A Dissertation on

SERUM CALCIUM AS A SEVERITY MARKER IN ACUTE ISCHEMIC STROKE

Submitted to

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INTRODUCTION

Stroke is defined as the syndrome of rapid onset of cerebral deficit, usually focal, lasting for more than 24 hours or leading to death with no cause apparent other than the vascular one \(^{(1)}\). As a result of this explanation transient ischemic attack (TIA), which is defined to last less than 24 hours, and patients with symptoms similar to stroke due to various causes such as subdural hemorrhage, tumors, poisoning, or trauma are barred \(^{(2)}\). Stroke may lead to the long term complications which caters under the most common causes for mortality and the morbidity both international as well as national level \(^{(3)}\) and stroke itself is the second commonest cause for increasing mortality worldwide \(^{(4)}\). Hence stroke is considered as an significant health issue as it has its impact strongly not over the individual alone but also over the social factors \(^{(5)}\).

The main risk factors associated with the occurrence of stroke are elevated blood pressure, uncontrolled diabetes, dyslipidemia, smoking and alcoholism. Though new modalities of treatment have evolved, still the prognosis is considered to be poor due to all these risk factors implications over the treatment \(^{(6)}\).
Based on several ways stroke can be classified as follows: \(^{(7)}\)

1. According to Clinical features
   
   1. Completed stroke.
   
   2. Stroke in Evolution.
   
   3. Transient Ischemic Effects.
   
   4. Reversible Ischemic Neurological Deficit.

2. According to anatomic site
   
   a. Supra-tentorial which includes lobar and Capsulo-ganglionic
   
   b. Infra-tentorial which includes brainstem and cerebellum.

3. According to pathophysiology:
   
   I. Infarct
      
      Thrombotic
      
      Embolic
   
   II. Hemorrhagic stroke.

   Among the various types of stroke the two main types are ischemic stroke and the hemorrhagic stroke. Ischemic stroke is due to the blockage of blood supply to the brain due to arterial occlusion, which can cause
damage to brain cells. Hemorrhagic stroke is the one caused when a blood vessel bursts within or on the surface of the brain (8). Ischemic stroke accounts for about 50% -85% of stroke all over the world (9).

**Acute ischemic stroke**

The greater part of strokes happen when blood vessels to the brain turn out to be lessened or congested with fatty deposits called plaque which cuts off blood flow to the brain cells. The stroke due to the deficiency in the blood flow reaching part of the brain is called an ischemic stroke (10).

Ischemic stroke is categorized into two types namely (10)

1. Thrombotic stroke
2. Embolic stroke

**Common causes** (20)

1. Thrombosis
   a. Lacunar
   b. Large vessel thrombosis
2. Embolic

a. Artery to artery embolic occlusion- at carotid bifurcation, aortic arch
b. Cardio embolic –

   Atrial fibrillation
   Mural thrombus
   Myocardial infarction 2-3% incidence
   Valvular lesions like [MS, bacterial endocarditis, mechanical valve]

c. Paradoxical embolus like ASD, patent foramen ovale
d. Stimulant drugs – cocaine, Amphetamine

Uncommon causes

1. Hypercoagulable states-
   APLA, Protein-C deficiency, Protein S deficiency,
   Sickle cell anemia, Homocystinemia.
2. Venous sins thrombosis
4. Fibro muscular dysplasia
5. Cardiogenic- Marantic endocarditis, atrial myxoma.

Genes involved in stroke

a. The presence of Apo ε 4 allele along with elevated triglycerides, hypertension, and age could predict the development of stroke.

b. MTHFR C677T mutations (MTHFR gene is involved with metabolism) was found to be strongly associated with arterial stroke, especially in young\(^{(11)}\)
c. F2 and F5 genes increase the risk of thrombosis.

d. Cerebral arteriopathy, autosomal dominant, with subcortical infarcts and leucoencephalopathy (CADASIL), is caused by mutations in the NOTCH3 gene\(^{(12)}\)

e. 2 single nucleotide polymorphisms on 2q23.3 is involved in early onset ischemic stroke.

f. HDAC9, PITX2, and ZFHX3 genes involved on large vessel stroke\(^{(13)}\)

g. Mutations in the CST3 gene are inherited in an autosomal dominant manner results in Amyloid angiopathies are also known to increase risk for stroke and dementia\(^{(14)}\)

Mutations in the following genes also are known to increase the risk of stroke\(^{(15)}\)

1. NOS3: A nitric oxide synthetase gene; involved in vascular relaxation

2. ALOX5AP: Involved in the metabolism of arachidonic acid

3. PRKCH: Involved in major signal transduction systems
**Thrombotic stroke**

Thrombogenic factors may cause injury to endothelial cells; results in platelet activation by the sub endothelium, activation of the clotting cascade, inhibition of fibrinolysis, and blood stasis.

Thrombotic strokes are generally thought to originate on ruptured atherosclerotic plaques. Arterial stenosis can cause turbulent blood flow, which can promote thrombus formation; atherosclerosis (i.e., ulcerated plaques); and platelet adherence. All cause the formation of blood clots that either embolize or occlude the artery. Intracranial atherosclerosis may be the cause of thrombotic stroke in patients with widespread atherosclerosis.\(^{(16)}\)

**Embolic stroke:**

20% of ischemic stroke. Stroke is due to embolism of thrombotic material formed on arterial or ventricular wall or left heart valves. Emboli may arise from the heart, the extra cranial arteries, including the aortic arch or, rarely paradoxical emboli arising from right sided circulation with subsequent passage through a patent foramen ovale.\(^{(17)}\)

Sources of cardiogenic emboli include the following:

- Valvular thrombi (eg, in mitral stenosis or endocarditis or from use of a prosthetic valve)
- Mural thrombi (e.g., in myocardial infarction, atrial fibrillation, dilated cardiomyopathy, or severe congestive heart failure)

- Atrial myxoma.

Emboli from heart mostly lodge in intracranial internal carotid artery, MCA, PCA, infrequently in ACA. Large emboli of size 3-4 mm can occlude the stem of MCA and cause large infarcts. Location and size of infarct depends on collateral circulation. Emboli originating from the aortic arch and diffuse thrombotic or inflammatory processes that can lead to multiple small-vessel occlusions or bilateral infarcts \(^{18,19}\)

Non rheumatic atrial fibrillation is the most common cause of cerebral embolism. Embolic strokes tend to have a sudden onset, and neuroimaging may demonstrate previous infarcts in several vascular territories or may show calcific emboli.

