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Association of Serum Hypoalbuminemia with Severity and Short-Term Prognosis in Acute Ischemic Stroke

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KEYWORDS

Acute ischemic stroke, Hypoalbuminemia , Stroke severity, Functional outcomes, Prognostic marker

ABSTRACT:

Background: Stroke is a leading cause of disability and mortality. Serum albumin, a key indicator of nutritional and inflammatory status, has been linked to stroke severity and recovery.

Objectives: To evaluate serum albumin levels at admission in acute ischemic stroke (AIS) patients, assess stroke severity, and examine the correlation between serum albumin levels and functional outcomes.

Methods: This was a prospective cohort study conducted in the Department of General Medicine, Aarupadai Veedu Medical College and Hospital, Puducherry, India between July 2023 and December 2024.

Results: Among the 90 study participants, those with moderate to severe stroke (NIHSS ≥ 5) were significantly older, with a mean age of 60.9 years, compared to 53.8 years in those with minor stroke ($p = 0.037$). Gender distribution was similar between groups, and no significant differences were observed regarding smoking, alcohol consumption, hypertension, or diabetes. Similarly, those with moderate to severe disability or death (mRS ≥ 3) were older (mean: 61.8 years) than those with no significant or slight disability (mean: 53.8 years) ($p = 0.013$). Patients aged >60 years were more likely to have moderate to severe disability or death (55.6%) compared to those with no or slight disability (33.3%) ($p = 0.025$). Gender and other vascular risk factors showed no significant differences between the groups. Serum albumin levels were significantly lower in patients with moderate to severe stroke (mean: 2.8 g/dL) compared to those with minor stroke (mean: 3.8 g/dL) ($p < 0.001$). Similarly, lower albumin levels were associated with poor functional outcomes ($p < 0.001$). A significant negative correlation was found between albumin levels and both NIHSS ($r_p = -0.521$) and mRS ($r_p = -0.484$) scores. ROC analysis confirmed hypoalbuminemia (<3.4 g/dL) as a strong predictor of stroke severity and short-term prognosis.

Conclusion: This study highlights the strong association between hypoalbuminemia and both stroke severity and poor short-term functional outcomes. Serum albumin levels may serve as a valuable prognostic marker for assessing stroke prognosis and guiding early interventions.

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INTRODUCTION

Acute ischemic stroke (AIS) is a major cause of morbidity and mortality worldwide, accounting for approximately 85% of all stroke cases.(1) The extent of brain injury in AIS is influenced by various factors, including oxidative stress, inflammation, and endothelial dysfunction.(2) Serum biomarkers have gained significant attention in predicting stroke severity and prognosis, among which serum albumin is emerging as a potential prognostic marker.(3) Albumin, a multifunctional protein synthesized by the liver, plays a crucial role in maintaining oncotic pressure, acting as an antioxidant, regulating inflammation, and stabilizing endothelial function.(4) Given these functions, its role in stroke pathophysiology is of particular interest. Hypoalbuminemia, commonly observed in critically ill patients, has been associated with worse outcomes in several neurological disorders, including stroke.(5)

In AIS, oxidative stress and inflammation contribute to neuronal injury and blood-brain barrier (BBB) disruption. Albumin exerts neuroprotective effects by scavenging free radicals, inhibiting pro-inflammatory cytokines, and maintaining vascular integrity.(6) Additionally, albumin enhances cerebral perfusion by reducing blood viscosity and improving microcirculatory flow.(7) Therefore, a decline in albumin levels may exacerbate ischemic damage and increase stroke severity. Several studies have reported an inverse relationship between serum albumin levels and stroke severity, with lower albumin levels being associated with higher National Institutes of Health Stroke Scale (NIHSS) scores at presentation.(8) Furthermore, hypoalbuminemia has been linked to poor functional outcomes,(9) as measured by the modified Rankin Scale (mRS), and higher mortality rates in stroke patients.(10)

