

## Original Research Article

# Prognostic significance of serum cortisol and serum albumin in patients of ischemic stroke

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## ABSTRACT

**Background:** Stroke is the second most common cause of mortality worldwide and a major contributor to morbidity and chronic adult disability. To study the prognostic significance of serum cortisol and serum albumin in patients of ischemic stroke was the objective.

**Methods:** This hospital based observational cohort prospective study was undertaken in the Department of Medicine in collaboration with the Departments of Radio diagnosis and Pathology, Jawahar Lal Nehru Medical College and Hospital, AMU, Aligarh from January 2017 to November 2018. By convenience method for sampling, 102 patients who were admitted with the diagnosis of acute ischemic stroke to IPD of JNMCH, Aligarh, on clinical as well as radiological grounds were taken into study.

**Results:** Mean cortisol was  $450.84 \pm 190.35$  nmol/L. The (mean $\pm$ SD) of serum cortisol was  $258.10 \pm 77.91$  ng/ml in patients with good outcome and  $585.77 \pm 113.34$  ng/ml in patients with poor outcome. ( $p < 0.05$ ,  $r = 0.812$ ). Mean serum albumin was  $2.83 \pm 0.76$  gm/dl. The (mean $\pm$ SD) of serum albumin was  $3.47 \pm 0.64$  mg/dl in patients with good outcome and it was comparatively lower in patients with poor outcome ( $2.38 \pm 0.45$  mg/dl). ( $p < 0.01$ ,  $r = -0.659$ ).

**Conclusions:** Serum albumin, serum cortisol are prognostic indicators of functional outcome at 3 months in patients of ischemic stroke.

**Keywords:** Ischemic stroke, Prognostic significance, Serum albumin, Serum cortisol

## INTRODUCTION

Stroke is classically characterized by a neurological deficit attributed to an acute focal injury of the central nervous system (CNS) by a vascular cause, including cerebral infarction, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH), and is a major cause of disability and death worldwide.<sup>1</sup>

The term “stroke” can be used to address broadly all cerebrovascular events. Ischemic stroke is an episode of neurological dysfunction lasting for more than 24 hours caused by focal cerebral, spinal, or retinal infarction as

evident on pathological, imaging or objective clinical studies.<sup>1</sup>

The stroke incidence in developing countries like India is much higher than in western industrialised countries. Also, stroke in developing countries is reported to have a younger mean age at onset as compared to developed countries.<sup>2</sup>

Studying long-term stroke outcomes including body functioning (neurologic and neuropsychological impairments) and activity limitations and participation is essential for long-term evidence-based rehabilitation and

service planning, resource allocation, and improving health outcomes in stroke.<sup>3</sup>

Functional outcome after stroke is subject to complex interactions with multiple factors, including age, gender, ethnicity, pre-existing morbidity, stroke severity, acute interventions, and post stroke care. Other important predictors of outcome include causal type of stroke, sedentary lifestyles, alcoholism and cigarette smoking, hypertension, diabetes, dyslipidemia, coronary artery disease, atrial fibrillation, and previous history of stroke or TIA. However, the need to identify better biomarkers as predictors of outcome in acute ischemic stroke still exists. This study was conducted to study the prognostic significance of serum cortisol and serum albumin in patients of ischemic stroke.

## METHODS

This hospital based observational cohort prospective study was undertaken in the Department of Medicine in collaboration with the Departments of Radio diagnosis and Pathology, Jawahar Lal Nehru Medical College and Hospital, AMU, Aligarh, during the period lasting from January 2017 to November 2018. By convenience method for sampling, 102 patients who were admitted with the diagnosis of acute ischemic stroke to Inpatient department of JNMCH, Aligarh, on clinical as well as radiological grounds were taken into study. All the participants were informed of all possible expected benefits and risks ensuing from the study. Written consent of all patients was taken before enrolling in the study.

### Inclusion criteria

All patients age  $\geq 18$  years presenting with acute ischemic stroke.

