STUDY OF SERUM ALBUMIN AS A PREDICTOR OF SHORT-TERM FUNCTIONAL OUTCOME IN ACUTE ISCHAEMIC STROKE

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ABSTRACT

BACKGROUND

Stroke or cerebrovascular accident is a life-threatening neurological disorder comprising more than 50% of admissions in a hospital. Identification of predictors of mortality, especially modifiable ones is vital so that prompt therapeutic measures can be instituted to improve outcome.

This study has been undertaken with the intention to determine the association if any between serum albumin and the severity as well as the short-term outcome of acute ischaemic stroke.

MATERIALS AND METHODS

This observational study was conducted in a tertiary care hospital in South India over a period of 1 year. The study population comprised of 100 patients who got admitted in medical wards with first ever acute ischaemic stroke within 72 hours of onset of symptoms. Stroke severity at admission was graded using the Scandinavian Stroke Scale and functional status on 7th day was assessed using Modified Rankin Scale.

RESULTS

The mean age of the study population was 58.44 ± 14.42 years. A significant association was observed between serum albumin and severity of stroke at presentation. A strong negative correlation was found between serum albumin at admission and MRS score, indicating a strong association between serum albumin and the functional outcome at 7 days. There was also significant association between the severity of stroke at admission and the functional outcome at 7 days.

CONCLUSION

The study found that the severity of stroke at onset had a definite association with outcome and serum albumin influences both stroke severity and outcome.

KEYWORDS

Serum Albumin, Ischaemic Stroke.

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BACKGROUND

Stroke or cerebrovascular accident is a life-threatening neurological disorder. It constitutes more than 50% of admissions in a hospital. It has been estimated that by the year 2020, stroke will emerge as the second leading cause of morbidity and mortality in developed countries.[1] Westernisation of lifestyle and the resulting demographic transition might increase the burden of stroke in developing countries as well. Early mortality from stroke is mostly directly related to stroke. Complications affect mortality only later in the course. Previous studies have thrown light on the various risk factors of stroke as well as the factors which influence mortality, some of which may serve as predictors of mortality. Stroke severity, type of stroke, increased age, level of consciousness, etc. are a few of them.[2,3,4] But most of these are non-modifiable and hence of limited value in clinical practice. Identification of predictors of mortality, especially modifiable ones is vital so that prompt therapeutic measures can be instituted to improve outcome.

Albumin is a multifunctional protein, which has been proven to have neuroprotective effects in animal studies. Albumin is also an indicator of the nutritional status. This fact holds importance, as out of 15 million stroke events occurring annually all over the world, two-third occurs in low income and middle income developing countries, where malnutrition is rampant. There have been several studies in the western world including interventional studies trying to explore the scope of albumin as a neuroprotective agent. Some of these have shown that albumin therapy is capable of minimising infarction volume and cerebral oedema.[5] Albumin reduces haematocrit as well as erythrocyte sedimentation rate by its affects erythrocyte aggregation.[6] Effect of albumin is mainly in the early reperfusion phase of acute ischaemic stroke, where it exerts an inhibitory effect on stagnation, thrombosis and leucocyte adhesion in microcirculation. This study has been undertaken with the foresight that if the association can be proven beyond doubt, it may be possible to

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institute corrective measures in order to improve the prognosis of the disease.

MATERIALS AND METHODS

This prospective observational study was conducted in a tertiary care hospital in South India over a period of 1 year. It was approved by the Ethical Committee of the Institution. The study population comprised of 100 patients who got admitted in medical wards with first ever acute ischaemic stroke within 72 hours of onset of symptoms. The patients were included in the study after getting informed consent, either from the patient himself or from the legal guardian. Patients presented after 72 hrs. after onset of symptoms, having previous history of stroke, haemorrhagic stroke, stroke due to tuberculoma, tumour or trauma, subarachnoid haemorrhage, patients with known renal or hepatic disease and patients with fever and infections were excluded from the study. Cases were defined as per WHO definition of stroke. Hypertension was diagnosed if there were records documenting the same or when at least 2 readings of blood pressure were ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic after the acute phase of stroke. Coronary artery disease was diagnosed in the presence of ECG changes or previous records. Patient was considered a smoker if he had a history of smoking in the past 5 years.

