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Relationship between Vitamin D Status in Acute Ischemic Stroke for Assessing Initial Severity and Short-Term Outcome in a Tertiary Level Hospital, Bangladesh

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Abstract

Recent studies suggest that vitamin D, a neuroprotective prohormone, which has a potential protective role against neurovascular injury. Low vitamin D levels were modestly associated with risk of stroke and stroke fatality. Objective: This study aimed to investigate the relationship of vitamin D status among acute ischemic stroke patients for assessing initial severity and short-term outcome. Methods: Fifty one acute ischemic stroke patients and 51 matched healthy control subjects participated in the study. Subjects were divided according to vitamin D level into deficient, insufficient, and sufficient groups. National Institute of Health Stroke Scale (NIHSS) on admission and after 72h and modified Rankin Scale (mRS) on discharge and after 3months were performed for all patients. **Results:** Acute ischaemic stroke patients (9.8%) had significantly lower serum vitamin D levels compared to healthy subjects (5.8%). In patients, serum vitamin D level ranged from 5 to 41ng/ml with a mean of 19.4±9.98ng/ml. In controls, serum vitamin D levels ranged from 6 to 48ng/ml with a mean of 30.3±10.48 ng/ml. Vitamin D deficiency and insufficiency were significantly prevalent among stroke patients (66.7%) compared to healthy controls (51.9%). Significant correlation was detected between serum vitamin D and NIHSS scores on admission and after 72hrs (p=0.007). Significant correlation was also detected between serum vitamin D and mRS scores on discharge and after 3months (p=0.004). The patients with 'not sufficient' vitamin D (i.e. deficient and insufficient) were 11.2 time more likely to report severe stroke (p=0.006). Conclusion: Vitamin D deficiency increases the risk of acute ischemic stroke and is associated with increased initial stroke severity and worse short-term outcome.

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Introduction

Stroke is the second leading reason for death worldwide, accounting for over 10% or 5.7 million deaths annually, with the whole number of cases predicted to rise over the next few decades (Kim and Johnston, 2013). Although stroke mortality has declined in developed countries because of strict pressure control, the burden of stroke remains rising thanks to an increase within the older population (Kim and Johnston, 2013; Feigin *et al.,* 2017).

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Moreover increased longevity in developing nations has a junction rectifier to rising stroke prevalence in middle-income countries(Kim and Johnston, 2013; Feigin *et al.,* 2017). Vitamin D (VD) is an organic compound consisting of fat-soluble ecosteroids mainly to blame for the regulation of calcium and phosphorous levels, among other physiological functions (Al-Mheid and Quyyumi, 2017; Alkhatatbeh *et al.,* 2017).

Vitamin D deficiency has been identified as a frequent problem in stroke survivors with an estimated prevalence of 71% (Gupta *et al.,* 2016). Reasons for Geographic and Racial Differences in Stroke (REGARDS) study of over 16,000 black and white patients showed that those who lived in areas that had shorter exposure to sunlight encompasses a 56% increased risk of stroke, and it showed that persons with a better level of via sterol in their diet had a decreased risk of stroke and cognitive impairment (Nair and Maseeh, 2012). The prevalence of osteoporosis in post-stroke survivors (Uluduz *et al.,* 2014). likewise because the identification of D receptors (VDR) and 1a-OHase activity within the brain (Eyles *et al.,* 2005). paved the way for more studies exploring the connection between fat-soluble vitamin status and stroke. Large epidemiological studies indicated an association between vitamin D status and thus the chance of stroke (Makariou *et al.,* 2014). However, the link between vitamin D status and acute ischemic stroke patients further exploring vitamin D as an independent risk factor for acute ischaemic stroke needs more elucidation (Zhou *et al.,* 2018; Park *et al.,* 2015; Sun *et al.,* 2012). Studies have also shown that serum Vitamin D is expounded to outcomes after cerebrovascular accidents. This provides a rationale to further investigate vitamin D as a biomarker for cerebral ischemic vulnerability and identify patients at high risk for poor post-stroke outcomes and also the potential of vitamin D supplementation for secondary stroke prophylaxis (Turetsky *et al.,* 2015).