### Exclusion criteria

Age  $< 18$  years, Hemorrhagic stroke, Previous TIA/ ischemic attack, Hyperuricemia, known patients of gout, Fever at presentation

Patients who had surgery within last 3 weeks, Patients on immunosuppressive agents or steroids. Only patients who presented with a focal or global disturbance of cerebral function within 48 hours were considered. A detailed clinical history was taken and examination findings were recorded.

Complete blood counts, RFT, Blood sugar levels, lipid profile, ESR, TSH, chest X-ray, ECG, and brain imaging (NCCT head/ MRI brain) were done in all the patients. Besides these investigations, serum albumin, serum cortisol were done. At baseline, demographic data (age and sex) and history of conventional vascular risk factors (hypertension, diabetes mellitus, atrial fibrillation,

coronary artery disease, smoking and alcohol abuse) were obtained.

### Measurement of outcome

Neurological and functional outcome was assessed by Modified Rankin Scale at day 90. We defined poor outcome as mRS 2 or more (m RS  $> 2$ ), because it was suggested that using this cutoff point makes it easier to define poor outcome.<sup>4</sup>

### Biochemical parameters used in study

The investigations were carried out in Central lab 1 of JNMCH, Aligarh and Chemical lab, department of pathology, medical central and renal lab of department of medicine, JNMCH, AMU, Aligarh.

- Complete blood counts: By automated machine (NIKOH KOHDEN Celltac hematology analyser)
- Normal value: TLC 4000-11000/microlitre
- Hb 12-18 g/dl
- PLATELET COUNT 150000-400000/microliter
- ESR: By wintrobe's method
- Normal value: male  $< 12$ mm/hr Female  $< 20$ mm/hr.

### Serum cortisol

Using VIDAS (Vitek Immuno Diagnostic Assay System). The technology used, which is adaptable to a wide range of assays, combines the EIA method with a final fluorescence reading: this technology is known as ELFA (Enzyme Linked Fluorescent Assay)

The enzyme used in the VIDAS range is alkaline phosphatase. The substrate is 4-methyl umbelliferyl phosphate (4-MUP) hydrolyzed into 4-methyl umbelliferone. Umbelliferone fluoresces at 450 nm after excitation at 370 nm. Each VIDAS assay kit contains the reagents required to run a specific assay. Kit contents vary for each assay, but generally a kit contains:

- Single or dual reagent strips,
- SPR®s (Solid Phase)
- control(s),
- the necessary standard(s),
- a diluent (as required),
- a package insert.

The SPR is the solid phase base for the immunological reaction. Its interior walls are coated with antibodies or antigens that capture a target analyte. The SPR is used to pipette samples and reagents and eliminates cross-contamination between reagent and instrument. The VIDAS single reagent strip contains ten wells. The sample is placed in the first well. The other eight wells contain the necessary reagents (conjugate, diluent, wash buffer). The last well is the optical cuvette in which the fluorescence of the substrate is measured. A small tab

ensures that the strip is correctly positioned in its channel guides.

The sample (serum or pre-treated) must be placed in the sample well on the reagent strip as indicated in the appropriate assay package insert. The sample volume required varies according to the test and is given in the assay package insert. The reagent strip slides horizontally to position the required well under the SPR. The SPR moves up and down so it can perforate the foil seal and pipette the required reagents.

**Dynamic reactions:** At each stage, the reagent is cycled in and out of the SPR several times. This increases reaction kinetics and reduces incubation times. The intensity of the final reaction is measured in the optical cuvette on the reagent strip.

**Detection of haptens (hormones):** The interior wall of the SPR is coated with a limited quantity of antibody. The hapten to be detected competes with the labeled hapten. The fluorescence level measured is inversely proportional to the quantity of haptens present in the sample.

**Specimen collection:** Blood samples of patients were obtained at 6:00 AM in the next morning of the day of the admission in plain vacutainers from heparinised butterfly catheters inserted the previous night.

**Normal value:** The normal range of morning serum cortisol concentration in our hospital laboratory was 55-288ng/ml (150 - 790nmol/L) which is broadly similar to other laboratories.

#### Serum albumin

Quantitative estimation of serum albumin was done using BeneSphera semiauto-analyser.

Principle involves, under acidic conditions albumin present in the serum sample binds to bromocresol green to form a green coloured albumin-BCG complex, which is photometrically measured at 628 nm. Intensity of the colour formed is directly proportional to albumin concentration in the sample.