About 212 consecutive patients who were admitted with first ever attack of stroke were screened to get the study population of 100. Patients first underwent a CT scan of the brain to rule out haemorrhagic stroke or any obvious mass lesions. A detailed history was elicited followed by general examination, an elaborate CNS examination and relevant examination of other systems. Stroke severity was graded using the Scandinavian Stroke Scale (Figure 1). Blood and urine investigations were done including complete haemogram, blood sugar, renal function test, liver function test with serum proteins, lipid profile and urine routine examination. ECG was also taken. Cases who met the exclusion criteria were excluded. Patients received treatment as per Institution guidelines. Patients were followed up and on the 7th day after onset of stroke their functional status was assessed using Modified Rankin Scale (Figure 2) either in person if patient still in hospital or over the phone if discharged. Serum albumin levels were measured using Bromocresol Green.

Scandinavian	**Patient Name**:	_____ _____	
Stroke	**Rater Name:**	_____ _____	
Scale	**Date:**	_____ _____	
Function	**Score**	**Prognostic Long Term**	
		Score Score	
Consciousness			
-Fully conscious	6	___	
-Somnolent, can be awaken to full consciousness	4		
-Reacts to verbal command, but is not fully conscious	2		
Eye Movement			
-No gaze palsy	4	___	
-Gaze palsy present	2		
-Conjugate eye deviation	0		
Arm, Motor Power*:			
-Raises arm with normal strength	6	___	___
-Raises arm with reduced strength	5		
-Raises arm with flexion in elbow	4		
-Can Move, but not against gravity	2		
-Paralysis	0		
Hand, Motor Power*:			
-Normal strength	6		___
-Reduced strength in full range	4		
-Some movement, fingertips do not reach palm	2		
-Paralysis	0		
Leg, Motor Power*:			
-Normal strength	6	___	___
-Raises straight leg with reduced strength	5		
-Raises leg with flexion of knee	4		
-Can move, but not against gravity	2		
-Paralysis	0		

Orientation			
-Correct for time, place and person	6		___
-Two of these	4		
-One of these	2		
-Completely disorientated	0		
Speech			
-No aphasia	10		___
-Limited vocabulary or incoherent speech	6		
-More than yes/no, but not longer sentences	3		
-Only yes/no or less	0		
Facial Palsy			
-None/dubious	2		___
-Present	0		
Gait:			
-Walks 5 m without aids	12		___
-Walks with aids	9		
-Walks with help of another person	6		
-Sits without support	3		
-Bedridden/wheelchair	0		
Maximal Score	___	22	48

Table 1. Scandinavian Stroke Scale

* Motor power is assessed only on the affected side.

Modified	**Patient Name**:	_____
Rankin	**Rater Name:**	_____
Scale (MRS)	**Date:**	_____

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead
	Total (0–6): ____

Table 2. Modified Rankin Scale

The obtained data was entered into a Microsoft Excel spreadsheet and analysed statistically using SPSS (Statistical Package for Social Sciences) (Version 18). The significance of association was tested using Chi-square test and correlation was measured by Pearson Correlation Coefficient. The statistical analysis was done to find out the significance of association if any between serum albumin value at admission and the severity of stroke at admission as well as the functional outcome at 7 days and also to find out the correlation between these variables.

RESULTS

Of the 100 patients included in the study, majority were in the 40 – 60 years' age group. Mean age of the study group was 58.44 ± 14.42 yrs. (Table 1). The study group had a near equal proportion of males and females with slight male predominance (Figure 3, 4). The mean age of males was 55 and that of females was 62. The CT brain results were analysed, in which around 53% showed MCA infarct followed by lacunar stroke (25%) and multi-infarct (17%) (Table 2). Associations of lesions with age is depicted in Figure 5. Systemic hypertension was found to be the most frequently associated comorbidity followed by dyslipidaemia and a combination of hypertension and diabetes mellitus (Figure 6). 35% of the population were having the habit of tobacco/smoking and 10% had alcohol addiction (Table 3). In young stroke (below the age of 40), rheumatic heart disease was the major associated comorbidity, whereas in older age groups hypertension predominates the picture.

