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# Association of serum albumin and serum high-sensitivity C-reactive protein levels with acute ischemic stroke severity.

**Mohit Choudhary** [1] - A,B,C,H,I,K,L,M,N,O. ORCID www.orcid.org/0009-0002-3310-2583
**Shailesh Kumar** [1] - A,B,C,E,H,J,K,L,M,N,O. ORCID www.orcid.org/0009-0002-9216-0572
**Rupesh Yadav** [2] - A,B,C,F,G,H,I,K,L,M,N,O. ORCID www.orcid.org/0000-0002-6379-6101

[1] *Department of Medicine, Atal Bihari Vajpayee Institute of Medical Sciences and Dr RML Hospital, New Delhi, India*
[2] *Department of Anesthesiology, Atal Bihari Vajpayee Institute of Medical Sciences and Dr RML Hospital, New Delhi, India*

**Address for correspondence:**
Rupesh Yadav, MD, Prof. *Department of Anesthesiology, Atal Bihari Vajpayee Institute of Medical Sciences and Dr RML Hospital, New Delhi, India -110001; e-mail: drrupesh.yadav98@gmail.com; tel: +91 9460720444*

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## ABSTRACT

**INTRODUCTION:** Acute ischemic stroke, a type of cerebrovascular disease, is one of the most common causes of mortality and morbidity around the world. Albumin-induced neuroprotection can be attributed to properties such as reversal of thrombosis, improvement in microvascular blood perfusion, reduction in brain swelling. The increase in high-sensitivity C-reactive protein levels (hs-CRP) after an ischemic stroke suggests a systemic inflammatory response and reveals the degree of brain damage. The purpose of the study was to assess the association of serum albumin and serum high-sensitivity C-reactive protein levels with acute ischemic stroke severity.

**MATERIALS AND METHODS:** Prospective cross-sectional observational study involving 90 patients admitted to the emergency department that met the inclusion and exclusion criteria. At the time of admission blood samples were taken for measurement of serum albumin level (normal albumin level ≥3.5 g/dl and hypoalbuminemia <3.5 g/dl), hs-CRP (low risk <1.0 mg/L; average risk 1.0-3.0 mg/L; high risk >3.0 mg/L). The severity of stroke was assessed using the National Institutes of health stroke scale (NIHSS) score.

**RESULTS:** 60% of the cases had a normal albumin level, while 40% of the cases had hypoalbuminemia. 82.22% of the cases had a high risk level of hs-CRP, while only 1.11% of the cases had a low risk level of hs-CRP. The association of hypoalbuminemia and hs-CRP with stroke severity on the NIHSS score measured at the time of admission. It was observed that there was a statistically significant correlation between hypoalbuminemia with stroke severity (p-value <0.002) and between hs-CRP levels with stroke severity (p-value <0.013).

**CONCLUSIONS:** The study concluded that the association between low serum albumin level and elevated hs-CRP levels with the severity of acute ischemic stroke was statistically significant.

**KEY WORDS**: Acute ischemic stroke, albumin, C-reactive protein, mortality.

## INTRODUCTION

Acute ischemic stroke, a type of cerebrovascular disease, is one of the most common causes of mortality and morbidity around the world. Stroke is defined as a sudden-onset focal neurological deficit lasting more than 24 hours and can be attributed to a defined vascular territory. Broadly, stroke is of two types: Ischemic and hemorrhagic. Ischemic stroke is mainly caused by thrombosis of cerebral vessels or due to embolus from other vessels thereby causing infarction and death of the brain tissue. Hemorrhagic stroke is caused by bleeding into and around the brain parenchyma. The clinical manifestations of stroke exhibit significant variability due to the complex anatomy of the brain and its vasculature. When blood flow is quickly restored, brain tissue has the potential for full recovery and the patient's symptoms are only transient. This condition is referred to as a transient ischemic attack (TIA). The definition of TIA stipulates that all neurological signs and symptoms must resolve within 24 hours without evidence of brain infarction on imaging [1,2].

Several etiopathological factors are involved in the pathogenesis of stroke. Albumin, a major plasma protein, consists of a single polypeptide chain of 585 amino acids with a molecular mass of approximately 67 kDa. It is synthesised primarily in a liver at the rate of 10-15 g/day. The synthesis of albumin is regulated at both the transcriptional and posttranscriptional levels. Several conditions, including trauma, sepsis, hepatic diseases, diabetes, and fasting, can influence the rate of albumin transcription. Albumin homeostasis is preserved through balanced catabolism that takes place in all tissues. However, a significant portion of albumin (40-60%) is primarily in the muscle and skin [3].