- Reagent 1: BCG reagent
- Succinate buffer, pH 4.2
- Bromocresol green
- Reagent 2: Calibrator
- Human albumin

Serum or heparinised plasma can be used as specimen. Samples should be preferably used on the same day. May be preserved upto one week if stored at 2-8 °C. Samples must be brought to room temperature prior to use.

Normal value: 3.2- 5.5 gm/dl.

#### Statistical analysis

Statistical analysis was done using SPSS version 20. Results were expressed as mean±standard deviation and percentage. Univariate analysis was performed using Independent t test for continuous variables and Chi Square test for categorical variables. Spearman's correlation coefficient (r) was used to show correlation between variables.

#### RESULTS

Mean age of the patients was 64.69±8.735 years, minimum age was 43 years and maximum age was 82 years. All patients of ischemic stroke was divided into various age groups and percentage of patients in various age groups was found. Maximum patients were in age group 60-69 years (Table 1).

**Table 1: Age distribution of study group (in years).**

Age (in years)	N (no. of patients)
≤50	6 (6%)
50 - 59	24(23.5%)
60 - 69	38(37%)
70 - 79	30(29.5%)
≥80	4(4%)

Out of 102 patients, 60 (59%) were males and 42 (41%) were females. Males outnumbered females in all age groups except in age ≤50 years, where number of females was greater. In age group ≥80 years, the number of male and female patients was equal.

Out of 102 patients, 40 (39%) were smokers, amongst which 38 (95%) were males and 2 (5%) were females. 22 out of 102 patients of acute ischemic stroke were alcoholic, and all were males.

In this study, 58 (57%) patients were known cases of hypertension. Other than those who were known cases of hypertension, 10 patients presented with BP ≥140/90 for the first time. Total number of patients who presented with raised BP was 68. The mean Systolic BP was 149.84±26.43 mm Hg. The mean Diastolic BP was 99.80±19.59mm Hg.

Out of 102 patients, 26 (25%) patients were found to be known cases of diabetes mellitus. The mean BS (f) levels were 175.90±97.78 mg/dl and the mean HbA1c levels were 6.55±1.62%. Out of 102 patients, 20 patients were known cases of coronary artery disease, 18 out of 102 patients presented with atrial fibrillation.

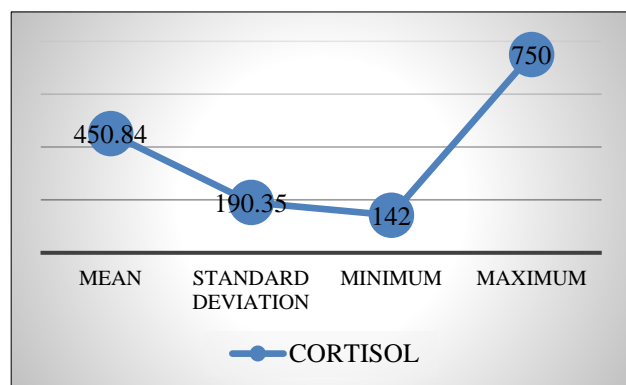
Dyslipidemia was diagnosed in any patient with serum Triglycerides TG>150, LDL>130 and HDL<40 in males and <50 in females.

Mean HDL was  $47.82 \pm 7.46$  mg/dl. Minimum HDL was 35 mg/dl and maximum HDL was 62 mg/dl. Mean LDL was  $110.84 \pm 19.9$  mg/dl. Minimum LDL was 81 mg/dl and maximum LDL was 152 mg/dl. Mean TG was  $147.92 \pm 13.93$  mg/dl. Minimum TG was 119 mg/dl and maximum TG was 178 mg/dl. Mean TC was  $199 \pm 24.1$  mg/dl. Minimum TC was 170 mg/dl and maximum TC was 290 mg/dl (Table 2).

