



## “CORRELATION OF SERUM CALCIUM LEVELS WITH SEVERITY OF STROKE USING MODIFIED RANKIN SCALE IN ACUTE ISCHEMIC STROKE PATIENTS”

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### Abstract

**Background:** Recent studies have shown that elevated serum calcium levels at admission in patients with stroke have been associated with less severe clinical deficits and with better outcomes. The objective of this study was to assess the role of serum calcium in severity of stroke in acute ischemic stroke patients.

**Materials and Methods:** This was a cross-sectional study done over a period of 3 months in the department of General Medicine, Krishna institute of medical sciences, Karad. A total of 73 patients admitted in the ward with CT confirmed ischemic stroke were included in the study.

**Results:** Low blood calcium levels occurred in 75% of patients with mRS score 3-6 (Severe Stroke category) compared to patients with score 0-2 (Minor Stroke category) among ischemic stroke patients. The relationship between serum calcium levels and mRS scores, a significant (p-value of 0.0001) negative correlation was observed with a Spearman coefficient (r) of -0.43.

**Conclusion:** We conclude that Serum calcium has statistically significant correlation with severity of acute ischemic stroke.

**Keywords:** Serum calcium, Acute ischemic stroke, mRS score.

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## 1. Introduction

The World Health Organization (WHO) defines stroke as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than vascular origin”.<sup>1</sup>Stroke is the 3rd most leading cause of death worldwide following coronary heart disease and cancer, especially ischemic stroke.<sup>2</sup>Based on the pathophysiology stroke is divided into two broad categories. Haemorrhagic and ischemic stroke. Haemorrhage is characterized by too much blood within the closed cranial cavity, while ischemia is characterized by too little blood to supply an adequate amount of oxygen and nutrients to a part of the brain. Acute ischemic stroke is caused by stenosis of artery supplying to brain. 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. 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 hyperlipidaemia 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.<sup>3</sup> 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<sup>+</sup>) and calcium (Ca<sup>2+</sup>) into the cells.<sup>4</sup> 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.<sup>5</sup> 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, Excessive intracellular calcium accumulation triggers a cascade of cytotoxic events that lead to the activation of enzymes involved cell death. In preclinical models, low extracellular serum calcium levels paradoxically enhance this overloading of intracellular serum calcium and potentiate cell death<sup>6</sup>.

High dietary intake of Ca<sup>2+</sup> has been associated with reduced risk of stroke. Whether serum calcium levels affect serum calcium level-dependent excitotoxic pathways in the setting of human acute cerebral ischemia remains unclear, but mounting data indicate that higher serum calcium levels at admission are associated with better clinical outcomes after ischemic stroke<sup>7,8</sup>.

The Rankin scale is named after the Scottish physician John Rankin who made this scale in view to access the disability of the patient with specific reference to the mobility of the patient. Initially this scale was made to access the patient who suffered from stroke to access the global disability of these patients was later to be used in clinical trial and the name Modified Rankin Scale (mRS). It is now widely used to assess the functional outcomes of patients who suffer from stroke.<sup>9</sup> (Table 1)

Table 1: Modified Rankin Scale (mRS)

Score	Description
0	No symptoms
1	No significant disability 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

The present study has been done with the aim of determining the role of serum calcium in assessing the severity and prognosis of acute ischemic stroke patients.

### Aims and Objectives

1. To correlate serum calcium level with severity of stroke using Modified Rankin scale for stroke.

2.To find association of demographic parameters and risk factors with severity of stroke using Modified Rankin scale for stroke.

## 2. Methodology

Study Design:Cross-sectional study.

Study Duration: 3 months.

Inclusion Criteria:

- 1) Age group from 18 to 80 years.
- 2) Acute ischemic stroke diagnosed by clinical examination and CT brain plain.
- 3) Patients who are willing to participate in the study –consent form signed by patient or attender.
- 4) Modified Rankin Scale (MRS) stroke score 1 to 6.

Exclusion Criteria:

- 1) Patients with age more than 80 years were excluded.
- 2) Patients with malignancy, sepsis, trauma, recent surgery.
- 3) Patients with a cerebral aneurysm, cerebral haemorrhage, brain tumour, brain contusion.
- 4) Intracranial haemorrhage as shown in a CT or MRI.
- 5) Patients with prior history of transient ischemic attacks or reversible ischemic neurological deficit.

Sample Size:The Sample size was estimated by using the prevalence of patients of acute ischemic stroke. Acute Ischemic Stroke patients as 21.2% from a previous study (UMEMURA 2013) using the formula

Sample size =  $Z_{1-\alpha/2} \sqrt{p(1-p)} / d^2$  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  $65 + 6.5 \sim 73$  patients was included in the study.