Albumin has some other functions in addition to the fluid and electrolyte balance. It also has immunomodulatory and neuroprotective functions. The proposed mechanism includes binding to free fatty acids, inhibition of free oxygen radicle production, and support of endothelial functions. Albumin-induced neuroprotection can be attributed to properties such as reversal of thrombosis, improvement in microvascular blood perfusion, reduction of brain swelling, and replenishment of polyunsaturated fatty acids (PUFA) in the brain [4,5].

Hypoalbuminemia in individuals with chronic diseases, such as chronic renal failure, arises from the synergistic impact of inflammation and insufficient protein and caloric intake. Both inflammation and malnutrition contribute to the concentration of albumin by reducing its synthesis rate. Solely, inflammation is associated with an elevated fractional catabolic rate (FCR), and in severe cases, there is a greater transfer of albumin out of the vascular compartment. This initiates a detrimental cascade, where inflammation induces anorexia, hampers the effective utilisation of dietary protein and energy intake, and intensifies the catabolism of the crucial somatic protein, albumin. In addition, inflammation is correlated with vascular disease and is likely to induce injury to the vascular endothelium, resulting in hypoalbuminemia as a distinct manifestation of the inflammatory process. Hypoalbuminemia also worsens the prognosis by decreasing cellular immunity and increasing the risk of infection and pressure sores in stroke patients.

Stroke patients with hypoalbuminemia at admission had an increased risk of infectious complications, death, and poor function outcome [6,7]. C-reactive protein (CRP) is an acute-phase protein produced by hepatocytes in a soluble form. CRP plays multiple roles in the human body, participating in immunomodulation and regulating the immune system and inflammation through functions such as complement pathway activation, chemotaxis, and opsonisation. The levels of serum high-sensitivity C-reactive protein (hs-CRP) depend on various characteristics of the individual. A variety of demographic factors, as well as socioeconomic status and physiological variables, such as birthweight, blood pressure, physical activity, and alcohol consumption, have been associated with CRP concentration. Vascular risk factor exposure, such as smoking, arterial hypertension, diabetes mellitus, hypercholesterolemia, and atrial fibrillation, as well as drug use, such as oral contraceptive use, postmenopausal hormone replacement therapy, and cocaine exposure, have also been connected to CRP concentration in serum [8,9].

There is still uncertainty about the methods by which CRP may be linked to stroke. Cerebral atherosclerosis is the most important underlying factor in most acute ischemic stroke cases. CRP might be a sign of inflammation that coexists with atherosclerosis but is not the cause. There is a chance that the degree of brain tissue damage and the elevated CRP are closely correlated. However, increasing data points to the possibility that CRP contributes to atherosclerosis directly or indirectly or acts as an additional risk factor. Increased hs-CRP levels after an ischemic stroke are indicative of a systemic inflammatory response and are related to the severity of the stroke. hs-CRP may also serve as a potential indicator of future vascular events and has a prognostic value for stroke. The increase in hs-CRP level after an ischemic stroke suggests a systemic inflammatory response and reveals the degree of brain damage and concomitant infections, and thus is related to the severity of stroke. Furthermore, due to its link to generalized atherosclerosis, hs-CRP may serve as a potential indicator of how future vascular events will develop [10].

Whether hypoalbuminemia and high HRP affect disease severity and clinical outcomes has been the subject of much debate. Despite the increased progress in the medical sciences, patients with acute ischemic stroke are still at high risk for mortality and morbidity. Some of these risk factors are modifiable and their identification and management can improve the outcome. The purpose of the study was to assess the association of serum albumin and serum high-sensitivity C-reactive protein levels with acute ischemic stroke severity.

## MATERIALS AND METHODS

The prospective cross-sectional observational study was conducted after approval of the institutional ethics committee (IEC/ABVIMS/RMLH/947). Inclusion criteria consisted of patients in the age group 20-70 years of either gender, diagnosed with acute ischemic stroke for the first time and admitted to the emergency medicine department within 24 hours from onset of symptoms were included in the study. Informed written consent was obtained from all conscious orientated patients and informed written consent was obtained from the relative of the patient if patients who had a limited state of consciousness due to

stroke or unconsciousness. Exclusion criteria included refusal of consent, diagnosed with chronic liver disease and chronic kidney disease, diagnosed with chronic inflammatory diseases such as tuberculosis, systemic lupus erythematosus, rheumatoid arthritis, history of recent myocardial ischemia, history of any recent infection, fever, and dehydration, patients taking steroids, antiplatelet agents, and oral contraceptive pills.

