RESEARCH
www.commprac.com
ISSN 1462 2815

A STUDY ON THE ROLE OF SERUM CALCIUM, ALBUMIN AND URIC ACID AS PREDICTORS OF NEUROLOGICAL SEVERITY AND SHORT TERM OUTCOME IN ACUTE ISCHEMIC STROKE

Dr. Dhanush Balaji. S [1]*, Dr. Abinaya Srinivasa Rangan [2], Karpaka Vinayakam Gopalakrishnan [3], Dr. S. Prasanna Karthik [4], Raghunathan E.G.[5] and Manoj Kumar S [6]

[1,2,4,5,6] Department of General Medicine, Saveetha Medical College and Hospital, Tamil Nadu.
[3] Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai, India.
*Corresponding Author Email: dhanushbalajis@gmail.com

DOI: 10.5281/zenodo.11480896

Abstract

Background: Worldwide, stroke is the main reason for disability and takes the second and third position in causing dementia and death, respectively. Ischemic injury in stroke leads to intracellular calcium accumulation, which activates the enzyme cascade causing cell death. It is not clear whether Serum Uric Acid promotes or do protects against the cerebrovascular disease. The predictors of severity and outcome in acute ischemic stroke (AIS) are not well elucidated, and the usual causative factors have not been shown to predict prognosis. To study and assess the role of Serum uric acid, Serum calcium and Serum albumin in acute ischemic stroke and its effect on stroke outcome. **Materials & Methods:** A cross-sectional study was carried out in Kurnool Medical College, Kurnool, over a period of 18 months in which 50 cases of who attained the inclusion criteria were studied. Individuals presenting within 72 hours of onset and aged >= 40 years were included in this study. Apart from routine investigations, serum albumin, calcium & uric acid levels were done in all patients. **Results:** Out of 50 patients, 62% were males, and 38% were females. The ratio was 1.6:1. Most of the stroke population are between 50 to 69 years. Hypertension constitutes the major risk factor in this population as 84% of the population is hypertensive. Serum calcium, albumin & uric acid values had a highly significant correlation with neurological severity by the NIHSS scores ($p<0.001$) and with the short-term outcome by Barthel index ($p< 0.001$). **Conclusion:** Serum albumin, Serum Calcium & Serum Uric acid values can predict initial neurologic severity and short-term outcome in AIS.

Keywords: Calcium, Albumin, Uric acid, Acute Ischemic Stroke, NIHSS Score, Barthel Index, Prognosis.

INTRODUCTION

The World Health Organization defines a stroke as "Rapidly developing clinical signs of focal (or global) disturbance of cerebral function with symptoms lasting twenty four hours or longer or leading to death, with no apparent cause other than a vascular origin [1]. Stroke is the third most common cause of death in the United States. Though the death rate from stroke has been decreasing from last 20 yrs, the incidence has been increasing as per AHA. Stroke assumes importance both because of its high rate of mortality and the residual disability that it causes. Its occurrence has far wider implications when viewed from an international perspective.78 lakh deaths are due to stroke contributing 13% totally among other reasons of death taking one of the top 5 causes of death as per WHO, 2004. They account for 3.6 percent of the total disability-adjusted life years (DALYs) hence acquiring place in top ten disability causes not related to country's development status [2]. Studies have elucidated the stroke pattern to a considerable extent in our country, with a prevalence rate of 471.58/100000 population [3]. As per studies, stroke constitutes to significant percentage of hospital admissions and death rate.