This study was designed to assess vitamin D status among acute ischaemic patients and examine its relation to initial stroke severity and short-term outcome. Stroke has been increasing; it is a significant issue of public health concern currently because the common lifespan at birth rises to 72 years in Bangladesh. Management of patients with stroke in low and middle-income countries is just too expensive that just about all governments are unable to afford it, and resources and budgets that are allocated are unable to satisfy the burden of treatment. The magnitude of stroke in Bangladesh isn't called there are not any national registries for this disease. However, studies have reported a better prevalence of stroke among increasing the age of patients. The association between vitamin D status and stroke in our country isn't exactly evaluated. If we evaluate the evaluated the connection between Vitamin D and stroke we should make an additional plan in treatment to the prevention of stroke. Limited data is obtainable on the association between serum vitamin D levels and stroke in Bangladesh. So we would favor commencing measuring the vitamin D status in stroke patients in Bangladesh to look out for their association in order that the study result might open a fresh era of future research regarding alternative management and prevention of stroke.

Materials and Methods

Study design, population and settings

This study was conducted the Department of Neurology of Sir Salimullah Medical College & Mitford Hospital, Dhaka Bangladesh from July 2020 to June 2021. 51 patients with acute ischaemic stroke (30 male and 21 female) and 51 control subjects (27 male and 24 female) were included within the study. Subjects were selected according to inclusion and exclusion criterias. Patient were included after obtaining written consent .The included patients were examined by a neurologist and diagnosed acute ischaemia

clinically and evidenced by neuroimaging (Computed tomography or Magnetic resonance imaging of the brain), age≥20years . Exclusion criteria were patient with intracerebral hemorrhage, endocrinal disorders which will affect bone health (thyroid, parathyroid, and adrenal disorders), chronic illness that will affect bone health, patients receiving drugs that will affect bone health (corticosteroids, chemotherapy), a history and current risk of debilitating diseases, like malignancies, patients receiving vitamin D supplementation, and pregnant, lactating, and menopausal females.

The Assessment of initial stroke severity by using the National institute of Health Stroke Scale (NIHSS) on admission and after 72h. The scale consists of 5 score sections, score 0 (no stroke symptoms), score 1–4 (minor stroke), score 5–15 (moderate stroke), score 16–20 (moderate to severe stroke), and score 21–42 (severe stroke) (Kasner 2006) (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group 1995).

The Assessment of the functional outcome by using the modified Rankin Scale (mRS) on discharge and after 3months. The scale runs from 0 to 6, running from perfect health without symptoms to death. Favorable (good) outcome is indicated by mRS≤2, while poor outcome is indicated by mRS≥3 (Sulter *et al.,* 1999).

Routine laboratory workup included complete blood count, liver function tests, kidney function tests, fasting blood glucose, and electrolytes (including sodium, potassium, calcium, and phosphorus levels) Serum vitamin D assay by using enzyme-linked immunosorbent assay (ELISA). Blood samples were collected then centrifuged to urge serum. The kit was used for the quantitative measurement of total 25-OH vitamin D3 in serum. According to vitamin D status, patients and controls were sub-divided into three subgroups: deficient (vitamin D levels <10ng/ml), insufficient (vitamin D levels 10–29ng/ml), and sufficient (vitamin D levels ≥30ng/ ml) (Yarlagadda *et al.,* 2020).

Data management and analysis

Exploratory data analyses were distributed to explain the study population where Quantitative data were expressed as mean± variance (SD). Qualitative data were expressed as frequency and percentage. For quantitative data, independent t test was used to compare between two independent variables with parametric data and paired t test to compare between two dependent variables .A one-way analysis of variance (ANOVA) was accustomed compare between over two variables. Post hoc was done to test possible combinations of groups to determine where the significant differences are located. For qualitative data, chi-square was used for differences between proportions and Fisher exact for variables with small expected numbers. Pearson correlation coefficient was used for correlation between variables. A logistic regression analysis was conducted to evaluate the independence of vitamin D role within the disease status. . All statistical analyses were performed using the Statistical Program for Social Science (SPSS) version 25, IBM Corp., Chicago, USA, 2017. p value <0.05 was considered significant, and p value < 0.01 was considered highly significant.

Results and Discussion

51 patients with acute ischemic stroke (30 male and 21 female) and 51 control subjects (27 male and 24 female) were included in the study. The age of patients ranged from 39 to 82 years with a mean of 59.55±10.88 years while the age of control subjects ranged from 26 to 70 years with a mean of 56.34±12.59 years (p =0.613). (Table1). Among patients and controls 57 (55.9%) were males and 54 (44.1%) were females.

Forty one patients (80.4%) were hypertensive, 31 patients (60.8 %) were diabetic, 13 patients (25.5%) had ischemic heart disease, 13 patients (25.5%) had atrial fibrillation and 28 patients (54.9%) were smokers (Table 2).

Table 1. Distribution of age by group.