**Table1.** National institutes of health stroke scale (NIHSS).

| | |
|---|---|
| **1a. Level of consciousness** | 0 = Alert keenly responsive<br>1 = Not Alert but arousable by minor stimulation<br>2 = Not Alert; requires repeat stimulation<br>3 = Unresponsive or responds only with reflex |
| **1b. LOC Questions**<br>*What is your age?*<br>*What is the month ?* | 0 = Answers both questions correctly<br>1 = Answers one question correctly<br>2 = Answers neither questions correctly |
| **1c. LOC Commands**<br>*Open and close eyes your eye*<br>*Grip & release your hand* | 0 = Performs both tasks correctly<br>1 = Performs one task correctly<br>2 = Performs neither task correctly |
| **2. Best Gaze.** | 0 = Normal<br>1 = Partial Gaze Palsy<br>2 = Forced deviation |
| **3. Visual** | 0 = No visual loss<br>1 = Partial hemianopia<br>2 = Complete hemianopia<br>3 = Bilateral hemianopia |
| **4. Facial Palsy** | 0 = Normal symmetrical movement<br>1 = Minor paralysis<br>2 = Partial paralysis<br>3 = Complete paralysis of one or both sides |
| **5. Motor Arm**<br>*Left arm*<br>*Right arm* | 0 = No drift<br>1 = Drift<br>2 = Some effort against gravity<br>3 = No effort against gravity<br>4 = No movement |
| **6. Motor leg**<br>*Left leg*<br>*Right leg* | 0 = No drift<br>1 = Drift<br>2 = Some effort against gravity<br>3 = No effort against gravity<br>4 = No movement |
| **7.Limb Ataxia** | 0 = Absent<br>1 = Present in one limb<br>2 = Present in two limbs |
| **8. Sensory** | 0 = Normal, no sensory loss<br>1 = Mild/moderate sensory loss<br>2 = Severe/total sensory loss |
| **9.Best Language** | 0 = No aphasia, normal<br>1 = Mild / moderate aphasia<br>2 = Severe aphasia<br>3 = Mute global aphasia |
| **10.Dysarthria** | 0 = Normal<br>1 = Mild / Moderate dysarthria<br>2 = Severe dysarthria |
| **11.Extinction & Inattention** | 0 = No abnormality<br>1 = Visual, tactile, auditory, spatial or personal inattention<br>2 = Profound hemi-inattention or extinction |
| Score = 0-42 | |

The sample size was calculated using a study in which Haq EU et al. [11] observed that hypoalbuminemia was found in 30 patients from 100 patients with acute stroke (30%). Taking this value as a reference, the minimum required sample size with 10% margin of error and 5% level of significance, 80% power is 81 patients. So the total sample size taken is 90.

In this study, patients with acute ischemic stroke who were admitted to the emergency medicine department that met the inclusion and exclusion criteria. Patients involved in this study were informed about the study and consent was taken and then a detailed history including age, sex, any comorbidities, clinical examination and body mass index (BMI). Non-contrast computed tomography (NCCT) head done within 24 hours of onset of symptoms. Blood samples were taken at the time of admission under aseptic precaution from peripheral veins for the measurement of serum albumin level (normal albumin level ≥3.5 g/dl and Hypoalbuminemia <3.5 g/dl), hs-CRP level (low risk <1.0 mg/L, average risk 1.0-3.0 mg/L, high risk >3.0 mg/L). The severity of stroke was assessed using the National Institutes of health stroke scale (NIHSS) score (Table 1; Table 2).

In statistical analysis categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested using the Kolmogorov-Smirnov test. If normality was rejected, then nonparametric test was used. Quantitative variables were compared using the unpaired t-test / Mann-Whitney test (when the data sets were not normally distributed) between the two groups. Qualitative variables were compared using the Chi square test / Fisher's exact test. The Pearson correlation coefficient/Spearman rank correlation coefficient was used to find the correlation coefficient of quantitative parameters with each other. A p value of <0.05 was considered statistically significant. Data were entered in MS EXCEL spreadsheet and analysis was performed using Statistical Package for Social Sciences (SPSS) version 25.0.