Stroke with other chronic illness constitutes for majority of mortality in older individuals [4] as per studies. Strokes due to infarction comprises for more than eighty percent of total stroke events [5]. Primary prevention strategies could be used if these individuals are recognized initially [6]. Calcium decreases aggregation of platelets, decreases blood pressure, in addition triggers cytotoxic events if intracellular calcium increases. Increased intake of calcium decreases the risk of stroke. Finally, it is associated with severity and outcome of stroke suggesting a treatment option [7]. Human serum albumin has neuroprotective properties with Experimental studies showing substantially improved neurological function, with albumin therapy markedly reduces the volume of cerebral infarction, and eliminates brain swelling in animals with acute stroke. Experimental studies of focal cerebral ischemia showed that high-dose (2.0 to 2.5 g/kg) or moderate-dose (0.63 to 1.25 g/kg) human albumin therapy, if administered promptly (2 to 4 hours) after stroke onset, is highly effective in improving neurological status and in reducing infarction volume and extent of brain swelling [8-10]. Thus, the correlation of albumin levels with clinical severity of acute stroke is being given interest to use it for medical intervention [11].

The concentration of Uric Acid is the key point of the mechanisms underlying the association of Uric Acid with development of stroke. As one of the most abundant antioxidant molecules in humans, UA has the valid ability to clear out peroxynitrite, nitric oxide, and hydroxyl radicals; hence, it can prevent proteinnitration and lipid peroxidation [12,13].

Studies in animal models have shown that administration of Uric Acid or soluble Uric Acid analogs that retain the antioxidant properties of Uric Acid protect the brain against ischemic injury [14-16]. These findings from experimental, epidemiological, and clinical studies of UA suggested that elevated Serum Uric Acid could be associated with vascular diseases and clarified the important role played by Serum Uric Acid levels in illustrating the possible pathophysiological association with hypertension, atherosclerosis, and stoke.

This study aims to analyse neurologic severity and short term outcome in cases of acute ischemic stroke (AIS) and its correlation with serum calcium levels at admission. Also to find the Correlation of serum albumin levels on admission with initial neurologic severity and short-term outcome in Acute Ischemic Stroke and to study the clinical relevance regarding severity and short term outcome of acute ischemic stroke (AIS) by estimating serum uric acid levels at admission Neurologic severity assessed through NIHSS score (National Institute of Health Stroke Scale) at admission and short-term outcome through Barthel index at seven days.

METHODOLOGY

Our present study was done in the Department of General Medicine, Kurnool Medical College / Govt. General Hospital, Kurnool, in one year from October 2020 to September 2021 and was performed on patients with the first attack of Acute Ischemic stroke admitted to the Medical ward in the Kurnool Medical College, Kurnool. This is a longitudinal study with a sample size of 100.

Data could be accrued by a pretested proforma that satisfies the objectives of the present study. History in detail, physical examination and required laboratory tests will be undertaken. The purpose of the present study could be explained to the individual and informed consent acquired.

Inclusion criteria:

- Patients aged > 40 years irrespective of gender.
- Individuals diagnosed to have an acute ischemic cerebrovascular stroke within the previous two hours by general examination and confirmed through either a non-contrast C.T. scan or through an MRI Scan were included.

Exclusion Criteria:

- Age < Forty years
- Patients presenting with (ICH) hemorrhagic stroke/ subarachnoid hemorrhage cerebral venous Sinus(CSVT) thrombosis
- Individuals with ischemic stroke after seventy two hours of onset weren't entertained in the study.
- Cases with old TIA or similar history.
- Cases who receive thiazide (for causing hypocalcemia) diuretics known(K/C/O) cases of gout (for causing raised uric acid levels) or show clinical evidence of gout/ Chronic renal Disease (CKD).
- Patients who suffer from cardiac diseases, which could be sources of emboli or whose echocardiogram showed sources of emboli.
- Patients with haematological abnormalities (Leukemia, Other Myeloproliferative disorders).

Clinical history was taken either from the case or their family members or attendant, with special concern towards raised ICT features. Information about comorbidities taken in detail. Information about addictions like tobacco, alcohol consumption also about dietary habits, recorded. NIH (NIHSS) stroke scoring was done in all patients to evaluate the neurological disability, and the Barthel index done to assess prognosis at discharge. Complete CNS examination was performed as per our proforma. In addition, examination of cardiovascular system, Gastrointestinal system, and Respiratory system were done in detail. Serum Calcium, Serum Alb, SUA tests were performed for all cases while admission. Complete investigations such as haemoglobin, Total Leucocyte Count with differential count, total bilirubin with fractionation, liver enzymes, blood urea, serum creatinine, Urine examination, Fasting Blood Sugars, cholesterol levels with its battery of tests, Electro Cardio Gram, Chest X-ray, 2D- Echocardiogram, ultrasound Neck vessel Doppler had been executed. In all cases, non contrast Computed Tomography Brain was performed. Magnetic Resonance Imaging of brain has been performed as required.