	Group		
Age (in year)	Case	Control	p value*
≤50	10 (19.6) #	12 (23.5)	0.613
50 -59	16 (31.4)	17 (33.3)	
60 -69	15 (29.4)	14 (27.5)	
>70	10(19.6)	8(15.7)	
Total	51 (100.0)	51 (100.0)	
Mean ± SD	59.55±10.88	56.34±12.59	

*t test was done to measure the level of significance.
#Figure within parentheses indicates in percentage.

Table 2. Risk factors of stroke.

Response	Number	Percent
Hypertension		
No	10	19.6
Yes	41	80.4
Diabetes mellitus		
No	20	39.2
Yes	31	60.8
Atrial fibrillation		
No	38	74.5
Yes	13	25.5
Smoker		
No	23	45.1
Yes	28	54.9
Previous stroke		
No	39	76.5
Yes	12	23.5
Previous TIA		
No	40	78.4
Yes	11	21.6
Ischemic heart disease		
No	38	74.5
Yes	13	25.5
Heart failure		
No	46	90.2
Yes	5	9.8

On presentation, the NIHSS scores ranged from 3 to 29 with a mean of 10.6±5.9. Nine patients (17.6%) had mild stroke, 31 patients (60.8%) had moderate stroke, 9 patients (17.6 %) had moderate/severe stroke, and 2 patients (3.9%) had severe stroke. After 72hrs, the NIHSS scores ranged from 1 to 25 with a mean

of 7.8±5.2. Twelve patients (23.5%) had mild stroke, 34 patients (66.7%) had moderate stroke, 3 patients (5.9%) had moderate/severe stroke, and 2 patients (3.9%) had severe stroke (Table 3).

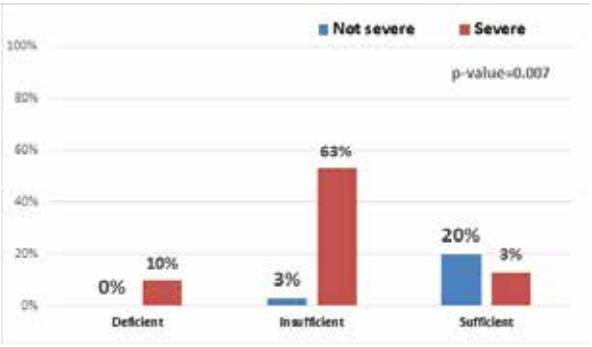

Fig. 1. Level of Vit D and stroke severity according to NIHSS after 72hours.

Table 3. Stroke severity on admission and after 72 hrs regarding NIHSS score.

NIHSS score	Number	Mean	Std	Median	Minimum	Maximum
Initial NIHSS score	51	10.6	5.9	10.0	3.0	29.0
NIHSS score after 72 h	51	7.8	5.2	6.0	1.0	25.0

Table 4. Comparison of mean serum vitamin D level between study subgroups (ANOVA).

Subgroup	Number	Mean	Std	95% confidence interval		p-value
				lower bound	upper bound	
Control	51	30.3	10.48	25.4	31.2	0.056*
Patient	51	21.4	9.98	21.6	27.2	

Table 5. Types Vit D status among patient and control.

Vit D status	Control	Patient	Control	Patient	P value
Deficient	3	5	5.9%	9.8%	
Insufficient	13	29	25.5%	56.9%	
Sufficient	35	17	68.6%	33.3%	
	51	51	100.0%	100.0%	0.002*

Twelve patients (23.5%) had mild stroke, 34 patients (66.7%) had moderate stroke, 3 patients (5.9%) had moderate/severe stroke, and 2 patients (3.9%) had severe stroke.

Serum vitamin D level

In patients, serum vitamin D level ranged from 5 to 41ng/ml with a mean of 21.4±9.98ng/ml. In controls, serum vitamin D levels ranged from 6 to 48ng/ml with a mean of 30.3±10.48 ng/ml. A statistically significant difference was found between the two groups as regards mean serum vitamin D level, being significantly lower in stroke patients (p value =0.056.) (Table: 4).

According to vitamin D status, patients and controls were sub-divided into three subgroups: deficient (vitamin D levels <10ng/ml), insufficient (vitamin D levels 10–29ng/ml), and sufficient (vitamin D levels ≥30ng/ ml)[16]. A statistically significant difference was also detected between subgroups of patients and controls regarding vitamin D status (p value =0.002) (Table 5).

On comparing Vit D status and NIHSS score between patient subgroups, there was a statistically significant difference detected between patient subgroups regarding initial scores of NIHSS, being significantly higher in the deficient group (p=0.003) (Table: 6).