![Ischemic stroke](image)

**Figure 1: Ischemic stroke**
Figure 2: Transient ischemic stroke

Mechanism of stroke

Large-Vessel Atherothrombosis \(^{(60)}\)

It affects both extra cranial and intracranial arteries due to the lipid-laden atherosclerotic plaques deposition on the inner wall of a large vessel. This plaques formation is more common at the bifurcations of the common carotid arteries, the origins of the vertebral arteries, and the course of the middle cerebral artery prior to its trifurcation. Risk factors for deposition are high blood pressure, diabetes mellitus, and dyslipidaemia. There will be gradual reductions in CBF over a long period without any infarcts until stenosis is reached at a critical level. Depending on the vessels involved and the presence or absence of anastomoses, this mechanism typically results in a single large territorial stroke.
In the case of so-called atheroembolism, a thrombus that has formed on the wall of a particular vessel may break apart and lodge along the branches of small arteries, resulting in multiple smaller infarcts within the expected branches of the parent vessel.

**Small-Vessel Disease**

Occlusive disease involving the microcirculation of the brain results in small vessel ischemic disease.

Lacunar infarct causes includes

- Microatheroma
- Lipohyalinosis
- Fibrinoid necrosis as a result of hypertension or Vasculitis.

Common locations for small-vessel disease include deep areas of the hemispheric white matter such as

1. The corona radiata
2. The internal capsule, adjacent to the proximal middle cerebral artery which is supplied by its penetrating branches;
3. The pons in the mid-brainstem, supplied by penetrators arising from the basilar artery;
4. The thalamus, reliant primarily on branches of the posterior cerebral arteries.

Infarctions of these typical regions are classically small (<1.5 cm). Depending on the location within the brain usually produce one of the classic lacunar syndromes depends upon site of lacunar infarct.

- Pure motor symptoms, usually face + arm or arm + leg, comprising 33–50 % of all small-vessel strokes;
- Pure sensory;
- Mixed sensorimotor
- Ataxic hemiparesis, which features weakness of one side with disproportionate clumsiness (ataxia) of the same side; and
- Clumsy hand- dysarthria, clumsiness of either hand, out of proportion to any weakness of the limb, combined with slurred speech.

Other lacunar syndromes referable to the posterior circulation have been recognized, such as hemiballism, hemichorea, and isolated dysarthria, but they are less commonly seen as results of acute stroke.
**Watershed infarcts**

Vascular watershed infarctions occur at the most distal areas between arterial territories occurs secondary to embolic phenomenon or to severe hypoperfusion, as occurs, for example, in carotid occlusion or prolonged hypotension.\(^{(21,22,23)}\)

**Hemorrhagic stroke\(^{(20)}\)**

Hemorrhagic stroke occurs when a blood vessel bursts inside the brain. The brain is very sensitive to bleeding and bleeding irritates the brain tissue, causing swelling. Bleeding collects into a mass called a hematoma. Bleeding also increases pressure on the brain and presses it against the skull.

There are two possible causes of a ruptured blood vessel in the brain.

The most common cause is an aneurysm.

A rarer cause of an ICH is an arteriovenous malformation (AVM).’

An aneurysm occurs when a section of a blood vessel becomes enlarged from chronic and dangerously high blood pressure or when a blood vessel wall is weak, leading to thinning of the vessel wall, and ultimately to a rupture.
RISK FACTORS OF STROKE:

Non modifiable risk factors (24)

a. Age

b. Race  (Africo-Caribbean population >Asian population> European population

c. Sex

d. Ethnicity

e. History of migraine headaches

f. Fibro muscular dysplasia

g. Heredity: Family history of stroke or transient ischemic attacks (TIAs)
Modifiable risk factors \(^{(25)}\)

- Hypertension (the most important)
- Diabetes mellitus
- Cardiac disease: Atrial fibrillation, valvular disease, heart failure, mitral stenosis, structural anomalies allowing right-to-left shunting (eg, patent foramen ovale), and atrial and ventricular enlargement
- Hypercholesterolemia
- Transient ischemic attacks (TIA)
- Carotid stenosis
- Hyperhomocystinemia
- Lifestyle issues: Excessive alcohol intake, tobacco use, illicit drug use, physical inactivity \(^{(26)}\)
- Obesity
- Oral contraceptive use/postmenopausal hormone use
- Sickle cell disease
**Pathogenesis:**

Acute ischemic stroke occurs due to vascular occlusion secondary to thromboembolic disease. Ischemia causes cell hypoxia and depletion of cellular ATP, due to this loss of energy to maintain ionic gradients is lost across the cell membrane leading to cellular depolarization \(^{(16)}\).

**Ischemic core and penumbra**

An acute vascular occlusion produces heterogeneous regions of ischemia in the affected vascular territory.

Affected regions with cerebral blood flow of lower than 10 ml/100g of tissue/min are referred to as the core.

Affected regions with cerebral blood flow of lower than 25 ml/100 g of tissue/min are referred to as ischemic penumbra \(^{(27)}\).

**Ischemic cascade**

Sodium - potassium pump fails due to depletion of ATP resulting in intracellular increase in sodium, thereby increasing intracellular water content. This cellular swelling produces as cytotoxic edema and occurs very early in cerebral ischemia. Also the Cerebral ischemia impairs the normal sodium-calcium exchange protein resulting in calcium influx , leading to release of neurotransmitters, such as glutamate, activating N -
methyl-D-aspartate (NMDA) and other excitatory receptors present in neurons. Cell membrane and other neuronal structures get destructed (28).

**Haemorrhagic transformation of ischemic stroke**

5% of uncomplicated ischemic strokes goes for hemorrhagic transformation in the absence of fibrinolytic therapy (29).

**Mechanism:**

1] Reperfusion of ischemically injured tissue, either from recanalisation of an occluded vessel or from collateral blood supply to the ischemic territory

2] Disruption of the blood-brain barrier and extravasation of red blood cells from the weakened capillary bed, producing petechial haemorrhage or more frank intraparenchymal hematoma (5).