The information collected regarding all the cases will be recorded in a Master Chart. The statistical software SAS 9.2, SPSS 15.0, State 10.1, Med Cale 9.0.1, Sy stat 2.0 and R environment ver.2.11.1, had used for the evaluation of data and Microsoft Word, Microsoft Excel had used to generate graphs, tables etc. Using this software, frequencies, percentage, mean, standard deviation, x2, and 'p' Values will be calculated. Descriptive and inferential statistical evaluation has been carried out in the present study. Results on continuous measurements are presented on Mean + S.D. (Min-Max), and results on categorical measurements are presented in number (%). Significance is assessed at a 5 % level of significance.

ISSN 1462 2815

RESULTS

The proposed study was conducted in the Department of General Medicine, Kurnool Medical College, Kurnool, Andhra Pradesh 518001 during a period of one year from October 2020 to September 2021. Our study had 100 patients out of which 62 were male and 38 were female. The patients aged between 50 to 70 years had the highest incident of stroke.

The risk factors among patients was analysed and Hypertension was present in 84% of patients with 78% of males and 94% of females. Smoking and alcohol was present in sixty five percent of males. Women wasn't involved in alcohol or tobacco usage. Diabetes and dyslipidemia observed in 34% and 20% people respectively [table 1].

Table 1: Distribution of Risk Factor in Study Population

Risk factor	MEN		WOMEN		Total	
	No.	%	No.	%	No.	%
Hypertension	24	78	18	94	42	84
D.M.	11	35	6	31	17	34
Dyslipidemia	6	19	4	21	10	20
Smoking	20	65	0	0	20	40
Alcoholism	21	68	0	0	21	42

There are diverse range of symptoms experienced by patients in stroke patients highlighting the multifaceted nature of this condition. 100% cases had motor weakness. 44% had facial nerve palsy, 16% had dysarthria.14% had Sensory disturbance. Headache, vomiting in 10% and 10% cases respectively [table 2].

Table 2: symptoms at presentation in study population

Symptoms	Men		Women		Total	
	No.	%	No.	%	No.	%
Central Facial Palsy	15	48	7	37	22	44
Headache	3	10	2	10	5	10
Nausea/Vomiting	2	6	3	15	5	10%
Motor Weakness	31	100	19	100	50	100
Altered Consciousness	4	13	0	0	4	8
Speech Disturbance	7	22	1	5	8	16
Vertigo	1	3	1	5	2	4
Tingling/Numbness	5	16	2	10	7	14
Seizures	0	0	0	0	0	0

NIHS score and study variables were correlated. Raised uric acid levels in 54% of cases with 41% of these scoring NIHSS >10. Low albumin levels in 52% of cases, with 100% of these scoring NIHSS >10. Low calcium levels in 58% seen, with 90% of these scoring NIHSS >10. Significant p-value between serum calcium, serum albumin, and NIHSS score [table 3].

Table 3: NIHSS Score and Study Variables

Study Variable	NIHSS SCORE		Total (n=50)	P-value
	<=10 (n=24)	>10 (n=26).		
	Serum uric acid			
Normal	8(35%)	15(65%)	23(46%)	x2=2.9811
Hyperuricemia	16(59%)	11 (41%)	27(54%)	p=0.08
	Serum Albumin			
<3.5	0	26(100%)	26(52%)	X2=42.30
≥3.5	24(100%)	0	24(48%)	p<0.0001
	Serum calcium			
<8.6	3(10%)	26(90%)	29(58%)	X2=35.44
≥8.6	21(100%)	0	21(42%)	p<0.0001
	Albumin corrected Calcium			
<8.6	6(48%)	7(54%)	13(26%)	X2=0.029
≥8.6	18(49%)	19(51%)	37(74%)	p=0.87

Similarly, study variables were correlated with Barthel index and Raised uric acid levels seen in 54 % cases, Barthel score was <60 in 100% of these population. Low albumin levels was documented in 52% of cases with 100 % having poor outcomes by the Barthel index (<60). Hypocalcemia was documented in 58% cases, with 93%, Barthel score <60 [Table 4].