Studies have suggested that hypoalbuminemia at admission is an independent predictor of poor short-term prognosis in AIS patients. For instance, a study by Zhou et al.(7) (2021) demonstrated that patients with low serum albumin levels had significantly worse neurological outcomes at one week and three months post-stroke. Another study highlighted that hypoalbuminemic patients had higher rates of early neurological deterioration and post-stroke complications.(3) Given these findings, evaluating albumin levels at admission and during the acute phase of stroke could provide valuable insights into disease severity and prognosis. However, there is limited data on short-term outcomes in relation to albumin fluctuations during hospitalization, making this an important area for further investigation. Against this background, the present study aimed to evaluate serum albumin levels at admission in acute ischemic stroke patients, assess stroke severity using the NIHSS score, and analyze functional outcomes via the modified Rankin Scale (mRS) at one week.

MATERIALS AND METHODS

This was a single centre, hospital based, prospective cohort study conducted in the outpatient department and/or inpatient wards of the Department of General Medicine, Aarupadai Veedu Medical College and Hospital, Puducherry, India for a duration of 18 months between July 2023 and December 2024. The study was approved by the Institutional Human Ethics Committee (IHEC) with reference number AV/IHEC/2023/048 dated 25/05/2023. The participants (or their attenders) were given the Participant Information Sheet (PIS) in their native language, and its contents were verbally explained to ensure their understanding and satisfaction. Enrolment into the study proceeded upon receipt of written informed consent. Patients between 18 and 80 years of age, of both gender, presenting with AIS, within 48 hours of onset, with clinical and radiological (including NCCT brain, MRI brain) evidence of AIS were included. However, patients presenting after 48 hours of symptom onset; with cerebral haemorrhage of any etiology; chronic kidney disease; protein losing enteropathies; malignancy; bronchiectasis; decompensated chronic liver disease; pregnant and lactating women were excluded.

The sample size was calculated based on reported albumin sensitivity of 0.667 for predicting stroke outcomes,(11) using a statistical formula for sensitivity estimation with 12% relative precision and a 5% significance level, resulting in a minimum required sample of 90. We used nonprobability sampling technique – purposive sampling/consecutive enumeration to enrol patients. Demographic and clinical data were collected for each participant at the time of

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admission. Blood samples were drawn to analyse serum albumin levels upon hospital admission. Based on the albumin levels, patients were categorized into groups with normal albumin levels and hypoalbuminemia. Further clinical evaluation was conducted for each group. The severity of stroke was assessed using the NIHSS (non-invasive assessment). One week after admission, patient outcomes were evaluated using the mRS to determine the degree of functional recovery or disability.

Statistical analysis: The data collected was manually entered in Microsoft Excel, coded, recoded, and analysed using Software for Statistics and Data Science (Stata) v16 (StataCorp, 2019). Descriptive analysis was presented using numbers and percentages for categorical variables; mean and standard deviation (SD) for continuous variables (based on data normality tested using Kolmogorov–Smirnov test and the Shapiro–Wilk test). Appropriate graphs were used. Chi square test of significance (two-sided) for categorial and independent 't' tests (two-sided) for continuous variables was applied to test for association between independent and dependent study variables. Pearsons's correlation coefficient was estimated to assess the correlation between serum albumin levels, NIHSS and mRS scores. Receiver operating characteristics (ROC) analysis was conducted to determine the area under the curve of serum albumin levels in moderate to severe stroke (based on NIHSS) and moderate to severe disability or death (assessed using mRS). Statistical significance was considered at $p<0.05$.

RESULTS

The study included 90 acute ischemic stroke patients with a mean age of 59.4 years (SD: 14.0). Nearly half (48.9%) were older than 60 years, while 41.1% were between 41 and 60 years, and 10% were under 40 years. The gender distribution was equal, with 50% male and 50% female participants. Smoking and alcohol consumption were reported in 13.3% and 17.8% of participants, respectively. Hypertension was present in 50% of patients, while 33.3% had diabetes mellitus. The mean serum albumin level was 3.0 g/dL (SD: 0.8). Stroke severity, assessed using the NIHSS, had a mean score of 14.7 (SD: 8.5), while functional outcomes, measured by the modified Rankin Scale, had a mean score of 3.4 (SD: 1.5).

