Original Article

Anemia as a Predictor of Functional Disability in the Early Stage of Ischemic Stroke in a South Asian Population

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Abstract

Background: 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. There is a paucity of data on the impact of anemia on early functional outcomes. **Aims:** To determine the association of anemia on early functional outcomes in a cohort of patients with ischemic stroke. **Methods:** This prospective study was conducted among 190 participants with acute ischemic stroke presenting to the National Hospital of Sri Lanka. Data were collected on socio-demographic determinants, clinical presentation, co-morbidities, subtype of stroke, and stroke severity (NIHSS score). Early functional outcomes were assessed by the Modified-Rankin-Score (mRS) and Barthel index (BI) within 48 h of the onset. Anemia was defined as Hb <13 g/dl in males and <12 g/dl in females. **Results:** The mean age of the population was 62.4 years (SD = 11.8). Most participants (75.8%) were males. Anemia was noted in 56.4% of the total study population (59.0% males; 56.5% females) with a mean Hb of 11.7 g/dl. A total of 20% of patients had moderate to severe stroke severity as defined by an NIHSS of ≥16. Functional status assessment revealed that 67.9% had mRS <3 and 85.8% had BI <75. Furthermore, 85.8% had a composite MRS <3 and/or BI 75. Univariate analysis revealed that anemia was significantly associated with "moderate-severe" functional disability. On logistic regression analyses, this retained significance when the functional disability was assessed by mRS >3 (adjusted OR = 2.36; 95% CI = 1.1–5.1). Receiver operator characteristics (ROC) curves indicated a Hb% of 10.65 g/dl as the cut-off that would predict stroke-related disability assessed by mRS >3 [sensitivity = 86.7%; specificity = 34.2%; and AUC = 0.659 ($P < 0.0001$)]. **Conclusions:** Anemia is an independent determinant of poor functional disability in early acute ischemic stroke.

Keywords: Anemia, outcome, stroke

Introduction

In spite the recent surge of therapeutic options in treating acute stroke that has shifted from time-locked thrombolytic therapy to tissue-based mechanical thrombectomy that has extended the therapeutic window up to 24 h,[1] stroke remains a leading cause of adult disability.[2,3] Among the many reasons as to why successful therapeutic reperfusion of acute ischemic strokes does not always result in complete recovery, anemia has been considered a possible factor. On one hand, it is shown that anemia 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, while on the other hand, anemia may have a direct effect on functional disability.[4] Recent evidence according to retrospective analyses clearly informs that anemia is a predictor of death following a stroke.[5,6] However, subsequent prospective studies have found an uncertain relationship between anemia and stroke outcomes when adjusted for confounders such as smoking and blood pressure.[7] Furthermore, the main focus of previous studies has been on the impact of anemia on mortality related to stroke, whereas studies conducted on the impact of anemia on functional outcomes are scarce. Studying this relationship at an early time point is relevant because 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 anemia in the individual patient is likely to determine the individual's prognosis after stroke, whereas the prevalence of anemia is likely to impact on the outcome of acute reperfusion therapies in the population at large.

Sri Lanka is a low- and middle-income country with a population of approximately 21 million and is estimated to have one of the highest age-standardized stroke mortality and stroke mortality-to-incidence ratios.[8] Although the prevalence of stroke in urban Sri Lanka lies between high-income and low- and middle-income countries, it remains a major cause of long-term disability in Sri Lanka.[9]

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The prevalence of anemia among non-pregnant adult females in Sri Lanka is approximately 39%.[10] Although centers for stroke thrombolysis have been established in the free state health service in every province in Sri Lanka, the outcome of reperfusion therapy is likely to be dampened by the high prevalence of anemia in the population.

Given the relatively high prevalence of stroke and anemia in Sri Lanka, this study aimed to determine the impact of anemia on functional outcome of stroke in the early stage of disease in a high anemia prevalence setting while adjusting for confounding factors.

Methods

The authors declare that all supporting data are available within the article. Ethics approval was obtained from the Ethics Review Committee, Faculty of Medicine, University of Colombo. July 2014.