**Post stroke cerebral edema and seizures**

Although clinically significant cerebral edema can occur after anterior circulation ischemic stroke, it is thought to be somewhat rare (10-20%). Edema and herniation are the most common causes of early death in patients with hemispheric stroke (5).
Seizures occur in 2-23% of patients within the first days after ischemic stroke. A fraction of patients who have experienced stroke develop chronic seizure disorders.

**SIGNS AND SYMPTOMS**\(^{(9, 30, 20)}\)

Consider stroke in any patient presenting with acute neurologic deficit or any alteration in level of consciousness. Common stroke signs and symptoms include the following:

- Abrupt onset of hemiparesis, monoparesis, or (rarely) quadriplegia
- Hemisensory deficits
- Monocular or binocular visual loss
- Visual field deficits
- Diplopia
- Dysarthria
- Facial droop
- Ataxia
- Vertigo (rarely in isolation)
- Nystagmus
- Aphasia
- Sudden decrease in level of consciousness
STROKE SYNDROMES

Middle cerebral artery stroke

The MCA supplies the upper extremity motor strip. Consequently, arm and face weakness is more than that of the lower limb.

Middle cerebral artery (MCA) occlusions commonly produce the following:

- Receptive or expressive aphasia, if the lesion occurs in the dominant hemisphere
- Gaze preference toward the side of the lesion
- Contralateral hemiparesis
- Contralateral hypoesthesia
- Ipsilateral hemianopia
- Agnosia

Anterior cerebral artery stroke

It primarily affects frontal lobe function. Findings in ACA stroke may include the following:

- Altered mental status
- Impaired judgment
- Disinhibition and speech perseveration
- Primitive reflexes (eg, grasping, sucking reflexes)
- Contralateral weakness (greater in legs than arms)
- Contralateral cortical sensory deficits
- Gait apraxia
- Urinary incontinence

**Posterior cerebral artery stroke**

It affects vision and thought. Manifestations include the following:

- Impaired memory
- Altered mental status
- Contralateral homonymous hemianopia
- Cortical blindness
- Visual agnosia

**Vertebro basilar artery occlusion**

It may cause a wide variety of cranial nerve, cerebellar, and brainstem deficits. Wallenberg's syndrome occurs due to the Posterior inferior cerebellar artery occlusion (PICA), vertebral, or superior, middle or inferior lateral medullary arteries. This syndrome is characterized by contralateral impaired pain and temperature sensation (spinothalamic tract involvement) and the same side numbness over half of the face, ataxia, Horner’s syndrome, dysphagia, vertigo, Hiccups and loss of taste sensation. The main feature of posterior circulation stroke is the presence
of crossed findings: Ipsilateral cranial nerve deficits and contralateral motor deficits.

**LACUNAR STROKE TYPES**

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Structure involved</th>
</tr>
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<tbody>
<tr>
<td>Pure motor hemiparesis</td>
<td>Infarct in the basis pontis, posterior limb of Internal capsule</td>
</tr>
<tr>
<td>Pure sensory stroke</td>
<td>Ventral thalamus infarct</td>
</tr>
<tr>
<td>Ataxic hemiparesis</td>
<td>Pons - Ventral portion infarct</td>
</tr>
<tr>
<td>Dysarthria and clumsy hand syndrome</td>
<td>Genu of internal capsule infarct</td>
</tr>
</tbody>
</table>

**Neurologic examination:**

Accurate neurologic examination on patients with suspected stroke syndromes.

The goals of the neurologic examination include the following:

- Confirming the presence of a stroke syndrome
- Distinguishing stroke from stroke mimics
Establishing a neurologic baseline (including documenting an NIH Stroke Scale)

Establishing stroke severity to assist in prognosis and therapeutic selection (based on potential disability due to current neurologic deficits)

Essential components of the neurologic examination include the following evaluations:

- Cranial nerves
- Motor function
- Sensory function
- Cerebellar function
- Gait
- Language (expressive and receptive capabilities)
- Mental status and level of consciousness

Examining the skull and spine and signs of meningismus should be sought.

Stroke mimics commonly confound the clinical diagnosis of stroke.

The most frequent stroke mimics include the following:

1. Seizure (17%)
2. Systemic infection (17%)
3. Brain tumour (15%)
4. Toxic-metabolic disorders, such as hyponatremia and hypoglycaemia (13%)\(^{(58)}\)

5. Positional vertigo (6%)

6. Conversion disorder

Ischemic stroke is distinguished from hemorrhagic stroke by neuroimaging; the following clinical findings increase the probability of hemorrhagic stroke:

- Coma
- Neck stiffness
- Seizures accompanying the neurologic deficit
- Diastolic blood pressure >110 mm Hg
- Vomiting
- Headache

The probability of haemorrhages decreased if there is cervical bruit and prior transient ischemic attack.

**IMAGING STUDIES**

- CT angiography and CT perfusion scanning
- Magnetic resonance imaging (MRI)
- Carotid duplex scanning
- Digital subtraction angiography.
CT scans

CT scan helps in the clear differentiation between haemorrhages and infarct and it also helps to detect abscess, tumour mass lesions, and extra parenchymal haemorrhages.

![Infarct](image1.png) ![Haemorrhage](image2.png)

Figure 4: Infarct  Figure 5: Haemorrhage

CT Angiography

Carotid disease and intracranial vascular occlusions are readily identified by this method.

Merits:

1. Helps the treating physician to decide the line of management by distinguishing infarct and hemorrhage.
2. Highly sensitive in detecting Subarachnoid Hemorrhage.
4. Cost effective than MRI.
Demerits:

1. CT not usually detects the infarct within first 24 to 48 hours.
2. Small infarct on the cortical surface will be missed.
3. Usually CT scans will not detect the posterior fossa lesions due to artifact (bone).

MRI Scan

1. Posterior fossa infarction and cortical infarction can be easily identified in MRI
2. Early brain infarction can be easily determined by DW Images.
3. Stenosis of intracranial vessels and extra cranial internal carotid arteries stenosis were detected by MR Angiogram.

Merits:

In TIA patient, MRI more likely to detect new infarction, which is a strong predictor of subsequent stroke.