Table 4: Barthel Score and Study Variables

	Barthel index			
	<60 n=31	**>60 n=19**	**Total**	
Normal	4(17%)	19(83%)	23(46%)	X2=32.21
Hyperuricemia	27(100%)	0	27(54%)	p value =0.0001
	Serum albumin			
<3.5	26(100%)	0	26(52%)	X2=29.30
>=3.5	5(21%)	19(79%)	24(48%)	p=0.0001
	Serum calcium			
<8.6	27(93%)	2(7%)	29(58%)	X2=28.35
>=8.6	4(19%)	17(81%)	21(42%)	p=0.0001
	Albumin corrected Calcium			
<8.6	7(54%)	6(46%)	13(26%)	X2=0.495
>=8.6	24(65%)	13(35%)	37(74%)	p=0.481

The correlation analysis report in given table 5 and all the values were statistically significant.

Table 5: Correlation Analysis Report

	CORRELATION	SUA	ALBUMIN	CALCIUM	ALB Cor Cal
NIHSS admission	Pearson Correlation	0.784	-0.878	-0.806	-0.108
	P value	<0.001	<0.001	<0.001	0.454
	N	50	50	50	50
Barthel index after 1 week	Pearson correlation	-0.738	0.770	0.6781	0.026
	P value	<0.001	<0.001	<0.001	0.856
	N	50	50	50	50

DISCUSSION

Worldwide, stroke is the main reason for disability and takes the second and third position in causing dementia and death, respectively. Despite of many known risk factors attributing to stroke, their contribution does not explain all the stroke cases. Hence our study aimed to find for other factors contributing to stroke which are calcium, albumin, and uric acid as neurological severity predictors and short term outcomes in AIS. 61.31+ 7.15 years was patients mean age in our study. The range was between 48 and 80 years. The ratio was 1.6:1 for men to women. Age as known, is the important and significant non modifiable risk element for cerebrovascular disease. As age increases, stroke risk and morbidity from stroke increases proportionately. People mean age in the study with stroke was 66 and 67 years, in Mumbai and Trivandrum [17] registries respectively. But, in the Bangalore study, it was 54.5 years [18]. **Analysis done retrospectively by Yu-Fang Wang et al.** on 1166 patients with ischaemic stroke hospitalized, from 2008 to 2012 over 51 months on prognostic outcomes.

Our Study findings are favoured with the data proposed by **Pandiyan** et al., with a men: women ratio of 1.9:1 and with stroke individuals mean age as 61.7 + 13.4 years [19]. Fifth and sixth decade are thus prone to develop or at increased risk of developing ischemic stroke and the concomitant comorbidities that occur as age increases adds to incidence risk in elderly individuals. This study thus helps in selecting individuals at increased risk of stroke, concluding age to be important risk factor in stroke epidemiology. SUA mean were more among men than females; however, this distinction did not attain statistical significance. **Pearce et al**. observed greater SUA values as compared to women (5.28 + 0.66 vs 4.47 + 0.78 mg/dl) [20]. **Longo-Mbenza et al**. determined significantly higher SUA level in men (6.6+7 vs 5.8 + 6 mg dl, P <0.01) [21]. Similar outcomes had been obtained in the study by **Milionis et al**.and in the **Rotterdam study [22-23]**. **Framingham heart study** also showed higher SUA levels in males [24].