**Table 2: Mean HDL, LDL, TG, TC in study group.**

	Mean	Standard deviation	Minimum	Maximum
HDL	47.82	7.46	35	62
LDL	110.84	19.9	81	152
TG	147.92	13.93	119	178
TC	199	24.1	170	290

Mean cortisol was  $450.84 \pm 190.35$  nmol/L. Minimum cortisol was 142 nmol/L and maximum cortisol was 750 nmol/L (Figure 1).



**Figure 1: Mean cortisol in study group.**

The (mean $\pm$ SD) of serum cortisol was  $258.10 \pm 77.91$  nmol/l in patients with good outcome and  $585.77 \pm 113.34$  nmol/l in patients with poor outcome. The difference between the 2 groups was statistically significant ( $p < 0.05$ ) (Table 3).

**Table 3: Difference in mean cortisol in the 2 outcome groups.**

	Serum cortisol (mean $\pm$ SD)	p value
m RS $\leq 2$	$258.10 \pm 77.91$	<0.05
m RS $> 2$	$585.77 \pm 113.34$	

There was a positive correlation between serum cortisol and functional outcome according to m RS. As serum cortisol increased, m RS grade also increased with a correlation coefficient of 0.812 and the result was statistically significant ( $p < 0.01$ ).

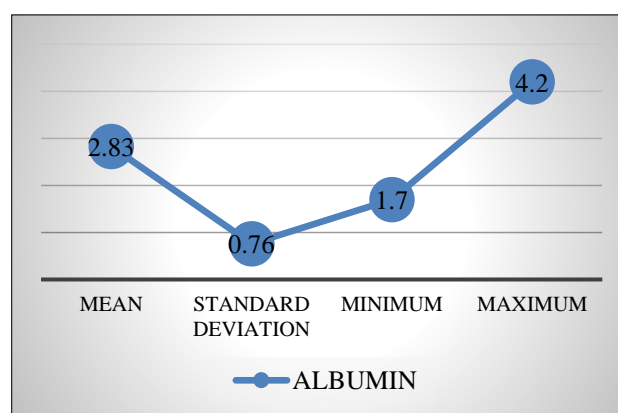
Mean serum albumin was  $2.83 \pm 0.76$  gm/dl. Minimum albumin was 1.7 gm/dl and maximum albumin was 4.2 gm/dl. The (mean $\pm$ SD) of serum albumin was

$3.47 \pm 0.64$  mg/dl in patients with good outcome and it was comparatively lower in patients with poor outcome ( $2.38 \pm 0.45$  mg/dl) and this difference was statistically significant ( $p < 0.01$ ).

there was a negative correlation between serum albumin and functional outcome according to m RS. As serum albumin increased, m RS grade decreased with a correlation coefficient of -0.659 and the result was statistically significant ( $p < 0.01$ ) (Table 4, Figure 2).

**Table 4: Difference in mean cortisol in the 2 outcome groups.**

	Serum albumin (mean $\pm$ SD)	p value
m RS $\leq 2$	$3.47 \pm 0.64$	<0.01
m RS $> 2$	$2.38 \pm 0.45$	



**Figure 2: Awareness of disease caused by dog bite.**

## DISCUSSION

the (mean $\pm$ SD) of serum cortisol was  $258.10 \pm 77.91$  nmol/l in patients with good outcome and  $585.77 \pm 113.34$  nmol/l in patients with poor outcome. The difference between the 2 groups was statistically significant ( $p < 0.05$ ). On regression analysis, serum cortisol was found to be an independent predictor of poor functional outcome. Zi and Shuai et al, conducted a study on 226 patients and found that the mean cortisol was 441 nmol/L in patients with good outcome and 643 nmol/L in patients with poor outcome and the difference was statistically significant.<sup>5</sup> Marklund et al, conducted a study on 88 patients and found that patients with severe functional impairment had higher cortisol levels ( $543 \pm 330$  vs.  $387 \pm 253$  nmol/L) ( $p < 0.05$ ) when compared with patients with mild symptoms.<sup>6</sup> Christensen et al, studies 172 patients and found mean serum cortisol in deteriorating patients was 649 nmol/l (95% CI 511-826 nmol/l) and in not deteriorating patients, mean s-cortisol was 525 nmol/l (95% CI 483-571 nmol/l), which was significantly lower.<sup>7</sup> These results agree with the results obtained by most authors, who have shown that hypercortisolemia is related to a greater neurological deficit. Neidert et al, studied 281 patients and reported that cortisol was an independent prognostic marker of



