## Original Research Article

# Correlation of serum calcium levels with infarct size and severity of stroke using National Institute of Health Stroke Scale in patients with acute ischemic stroke

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### ABSTRACT

**Background:** Normal cerebral membrane integration is important to maintain the cellular calcium homeostasis. Recent studies have suggested that elevated serum calcium levels at presentation correlates well with the infarct size and severity of stroke.

**Methods:** A total of 73 patients with acute ischemic stroke satisfying inclusion and exclusion criteria were included in the study from November 1st 2017 to April 30th 2019 at a tertiary care centre in Kolar, Karnataka. Serum calcium (total, ionized and albumin corrected calcium) levels were measured at the time of presentation and compared with the infarct size and severity of stroke using NIHSS score (National Institute of Health Stroke Scale).

**Results:** The levels of total calcium, albumin-corrected calcium, and ionized calcium were 9.13±0.89 mg/dL (range: 8.24-10.02), 9.56±0.82 mg/dL (range: 8.74-10.38), and 4.79±0.47 mg/dL (range: 4.3-5.2), respectively. Mean stroke size as measured on the CT scan was 47.38±17.7 cm (range: 21-88). Analysis revealed significant negative correlation between calcium levels (total, corrected, and ionized) and infarct size and severity of stroke.

**Conclusions:** In this study, it was found that there was a statistically significant negative correlation between total, ionized and corrected calcium with the infarct size in patients with ischemic stroke and also the total calcium at presentation and severity of stroke calculated using NIHSS score.

**Keywords:** Acute ischemic stroke, Infarct size, NIHSS, Total calcium

## INTRODUCTION

Stroke is the 3rd most leading cause of death worldwide following coronary heart disease and cancer, especially ischemic stroke.[1] It is more often disabling than fatal and is a major cause of long-term disability among patients and has enormous emotional and socio-economic consequences. Stroke is defined as "rapidly developing clinical signs or symptoms of focal (at times global) disturbance of cerebral function with symptoms lasting more than one-day (I.e., 24 hours) or leading to death with no apparent cause other than that of vascular origin".[2] More than four-fifth of all strokes are occurring in developing countries .[3] The average incidence rate of stroke per annum in India currently is 145 per 100,000 populations, which are higher compared to western nations.[4]

Rapid socio-economic changes are leading to change in people's lifestyles, work-connected stress, altered food habits and the risk of developing hypertension, diabetes, and hyperlipidemia these risk factors along with increased lifespan has resulted in an increase in the incidence of stroke.

Normal Cerebral Blood Flow (CBF) in man is usually in the range of 45-50 ml/min/100 g with a mean arterial pressure of 60 and 130 mmHg.[5] When this blood flow falls below 20-30 ml/min/100 g, severe disturbances in brain metabolism begin to occur, such as water and electrolyte shifts and regional areas of the cerebral cortex experience decreased perfusion. At blood flow rate below 10 ml/min/100g, there will be sudden depolarization of the neurons leading to depletion of high-energy compounds such as adenosine tri phosphate (ATP), shift of intracellular potassium (K) to the extracellular space, and shift of sodium ($Na^+$) and calcium ($Ca^{2+}$) into the cells.[6] Decreased brain perfusion leads to interruption in the oxygen-dependent production of high-energy compounds eliminating three of the four mechanisms of cellular calcium homeostasis resulting in rapid and massive shift of calcium into the cell.[7]

Increased intracellular calcium results in activation of membrane phospho-lipases and protein kinase leading to increased production of free fatty acids and also loss of membrane integrity resulting in further influx of calcium.[8]

A study carried out by Chung et al, found that higher albumin-corrected calcium levels were of prognostic significance in terms of early neurologic outcome and long-term mortality after acute ischemic stroke.[9] Serum calcium also correlates with the size of cerebral infarct and clinical outcomes as shown by Buck et al. and Ovbiagele et al.[10,11]

## METHODS

Study population of all the patients with acute ischemic stroke enrolled in the General Medicine OPD and Emergency department at R L Jalappa hospital, Kolar were enrolled for the study. Out of total 95 patients only 73 were included in the study considering all inclusion and exclusion criteria and patients were categorized into groups based on severity of stroke using NIHSS scale into mild, moderate and severe. The study protocol was approved by the Institutional Ethics Committee, and the written informed consent was taken from all participants before their inclusion in the study.

It was observational prospective study.

### Study period

Data was collected from all patients admitted with diagnosis of ischemic stroke for 1 and half year between time periods of 1st November 2017 to 30th April of 2019.

The Sample size was estimated by using the proportion of patients with END among.