Patients and setting

A hospital-based cross-sectional analytical study was conducted among patients aged 18 years or more with new-onset acute ischemic stroke who were admitted to the National Hospital of Sri Lanka. This is the apex tertiary referral hospital in the country located in the district of Colombo, which has the highest population density (3,300/km^2) with 2.3 million inhabitants. Patients are referred to this hospital from Colombo and all other districts in Sri Lanka. We identified the eligible patients for the study according to the World Health Organization (WHO) definition of stroke as "a focal (or at times global) neurological impairment of sudden onset, and lasting more than 24 hours, and of presumed vascular origin",[11] whereas hemorrhage and alternative diagnoses for the patients' neurological deficits were excluded using cranial computerized tomography (CT). A normal cranial CT or an area of cerebral hypodensity corresponding to the neurological deficit was considered consistent with an acute ischemic stroke. Patients with hematological disorders other than anemia were excluded. The sample required was calculated using the equation for detecting a given odds ratio in a cross-sectional analytical study design,[12] considering an anticipated odds ratio of anemia (exposure) for functional disability in stroke (outcome) of 2.09 from the previous study;[13] probability of anemia prevalence (exposure) in the general population (without disease) of 0.34 from Demographic and Health Survey Sri Lanka 2007;[14] 95% level of confidence; and relative precision of 50%. Assuming that 35% of the stroke patients would be identified as having a functional disability, the final sample size was 191. The sample of patients was obtained consecutively from the patient admission registers.

Assessments

Data were collected by two trained pre-intern medical graduates. An interviewer-administered questionnaire was used to record socio-demographic data, co-morbidities, and risk factors (hypertension, dyslipidemia, diabetes mellitus, ischemic heart disease, congestive cardiac failure, atrial fibrillation, history of stroke and transient ischemic attack, smoking, and alcohol consumption) from medical records and self-report. In patients unable to participate in an interview, the spouse or first-degree relatives were interviewed on their behalf.

Patients were evaluated systematically within 48 h of the onset of stroke for stroke type, subtype, stroke severity, and functional disability. Stroke was classified according to the Oxfordshire Community Stroke Project.[15] Stroke severity was assessed using the National Institute of Health Stroke Scale (NIHSS). Functional disability was assessed using the modified Rankin Scale (mRS) and the Barthel index (BI). Hemoglobin (Hb) concentrations were estimated on admission using a Beckmann Coulter auto-analyzer in accordance with the manufacturer's instructions.

Definitions

Anemia was defined using the WHO criteria, as Hb concentration less than 13 g/dl in men and less than 12 g/dl in women.[16] "Moderate-severe" level of stroke severity was defined by an NIHSS score of 16 or more.[17] "Moderate-severe" level of functional disability, the degree at which patients were considered to be functionally dependent, was defined from three independent classifications: mRS score more than 3; BI score less than 75; and composite index of mRS more than 3 and/or BI score less than 75. The mRS of 3 has been shown to be the corresponding score for a BI of 75 and recommended as the optimal cut-off values for defining stroke functional outcomes.[18]

Data analysis

Univariate analysis (analysis repeated for each classification on functional disability) was performed first to determine the factors associated with "moderate-severe" level of functional disability at the early stage of the disease, using Chi-square test with significance tested at 0.05 level. To adjust for confounders, logistic regression (LR) analysis (analysis repeated for each classification on functional disability) was performed, in which the dependent variable was the level of functional disability, whereas the independent variables were those significant in the univariate analysis. Backward LR method was utilized in model generation (exit at a significance level of 0.1). Adjusted odds ratio (OR) and 95% CI were derived for the variables in the final models.

Using the functional disability outcome that showed a significant association with anemia in the final LR model, optimal cut-off values of Hb that predict the functional disability in stroke were derived using receiver operator characteristic (ROC) curves. The area under the curve (AUC) determined the goodness of fit of the ROC curve.

Further, correlations of the Hb concentration with functional disability (according to mRS and BI scores) were assessed using Spearman correlation coefficient (r_s). Further, simple

regression analysis was carried out to assess the performance of Hb concentration (g/dl - X-axis) as a predictor of the functional disability (BI or mRS scores - Y-axis) of patients (dose-response effect). The analysis generated model summary statistics, parameter estimates, and a regression equation to describe the statistical relationship between the predictor variable and response variable.

Ethical considerations

Ethics approval was obtained from the Ethics Review Committee of the Faculty of Medicine, University of Colombo, Sri Lanka. Written informed consent was obtained from the patient or in incapacitated patients, from the next-of-kin/guardian.