Demerits:

1. More expensive and time consuming.
2. Not readily available everywhere.
MANAGEMENT

**Primary stroke prevention** refers to the treatment of individuals with no previous history of stroke.

Platelet antiaggregants

- Statins
- Exercise
- Lifestyle interventions (eg, smoking cessation, alcohol moderation)

**Secondary prevention** refers to the treatment of individuals who have already had a stroke.

- Platelet antiaggregants
- Antihypertensive
- Statins
- Lifestyle interventions

**Emergency Management**

The goal for the emergent management of stroke is to complete the following within 60 minutes or less of patient arrival \(^{(24)}\):

- Assess airway, breathing, and circulation (ABCs) and stabilize the patient as necessary
- Complete the initial evaluation and assessment, including imaging and laboratory studies
- Initiate reperfusion therapy, if appropriate

Critical treatment decisions focus on the following:

- Airway management
- Optimal blood pressure control
- Identifying potential reperfusion therapies (eg, intravenous fibrinolysis with rt-PA (Alteplase) or intra-arterial approaches.

Treatment of comorbid conditions may include the following:

- Reduce fever
- Correct hypotension/significant hypertension
- Correct hypoxia
- Correct hypoglycaemia

**ISCHEMIC STROKE THERAPY**

Ischemic stroke therapies include the following:

- Antithrombotic treatment
- Fibrinolytic therapy

- Mechanical thrombectomy
ANTITHROMBOTIC TREATMENT

Platelet inhibition:

1. Aspirin (ASA):

   Aspirin blocks prostaglandin synthetase action, which in turn inhibits prostaglandin synthesis and prevents the formation of platelet-aggregating thromboxane A2. It also reduces fever by acting on the hypothalamic heat-regulating center (32)

   For ischemic Stroke & Transient Ischemic Attack:

   50-325/day Per oral within 48 hours of stroke or TIA, then 75-100 mg/day Per Oral

2. Dipyridamole and Aspirin:

   The combination of extended-release Dipyridamole and Aspirin reduces the relative risk of stroke, death, and myocardial infarction (MI). It is used for the secondary prevention of ischemic stroke and TIA.

ANTICOAGULATION (33)

Anticoagulation should be advised for all patients with atrial fibrillation due to nonvalvular heart disease and cardiac disease. Cerebral embolism can be prevented by maintaining INR between 2-3.
Indications of anticoagulation for 3 months include:

1. Left ventricular dysfunction
2. Atrial fibrillation
3. Anterior Q–wave infarction
4. Mural thrombus
5. Congestive cardiac failure

**STATINS** (34)

These drugs were effective in reducing the cholesterol levels particularly Low density lipoproteins and very effective in reducing the incidence of Coronary artery disease and cerebrovascular accidents.

These statins has the following properties:

1. Normalizes the vascular endothelium
2. Reducing inflammation
3. Stabilizes the plaques mainly the central lipid core mass.

**FIBRINOLYTIC THERAPY** (35)

Alteplase(rt-PA), the only fibrinolytic agent that has been shown to benefit selected patients with acute ischemic stroke. In May 2009 the AHA/ASA revised the guidelines for the administration of rt-PA after
acute stroke, expanding the window of treatment from 3 hours to 4.5 hours to provide more patients with an opportunity to benefit from this therapy.

Table 1: Indication and Contraindication for Fibrinolytic therapy

<table>
<thead>
<tr>
<th>Indication for rt-PA</th>
<th>Contraindication for rt-PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. CT showing haemorrhage or oedema of &gt;1/3 of MCA territory.</td>
<td>1. Platelet &lt;1 lakh; Hct&lt;25%;</td>
</tr>
<tr>
<td>2. Symptom onset to drug administration time &lt;4.5 hours</td>
<td>2. Blood glucose &lt;50 or &gt;400</td>
</tr>
<tr>
<td>3. Age &gt;18 years</td>
<td>3. Sustained BP &gt;185/110;</td>
</tr>
<tr>
<td>4. Consent by patient or relatives</td>
<td>4. Use of heparin within 48 hours</td>
</tr>
<tr>
<td></td>
<td>5. Recent head injury within 3 months or any GI surgery within 2 weeks.</td>
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<tr>
<td></td>
<td>6. Recent MI</td>
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<tr>
<td></td>
<td>7. Rapidly improving symptoms.</td>
</tr>
</tbody>
</table>

Mechanical Thrombectomy or endovascular revascularisation: (36)

In large vessel occlusions like MCA, intracranial ICA, basilar artery, the clot fails to open with rt-PA alone. So intravascular route of thrombolytics used. It is an alternative for patients in whom fibrinolysis is ineffective or contraindicated. In 2015, The American Heart
Association/American Stroke Association issued updated guidelines for the emergency treatment of patients with acute ischemic stroke, recommending endovascular treatment using the newer generation stent retrievers $^{(37)}$. Currently, 4 devices are approved by the FDA for the endovascular treatment of acute ischemic stroke.

**STEM CELL THERAPY:**

Chronic ischemic stroke has potential benefit with stem cell therapy by not only through formation of neurons at infarct zone but also as cellular mediators of many of the biological mechanisms.

Intravenously administered stem cell will help in up regulation of growth factors within the body and brain making the host environment conducive for behavioural recovery in the form of ‘learning’ $^{(38)}$. They observed that autologous bone marrow-derived mononuclear cells are safe in chronic ischemic stroke.

**NEUROPROTECTION**

Neuroprotective drugs blocks the neuro- excitatory amino acid pathway and it promotes the tolerance of brain to ischemic effects.

1. Calcium Channel Antagonists (e.g., Flunarizine, and Darodipine)$^{(39)}$
2. Non-competitive N-methyl-D-aspartate receptor antagonists (e.g., Dextromethorphan, Eliprodil)

3. Phosphatidyl choline synthesis (e.g., Citicholine)
   Citi choline - is an exogenous form of cytidine-5’-diphosphocholine (CDP-choline) used in membrane biosynthesis. Citi choline decreasing free radical formation by reducing ischemic injury and stabilizing the membranes.\(^{(40)}\)

Treating Associated Co-morbidities:\(^{(20)}\)


2. Blood pressure is lowered if associated malignant hypertension, or if BP>185/110, if thrombolytic therapy is anticipated.
   Beta blocker (Esmolol) is used.