Patients with moderate to severe stroke (NIHSS ≥5, N = 71) were older, with a mean age of 60.9 years (SD: 14.2), compared to 53.8 years (SD: 12.2) in those with minor stroke ($p = 0.037$). A significantly higher proportion of minor stroke patients were aged 41–60 years (68.4%) compared to those with moderate to severe stroke (33.8%), while a greater proportion of severe stroke cases were above 60 years (54.9% vs. 26.3%, $p = 0.024$). Gender distribution, smoking, alcohol consumption, hypertension, and diabetes mellitus did not significantly differ between the groups. However, serum albumin levels were significantly lower in the moderate to severe stroke group (mean: 2.8 g/dL, SD: 0.7) compared to the minor stroke group (mean: 3.8 g/dL, SD: 0.7, $p < 0.001$).

Patients with moderate to severe disability or death (N = 63) were significantly older, with a mean age of 61.8 years (SD: 12.7), compared to 53.8 years (SD: 15.5) in those with no significant or slight disability ($p = 0.013$). A significantly higher proportion of patients with better outcomes were under 40 years (18.5% vs. 6.3%), whereas those with worse outcomes were more likely to be over 60 years (55.6% vs. 33.3%, $p = 0.025$). Gender, smoking, alcohol consumption, hypertension, and diabetes mellitus showed no significant differences between the groups. However, serum albumin levels were significantly lower in the moderate to severe disability or death group (mean: 2.8 g/dL, SD: 0.7) compared to those with no significant or slight disability (mean: 3.7 g/dL, SD: 0.7, $p < 0.001$), suggesting an association between hypoalbuminemia and poor functional outcomes.

A significant negative correlation was observed between serum albumin levels and both NIHSS and mRS scores. Serum albumin levels showed a moderate negative correlation with NIHSS ($r_p = -0.521$, $p < 0.001$), indicating that lower albumin levels were associated with greater stroke severity. Similarly, serum albumin levels demonstrated a moderate negative correlation with mRS scores ($r_p = -0.484$, $p < 0.001$), suggesting that lower albumin levels were linked to worse functional outcomes and higher disability at one-week post-stroke.

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ROC analysis demonstrated that serum albumin levels were a significant predictor of both moderate to severe stroke (based on NIHSS) and moderate to severe disability or death (based on mRS). The AUC for predicting moderate to severe stroke was 0.809 (95% CI: 0.692–0.927, $p < 0.001$), with a serum albumin cutoff of <3.4 g/dL yielding a sensitivity of 81.7% and a specificity of 73.7%. Similarly, the AUC for predicting moderate to severe disability or death was 0.822 (95% CI: 0.727–0.917, $p < 0.001$), with the same serum albumin cutoff of <3.4 g/dL, providing a sensitivity of 85.7% and a specificity of 70.4%.

DISCUSSION

Our study demonstrated that patients with moderate to severe stroke (NIHSS ≥ 5) had a significantly higher mean age (60.9 years) compared to those with minor stroke (53.8 years, $p = 0.037$). This finding is consistent with prior studies indicating that advanced age is associated with increased stroke severity.(12) The higher prevalence of moderate to severe stroke in individuals over 60 years (54.9%) compared to younger individuals suggests that aging-related vascular changes, increased arterial stiffness, and a higher burden of comorbidities may contribute to worse stroke severity.(13, 14) Similar patterns have been observed in previous research. For instance, a meta-analysis by Thuemmler et al.(15) (2024) reported that older stroke patients had a higher risk of poor outcomes due to age-related endothelial dysfunction and reduced neuroplasticity. The association between older age and increased stroke severity might also be due to higher levels of systemic inflammation and impaired cerebrovascular autoregulation, leading to greater infarct expansion and neurological impairment.(16)