Results

Patient characteristics

The study recruited 190 participants with new-onset ischemic stroke. The majority were males (n = 144, 75.8%). Mean age of the sample was 62.4 years (SD = 11.8), ranging from 24 to 85 years. Of the stroke subtypes, total anterior circulation infarction (TACI) and lacunar circulation infarction were the most common. The most common traditional risk factors for stroke were hypertension (62.6%), smoking (52.1%), diabetes mellitus (47.4%), and dyslipidemia (36.8%). Of all patients, 20% indicated "moderate-severe" level of stroke severity. Mean Hb was 11.7 g/dl (SD = 2.2) [men = 11.7 (SD = 2.3); women = 11.65 (SD = 1.9)].A total of 111/190 (58.4%) patients had anemia (men = 59.0%; women = 56.5%). The basic characteristics of patients by their anemic status are shown in Table 1. None of the characteristics were significantly different between the anemic and non-anemic patients ($P > 0.05$) except past stroke ($P = 0.001$) and family history of stroke ($P = 0.01$).

Functional outcome in early stage of disease among patients with stroke

As shown in Table 2, "moderate-severe" level of functional disability was found in 67.9% according to the mRS classification, and 85.8% according to the BI classification. When both classifications were considered together (mRS >3 and/or BI <75), it was 86.3%.

Association of anemia with functional disability of stroke

In the univariate analyses performed for all three classifications of functional disability [Table 3], a significantly higher proportion of "moderate-severe" level of functional disability was seen among anemic patients than that of the non-anemic ones [Table 3]. Other variables significantly associated with such disability were history of stroke, TACI stroke subtype, and "moderate-severe" level of stroke severity.

In the logistic regression analyses performed to identify the role of anemia on functional disability independent of other

Table 1: Basic characteristics of stroke patients by their anemic status

Characteristic	No. (%)		
	Anemia (n=111)	No anemia (n=79)	Total (n=190)
Patient characteristics			
Age over 45 years	103 (92.8)	70 (88.6)	173 (91.1)
Males	85 (76.6)	59 (74.7)	144 (75.8)
High level of education[1]	59 (53.2)	52 (65.8)	111 (58.4)
Monthly family income Rs. >25,000	31 (27.9)	22 (27.8)	53 (27.9)
Clinical conditions			
Hypertension	73 (65.8)	46 (58.2)	119 (62.6)
Diabetes mellitus	56 (50.5)	34 (43.0)	90 (47.4)
Dyslipidaemia	36 (32.4)	34 (43.0)	70 (36.8)
Ischemic heart disease	40 (36.0)	19 (24.1)	59 (31.1)
Valvular heart disease	6 (5.4)	10 (12.7)	16 (8.4)
Atrial fibrillation	6 (5.4)	6 (7.6)	12 (6.3)
Congestive cardiac failure	8 (7.2)	3 (3.8)	11 (5.8)
Current or ex-smoker	59 (53.2)	40 (50.6)	99 (52.1)
Current or ex-consumer of alcohol	60 (54.1)	49 (62.0)	109 (57.4)
Family history of stroke	22 (19.8)	28 (35.4)	50 (26.3)
History of stroke	37 (33.3)	9 (11.4)	46 (24.2)
History of TIA	16 (14.4)	14 (17.7)	30 (15.8)
"Moderate-severe" level of stroke severity[2]	22 (19.8)	16 (20.3)	38 (20.0)
Stroke subtype (n=164)[3]			
Total anterior circulation infarct (TACI)	39 (37.9)	24 (39.3)	63 (38.4)
Partial anterior circulation infarct (PACI)	25 (24.3)	6 (9.8)	31 (18.1)
Lacunar infarct (LACI)	21 (20.4)	21 (34.4)	42 (25.6)
Posterior circulation infarct (POCI)	18 (17.5)	10 (16.4)	28 (17.1)

[1]General Certificate of Education (Ordinary Level) or above, [2]Based on NIHSS ≥16,[3] Missing data in 26 patients

Table 2: Functional disability in the early stage of disease among patients with stroke