poor functional outcome and death within 90 days and at 1 year.<sup>8</sup> Hence, the main finding in this study is that cortisol is an independent prognostic marker of functional outcome and death in patients with ischaemic stroke. Acute ischaemic stroke acts as a stressor and thus stimulates the HPA axis resulting in increased glucocorticoid levels. The higher cortisol levels observed in patients with worse functional outcome or subsequent death reflect a higher degree of stress. Hypercortisolism has been suggested to potentiate ischaemic neuronal injury. In addition, patients with stroke and high cortisol levels have been shown to be more prone to adverse cardiac events (e.g. arrhythmias or myofibrillar degeneration), which might lead to higher mortality rates. Another major cause of a bad prognosis after stroke is the development of infectious disease which is related to an immune dysregulation resulting from neuroendocrine disturbance after stroke. A systematic review of 48 studies conducted by Barugh et al, found that elevated cortisol levels were associated with higher dependency, length of hospital stay, depression, delirium, and mortality.<sup>9</sup> Whether other factors like initial severity of stroke, increasing age, and other co morbidities constitute part of the stressor response which leads to hypercortisolemia remains to be elucidated. Study concludes that hypercortisolemia is associated with poor functional outcome in patients of acute ischemic stroke.

The (mean±SD) of serum albumin was 3.47±0.64mg/dl in patients with good outcome and it was comparatively lower in patients with poor outcome (2.38±0.45mg/dl) and this difference was statistically significant ( $p < 0.01$ ). Famakin et al, studied 1477 patients and found the mean serum albumin levels were significantly higher (3.71±0.05) in patients with good outcome as compared to those with poor outcome (3.39±0.10).<sup>10</sup> Idicula et al, conducted a study on 444 patients and showed that high albumin levels were an independent predictor of good functional outcome and lower mortality. Dziedzic et al, recruited 818 subjects in whom the mean albumin levels were 3.41 g/dl in patients with poor outcome and 3.68 g/dl in patients with good outcome ( $p < 0.01$ ).<sup>11</sup> Abu bakar et al, reported mean serum albumin levels of 2.08 g/dl in patients with poor outcome and 3.03 g/dl in patients with good outcome.<sup>12</sup> Similar findings were recorded by Sandeep et al, along with a negative correlation between serum albumin and mRS. A study conducted by Zhang et al, concluded that lower serum albumin levels increased the risk of recurrence in patients with acute ischemic stroke.<sup>13,14</sup> Babu et al, studied 560 ischemic stroke patients and recorded that mean serum albumin levels were significantly lower (2.3g/dl) in patients with poor outcome as compared to those having good outcome (3.8g/dl).<sup>15</sup> Chakraborty et al, also reached the same results.<sup>16</sup> Moderate to high dose albumin therapy has been shown to be neuroprotective in animal models with focal as well as global cerebral ischemia. Albumin exerts its neuroprotective effect by virtue of its antioxidant properties, induces hemodilution, maintains microvascular stability and prevents post ischemic

thrombosis. The ALIAS (Albumin in Acute Ischemic Stroke) part 1 and 2 trials evaluated whether 25% human serum albumin improves clinical outcomes after acute ischemic stroke but did not yield satisfactory results and had to be terminated prematurely. The National Institutes of Health has funded a large randomized multicenter placebo-controlled efficacy trial, the ALIAS Phase III Trial that is still ongoing to test the benefits of albumin therapy in humans. We thus conclude that higher albumin levels are neuroprotective in ischemic stroke, but further studies are required to confirm whether moderate to high dose albumin could be used as a therapeutic intervention in patients of ischemic stroke.

## CONCLUSION

Serum albumin, serum cortisol are prognostic indicators of functional outcome at 3 months in patients of ischemic stroke. Serum cortisol level was found to have a significant positive correlation with worsening functional outcome. Serum albumin was to have a neuroprotective effect. Increased levels of albumin was associated with better functional outcome.

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*Ethical approval: The study was approved by the Institutional Ethics Committee*

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