A similar trend was observed in our study regarding stroke prognosis, as patients with moderate to severe disability or death (mRS ≥ 3) had a significantly higher mean age (61.8 years) compared to those with mild or no disability (53.8 years, $p = 0.013$). This aligns with the findings of Violi et al.(17) (2023), who reported that older age was an independent predictor of poor stroke outcomes. Additionally, our study found that the proportion of patients aged >60 years was significantly higher in the moderate to severe disability or death group (55.6%) than in the mild or no disability group (33.3%), reinforcing the impact of aging on stroke recovery and mortality risk. Research by Wang et al.(8) (2023) and Zhang et al.(18) (2016) has highlighted that low serum albumin levels, which are more common in elderly individuals, may contribute to worse stroke outcomes. Albumin has neuroprotective properties, including antioxidant and anti-inflammatory effects, which decline with age, potentially explaining why older individuals experience worse post-stroke recovery.(5)

Our study found no significant differences in gender distribution between stroke severity and prognosis groups ($p = 0.796$ and $p = 0.818$, respectively). This finding is in line with a report from Framingham Heart Study by Petrea et al.,(19) (2009) which found that gender did not significantly influence stroke severity or prognosis. However, some studies have reported that women tend to have worse functional outcomes post-stroke due to factors such as higher age at stroke onset and differences in pre-existing comorbidities.(20) Interestingly, common vascular risk factors, including smoking, alcohol consumption, hypertension, and diabetes mellitus, were not significantly associated with stroke severity or prognosis in our study (all p-values > 0.05). This contrasts with several previous studies that have identified these factors as major contributors to stroke outcomes.(21-23) However, the lack of significant associations in our study may be due to the relatively small sample size (n = 90) and the possibility that other unmeasured factors, such as medication use and stroke subtype, influenced the outcomes. Previous research has shown that low albumin levels are associated with higher stroke severity and poorer prognosis, independent of traditional vascular risk factors.(18, 24) Therefore, while risk factors like hypertension and diabetes are well-established contributors to stroke incidence, their impact on severity and prognosis may be mediated by additional factors, such as inflammation and nutritional status.

Our study revealed that serum albumin levels were significantly lower in patients with moderate to severe stroke (mean: 2.8 g/dL) compared to those with minor stroke (mean: 3.8 g/dL) ($p < 0.001$). Furthermore, a moderate negative correlation was found between albumin levels and NIHSS scores ($r = -0.521$, p <

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0.001), indicating that lower albumin levels were associated with increased stroke severity. These findings are consistent with previous research. A study by Shaikh et al.(10) (2021) found that hypoalbuminemia was common among stroke patients and significantly correlated with higher NIHSS scores. Similarly, Thuemmler et al.(15) (2024) reported that stroke patients with low albumin levels had worse neurological deficits, with low-normal albumin levels (<37 g/L) increasing the risk of in-hospital and long-term mortality. Hypoalbuminemia is believed to contribute to stroke severity due to its role in inflammation, endothelial dysfunction, and impaired cerebral perfusion.(17) Additionally, Wang et al.(8) (2023) demonstrated that lower serum albumin levels were significantly associated with an increased risk of ischemic stroke, particularly among non-diabetics and hypertensive patients. Albumin's neuroprotective properties, including its antioxidant and anti-inflammatory effects, are diminished in hypoalbuminemic patients, which may exacerbate ischemic injury and worsen stroke severity.(5)

In our study, serum albumin levels were also significantly lower in patients with moderate to severe disability or death (mRS ≥ 3, mean: 2.8 g/dL) compared to those with mild or no disability (mRS < 3, mean: 3.7 g/dL) (p < 0.001). A moderate negative correlation was observed between albumin levels and mRS scores (r = -0.484, p < 0.001), indicating that lower albumin levels were linked to worse functional recovery at one-week post-stroke. These findings are in agreement with previous research. Zhou et al.(7) (2021) found that patients with albumin levels <35 g/L had significantly worse functional outcomes at discharge and higher mortality rates at one year. A study by Idicula et al.(24) (2009) confirmed that each 1 g/L decrease in albumin levels slightly increased the risk of poor functional outcomes (OR 1.03) and mortality (HR 1.07). The relationship between hypoalbuminemia and poor recovery may be explained by multiple mechanisms. First, albumin has been shown to reduce cerebral oedema and oxidative stress, playing a critical role in protecting neurons from ischemic injury. Second, hypoalbuminemia is often indicative of malnutrition and systemic inflammation, both of which are associated with worse stroke recovery and higher mortality.(11)