Acute Ischemic Stroke patients as 21.2% from a previous study (UMEMURA 2013) using the formula:

Sample size = Z1-alpha/22p(1-p)/d2 Here

Z=Standard normal variate [at 5% type 1 error (p<0.05), it is 1.96 and at 1% type 1 error (p<0.01), it is 2.58].

As in the majority of studies, p values are considered significant below 0.05, hence Z =1.96 is used in the formula.

p=Expected proportion in population-based on previous studies or pilot studies.

Here, p = 21.2 or 0.212 and q, (1-p) = 78.9 or 0.789.

d=Absolute error or precision which is decided by researcher.

d =10% or 0.1

Using the above values at 99% Confidence level, a sample size of 65 subjects with acute ischemic stroke should be included in the study. Considering 10% nonresponse, a sample size of 65+6.5 ~73 subjects were included in the study.

### Inclusion criteria

- All the patients of acute ischemic stroke who are more than 18 years of age.
- Patients with a first episode of acute ischemic stroke presenting within the first 24 hours after onset of symptoms reassured by clinical examination and confirmed by a computed tomography (CT) scan were included in the study.

### Exclusion criteria

- Patients with evidence of hemorrhagic stroke.
- Patients with a transient ischemic attack.
- Patients with co-morbid conditions like a congestive cardiac failure (CCF), renal failure and decompensated cirrhosis of the liver.

The study was conducted among acute ischemic stroke patients presenting to the department of General medicine, RLJH satisfying the inclusion criteria. Written informed consent was obtained from the patients or their relatives.

A detailed history was taken and a thorough general physical and systemic examination was performed. The following details were noted: age; sex; presenting complaints; a history of any comorbidities and signs on examination. The neurological status of the patients and the severity of stroke was assessed by using the NIHSS scoring system NIHSS (National Institute of Health Stroke Scale). NIHSS score was calculated immediately at the time of admission, then subsequently after 24 after the onset of symptoms. Patients for whom the NIHSS score returned to zero within the initial 24 h will be

classified as having a transient ischemic attack (TIA) and were excluded from the study.

Measurement of total (TCa) and ionized (ICa) calcium was done in Caretium ISE analyzer. Albumin corrected calcium (CCa) was calculated using the formula= serum total calcium level + 0.8 × (4 - patient's albumin level) (Normal serum albumin level taken as 4 mg/dL). CT imaging was done with a Multislice (128 slices) CT scan (Definition AS + Excel Siemens, Germany, No-1) in all patients. For analysis of stroke, the formula shown by Sims et al. was used.12 According to this formula, the largest lesion slice was selected. The longest lesion axis on this slice was measured with the ruler tool. A second line was drawn perpendicular to the first at the widest dimension. These two measurements were called the x (A) and y (B) axes. A third axis, the z (C) axis, was computed by multiplying the number of slices by slice thickness. The scan slice for CT was 5 mm. Final size of stroke was measured as ABC/2.

### Statistical analysis

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency, and proportion for categorical variables. Data was also represented using appropriate diagrams like a bar diagram, pie diagram, and cluster bar.

The association between categorical explanatory variables and the quantitative outcome was assessed by comparing the mean values. The mean differences along with their 95% CI were presented. An independent sample t-test was used to assess statistical significance. The association between explanatory variables and categorical outcomes was assessed by cross-tabulation and comparison of percentages. Univariate logistic regression was done to assess the factors associated with the occurrence of END. Unadjusted odds ratios along with their 95% CI were presented. Factors showing statistical significance in univariate analysis were included in the multivariate analysis. Adjusted odds ratios along with 95% CI and p-values were presented.

p-value <0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.[17]

### RESULTS

Data were collected from 73 patients out of 95 patients who had presented with ischemic stroke within 24 hrs of onset of symptoms after due consideration to all relevant inclusion and exclusion criteria. There were 48(65.75%) were males and 25(34.24%) constitute females, ranging from 48 years to 92 years in age. The mean age of the patients was 68.89±8.92 years. The levels of total calcium, albumin-corrected calcium, and ionized calcium were 9.13±0.89 mg/dL (range: 8.24-10.02), 9.56±0.82 mg/dL (range: 8.74-10.38), and 4.79±0.47 mg/dL (range: 4.3-5.2), respectively. Mean stroke size as measured on the CT scan was 47.38±17.7 cm (range: 21-88). Analysis revealed no significant difference between males and females with respect to age, calcium levels (total, corrected, and ionized) or infarct size. Gender-wise distribution of baseline biochemical and radiological parameters are shown in (Table 1).