Our thesis resulted in a statistically significant (P =0.00) correlation of severity of Acute (AIS) Ischemic stroke with both calcium in blood and alb cor calcium in blood level (0.004). Both these values had positive correlation with NIHSS, p-value < 0.001 & 0.002 in both and Barthel index, p-value <0.002& <0.004, respectively for short term outcome after acute ischemic stroke in our study. Thus calcium levels in blood has a protective role in severity of stroke both corrected calcium in blood and total calcium levels in blood. All the above studies supported the role of serum calcium and its function in outcome assessment and functional outcome. All the above studies favoured our results in assessing severity through calcium levels that include total serum calcium, albumin corrected calcium, ionized calcium. It is important to understand the role of SUA, calcium and albumin in assessing stroke severity and outcome and their role as predictors in AIS, to treat the individuals with no other co morbidities known to play a part in their pathogenesis of stroke. Limitations includes Serum calcium was measured only once patients had been covered up to 72 h of onset, at the same time, previous studies have proven that serum calcium levels fluctuate quite significantly in the initial hours following a stroke. Also, the serum calcium and albumin levels had been measured on admission without a set time interval from the stroke beginning. Thus, this could cause bias in the analysis due to a lack of standardization of the timing of blood sampling.

CONCLUSION

Serum calcium level and albumin-corrected calcium level has a significant correlation with neurological severity and short-term outcome after acute ischemic stroke. As there had been only a few research studies of serum calcium levels and stroke prognosis correlation, our study adds to the knowledge available and proves calcium levels as a strong contender for a prognostic marker of early recovery and disability. Higher serum uric acid (SUA) levels independently predicted neurological severity and related to short-term outcomes in AIS. Thus, a low SUA concentration is related to a very good short-term outcome. Although uric acid role in stroke pathophysiology isn't clear and is controversial over decades, our findings support the hypothesis that SUA is a marker of cerebral infarction magnitude and proved to be an unbiased predictor of stroke outcome. Serum albumin can predict and assess initial neurologic severity and short-term outcome in Acute Ischemic Stroke. Relatively high serum albumin level decreases the risk of poor outcomes in these cases. Our results reinforce the available evidence and point towards a potential therapeutic approach as therapeutic correction of the hypoalbuminemia main a bid to improve the outcome for the patients. Though the results of the ALIAS trial are not encouraging, further studies are needed to test the function of Albumin on a bigger scale, at a different dose, over a longer duration of follow-up.

References

1) Sacco RL, Kasner SE, Broderick JP, Caplan LR, Culebras A, Elkind MS, et al. An updated definition of stroke for the 21st century a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013 Jul 1:44(7):2064-89

2) Adam RD, Victor M. Principles of Neurology. 10th ed. Chapter 34 Page 778 - 790. McGraw-Hill 2014; ISBN-10: 0071794794.

3) Das SK, Banerjee TK, Biswas A, Roy T, Raut DK, Mukherjee CS, et al. A prospective community-based study of stroke in Kolkata, India. Stroke. 2007 Mar 1;38(3):906-10.

4) Khare S. Risk factors of transient ischemic attack: An overview. Journal of mid-life health. 2016 Jan:7(1):2.

5) Ferri CP, Acosta D, Guerra M, Huang Y, Llibre-Rodriguez JJ, Salas A, et al. Socioeconomic factors and all-cause and cause-specific mortality among older people in Latin America, India, and China: a population- based cohort study. PLoS Med. 2012 Feb 28,9(2): e1001179.

6) Bonita R. Epidemiology of stroke.The Lancet.1992 Feb8;339(8789):342-4

7) Buckley BM. Healthy ageing: ageing safely. European Heart Journal Supplements. 2001 Nov 1;3(suppl N): N6-10.

8) Guven H, Çilliler AE, Koker C, Sarikaya SA, Comoglu SS. Association of Serum Calcium levels with clinical severity of acute ischemic stroke. ACTA NeurologicaBelgica. 2011 Mar 1;111(1):45.