Our study demonstrated that serum albumin is a significant predictor of both stroke severity and short-term prognosis. The ROC analysis showed that albumin had a strong predictive value for moderate to severe stroke, with an AUC of 0.809 (95% CI: 0.692–0.927, p < 0.001). A serum albumin cutoff of <3.4 g/dL yielded a sensitivity of 81.7% and a specificity of 73.7%. Similarly, for predicting moderate to severe disability or death, the AUC was 0.822 (95% CI: 0.727–0.917, p < 0.001), with the same cutoff providing a sensitivity of 85.7% and specificity of 70.4%. These results highlight the potential clinical utility of serum albumin as a prognostic biomarker for stroke severity and recovery. Previous studies have also demonstrated the predictive value of hypoalbuminemia in stroke outcomes. Zhang et al.(18) (2016) found that higher albumin levels were associated with a lower risk of stroke recurrence, while Violi et al.(17) (2023) identified hypoalbuminemia as an independent predictor of ischemic events and mortality. Moreover, Idicula et al.(24) (2009) suggested that monitoring albumin levels in stroke patients could help identify those at higher risk of poor functional recovery and mortality.

Given these findings, serum albumin could serve as a valuable biomarker for risk stratification in acute ischemic stroke patients. Early identification of hypoalbuminemia may allow for targeted interventions, such as albumin supplementation, nutritional support, and inflammation management, to improve patient outcomes. While previous trials have investigated albumin therapy in acute stroke (e.g., the ALIAS trial),(25) further research is needed to determine the optimal strategies for mitigating the adverse effects of hypoalbuminemia on stroke prognosis.

The present study has several limitations that should be acknowledged. First, as a single-centre study conducted at Aarupadai Veedu Medical College and Hospital, the findings may not be generalizable to broader populations with diverse demographic and socioeconomic backgrounds. Additionally, while serum albumin levels were measured at admission, dynamic changes in albumin over time were not assessed, which may have provided deeper insights into its role in stroke

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progression and recovery. The study also did not account for potential confounders such as nutritional status, inflammatory markers, and chronic comorbidities, which could influence both albumin levels and stroke outcomes. Furthermore, the short follow-up period of one week limits the ability to assess long-term prognostic implications, making it necessary for future studies to investigate whether the observed associations persist over extended recovery periods. Lastly, while the study establishes a strong association between hypoalbuminemia and stroke severity and prognosis, it does not establish causality, necessitating further interventional studies to explore whether albumin supplementation could improve outcomes in stroke patients.

CONCLUSION

The present study demonstrates a significant association between hypoalbuminemia and both stroke severity and short-term functional outcomes in patients with acute ischemic stroke. Patients with lower serum albumin levels at admission were more likely to present with moderate to severe stroke, as assessed by NIHSS, and had a higher likelihood of experiencing moderate to severe disability or death, as measured by mRS at one-week post-stroke. The negative correlation between serum albumin levels and both NIHSS and mRS scores further highlights the potential role of hypoalbuminemia as a prognostic marker in acute ischemic stroke. Additionally, ROC analysis confirmed the strong predictive value of albumin levels, with a cutoff of <3.4 g/dL demonstrating high sensitivity and specificity in identifying patients at greater risk for severe stroke and poor functional recovery.

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Table 1: Sociodemographic and clinical characteristics of AIS patients

		Frequency (N = 90)	**Percent**
		(n)	**(%)**
Age (in years), Mean (SD)		59.4 (14.0)	
Age (in years)	≤40	9	10.0
	41 to 60	37	41.1
	>60	44	48.9
Gender	Female	45	50.0
	Male	45	50.0