Age Group	Frequency
Less than 40	14
40 - 60 yrs.	43
60 - 80 yrs.	36
Above 80 yrs.	7
Total	**100**

Table 1. Age Distribution

MCA Infarct	53
Multi-Infarct	17
Posterior Circulation Stroke	5
Lacunar Stroke	25
Total	**100**

Table 2. Frequency of Lesions in CT Brain

Addiction	Frequency
Smoking/Tobacco Chewing	35
Alcohol	10
Alcohol/Tobacco	3
NIL	52
Total	**100**

Table 3. Prevalence of Addictions in the Study Population

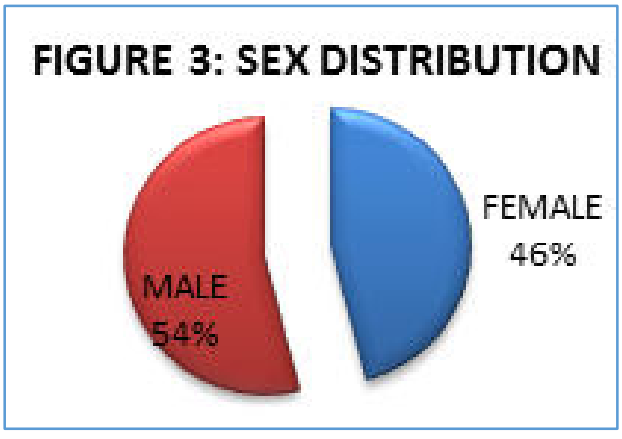

Figure 3. Sex Distribution

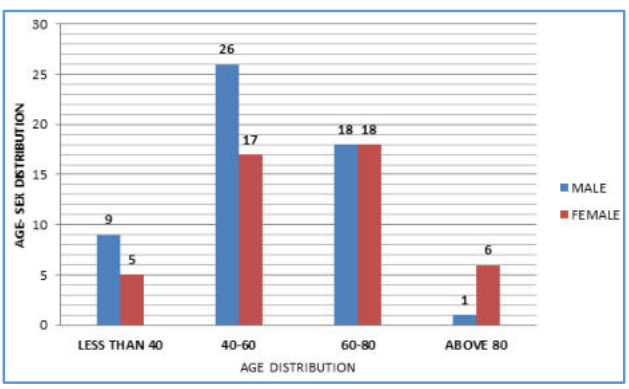

Figure 4. Age-Sex Distribution

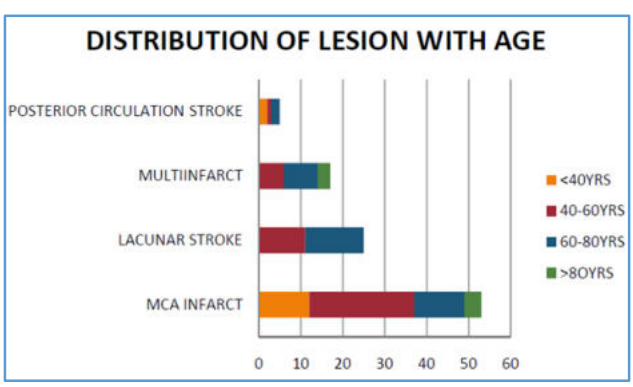

Figure 5. Association of Lesions with Age

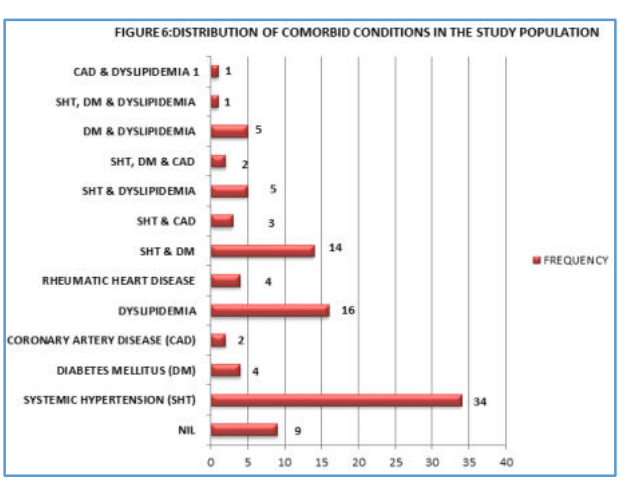

Figure 6. Distribution of Comorbid Conditions in the Study Population

There was no gross difference in the number of stroke patients included in the study with regard to the levels of serum albumin (Table 4). The chi-square value of 6.45 for the association between age and serum albumin is not significant ($p > 0.05$) (Figure 7). In our study population, there was a fairly uniform distribution of serum albumin values with no gross difference in the number of males and females with normal and low albumin levels (Figure 8). In the above table (Table 5), the chi-square value of 64.024 for the association between severity of the stroke as measured by the SSS score and the outcome as measured by the MRS score at 7 days is significant ($p < 0.05$). Hence, we can infer that there is significant association between the severity of stroke at onset and the outcome at 7 days. In the above table (Table 6), the chi-square