Calcium levels (total, corrected, and ionized) were collapsed into quartiles, and Pearson's correlation coefficient was used for comparing the levels with IS (Table 2). Total calcium, albumin-corrected calcium, and ionized calcium had a significant negative correlation with infarct size with r = -0.6673, -0.5671, and -0.6134, respectively and it was also found that total calcium at presentation also had significant negative correlation with NIHSS score on day 1 indicating the severity (Table 1).

**Table 1: demographic profile and base line characteristics of the study population.**

| Parameter | Range | | Mean±SD | | Significance(p) |
|---|---|---|---|---|---|
| | Male | Female | Male | Female | |
| Age | 48-92 | 51-84 | 59±10.43 | 58±11.2 | 0.823(NS) |
| Total calcium(mg/dl) | 7.92-11.8 | 8.3-11.5 | 9.82±1.04 | 9.76±1.01 | 0.610(NS) |
| Albumin corrected calcium(mg/dl) | 8.0-12.2 | 8.8-11.9 | 9.96±1.02 | 9.87±1.03 | 0.447(NS) |
| Ionised calcium(mg/dl) | 4.1-5.8 | 4.2-5.9 | 4.8±0.67 | 4.8±0.72 | 0.342(NS) |
| Infarct size(cm3) | 18-89 | 18-92 | 45.3±16.75 | 46.7±16.57 | 0.231(NS) |
| NIHSS day 1 | 8-32 | 10-36 | 21.2±-6 | 23.7±8.6 | 0.0432(S) |

P>0.005. NS: statistically not significant, SD=standard deviation.

### DISCUSSION

In this study, a total of 73 patients were included after considering all the inclusion and exclusion criteria. Patients were evaluated for correlation between serum calcium levels and infarct size in patients with acute ischemic stroke. In this study, it was found that serum calcium levels had a significant negative correlation with infarct size in patients with ischemic stroke and albumin corrected calcium levels and ionized calcium levels also

had a significant negative correlation with infarct size. This is in concordance with the findings of Buck et al. [11] and D'Erasmo et al.[13] Similar findings were also reported in a study done by Kasundra et al.[14] where a statistically significant ($p<0.05$) correlation of IS was found with both calcium level and corrected calcium level.

**Table 2: Correlation between serum calcium (total calcium, corrected calcium and ionized calcium) and infarct size.**

| Serum calcium | | Infarct size | |
|---|---|---|---|
| | | r | p |
| Total calcium(mg/dl) | 7.92-8.91 | -0.4567 | 0.0453 |
| | 8.92-9.91 | -0.4763 | 0.0317 |
| | 9.92-10.91 | -0.5123 | 0.0297 |
| | 10.92-11.91 | -0.6673 | 0.0067 |
| Corrected calcium(mg/dl) | 8-9.1 | -0.5326 | 0.0351 |
| | 9.2-10.1 | -0.4865 | 0.0432 |
| | 10.2-11.1 | -0.3956 | 0.0463 |
| | 11.2-12.2 | -0.5671 | 0.0156 |
| Ionized calcium | 4.1-4.5 | -0.5983 | 0.0276 |
| | 4.6-5.0 | -0.5142 | 0.0321 |
| | 5.1-5.5 | -0.5874 | 0.0215 |
| | 5.6-6 | -0.6134 | 0.0118 |

Therefore, the present study is conclusive that ischemic stroke patients with a larger infarct prone to have lower levels of serum calcium and those with smaller IS are prone to have a higher level of serum calcium. so, whenever CBF falls below the critical level, cellular hypoxia develops leading to failure of cellular homeostatic mechanisms and influx of calcium leading to ischemic cell death.[7]

The finding that there is a greater decrease in serum calcium in patients with ischemic stroke as compared with patients of transient ischemic attack also lends strength to this hypothesis.[15] however, to confirm shift of extracellular calcium to intracellular leading to increased infarct size cannot be confirmed unless author can measure intracellular calcium directly.

In this study, total calcium had a better correlation with infarct size compared to corrected calcium and ionized calcium. Total, corrected calcium and ionized calcium had a statistically significant correlation with ischemic infarct across all four quartiles. These findings are similar with Ovbiagele et al.[10], D'Erasmo et al.[13] and Kasundra et al.[14] who found total calcium to be a better predictor in the outcome of ischemic stroke as compared to corrected calcium. It was also found that the total calcium done on the day of admission was also correlating with SEVERITY OF NIHSS score on day 1 of admission, i.e., greater the NIHSS score, lower the serum total calcium ($p<0.0124$). This study also found a better correlation of infarct size with the highest quartile of calcium in all three cases (total, albumin corrected, and ionized), no reason identified. May be because smaller infarcts have

minimal membrane disturbance leading to minimal calcium influx.

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