3. Fever is detrimental and it is treated with antipyretics,

4. If massive infarct causing cerebral edema and brain herniation:
   Water restriction and IV Mannitol is used.

5. Blood glucose should be maintained <180mg% using insulin infusion if necessary.
STROKE REHABILITATION (24)

a) Speech therapy

b) Occupational therapy

c) Physical therapy

d) Pharmacological therapy

COMPLICATIONS OF STROKE (24)

1. Aspiration Pneumonia

2. Urinary tract infection

3. Bed sores

4. Pulmonary embolism with Deep vein thrombosis

5. Contractures

6. Dehydration

7. Hypoxemia

8. Hyperglycaemia

9. Frozen Shoulder and subluxation

10. Constipation

11. Hyponatremia and seizures.
Prognosis

In the Framingham and Rochester stroke studies, the overall mortality rate at 30 days after stroke was 28%, the mortality rate at 30 days after ischemic stroke was 19%, and the 1-year survival rate for patients with ischemic stroke was 77%. In ischemic stroke, prognosis varies in individual patients, depending on patient’s premorbid condition, age, and post stroke complications (32)

Stroke survivors from the Framingham Heart Study-

31% needed help caring for themselves,

20% needed help when walking, and

71% had impaired vocational capacity in long-term follow-up.

Role of Calcium in stroke

Calcium is the most prevalent cation in the human body. Approximately 1-1.3 kg of calcium can be found in a healthy adult, 99% of which is in the form of hydroxyapatite in the skeleton; the remaining 1% in the extracellular fluid (ECF). Serum (plasma) calcium exists in 3 distinct forms.

The serum calcium is divided into three fractions:

1. 50% of calcium ions in the active form,
2. 40% bound to serum proteins, principally albumin and
3. 10% bound to anions such as bicarbonate and citrate.

Calcium (Ca2+) ions play a physiological role in the multiple patho
mechanisms of cerebral ischemia \(^{(40)}\)

Normal CBF is between 45 and 60 ml blood/100 g/min. It is well
documented that time-dependent neuronal events are triggered in
response to reduced CBF \(^{(41)}\), there is an interruption in the oxygen
dependent generation of high-energy compounds, when the CBF falls
below 10 ml/min/100 g, this leads to a disturbance in cellular calcium
homeostasis. Cerebral ischemia results in intracellular accumulation of
calcium which activates cytotoxic enzyme leading to cell death \(^{(42)}\). A
rapid and massive influx of calcium into the cell results.
The reduction of blood flow supply to the brain during ischemic stroke results in oxygen and glucose deprivation and thus a reduction in energy available to maintain the ionic gradients. This results in excessive neuronal depolarization and deregulated glutamate release. If blood flow is reduced for a long period, Glutamate is released at high concentrations in the penumbral cortex \(^{43}\) and the amount of glutamate released correlates with early neurological deterioration in patients with acute ischemic stroke \(^{44}\).

After a stroke, as a consequence of excessive extracellular glutamates, NMDARs are excessively activated resulting in increased Ca2+ influx \(^{45}\). In the excitotoxic cascade, Calcium plays a critical role, because either removing Ca2+ from extracellular medium or preventing Ca2+ from entering mitochondria by uncouplers protects neurons against excitotoxic injury.

N-methyl-d-aspartate (NMDA) glutamate receptors are believed to be the key mediators of death during excitotoxic injury \(^{46}\). Mitochondrial dysfunction as a consequence of prolonged accumulation of Ca2+ is considered a major source of free radicals that are generated after ischemia-reperfusion \(^{47,48}\). Excitotoxicity causes a sudden increase in cytoplasmic Ca2+ concentrations in neurons after ischemia, which induces activation of several signalling pathways, leading to apoptotic or
necrotic neuronal death. Activation of calpains, caspases, other proteases, kinases and endonucleases, cause mitochondrial disturbance, overproduction of free radicals and DNA fragmentation, that synergistically leads to neuronal death.

Oxidative stress induced by excitotoxicity is considered the main event leading to brain damage after cerebral ischemia \(^{(49)}\). The most important free radicals induced by excitotoxicity are reactive oxygen species and reactive nitrogen species.

Low serum calcium found after acute ischemic stroke is significantly associated with greater severity of stroke as assessed by the National Institute of Health Stroke Score (NIHSS) than those with high calcium levels. Since about half of calcium in the blood is bound to albumin, an abnormally high or low level of albumin may affect the interpretation of calcium results and "free" or "ionized calcium" must be measured.

The first step in the evaluation of a patient with hypocalcaemia is to verify with repeat measurement (total serum calcium corrected for albumin or ionized calcium) that there is a true decrease in the serum calcium concentration.
Table 2: Conditions with decreased and increased calcium levels

<table>
<thead>
<tr>
<th>Conditions with increased calcium level</th>
<th>Conditions with decreased calcium levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperparathyroidism</td>
<td>Hypoparathyroidism</td>
</tr>
<tr>
<td>Malignancies like squamous cell carcinoma of lung, renal cell carcinoma,</td>
<td>Vitamin D deficiency</td>
</tr>
<tr>
<td>Vitamin D excess</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Hyperphosphatemia</td>
</tr>
<tr>
<td>Paget disease of bone</td>
<td>Massive transfusion</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Hypoalbuminemia</td>
</tr>
<tr>
<td>Drugs like some antacids, long term thiazides, lithium.</td>
<td>Chronic liver disease., biliary obstructive disease</td>
</tr>
<tr>
<td></td>
<td>Severe dietary calcium deficiency.</td>
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<tr>
<td></td>
<td>Severe sepsis</td>
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<tr>
<td></td>
<td>Tumor lysis syndrome.</td>
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</tbody>
</table>

Calcium in serum is bound to proteins, principally albumin. As a result, the total serum calcium concentration in patients with low or high serum albumin levels may not accurately reflect the physiologically important ionized (or free) calcium concentration. Each 1 g/dL reduction in the serum albumin concentration will lower the total calcium concentration by approximately 0.8 mg/dL (0.2 mmol/L) without
affecting the ionized calcium concentration and, therefore, without 
producing any symptoms or signs of hypocalcaemia.