Post hoc analysis revealed a statistically significant difference between deficient and insufficient groups compared to sufficient group (p value = 0.01, 0.01 respectively) (Table: 7). On discharge, a statistically significant difference was detected between patient subgroups regarding mean scores of mRS, being significantly higher in the deficient.

On discharge, mRS scores ranged in deficient from 1 to 5 with a mean of 3.80 ± 1.09 and insufficient was 3.21 ± 0.67. Ten patients (19.6%) had good outcome whereas 41 patients (85.4%) had poor outcome. After 3 months, mRS scores in deficient ranged from 1 to 6 with a mean of 2.60 ± 1.34 and insufficient was 1.97 ± 0.57. Eighteen patients (35.3%) had good outcome; however, 33 patients (64.7%) had poor outcome (Table: 8).

On discharge, a statistically significant difference was detected between patient subgroups regarding mean scores of mRS, being significantly higher in the deficient (p=0.05).

After 3months, a statistically highly significant difference was detected between patient subgroups regarding mean scores of mRS, being significantly higher in the deficient group (p=0.004). Eighteen patients (35.3%) had good outcome; however, 33 patients (64.7%) had poor outcome.

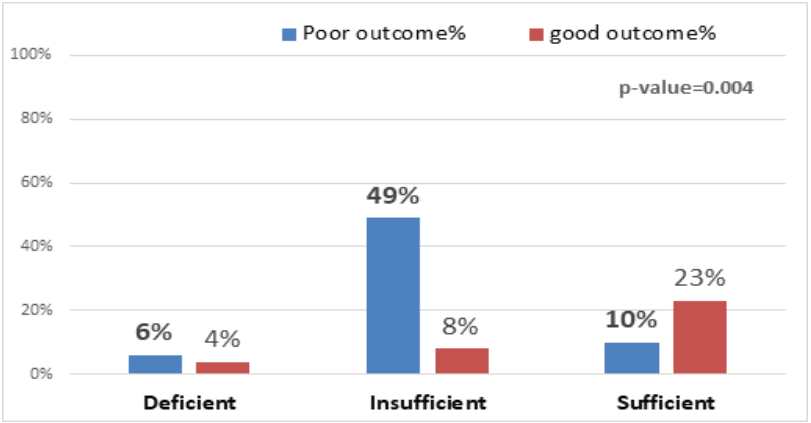

Fig. 2. Level of Vit D and functional outcome according to mRS after 3 months.

A logistic regression analysis was performed to evaluate the independence of vitamin D role in the diseasestatus apart from differences of age, gender distribution, and vascular risk factors. Vitamin D was found contributing to disease status (severity and outcome) independent of age, gender, and vascular risk factors. The Logistic Regression analysis revealed a significant impact of the Vit D status of the patients on the severity of stroke. The patients with 'not sufficient' Vit D (i.e. deficient and insufficient) were 11.2 time more likely to report severe stroke OR=11.2. (Table 9)

Vitamin D has a cappotential protecting function against neurovascular injury, particularly with a reduction of stroke risk and stroke fatality (Sulter *et al.,* 1999). Poor vitamin D status in stroke patients has additionally

Table 6. Comparison of vitamin D status and NIHSS scores.

Vit D status	Number	Initial NIHSS score (mean)	Std	95% confidence interval		p-value
				lower bound	upper bound	
Deficient	5	20.4	8.96	9.3	31.5	
Insufficient	29	10.9	4.06	9.4	12.4	0.003*
Sufficient	17	7.3	4.40	5.0	9.6	

Table 7. Relation between serum vitamin D and stroke severity on presentation and after 72 h by NIHSS.

NIHSS score	25 (OH) vit D (ng/ml)
NIHSS score on admission	
Pearson correlation	-0.508
p-value	<0.01
N	51
NIHSS score after 72 h	
Pearson correlation	-0.509
p-value	<0.01

Table 9. Logistic Regression analysis: Vit D status and severity of stroke.

Variable		B	Odds ratio	p-value
Vit D status	Sufficient	-	-	-
	Not sufficient	2.42	11.2	0.006*
Constant		0.36	1.4	0.469
* Significant at less than 1% level of significance				

been found to be intently related not most effective to increased risk for destiny stroke however additionally to poor functional outcome in stroke (Nair and Maseeh 2012). In this observation, a statistically significant distinction became observed in suggesting serum vitamin D between patients and controls was substantially decreased in stroke patients. Moreover, there was a large distinction between patient and control subgroups dispensed regularly with vitamin D status, in which vitamin D deficiency and insufficiency were more significantly encountered in stroke patients compared to control who mostly had enough vitamin D status. There are several previous researches that showed a modest affiliation between low 25 (OH) vitamin D levels and the hazard of ischemic stroke (Uluduz *et al.,* 2014; Eyles *et al.,* 2005; Kasner (2006); The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group 1995). Most of the previous studies had been primarily based totally on populations of Caucasian descent and indicated an inconsistent inverse relationship between vitamin D levels and the hazard of stroke.18 Recent