**Table 2.** National Institutes of health stroke scale (NIHSS) score.

| NIHSS Score | Stroke Severity |
|---|---|
| 0 | No Stroke Symptoms |
| 1-4 | Mild Stroke |
| 5-15 | Moderate Stroke |
| 16-20 | Moderate to Severe Stroke |
| 21-42 | Severe Stroke |

## RESULTS

In total, 90 patients with acute ischemic stroke were included in the study. It was observed that the mean age of the study group was 58.10 years. The youngest study participant was 22 years and the eldest study participant 70 years old. 51 (56.66%) patients fell in the age group of 61-70 years, while only 3 (3.33%) patients belonged to the age group 20-30 years. 56 (62.2%) male patients were observed and 34

(37.77) female patients in this study. It was observed that more than two-thirds (69%) of the cases in the study group had a BMI of more than 23 kg/m$^2$. The mean BMI of the study group was 25.21 kg/m$^2$. Four cases had a BMI greater than 30 kg/m$^2$. Almost two-thirds of the study group (62.2%) had a history of hypertension. More than one-third of the cases had diabetes mellitus, while 20 cases reported having a history of smoking (Table 3).

**Table 3.** Demographic details.

| **Age of the patient** | **Number of cases** (N = 90) |
|---|---|
| 20 - 30 years | 3 (3.33%) |
| 31 - 40 years | 4 (4.44%) |
| 41 - 50 years | 15 (16.66%) |
| 51 - 60 years | 17 (18.88%) |
| 61 - 70 years | 51 (56.66%) |
| Mean age of the patient in years | 58.10 |
| **Gender of the patient** | |
| Male | 56 (62.22%) |
| Female | 34 (37.77%) |
| **Body mass index** | |
| Underweight (Less than 18.5 kg/m$^2$) | 0 (0%) |
| Normal (18.5 – 22.9 kg/m$^2$) | 28 (31.11%) |
| Overweight (23 – 24.9 kg/m$^2$) | 9 (10%) |
| Obese I (25 – 29.9 kg/m$^2$) | 49 (54.44%) |
| Obese II (30 kg/m$^2$ or more) | 4 (4.44%) |
| Mean body mass index in kg/m$^2$ | 25.21 |
| **Comorbidity** | |
| Hypertension | 56 (62.22%) |
| Diabetes mellitus | 31 (34.44%) |
| Chronic smoker | 20 (22.22%) |

Blood samples were taken at the time of admission to measure the serum albumin level and hs-CRP level. The mean serum albumin (g/dL) value was 3.65 g/dl (SD = 0.66) with a range of 1.9-4.9 g/dl. The mean levels of hs-CRP were 10.65 mg/L with an SD of 8.71 mg/L and a range that varied between 0.87 and 34.77 mg/L. The distribution of cases according to serum albumin level at the time of admission. Hypoalbuminemia is defined as a serum albumin value less than 3.5 gm/dl. 60% of the cases had a normal albumin level, while 40% of the cases had hypoalbuminemia. The distribution of cases based on hs-CRP levels at admission reveals that 82.22% fell into the high-risk category (>3.0 mg/L), 16.66% into the average-risk category (1.0-3.0 mg/L), and only 1.11% into the low-risk category (<1.0 mg/L) (Table 4).

**Table 4.** Distribution of cases according to serum albumin levels and hs-CRP levels.

| **Albumin levels** | **Number of cases** (N = 90) |
|---|---|
| Hypoalbuminemia (<3.5 gm/dl) | 36 (40%) |
| Normal Albumin levels (≥3.5 gm/dl) | 54 (60%) |
| **hs-CRP levels** | |
| Low risk (<1.0 mg/L) | 1 (1.11%) |
| Average risk (1.0-3.0 mg/L)) | 15 (16.66%) |
| High risk (> 3.0 mg/L) | 74 (82.22%) |

**The distribution of cases according to the National Institutes of health stroke scale (NIHSS) score at the time of hospital admission**.

The mean NIHSS score for the study group was 10.74. 41.11% of the cases had a mild NIHSS score, 33.33% of the cases had a moderate NIHSS. 15.55% of the cases had severe NIHSS. (Table 5)

**Table 5.** Distribution of cases according to the NIHSS score.

| **NIHSS score** | **Number of cases** (N = 90) |
|---|---|
| Mild (1-4) | 37 (41.11%) |
| Moderate (5-15) | 30 (33.33%) |
| Moderate-severe (16-20) | 9 (10%) |
| Severe (21-42) | 14 (15.55%) |
| Mean NIHSS score (SD) | 10.74 (9.34) |

**The association of hypoalbuminemia with stroke severity in the NIHSS score measured at the time of admission.**

It was observed that there was a statistically significant correlation between hypoalbuminemia and stroke severity (p value <0.002) (Table 6). The association between hs-CRP levels with stroke severity on the NIHSS score at the time of admission. It was observed that there was a statistically significant correlation between hs-CRP levels and stroke severity (p-value <0.013) (Table 7).