Hypoalbuminemia is the most common cause of hypocalcaemia. 
Causes include

1. Cirrhosis,
2. Nephrosis,
3. Malnutrition,
4. Burns,
5. Chronic illness,

In patients who are critically ill, low calcium levels can be simply 
due to Hypoalbuminemia.

The reference range for albumin testing is as follows: (5)

- The normal range is 3.5 to 5.5 g/dL or 35-55 g/litre. This range may 
  vary slightly in different laboratories.

- Albumin composes 50%-60% of blood plasma proteins.

Calcium is maintained within a fairly narrow range from 8.5 to 10.5 
mg/dl (4.3 to 5.3 m Eq /L or 2.2 to 2.7 mmol /L). Normal values and 
reference ranges may vary among laboratories as much as 0.5 mg/dl. 
Concentrations of total calcium in normal serum generally range between 
8.5 and 10.5 mg/dL (2.12 to 2.62 mmol/L) and levels below this are 
considered to be consistent with hypocalcaemia.
The normal range of ionized calcium is 4.65 to 5.25 mg/dL (1.16 to 1.31 mmol/L).

**Formula**

Corrected Ca = \([0.8 \times (\text{normal albumin} - \text{patient's albumin})] + \text{serum Ca level}\).

Accordingly normal corrected calcium value is taken as 8.6 to 10.2.

**NATIONAL INSTITUTE OF HEALTH STROKE SCALE (NIHSS)**

For assessing the impairment due to stroke National Institute of Health Stroke scale was formed. The NIHSS was designed to be a uniform assessment of stroke patients by large multi-centre clinical trials (50). This scale has been accepted widely due to eminent levels of score consistency. Consistency of NIHSS scores has been established in inter-examiner and in test-retest scenarios (51). The NIHSS is repeated at customary intervals or following noteworthy changes in patient appearance. This scores can also be utilized to scrutinize the efficiency of the treatment method and enumerate the patient’s enhancement or turn down (52). The NIHSS can also be used for prospective observational study, to envisage 3 month outcomes of patients with under nutrition during hospital stays directly after a stroke (53).
National Institute of Health Stroke scale consists of eleven components, each score ranging from 0 - 4 based on the response. A score 0 indicates normal function, whereas a elevated score indicates impairment. Overall score vary from 0-42 with high values represent increased severity of infarcts.

The four vital areas to be taken into consideration are as follows:

1. Cranial Nerve/ Visual disturbances
2. Level of Consciousness
3. Motor weakness
4. Language/ Neglect

This clinical parameter can also be used to assess and the scores can be computed for assessing the severity of stroke.

**Advantages of National Institute of Health Stroke Scale** (5).

a. To assess the cerebro - vascular accidents.

b. To determine the stoke prognosis.

c. To establish functional disability

d. Speedy technique of assessing the study subjects, that hardly needs the duration of 10 minutes.
### NATIONAL INSTITUTE OF HEALTH STROKE SCALE (NIHSS)

#### Table 3: NIHSS

<table>
<thead>
<tr>
<th>S.NO</th>
<th>TESTED ITEM</th>
<th>TITLE</th>
<th>RESPONSE AND SCORE</th>
</tr>
</thead>
</table>
| 1    | 1A          | Level of consciousness      | 0-Alert  
1-Ready to fall asleep, lack of attention, respond to painful stimuli.  
2-Nott alert / oriented to time, place, remains in a state of confusion or delirium.  
3-comatose and not responding to painful stimuli. |
| 2    | 1B          | Orientation questions       | 0-Answers correctly to 2 simple questions.  
1-Patient will answer 1 question correctly.  
2-patient will not answer to any question correctly. |
| 3    | 1C          | Response to commands        | 0-Patient will do both work and tasks perfectly.  
1-Patient will do one task perfectly.  
2-Patient will not do both tasks. |
| 4 | 2 | Gaze | 0-Normal horizontal movements  
1-Partial gaze palsy  
2-Complete ophthalmoplegia |
| 5 | 3 | Field of vision | 0-Normal visual field  
1-Partial Hemianopia  
2-Complete Hemianopia  
3-Bilateral Hemianopia |
| 6 | 4 | Facial movements | 0-Normal  
1-Subtle facial palsy  
2-Incomplete facial weakness  
3-Unilateral complete facial palsy |
| 7 | 5 | Motor Functions  
(Arm)  
a) Left  
b) Right | 0-No fall of forearm and hand when stretched and kept in supination for 10sec  
1-Fall of forearm and hand but no hit in the bed  
2-Fall of forearm and hand and hits the bed  
3-No movement against gravity  
4-Total paralysis |
| 8 | 6 | Motor Functions  
(leg)  
a) Left  
b) Right | 0 – No fall of leg for 5sec  
1 – Fall of leg occurs but it doesn’t hit the bed.  
2 – Fall of leg occurs and hits the bed. |
<table>
<thead>
<tr>
<th>3</th>
<th>No movement against gravity</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Total paralysis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9</th>
<th>7</th>
<th>Limb Incoordination</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Incoordination of only one limb</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Incoordination of two limbs</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>10</th>
<th>8</th>
<th>Sensory</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Patient will not have any sensory loss</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Here sensory loss is mild</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Here patient will have severe sensory loss</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>11</th>
<th>9</th>
<th>Language</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Patient can communicate and comprehend the language properly</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>12</th>
<th>10</th>
<th>Articulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Articulation defect is mild</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Articulation defect is severe</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>13</th>
<th>11</th>
<th>Extinction or inattention (Neglect)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>One modality of sensation is loss</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Severe loss of sensation</td>
<td></td>
</tr>
</tbody>
</table>
Scores:

0 – No stroke

1-4 – Minor stroke

5-15 – Moderate stroke

15-41 – Severe stroke

NIHSS- A Good Predictor of Progress

NIHSS serves as the best prognostic indicator. A baseline NIHSS score larger than 16 indicates a sturdy probability of death of the patient, while a baseline NIHSS score lesser than 6 indicates a sturdy probability of patients recovery. On standard, an increase of 1 point in a patient’s NIHSS score reduces the probability of a brilliant result by 17% (32).