value of 13.81 for the association between SSS score and serum albumin is significant ($p < 0.05$). This implies that there is significant association between the severity of stroke at presentation and the serum albumin value. The chi-square value for the association between MRS score and serum albumin, 48.21 is statistically significant ($p < 0.05$). This implies that the stroke outcome at 7 days as measured by the Modified Rankin scale is significantly associated with the level of serum albumin at stroke onset (Table 7). In our study population, 84% of deaths was in the group with low serum albumin values. Among the patients with low serum albumin values, 93% landed up with severe disability or death compared to 24.5% in patients with normal serum albumin. This reemphasises the fact that serum albumin could be of prognostic significance in acute ischaemic stroke.

Serum Albumin	Frequency
Normal (3.5 – 5 g/dL)	57
Low (< 3.5 g/dL)	43
Total	**100**

Table 4. Distribution of Albumin in the Study Population

	Severity	MRS Score				
		Mild	Moderate	Severe	Death	Total
Score	Mild	6	0	0	0	6
	Moderate	17	12	7	0	36
	Severe	0	11	22	25	58
	Total	**23**	**23**	**29**	**25**	**100**

Table 5. Association of MRS Score at 7 Days with Severity of Stroke (SSS Score)

		Serum Albumin		
	Severity	Normal	Low	Total
Score	Mild	5	1	6
	Moderate	28	8	36
	Severe	24	34	58
	Total	**57**	**43**	**100**

Table 6. Association of Severity of Stroke (SSS Score) with Serum Albumin

		Serum Albumin		
	Severity	Normal	Low	Total
MRS Score	Mild	22	1	23
	Moderate	21	2	23
	Severe	10	19	29
	Death	4	21	25
	Total	57	43	100