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Smoking	Present	12	13.3
	Absent	78	86.7
Alcohol	Present	16	17.8
	Absent	64	82.2
Hypertension	Present	45	50.0
	Absent	45	50.0
Diabetes mellitus	Present	30	33.3
	Absent	60	66.7
Serum albumin levels (g/dL), Mean (SD)		3.0 (0.8)	
NIHSS, Mean (SD)		14.7 (8.5)	
Modified Rankin Scale, Mean (SD)		3.4 (1.5)	
SD, Standard deviation; NIHSS, National Institutes of Health Stroke Scale			

Table 2: Association between independent study variables and stroke severity assessed using NIHSS

		NIHSS		P value
		Moderate to severe stroke N = 71	**Minor stroke N = 19**	
		n (%)	**n (%)**	
Age (in years), Mean (SD)		60.9 (14.2)	53.8 (12.2)	0.037*
Age (in years)	≤40	8 (11.3)	1 (5.3)	0.024*
	41 to 60	24 (33.8)	13 (68.4)	
	>60	39 (54.9)	5 (26.3)	
Gender	Female	35 (49.3)	10 (52.6)	0.796
	Male	36 (50.7)	9 (47.4)	
Smoking	Present	9 (12.7)	3 (15.8)	0.723
	Absent	62 (87.3)	16 (84.2)	
Alcohol	Present	13 (18.3)	3 (15.8)	0.799
	Absent	58 (81.7)	16 (84.2)	
Hypertension	Present	36 (50.7)	9 (47.4)	0.796
	Absent	35 (49.3)	10 (52.6)	
Diabetes mellitus	Present	23 (32.4)	7 (36.8)	0.715
	Absent	48 (67.7)	12 (63.2)	
Serum albumin levels (g/dL)		2.8 (0.7)	3.8 (0.7)	<0.001*

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*Statistically significant at p<0.05 NIHSS, National Institutes of Health Stroke Scale; SD, Standard deviation

Table 3: Association between independent study variables and functional outcomes assessed using mRS

		Modified Rankin Scale		**P value**
		Moderate to severe disability or death **N = 63**	**No significant or slight disability** **N = 27**	
		n (%)	**n (%)**	
Age (in years), Mean (SD)		61.8 (12.7)	53.8 (15.5)	0.013
Age (in years)	≤40	4 (6.3)	5 (18.5)	0.025*
	41 to 60	24 (38.1)	13 (48.1)	
	>60	35 (55.6)	9 (33.3)	
Gender	Female	31 (49.2)	14 (51.9)	0.818
	Male	32 (50.8)	13 (48.1)	
Smoking	Present	9 (14.3)	3 (11.1)	0.685
	Absent	54 (85.7)	24 (88.9)	
Alcohol	Present	12 (19.0)	4 (14.8)	0.630
	Absent	51 (81.0)	23 (85.2)	
Hypertension	Present	33 (52.4)	12 (44.4)	0.490
	Absent	30 (47.6)	15 (55.6)	
Diabetes mellitus	Present	20 (31.7)	10 (37.0)	0.626
	Absent	43 (68.3)	17 (63.0)	
Serum albumin levels (g/dL)		2.8 (0.7)	3.7 (0.7)	<0.001*
*Statistically significant at p<0.05 SD, Standard deviation				