Modified Rankin Scale (MRS)

The modified Rankin Scale (MRS) is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. It has become the most widely used clinical outcome measure for stroke clinical trials (54).
# TABLE 4: MRS

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Score</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>Patient should not have any symptoms at all</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Patient should not have any significant disability in spite of presence of symptoms and can able to perform routine daily normal activities</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>Patient will have slight disability and the person cannot perform all routine activities but manages to do his personal work without help</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>Patient is having moderate disability and needs some help, but able to walk without assistance.</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>Patient will have moderately severe disability and cannot walk without help and unable to do his personal affairs without assistance</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>Here patient is having severe disability and the affected individual is bedridden, urinary incontinence will be present and needs continuous nursing care and attention</td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Total score of Modified Rankin Scale (MRS): 0-6.
Epidemiology

According to the World Health Organization (WHO), 15 million people suffer from stroke worldwide every single year. Of these, 5 million die, and another 5 million are left eternally disabled (55).

Stroke is the fifth leading cause of death in the United States and the leading cause of disability. Each year, approximately 795,000 people in the United States experience new (610,000 people) or recurrent (185,000 people) stroke (56). Epidemiologic studies indicate that 82-92% of strokes in the United States are ischemic (57).

Stroke is the second leading cause of death and fourth leading cause of disability worldwide. It is also the leading cause of functional impairment. 20% of survivor of stroke requires institutional care after 3 months and 15 to 30% are permanently disabled (58).

Globally 400-800 strokes per 1 million populations occur among which 5.7 million deaths occur. 15 million new acute strokes occur every year. It was estimated that 28.5 million DALYs were lost due to stroke worldwide (5).

Burden of stroke in India:

Stroke is the emerging disease in the India. 12% of all strokes occur in less than 40 years of age (59). Average age of stroke in developing
countries is 15 years younger than that of developed nations. 55.6 stroke cases occur per 1 million populations, among which 0.63 million deaths occur annually. The incidence of ischemic year stroke was 3.4 per 1000 per year, and the incidence of hemorrhagic stroke was 0.8 per 1000 per year. 1.44 to 1.64 million of acute stroke cases occurs every year. It was estimated that 6,398,000 DALYs were lost due to stroke. The case fatality rate is 18% to 41%. In India the case fatality rate is high compared to other western nations due to inadequate medical care and severity of lesion. Stroke prevalence among the rural India was found to be 1.1% and urban India was 1.9%. Stroke represents 1.2% of total death in India.
Muhammad Ishfaq, FahimUllah, et al. conducted a study titled “Correlation of serum calcium with severity of acute ischemic stroke”, a cross-sectional study. In this study serum calcium of all patients was measured and adjusted for serum albumin level. The mean serum calcium was 8.82±0.69 mg/dl (range: 6.84-10.48 mg/dl). The calcium level was underneath 8.7 mg/dl in 47 (34.06%) patients, 8.71-9.00 mg/dl in 32 (23.19%), 9.01-9.30 mg/dl in 31 (22.46%) and above 9.30 mg/dl in 28 (20.3%) patients. The mean NIHSS of the relevant groups was 20.19±7.865, 14.81±7.324, 19.81±6.199 and 14.82±7.727. Bivariate correlation was calculated between continuous data of serum calcium and NIHSS. The overall Pearson's correlation coefficient was r= -0.237 (p=0.005). The value was r= -0.256 (p=0.37) among men and r= -0.193 among women (p=0.10). From the inferences obtained author concluded the study stating that lower serum calcium levels may be associated with more severe clinical findings at the onset of stroke. Serum calcium levels may reproduce the brutality of ischemic injury hence more studies were in need to clarify and assess the role of calcium as the prognostic factor and the strategy for preventing stroke.

Meghna Borah, SriparnaDhar, Dipankar Mall Gogoi, et al., conducted a study titled “Association of Serum Calcium Levels with Infarct Size in Acute Ischemic Stroke: Observations from Northeast India” with the aim of determining the correlation between serum calcium (total, corrected, and ionized) and infarct size (IS) in patients with acute ischemic stroke. The result of the study revealed was, the levels of total calcium, albumin -corrected calcium, and ionized calcium was 9.61±
0.96 mg/dl (range: 7.84–11.5), 9.72 ± 0.97 mg/dl (range: 7.92–11.66), and 4.82 ± 0.51 mg/dl (range: 3.9–5.9). Mean IS as measured on the CT scan was 45.44 ± 18.2 cm³ (range: 16–94). The levels of total protein and albumin in the patients with ischemic stroke was 7.43 ± 0.61 g/dl (range: 5–8.4) and 3.87 ± 0.39 g/dl (range: 2.3–4.9). Total calcium, albumin - corrected calcium, and ionized calcium had a significant negative correlation with IS with $r = -0.578$, $-0.5396$, and $-0.5335$. Pearson’s correlation coefficient for serum albumin and IS was not statistically coefficient ($r = -0.0463$, $P = 0.7226$). Finally the author concluded the study stating that total, corrected, and ionized calcium had a statistically significant correlation with IS in ischemic stroke and from the inference of the study it was suggested that serum calcium can be used as a prognostic indicator in ischemic stroke as it directly correlates with the IS.

“Clinico-radiological correlation between serum calcium and acute ischemic stroke” the observational study conducted by Gaurav M Kasundra, IshaSood, et.,al…In this study the author stated that Higher Ca (Cca in some subgroups) is associated with better prognosis and recovery after AIS (except in posterior circulation strokes), and higher Ca and Cca are both associated with smaller IS. Serum Ca had a significant correlation with NIHSS at admission, NIHSS after 1 week, change in
NIHSS, BI, and IS (r-values: −0.3915, −0.4473, 0.2986, 0.5267, and −0.4256, respectively). Ca had significant (P < 0.05) correlation with NIHSS (admission) and highly significant (P < 0.001) correlation with BI. Among all patients, correlation of Ca with NIHSS was stronger after 1 week (r-value: −0.4473; P-value: 0.0011) than at admission (r-value: −0.3915; P-value: 0.0048). It was also found the calcium levels to have a better correlation, compared to the corrected calcium level. Cca had a significant (P < 0.05) correlation only with BI among all patients and the anterior circulation stroke subgroups and none of the other stroke subgroups or with NIHSS in any of the groups or subgroups analysed.

