclusion

Our study demonstrated an association between abnormal Hb level (both low level and high level) and the severity of stroke. It may be important to treat anemia in the presence of acute stroke because this treatment will improve the delivery of oxygen to the brain. Future research may include the examination of whether giving blood transfusion/treating a high Hb level will help and mentioning in improving the severity of stroke and mortality rate.

Authors' Declaration Statements

Ethics approval and consent to participate

Ethical approval obtained from Regional Committee of Bio-Ethics (REC) Qassim Region. The study was approved by the Institutional Ethics Committee.

Availability of data and material

Data and material available upon request.

Author's Contribution

NA participated in literature review, writing the manuscript, overall review of the whole paper; MSA and STA participated in data collection, data entry, literature review, writing the introduction.

References

1. Katan M, Luft A. Global burden of stroke. In: Seminars in Neurology. Vol. 38. United States: Thieme Medical Publishers; 2018. p. 208-11.

2. Asirvatham AR, Marwan MZ. Stroke in Saudi Arabia: A review of the recent literature. Pan Afr Med J 2014;17:14.

3. Alhazzani AA, Mahfouz AA, Abolyazid AY, Awadalla NJ, Katramiz K, Faraheen A, *et al*. In hospital stroke mortality: Rates and determinants in Southwestern Saudi Arabia. Int J Environ Res Public Health 2018;15:927.

4. Cassel CK, Ek K. Demography and epidemiology of age-associated neuronal impairment. In: Functional Neurobiology of Aging. United States: Academic Press; 2001. p. 31-50.

5. Alahmari K, Paul SS. Prevalence of stroke in Kingdom of Saudi Arabia-through a physiotherapist diary. Mediter J Soc Sci 2016;7:228.

6. Chang YL, Hung SH, Ling W, Lin HC, Li HC, Chung SD. Association between ischemic stroke and iron-deficiency anemia: A population-based study. PLoS One 2013;8:e82952.

7. Sims NR, Muyderman H. Mitochondria, oxidative metabolism and cell death in stroke. Biochim Biophys Acta 2010;1802:80-91.

8. Zahari WN, Supriyanto E, Mahmud N. Stroke risk prediction model. Int J Biol Biomed 2019;4:1-6.

9. 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. Scientific reports, 2016;6:p.26636.

10. Akins PT, Glenn S, Nemeth PM, Derdeyn CP. Carotid artery thrombus associated with severe iron-deficiency anemia and thrombocytosis. Stroke 1996;27:1002-5.

11. 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:e003019.

12. Furlan JC, Fang J, Silver FL. Acute ischemic stroke and abnormal blood hemoglobin concentration. Acta Neurol Scand 2016;134:123-30.

13. 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;135:596-602.

14. Mehta PJ, Chapman S, Jayam-Trouth A, Kurukumbi M. Acute ischemic stroke secondary to iron deficiency anemia: A case report. Case Rep Neurol Med 2012;2012:487080.

15. Milionis H, Papavasileiou V, Eskandari A, D'Ambrogio-Remillard S, Ntaios G, Michel P. Anemia on admission predicts short-and long-term outcomes in patients with acute ischemic stroke. Int J Stroke 2015;10:224-30.

16. Tanne D, Molshatzki N, Merzeliak O, Tsbari R, Toashi M, Schwammenthal Y. Anemia status, hemoglobin concentration and outcome after acute stroke: A cohort study. BMC Neurol 2010;10:22.

17. Naess H, Logallo N, Waje-Andreassen U, Thomassen L, Kvistad CE. U-shaped relationship between hemoglobin level and severity of ischemic stroke. Acta Neurol Scand 2019;140:56-61.

18. Diamond PT, Gale SD, Evans BA. Relationship of initial hematocrit level to discharge destination and resource utilization after ischemic stroke: A pilot study. Arch Phys Med Rehabil 2003;84:964-7.

19. Mayo Clinic. Hemoglobin Test: Results. 2019. Available from: https://www.mayoclinic.org/tests-procedures/hemoglobin-test/about/pac-20385075. [Last accessed on 2020 Apr 14].

20. Goldstein LB, Bertels C, Davis JN. Interrater reliability of the NIH stroke scale. Arch Neurol 1989;46:660-2.

21. Bushnell CD, Chaturvedi S, Gage KR, Herson PS, Hurn PD, Jimenez MC, *et al*. Sex differences in stroke: Challenges and opportunities. J Cereb Blood Flow Metab 2018;38:2179-91.

22. Li C, Baek J, Sanchez BN, Morgenstern LB, Lisabeth LD. Temporal trends in age at ischemic stroke onset by ethnicity. Ann Epidemiol 2018;28:686-90.

23. Al Rajeh S, Awada A, Niazi G, Larbi E. Stroke in a Saudi Arabian national guard community. Analysis of 500 consecutive cases from a population-based hospital. Stroke 1993;24:1635-9.

24. Yaqub BA, Shamena AR, Kolawole TM, Patel PJ. Cerebrovascular disease in Saudi Arabia. Stroke 1991;22:1173-6.

25. Al-Nozha MM, Abdullah M, Arafah MR, Khalil MZ, Khan NB, Al-Mazrou YY, *et al*. Hypertension in Saudi Arabia. Saudi Med J 2007;28:77.

26. Avan A, Digaleh H, Di Napoli M, Stranges S, Behrouz R, Shojaeianbabaei G, *et al*. Socioeconomic status and stroke incidence, prevalence, mortality, and worldwide burden: An ecological analysis from the global burden of disease study 2017. BMC Med 2019;17:191.