"Moderate-severe" level of functional disability[1]	No. (%)[2]		
	Males (*n*=144)	Females (*n*=46)	Total (*n*=190)
Classified based on mRS	95 (66.4%)	34 (73.9%)	129 (67.9%)
Classified based on Barthel Index	121 (84.0%)	42 (91.3%)	163 (85.8%)
Classified based on composite index	122 (84.7%)	42 (91.3%)	164 (86.3%)

[1]Assessed based on three independent classifications: mRS >3; Barthel index <75; composite index of mRS>3 and/or BI<75, [2]Percentages calculated out of the total number in each column

Table 3: Univariate analysis on factors associated with "moderate-severe" level of functional disability[1] in patients with stroke

Variable		"Moderate-severe" functional disability, No. (%)[2]		
		MRS >3 (*n*=129)	BI <75 (*n*=163)	Composite (*n*=164)
Anemia	Yes	**85 (77.3%)**	**100 (90.1%)**	**101 (91.0%)**
	No	**44 (55.7%)**	**63 (79.7%)**	**63 (79.7%)**
Sex	Female	34 (73.9%)	42 (91.3%)	42 (91.3%)
	Male	95 (66.4%)	121 (84.0%)	122 (84.7%)
History of stroke	Yes	**41 (89.1%)**	**45 (97.8%)**	**45 (97.8%)**
	No	**88 (61.5%)**	**118 (81.9%)**	**119 (82.6%)**
Age >45 years	Yes	118 (68.6%)	151 (87.3%)	152 (87.9%)
	No	11 (64.7%)	12 (70.6%)	12 (70.6%)
TACI	Yes	**50 (79.4%)**	**60 (95.2%)**	**60 (95.2%)**
	No	**79 (62.7%)**	**103 (81.1%)**	**104 (81.9%)**
PACI	Yes	**26 (83.9%)**	26 (83.9%)	26 (83.9%)
	No	**103 (65.2%)**	137 (86.2%)	138 (86.8%)
POCI	Yes	**12 (44.4%)**	21 (75.0%)	21 (75.0%)
	No	**117 (72.2%)**	142 (87.7%)	143 (88.3%)
LACI	Yes	**22 (52.4%)**	**32 (76.2%)**	33 (78.6%)
	No	**107 (72.8%)**	**131 (88.5%)**	131 (88.5%)
Hypertension	Yes	72 (68.6%)	94 (88.7%)	95 (89.6%)
	No	57 (67.9%)	69 (82.1%)	69 (82.1%)
Diabetes	Yes	55 (67.1%)	71 (85.5%)	71 (85.5%)
	No	74 (69.2%)	92 (86.0%)	93 (86.9%)
Moderate-severe stroke severity	Yes	**35 (92.1%)**	**38 (100.0%)**	**38 (100.0%)**
	No	**94 (62.3%)**	**125 (82.2%)**	**126 (82.9%)**

[1]Assessed according to three independent classifications: mRS >3; Barthel index <75; composite index of mRS>3 and/or BI<75, [2]Significant associations at $P<0.05$ are highlighted in bold font

factors [Table 4], anemic state, history of stroke, stroke subtype, and stroke severity were included as independent variables. Anemia remained a significant factor associated with the functional disability when assessed according to mRS >3 (adjusted OR = 2.36; 95% CI = 1.1–5.1), in contrast to the marginal significance observed when assessed according to composite index (adjusted OR = 2.19; 95% CI = 1.01–4.75) and no relationship according to BI ($P > 0.05$).

ROC curves were generated to identify the Hb concentration, which would predict "moderate-severe" functional disability based on mRS >3. The optimal cut-off Hb concentration was computed as 10.65 g/dl, which had a sensitivity of 86.7% and a specificity of 34.2% [Figure 1]. The AUC was 0.659 ($P < 0.0001$).