### Study Setting:

The study was conducted in Krishna institute of medical sciences, Karad. The samples were selected among the acute ischemic stroke patients presenting to inpatients who were admitted under the department of general medicine. 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 mRS scoring system mRS (Modified Rankin Scale for Stroke). mRS score was calculated immediately at the time of admission. Measurement of total serum calcium (TCa) was done in Caretium ISE analyzer. Normal serum calcium value 8.5 to 10.5 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.<sup>12</sup>

**Statistical Analysis:** Data collected entered in MS-EXCEL. Descriptive analysis was carried out by mean and standard deviation for quantitative variables. Spearman correlation analysis was used to find correlation between categorical variables (serum Ca and mRS Score). Fisher's exact test was applied to find association. p value <0.05 is considered as significant. All data analysed using Graphpad prism version 8.

## 3. Results

Data were collected from 73 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 49(67%) were males and 24(33%) constitute females, ranging from 18 years to 80 years in age. The mean age of the patients was  $60.55 \pm 9.94$  years. The levels of total calcium  $8.49 \pm 0.74$  mg/dL (range: 7.50-10.30)

Fig.1: Age distribution

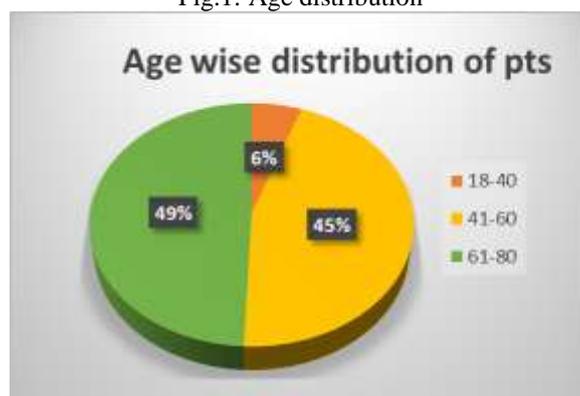


Fig.2: Gender distribution

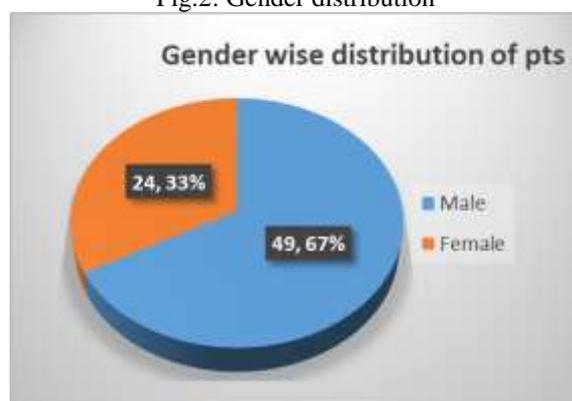


Fig.3: Risk factor wise distribution

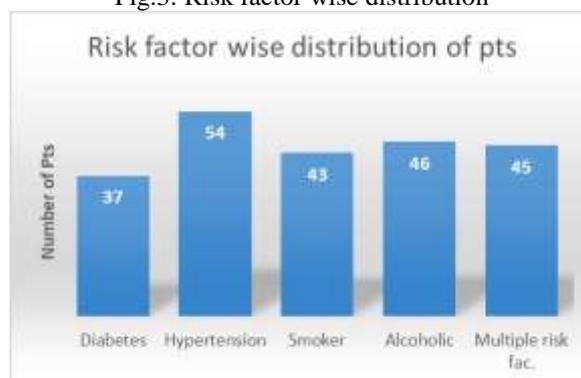


Table 1 showing mRS score with no of pts and serum Ca

Modified Rankin Scale	Number of Pts	Low ca	Normal ca
Mild (0-2)	18	4(22%)	14(78%)
Mod-severe (3-5)	51	35(69%)	16(31%)
Death (6)	4	4(100%)	0

Out of 73 patients 18 patients had mild (0-2) mRS score of these 18 only 4 patients had low serum Ca. 51 patients had mRS score (3-5) which indicates moderate severity of stroke of which 35 patients

had low serum Ca. 4 patients died indicating mRS score 6, all these patients had low serum calcium.