**Table 6.** Association of hypoalbuminemia with stroke severity on the NIHSS score.

| **Stroke severity on NIHSS score** | **Hypoalbuminemia** | | **p-value** |
|---|---|---|---|
| | **Present** | **Absent** | |
| Mild | 5 (13.88%) | 32 (59.25%) | <0.002* |
| Moderate | 15 (41.66%) | 15 (27.77%) | |
| Moderate-severe | 5 (13.88%) | 4 (7.4%) | |
| Severe | 11 (30.55%) | 3 (5.55%) | |

**Chi square test*

**Table 7.** Association of hs-CRP with stroke severity on the NIHSS score.

| Stroke severity on NIHSS score | hs-CRP | | p-value |
|---|---|---|---|
| | Low/Average risk | High risk | |
| Mild | 12 (75%) | 25 (33.78%) | 0.013* |
| Moderate | 4 (25%) | 26 (35.13%) | |
| Moderate-severe | 0 (0%) | 9 (12.16%) | |
| Severe | 0 (0%) | 14 (18.91%) | |

**Chi square test*

## DISCUSSION

The mean age of patients with acute ischemic stroke in our study is 58.10 years. This is correlated well with the study by Jones SP et al. [1] The mean age of stroke patients was found to be 62.2 years. Among the identified risk factors, hypertension emerged as the predominant comorbidity, with an incidence rate of 62.2%. Diabetes mellitus had an incidence of 34.4% and 22.2% were identified as chronic smokers. Similar findings were reported in the study conducted by Alam MN et al. [12], where 42% of patients had hypertension, 22% were smokers and 22% were diabetic. In this study, the frequency of hypoalbuminemia in patients with acute ischemic stroke was found to be 40% and the mean serum albumin (g/dL) was 3.65 g/dl. A similar result was 50% found in a study by Elbaih AH et al [13]. Mean albumin levels were comparable to previous studies, 3.55 g/dl in the study by Dziedzic et al [14]. The serum albumin level is influenced by ethnic and regional factors as well as determined by underlying malnourishment and disease processes.

In this study, the correlation between hypoalbuminemia and stroke severity (measured by the NIHSS score) was statistically significant ($p < 0.002$). Most studies favour a strong correlation between hypoalbuminemia and stroke severity, studies by Chakraborty B et al. [15] ($r2 = -0.86$; $p = 0.001$), Kasundra G et al. study [16] ($p < 0.001$), Elbaih AH et al. study [13] study ($p = 0.001$) showed statistically significant association. Hypoalbuminemia in patients with acute ischemic stroke could also be related to unidentified underlying chronic inflammatory diseases, which will also have detrimental effects on stroke severity and recovery. Furthermore, the correlation between albumin and protein energy malnutrition can exert a significant influence on the severity of stroke and its clinical outcomes [17]. A statistically significant ($p < 0.013$) was found between serum high-sensitivity CRP levels and stroke severity, as determined by the NIHSS score. Mean hs-CRP levels were 10.65 mg/L. The mean levels of hs-CRP were found similar, 9.69 ± 7.072 mg/L in the Mohan G et al [18] study, 8.04 mg/L (IQR 2.56, 16.23) in the Pu Y et al [19] study. A proportion of 82.2% of the patients fell into the high-risk hs-CRP group (>3 mg/L), a finding that aligns with the study by Alam MN et al [12]. There is also a probability that an increase in C-reactive protein (CRP) levels is a direct response to the extent of cerebral tissue injury, thus establishing a link to the severity of the stroke. Serum CRP levels at admission also influence prognosis, functional outcome, and mortality [19].

The limitations of the study include its small sample size and short duration, along with the recruitment exclusively from a single tertiary care hospital. The results would be more precise and generalised if the participants were recruited from multiple tertiary care hospitals. Studies with a larger sample size and a long duration of the study period are required to produce stronger findings. Furthermore, rather than relying solely on single measurements of serum albumin and serum high-sensitivity C-reactive protein levels at admission, exploring serial values and trends can offer deeper insights into associations and prognostic implications.

## CONCLUSIONS

The study concluded that the association between low serum albumin level and elevated hs-CRP levels with the severity of acute ischemic stroke was statistically significant. Implementing these findings into clinical practice has the potential to contribute to risk stratification and guide treatment decisions for patients with acute ischemic stroke.

### SUPPLEMENTARY INFORMATION

***Funding:*** *No fund was received related to this study.*
***Institutional Review Statement:*** *The study was conducted according to the guidelines of the Declaration of Helsinki.*
***Informed Consent Statement:*** *Not applicable*
***Data Availability Statement:*** *The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.*
***Conflicts of Interest:*** *The authors declare no conflicts of interest.*
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