Prediction of functional disability of stroke using hemoglobin concentration

The average mRS and BI scores on functional disability were 3.63 (SD = 1.19) and 38.3 (SD = 30.6), respectively. These scores showed significant correlations with the Hbconcentration (mRS: $r_s = –0.2$; $P = 0.003$; and BI: $r_s = 0.27$; $P = 0.000$). As shown by significant beta coefficients in the regression models [Table 5], Hb concentration was a significant predictor variable of functional disability. Both models were statistically significant (mRS model: F = 8.01; $P = 0.005$; BI model: F = 14.72; $P = 0.000$). The derived regression equations are as follows:

Functional disability based on mRS score = 4.895+ –0.108* Hb concentration

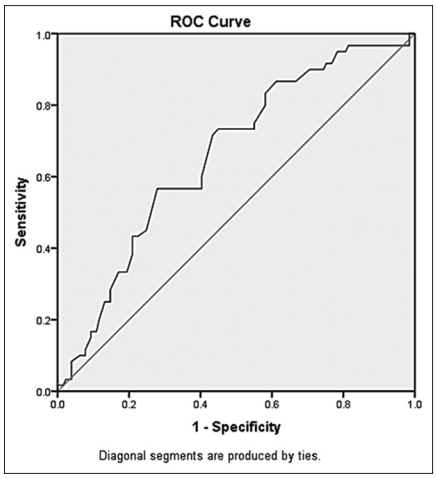

Figure 1: ROC curve for hemoglobin concentrations that predict "moderate-severe" level of functional disability (based on mRS >3) in early stage of stroke

Table 4: Logistic regression analyses on independent factors associated with "moderate-severe" functional disability in patients with stroke

Variables in the model[1]	Adjusted OR	95% CI	*P*[1]
Model for MRS >3			
Anemia	2.36	1.09-5.1	**0.029**
Past stroke	8.42	2.33-30.39	**0.001**
TACI	3.13	1.36-3.13	**0.007**
Moderate-severe stroke (NIHSS >16)	10.02	2.14-46.94	**0.003**
Model for BI <75			
Past stroke	5.16	1.79-14.83	**0.002**
TACI	8.33	2.50-3.13	**0.000**
Moderate-severe stroke (NIHSS >16)	6.35	1.38-29.26	**0.018**
Model for composite outcome of MRS >3 and/or BI <75			
Anemia	2.19	1.01-4.75	**0.045**
Past stroke	8.96	2.48-32.42	**0.001**
TACI	3.45	1.47-7.69	**0.004**
Moderate-severe stroke (NIHSS>16)	10.28	2.19-48.19	**0.003**

[1]Assessed according to three independent classifications: mRS >3; Barthel index <75; composite index of mRS>3 and/or BI<75 [1]Significant associations at *P*<0.05 are highlighted in bold font

Functional disability according to BI score = –4.962 + 3.688* Hb concentration

Discussion

We found that almost two-third of our study population presenting with acute ischemic strokes were anemic. Furthermore, anemia was an independent determinant of poor functional outcome assessed using the mRS or composite score classifications. Hb concentration less than 10.65 g/dl was associated with worse stroke-related functional outcome, whereas a significant dose-response relationship was noted between Hb concentration and functional disability scores. Our results also showed that a history of stroke and the stroke subtype of total anterior circulation infarct were independent determinants of poor functional outcome. Although stroke severity *per se* was an independent risk factor of functional outcome, only a fifth of our study population had moderate to severe strokes. None of our patients had received thrombolytic therapy as this study was done prior to provision of thrombolysis in the free National Health Service in Sri Lanka.

A meta-analysis of 13 cohort studies has shown anemia to be an independent risk factor of increased mortality following both ischemic and hemorrhagic strokes.[6] However, studies on the impact of anemia on functional outcome in early stroke are scarce and are often confounded by other risk factors such as hypertension, diabetes mellitus, and dyslipidemia or prognostic determinants such as stroke severity, previous strokes, and stroke subtypes. Our study provides evidence for an independent and significant effect of anemia on the functional outcome of acute ischemic stroke in its early stage, which is likely to determine long-term outcome. Our results were significant when the functional status was measured either by mRS or compositely with mRS with or without BI. However, the unfavorable relationship of functional outcome and anemia was not significant when the functional status was measured by BI alone. This may have been because mRS is a measure of global disability, whereas BI is a summed measure of individual activities of daily living. Thus, our results also suggest that mRS is a more reliable measure of disability in the acute phase after stroke while assessing activities of daily living is more reliable in later stroke to evaluate rehabilitation outcomes.