meta-analyses studies summarized the results of preceding studies and presented statistically significant pooled estimates of relative risks of stroke evaluating low vs high vitamin D status. (Brøndum-Jacobsen *et al.,* 2013; Michos *et al.,* 2012). Similarly, in a meta-analysis comparing lowest vs highest quartile of 25(OH)D concentrations, the multivariate adjusted OR of ischemic stroke was observed to be 1.54 (1.43–1.65) through Brøndum-Jacobsen *et al.,* (2013). These summarized estimates imply a potentially significant contribution of low vitamin D status to stroke risk. In line with these studies, we found a strong and significant affiliation between 25(OH) D3 status and risk of ischemic stroke in Bangladeshi population. Vitamin D deficiency has been related to greater stroke severity and poor submit stroke outcomes (Fahmy *et al.,* 2019). Lower serum 25(OH) D3 levels in patients with stroke are independently associated with higher infarct volumes, although causality has yet to be determined. 16 Overall stroke severities, assessed the usage of the National Institutes of Health Stroke Scale (NIHSS), changed into worse in 25(OH) D3-deficient patients with stroke, while patients with enough to optimal VD levels had decreased ratings thereon scale, or less severe strokes, at the average (Sulter *et al.,* 1999; Wei and Kuang 2018). A sturdy poor correlation changed into later found between vitamin D status and NIHSS scores after 72h, confirming the steady relation between vitamin D and stroke severity This came in agreement with preceding research which confirmed that a decrease in 25 (OH) vitamin D levels had been independently related to higher clinical severity.11, 23 The current observation found a significant difference between patient subgroups concerning stroke severity on a presentation in which decrease vitamin D levels were associated with higher NIHSS scores indicating severer strokes. The short-term post-stroke outcome, measured through the modified Rankin Scale (mRS) at patient discharge, became similarly poorer among 25(OH) D3-deficient patients with stroke (Park *et al.,* 2015; Rezaei *et al.,* 2021). 25(OH)D3-deficient patients also had higher mRS scores 3 months post stroke, reflecting particularly worse longer-time period outcomes (Park *et al.,* 2015; Sulter *et al.,* 1999; Rezaei *et al.,* 2021). In accordance with those studies, we observed that mRS on discharge and after 3 months confirmed an exceedingly significant difference between patient subgroups. A strong negative correlation changed additionally detected between vitamin D status and mRS on discharge and after 3 months. A logistic regression analysis revealed independence of vitamin D in the disease status in which vitamin D deficiency increases the severity 11.2 times. These findings got here in similar to Makariou and associates (Makariou *et al.,* 2014); and Zhou (Zhou *et al.,* 2018). At the end on this observation, vitamin D deficiency is related to the initial severity of the acute ischemic stroke and a predictor for a poor short-time period final result. These outcomes also acquit considering vitamin D supplementation in the primary prevention of stroke in patients with vascular risk factors and in secondary prevention in patients who develop stroke to reduce disability and improve functional outcomes.

Conclusions

This study has concluded that vitamin D deficiency is related to the initial severity of the acute ischemic stroke and a predictor of a poor short-term outcome of acute ischaemic stroke.

Abbreviations

IS: Ischemic stroke
VD: Vitamin D
25-OH-D: 25-Hydroxyvitamin D
CT: Computed tomography
MRI: Magnetic Resonance Imaging

NIHSS: National Institute of Health Stroke Scale
mRS: Modified Rankin scale

Limitations

Small sample size and this single hospital based study did not reflect exact scenario of the whole community. Patients from all socioeconomic status and all parts of the country did not come to seek medical attention in the study place.

Conflict of Interest

The authors stated that there is no conflict of interest in this study

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Ethical consideration

The study was conducted after approval from the ethical review committee. The confidentiality and anonymity of the study participants were maintained.

Authors' Contributions

AR was responsible for conception and design, obtaining funds, data interpretation, manuscript drafting and manuscript editing, and final approval data acquisition, data interpretation and critical revision for important intellectual contentconception and design, obtaining funds, data interpretation, manuscript editing, and final approval. MNQ was responsible for data analysis and statistical analysis. MJA and AHRwere responsible for data collection. All authors have read and approved the final version of the manuscript.

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