9) Belayev L, Busto R, Zhao W, Clemens JA, Ginsberg MD. Effect of delayed albumin hemodilution on infarction volume and brain edema after transient middle cerebral artery occlusion in rats. **J Neurosurg**. 1997; *87*: 595–601

10) Belayev L, Zhao W, Pattany PM, Weaver RG, Huh PW, Lin B, Busto R, Ginsberg MD. Diffusion-weighted magnetic resonance imaging confirms marked neuroprotective efficacy of albumin therapy in focal cerebral ischemia. **Stroke**. 1998; *29*: 2587–2599

11) Belayev L, Liu Y, Zhao W, Busto R, Ginsberg MD. Human albumin therapy of acute ischemic stroke. Marked neuroprotective efficacy at moderate doses and with a broad therapeutic window. **Stroke**. 2001; *32*: 553–560.

12) Kasundra G, Sood I. Prognostic significance of serum albumin levels in acute ischemic stroke. NJIRM 2014: 5(2): plSSN: 2230 -9969

13) Hooper DC, Bagasra O, Marini JC, Zborek A, Ohnishi ST, Kean R, et al. Prevention of experimental allergic encephalomyelitis by targeting nitric oxide and peroxynitrite: implications for the treatment of multiple sclerosis. Proc Natl Acad Sci USA. (1997) 94:2528–33.

14) Hooper DC, Spitsin S, Kean RB, Champion JM, Dickson GM, Chaudhry I, et al. Uric acid, a natural scavenger of peroxynitrite, in experimental allergic encephalomyelitis and multiple sclerosis. Proc Natl Acad Sci USA. (1998) 95:675–80.

15) Aliena-Valero A, Lopez-Morales MA, Burguete MC, Castello-Ruiz M, Jover-Mengual T, Hervas D, et al. Emergent uric acid treatment is synergistic with mechanical recanalization in improving stroke outcomes in male and female rats. Neuroscience. (2018) 388:263–73.76

16) Dhanesha N, Vazquez-Rosa E, Cintron-Perez CJ, Thedens D, Kort AJ, Chuong V, et al. Treatment with uric acid reduces infarct and improves neurologic function in female mice after transient cerebral ischemia. J Stroke Cerebrovasc Dis. (2018) 27:1412–6.

17) Brown RD, Whisnant JP, Sicks JD. O'Fallon WM, Wiebers DO. Stroke incidence prevalence, and survival: secular trends in Rochester, Minnesota, through 1989. Stroke a journal of cerebral circulation. 1996 Mar;27(3):373-80.

18) Dalal PM, Malik S, Bhattacharjee M, Trivedi ND, Vairale J, Bhat P, et al. Population-based stroke survey in Mumbai, India: incidence and 28-day case fatality. Neuroepidemiology.2008 Oct 20;31 (4):254-61.

19) Sridharan SE, Unnikrishnan JP, Sukumaran S, Sylaja PN, Nayak SD, Sarma Ps, et al. Incidence, types, risk factors, and outcome of stroke in a developing country the Trivandrum stroke registry. Stroke. 2009 Apr 1;40(4):1212-8.

20) Nagaraja D, Gururaj G, Girish N, Panda S, Roy AK, Sarma GR, et al. Feasibility study of stroke surveillance: data from Bangalore, India.

21) Sethi PK. Stroke-incidence in India and management of ischaemic stroke. Neurosciences. 2002 Jul:4(3):139-41.

22) Das SK, Banerjee TK. Stroke Indian Scenario. Circulation. 2008 Dec 16;118(25):2719-24.

23) He J, Klag MJ, Wu Z, Whelton PK. Stroke in the People's Republic of China I. Geographic variations in incidence and risk factors. Stroke. 1995 Dec 1;26(12):2222-7.

24) Milionis HJ, Kalantzi KJ, Goudevenos JA, Seferiadis K, Mikhailidis DP, Elisaf MS. Serum uric acid levels and risk for acute ischaemic nonembolic stroke in elderly subjects. Journal of internal medicine. 2005 Nov 1;258(5):435-41.