Table 5: Parameter estimates and the significance of best-fitting regression model to predict post-stroke functional disability depending on hemoglobin concentration (g/dl)

Independent Variable	Unstandardized coefficients		Standardized coefficients	*t*	*P*	95% CI for B	
	B	SE	Beta			Lower	Upper
On the basis of mRS scores							
Constant	4.895	0.455		10.754	0.000	3.997	5.792
Hb (g/dl)	–0.108	0.038	–0.203	–2.829	0.005	–0.183	–0.033
On the basis of BI scores							
Constant	–4.962	11.469		–0.433	0.666	–27.587	17.663
Hb (g/dl)	3.688	0.961	0.269	3.836	0.000	1.792	5.585

Dependent Variable: Functional disability; Beta=Regression coefficient; SE=Standard error of beta

There is a paucity of data on the functional outcomes of ischemic stroke in anemic patients in South Asia. This is concerning, especially owingto rising incidence of stroke in the region, as well as the heightened prevalence of anemia. Joshi *et al*. note a 42% prevalence of moderate anemia in a cohort of 50 patients with ischemic stroke from Nagpur, India.[19] Sukdev *et al*. describe an Indian patient with severe anemia presenting with ischemic stroke and explore the hypothesis of anemia as a risk factor in the pathogenesis.[20]

The relationship between the Hb concentration in blood and stroke outcome is complex. On one hand, increased hematocrit is likely to increase blood viscosity and interrupt normal flow dynamics, while on the other hand, reduced Hb is likely to impair tissue oxygenation. Lower Hb levels have been reported to be associated with increased stroke volumes as well as poorer stroke outcomes.[4,21,22] It has been suggested that in patients with acute ischemic stroke, anemia may cause aggravation of hypoxia in the penumbral lesions.[23] Consistent with this, recent retrospective analysis has found that moderate to severe anemia was associated with a poor outcome in spite successful revascularization with mechanical thrombectomy.[4] On the contrary, an inverse relationship between a higher hematocrit and cerebral blood flow has been reported.[24] Further complicating this relationship is the suggestion that anemia is a hyperkinetic state that alters endothelial function and predispose to thrombus formation and embolism. Furthermore, anemia induced erythropoietin secretion can lead to reactive thrombocytosis.[25] Thus, a U-shaped distribution has been proposed to denote the relationship between anemia and stroke outcome.[26] However, the optimal level of Hb that prevents infarction of critically ischemic cerebral tissue remains undetermined. Although we found a worse functional outcome below a cut-off Hb level of 10.65 g/dl, larger studies are required to determine a more accurate value with greater sensitivity and specificity.

The NIHSS score is considered a reliable measure of stroke severity and identified as a surrogate marker of lesion volume.[27] As expected, a greater stroke severity was associated with a worse functional outcome, but the occurrence of more severe strokes was not different between anemic and non-anemic patients in our study. It has been shown that the decrease in Hb after admission may be more relevant to stroke severity than baseline levels[28] suggesting that the development of collateral circulation may compensate in patients with anemia. Thus, our data support the observation that anemia acts independently to an initial lesion volume in determining the functional outcome of stroke.

The key finding of our study is the recognition of anemia as an independent risk factor of poor functional outcome following acute ischemic stroke. Our data also supports previous observations of a high prevalence of anemia among patients presenting with acute ischemic stroke. We focused on the acute phase of stroke presentation because this is the period in which therapeutic interventions have the greatest impact on prognosis. However, whether correction of anemia in the acute phase following stroke improves prognosis remains controversial.[25] However, our study lends justification for a randomized trial to test the therapeutic value of blood transfusions in patients with anemia presenting with acute ischemic stroke.

This study had a few limitations. The duration of anemia preceding stroke was not known. The causes or types of anemia was not determined, but sickle cell disease is exceptionally rare in Sri Lanka and is unlikely to have contributed significantly. Furthermore, the small sample size and cross-sectional design recruiting patients from a single center may have introduced statistical error and biases. A case-control design is not appropriate here, as functional disability was assessed using three independent classifications, thus leading to misclassification of cases (stroke patients with a disability).

Conclusions

Our study highlights the role of anemia as an independent determinant of poor functional outcome in the early stage of acute ischemic stroke. Furthermore, our data reaffirms that anemia is common among South Asians presenting with stroke. Until evidence becomes available to support treatment of anemia in the acute phase of stroke, intervention should focus on screening and treating anemia in the general population to minimize the deleterious effects of it in the event of acute ischemic stroke.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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