Table 2: Correlation of age and serum Ca with mRS

Correlation statistics	Age	Serum Ca
Spearman r	0.5494	-0.4336

95% confidence interval	0.3595 to 0.6956	-0.6078 to -0.2195
P (two-tailed)	<0.0001	0.0001

Correlation statistics was applied to find out correlation of age and serum Ca with magnitude of mRS score. The relationship between serum calcium levels and mRS scores, a significant (p-value of 0.0001) negative correlation was observed with a Spearman coefficient (r) of -0.43. which was

mild-moderately strong. The relationship between age and mRS scores, a positive correlation was observed with a Spearman coefficient of 0.54 indicating moderately strong correlation. It was statistically significant with a p-value of 0.0008

Fig.4: Scatter diagram for correlation of Serum Ca with mRS

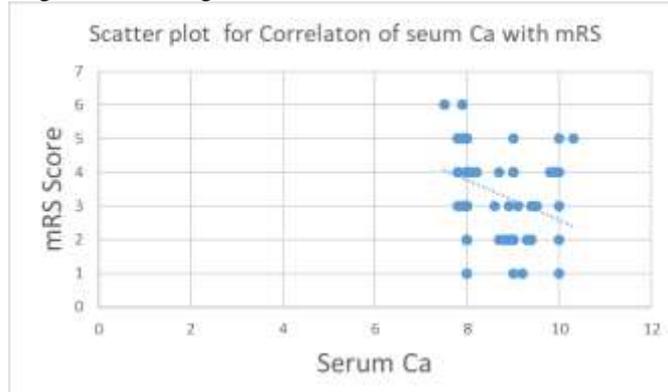


Table 3: Fisher's exact test for gender association with mRS

Modified Rankin Scale Score (p=0.5733)			
Gender	0-2	3-5	Total
Male	11	35	46
Female	7	16	23
Total	18	51	69

Table 4: Fisher's exact test for Smoking association with mRS

Modified Rankin Scale Score (p=0.0047)			
Smoker	0-2	3-5	Total
Yes	6	37	43
No	12	14	26
Total	18	51	69

Table 5: Fisher's exact test for association of Diabetes with mRS

Modified Rankin Scale Score (p=0.0025)			
Diabetes	0-2	3-5	Total
Yes	4	33	37
No	14	18	28
Total	18	51	65

Table 6: Fisher's exact test for association of Hypertension with mRS

Modified Rankin Scale Score (p=0.0017)			
Hypertension	0-2	3-5	Total
Yes	9	45	54
No	9	6	15

Total	18	51	69
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Table 7: Fisher's exact test for association of Alcoholism with mRS

Modified Rankin Scale Score (p=0.0394)			
Alcoholic	0-2	3-5	Total
Yes	8	38	46
No	10	13	23
Total	18	51	69

Table 8: Association of various parameters with mRS using Fisher's exact test

	Gender	Hypertension	Diabetes	Smoking	Alcoholism
P Value	0.5733	0.0017	0.0025	0.0047	0.0394
Significance	No	Yes +++++	Yes +++	Yes ++	Yes +

To find out association Fischer's exact test was applied. Significant association was noted between various risk factors with mRS score. Hypertension was very strongly associated (p= 0.0017), followed by diabetes, smoking, alcoholism. Gender had no association with mRS score.

#### 4. Discussion

In this study, a total of 73 patients were included after considering all the inclusion and exclusion criteria. Patients in age group 41-80 were more (94%) as compared to patients in age group 18-40 (6%).

Patients were evaluated for correlation between serum calcium levels and modified Rankin scale score in patients with acute ischemic stroke. Low blood calcium levels occurred in 75% of patients with mRS score 3-6 (Severe Stroke category) compared to patients with score 0-2 (Minor Stroke category) among ischemic stroke patients. Also it was found that serum calcium levels had a significant negative correlation with severity of stroke in patients with ischemic stroke This is in concordance with the findings of previous studies that examined serum calcium levels in patients with acute ischemic stroke like Gupta A et al<sup>13</sup>, Starkman S, et al<sup>14</sup>.

In our study, majority of the participants 43 (59%) had low levels of serum calcium than participants with normal calcium range (41%), similar finding reported in study done by Dr Amudalapalli L A Alekhya et al<sup>15</sup>. Among 43 participants with decreased serum calcium majority were males and females were comparatively less. Significant correlation was noted between the age distribution and serum calcium levels with p value < 0.0001. Also significant association noted between various risk factors like diabetes, hypertension, smoking and alcohol consumption which is in concordance with the study done by Gupta A et al<sup>13</sup>.

Conclusion: Acute ischemic stroke is more prevalent after the age of 40. Serum calcium has

statistically significant correlation with severity of acute ischemic stroke as evidenced by mRS scores. Also there is significant association between Hypertension, Diabetes, Smoking and Alcohol consumption with severity of acute ischemic stroke.

#### Limitations of the study:

Our study has a major limitation of small sample size; Results may vary when done in a large number of subjects. and no data was collected on ionized calcium which is a physiological active component of calcium.

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**Conflict of interest:** None declared.

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