Table 7. Association of MRS Score at 7 Days with Serum Albumin

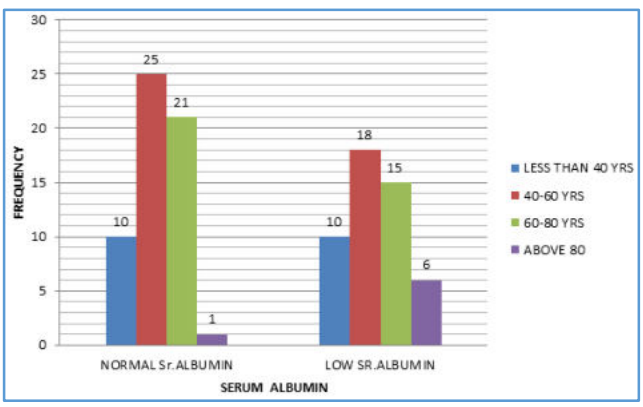

Figure 7. Association of Serum Albumin with Age

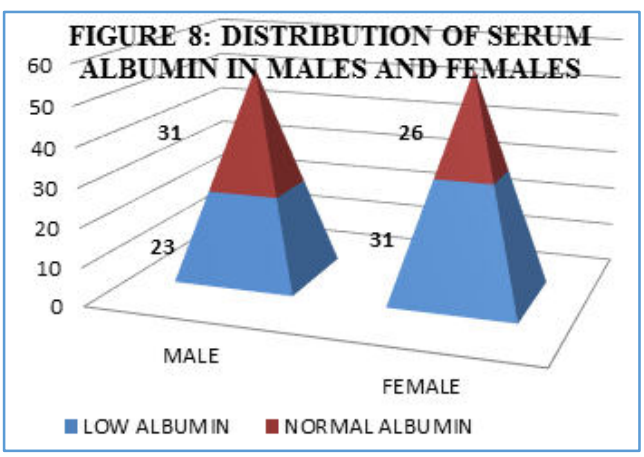

Figure 8. Distribution of Serum Albumin in Males and Females

		GCS	S. Albumin	SSS Score	MRS Score
GCS	Pearson Correlation	1	.612**	.859**	-.845**
	Sig. (2-tailed)		.000	.000	.000
	N	100	100	100	100
S. Albumin	Pearson Correlation	.612**	1	.558**	-.700**
	Sig. (2-tailed)	.000		.000	.000
	N	100	100	100	100
SSS Score	Pearson Correlation	.859**	.558**	1	-.865**
	Sig. (2-tailed)	.000	.000		.000

	N	100	100	100	100
MRS Score	Pearson Correlation	-.845**	-.700**	-.865**	1
	Sig. (2-tailed)	.000	.000	.000	
	N	100	100	100	100

Table 8. Correlation between Serum Albumin, GCS Score, SSS Score and MRS Score

GCS Score and Serum Albumin

The Pearson Correlation Coefficient of the correlation between serum albumin and the Glasgow Coma Scale score at admission 0.612 is statistically significant ($p < 0.05$). This shows that there is strong positive correlation between serum albumin value and the GCS at admission. So, higher the serum albumin value, better the GCS.

GCS and SSS Score

The correlation between GCS and SSS score has a Pearson Correlation Coefficient of 0.859, which is statistically significant ($p < 0.05$). This implies a strong positive correlation between the GCS score at admission and the SSS score at admission. This means that the Glasgow Coma Scale and The Scandinavian Stroke Scale go hand in hand in measuring the severity of stroke at admission.

GCS and MRS Score

The Pearson Correlation Coefficient for the correlation between GCS and MRS score is -0.845, which is statistically significant ($p < 0.05$). This suggests a strong negative correlation between the GCS at admission and the MRS score at 7 days. So a higher GCS at admission is associated with a lower MRS score or a better outcome at 7 days.

Serum Albumin and SSS Score

The correlation between serum albumin at admission and the SSS score at admission has a Pearson Correlation Coefficient of 0.558, which is statistically significant ($p < 0.05$). So there is a strong positive correlation between the serum albumin at admission and the Scandinavian Stroke Scale score. A higher albumin value is therefore associated with a less severe stroke as a higher SSS score indicates a milder stroke.

Serum Albumin and MRS Score

The Pearson correlation coefficient for the correlation between serum albumin value at admission and the MRS score -0.700 is statistically significant. So there is a strong negative correlation between the serum albumin level at admission and the Modified Rankin Scale at 7 days. A lower MRS score indicates a milder disability and better outcome. Hence, the higher the serum albumin level, the lower the MRS score and better the outcome (Table 8).

SSS Score and MRS Score

The Pearson Correlation Coefficient for the correlation between the SSS score and MRS score is -0.865, which is statistically significant ($p < 0.05$). So there is a strong negative correlation between the SSS score at admission and the MRS score at 7 days. This implies that higher the SSS score, lower the MRS score. That is less severe the stroke at admission, better the functional outcome at 7 days.