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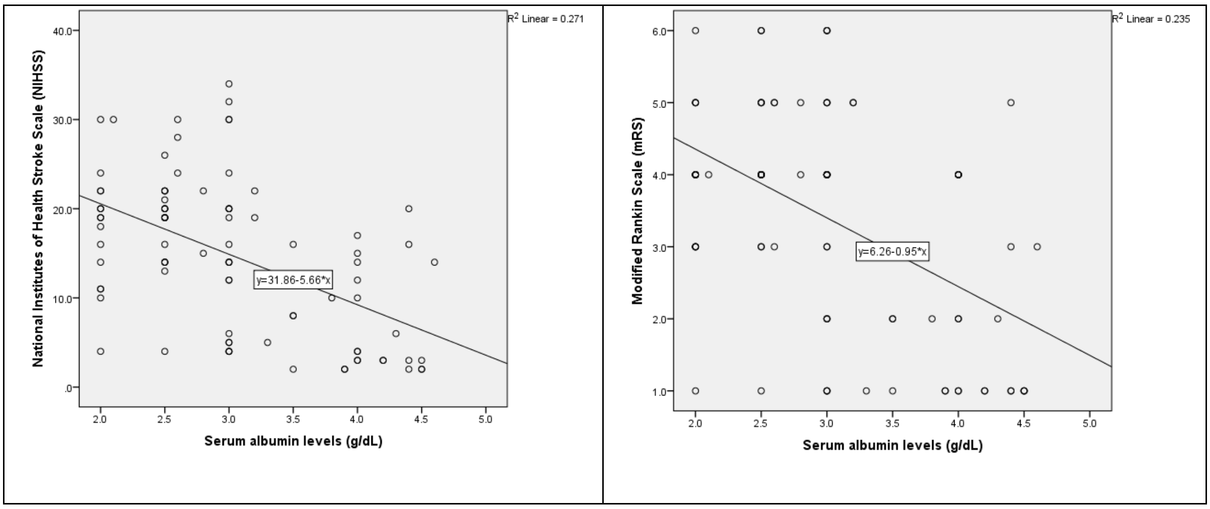

Figure 1: Correlation between serum albumin levels, NIHSS and mRS scores

Table 4: ROC analysis showing AUC of serum albumin levels in predicting moderate to severe stroke (based on NIHSS) and moderate to severe disability or death (assessed using mRS)

	AUC (95% CI)	**Cut off**	**Sensitivity (%)**	**Specificity (%)**	**P value**
Moderate to severe stroke (based on NIHSS)	0.809 (0.692 to 0.927)	≤3.4	81.7	73.7	<0.001*
Moderate to severe disability or death (based on mRS)	0.822 (0.727 to 0.917)	≤3.4	85.7	70.4	<0.001*

*Statistically significant at p<0.05

NIHSS, National Institutes of Health Stroke Scale; mRS, Modified Rankin Scale; AUC, Area under the curve; CI, Confidence interval

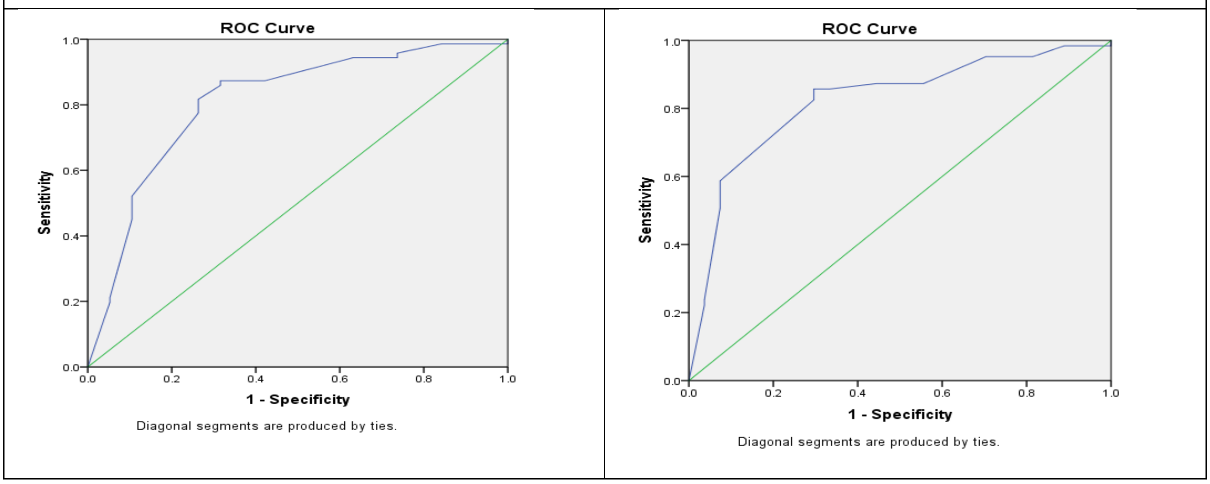

Figure 2: ROC analysis showing AUC of serum albumin levels in predicting moderate to severe stroke (based on NIHSS) and moderate to severe disability or death (assessed using mRS)