Study	Sample Size	Males	Mean Age	Mortality	Poor Outcome
Dziedzic et al[7]	759	49%	68.3	12.9%	36%
Abubakar et al	75	52%	57.68 ± 12.4	17.3%	52%
Idicula et al	444		70.4 ± 14.4	13%	
Our study	100	54%	58.44 ± 14.42	25%	54%

Serum Albumin		
Study	**Poor Outcome**	**Good Outcome**
Dziedzic et al	3.41	3.68
Reinhardt et al	< 3.4	> 3.5
Our Study	3.13	4.16

Table 9. Comparison of Mortality and Outcome with Other Studies

DISCUSSION

Albumin has well established important functions in health. Animal studies have shown neuroprotective effect of albumin in ischaemic stroke. But this has not been well studied in humans. Though there are quite a few studies from the western world, there are a very few Indian studies in this regard. Previous studies have concluded that in ischaemic stroke, serum albumin is an independent predictor of outcome. The study by Gariballa et al[8] has observed that serum albumin concentration is a strong and independent predictor of mortality. Of the various markers of nutritional status used in this study, only serum albumin showed a significant and independent association with stroke outcome. Aptaker et al[9] found that serum albumin concentrations at admission were significantly related to the rate of medical complications and functional outcome in stroke. Our study included 100 patients with ischaemic stroke. This sample size was small compared to most of the multicentric studies conducted in the western world. But the study results were comparable to that of previous studies. Males comprised 54% of patients in our study, which made the sex distribution similar to the study by Abubakar et al.[10] The mean age of our patients was 58.44 ± 14.42 as compared to 57.68 ± 12.4 in this study (Table 9).

Reflection of the nutritional status and may be causally related to the increased morbidity and mortality after stroke. A study by Mallemoggala et al[11] has found that recurrence of stroke also was high in patients with low levels of albumin compared to patients with high levels.

Our study found no significant association between serum albumin and age as opposed to the finding in the study by Idicula et al.[12] But the study by Abubakar et al supported our finding. Our study revealed higher mortality and more number of patients with unfavourable outcome compared to the study by Dziedzic et al.[7] This is probably because in the aforementioned study, patients with SSS score < 25 were excluded as they would be non-ambulatory. The study by Reinhardt et al has found that serum albumin levels of < 3.4 are associated with a high mortality of about 25%. This might explain the high mortality observed in our study. Our study as in the above-mentioned studies has come out with a significant association between serum albumin levels and the

severity of acute ischaemic stroke. There is also significant correlation between serum albumin level and the functional outcome at 7 days. We have also found out significant correlation between the severity of ischaemic stroke at onset and the functional outcome at 7 days. Albumin has been considered as a measure of health and disease. Malnutrition, liver disease, renal disease, etc. reduce serum albumin concentration. Catabolic state and neuroendocrine response that follow stroke alter the serum albumin concentration. Malnutrition also down-regulates protein synthesis. Nutrition is thought to be the single most important factor regulating albumin synthesis. Having excluded patients with hepatic and renal disease from the study population, the serum albumin concentration in our study is probably a reflection of the nutritional status and may be causally related to the increased morbidity and mortality after stroke. A study by Mallemoggala et al[11] has found that recurrence of stroke also was high in patients with low levels of albumin compared to patients with high levels.

A phase 3 trial, Albumin in acute ischaemic stroke trial (Alias) was conducted by the National Institute of Neurological Disorders and Stroke (NINDS) sponsored by the University of Miami, to determine whether human albumin administered within 5 hours of symptom onset improves 3-month outcome of subjects with acute ischaemic stroke. The study has been terminated, but the results are not yet available. More nutritional intervention studies are needed to prove beyond doubt that improving serum albumin concentration will improve clinical outcome.[13]

CONCLUSION

Though the risk of stroke increases with age, most of our patients were middle aged in the 40 - 60 years' age group. Smoking and hypertension are the most common modifiable risk factors associated. GCS is as good as SSS as a measure of stroke severity. There was no significant variation of serum albumin with age or sex. Severity of stroke at onset has a definite association with outcome. Serum albumin influences both stroke severity and outcome. Serum albumin being a marker of nutritional status, nutritional support may improve the functional outcome of acute ischaemic stroke.

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