From these inferences the author concluded the study stating that Serum calcium level, and not albumin-corrected calcium level, has a significant positive correlation with early (1 week post-stroke) recovery after ischemic stroke.

Serum calcium in acute ischemic stroke: correlation with stroke severity and outcome, the study done by Marwa Mohammed Ghanem and ThaKamelAloush. It was a cross sectional study and the main aim of the study was to correlate the serum calcium level on one hand and the size of infarction and the stroke outcome. The study results showed that serum calcium values were found to decrease in patients with cerebral infarction, higher serum calcium levels both early and late were
associated with smaller cerebral infarct volume on DWI and that an inverse correlation exists between late serum calcium level and stroke outcome; and this puts a highlight on the role of both calcium compounds and calcium antagonists in ischemic brain injury.

Agursuryawan, AABN Nuartha, et., al. conducted a study titled “Low adjusted serum calcium level as a predictor of poor outcome in patient with acute ischemic stroke”, a prospective cohort study. The main aim of the study was to determine whether calcium can be used as a predictor of poor outcome in patients with acute ischemic stroke. NIHSS score was used. Chi square was used for analysis. The study revealed that lower adjusted serum calcium levels accompanied by poor outcome with RR-3.2, 95% CI = 1.34 to 7.62, p-value 0.00, multivariate analysis done revealed serum calcium as independent predictor of poor outcome in patients with acute ischemic stroke. From all these inferences, author concluded the study stating that low adjusted serum calcium as an independent predictor of poor outcome in patients with acute ischemic stroke.
AIMS AND OBJECTIVES

AIMS

To determine serum calcium as a prognostic marker in Acute ischemic stroke.

OBJECTIVES

1. To study the role of serum calcium as a severity marker of acute ischemic stroke.

2. To correlate serum calcium level with severity of stroke using NIHSS stroke score and assessing the prognosis.
METHODOLOGY

Study design:

A cross sectional study

Study duration:

The ethical approval for the study was obtained from the institutional ethical committee in the month of April 2017 and the sample collection were collected following the ethical approval, and the study completed in the month of September 2017. The total study duration was 6 months.

Study setting:

The study was conducted in the Government Stanley medical college and hospital, Chennai. The samples were selected among the inpatients who were admitted under the department of general medicine. The patients diagnosed with acute ischemic stroke were listed and among the listed patients the samples are selected based on the inclusion criteria.

Study population:

Inclusion criteria:

1- Age group from 18 to 80 years.
2- Both sexes are included.
3- Acute ischemic stroke diagnosed by clinical examination and CT brain plain.

4- Patients who are willing to participate in the study –consent form signed by patient or attender.

Exclusion criteria:

1- Patients with age more than 80 years were excluded.

2- Patients with malignancy

3- Patients with clinical findings and blood investigations suggestive of infection were excluded.

4- Patients with prior history of transient ischemic attacks or reversible ischemic neurological deficit.

5- Patients with features of hemorrhage confirmed by CT.

6- History of recent surgery and trauma.

7- Patients who did not give consent and who were not willing to participate in the study.

8- Prolong drug history like steroids.

Study setting:

75 patients who were admitted in the ward as inpatient under the department of general medicine with CT confirmed ischemic stroke, in Government Stanley medical college and hospital, Chennai.
**Study tool:**

Questionnaire including the socio demographic factors and the standardized questionnaire for analysing the level of calcium in ischemic stroke.

**Study method:**

75 patients who diagnosed to be a case of ischemic stroke confirmed by CT /MRI were selected for study by simple random method. Data was collected using a standardized questionnaire either from the patient or the patient’s attender. General examination, clinical examination and neurological examination was done. The routine blood investigations such as complete blood count, renal function test, Liver function test, etc…were done for the selected patients. CT was done for confirmation of diagnosis. All the data inferred were recorded in the standard proforma. Corrected calcium was calculated using the $CCa=\text{Total calcium}+0.8(4 - \text{patients albumin level})$. The value obtained is correlated with NIHSS scoring. National Institute of Health Stroke Scale were calculated. Based on the scores, the patients are categorized as mild, moderate and severe. The patients were treated with standard treatment protocol. It was made sure that no patient involved in the study were thrombolysed. Only the measures to reduce the edema were undertaken and drugs such as Mannitol through intravenous route or oral glycerol are
used. Modified Rankin Scale was applied to the study patients and the score was calculated after 4 weeks of follow up period.

Department of General medicine

Patients attending the Outpatient department

Features suggestive of Stroke

CT –Brain plain

Confirmation of Ischemic stroke

After getting consent (Verbal /written )

Study samples (75)

Check for corrected calcium

Result associated with NIHSS

Severity assessed.

MRS score measured after 4 weeks
Statistical analysis:

The data collected entered in MS-EXCEL and coding done for further statistical analysis. The statistical analysis done using the SPSS software version 21. Multivariate analysis, Pearson correlation analysis and chi-square test is applied for significance. p value <0.05 is considered as significant. The results are represented in the form of frequency tables, graphs and figures.

Ethical consideration:

The study was conducted after obtaining the ethical approval from the institutional ethical committee of Government Stanley medical college and hospital on April 2017. The aim and objective of the study and purpose of the study, mentioning that the details shared will be kept confidential were included in the informed consent. The details are kept confidential.

Operational definitions

HYPERTENSION:

The risk of stroke is increased four to six times in hypertensive patients. Since hypertension promotes the atheroma formation in all sized vessels of brain, hypertension is considered as important risk factor for
stroke. Prolonged treatment of diastolic BP to produce a fall of 6mm Hg decrease the stroke risk by 40% and the benefits occur within 3 years.

**DIABETES:**

Diabetic individuals are three times more prone for than individuals who are not diabetic. Diabetes also promotes the atheroma formation, thereby increasing the rate of occlusion of intracranial arteries. Impaired glucose tolerance may be a risk factor and elevated glycosylated haemoglobin may be found in up to 42% patients with cerebral infarcts not previously known to have diabetes.

**SMOKING:**

Smoking increases the stroke risk by two times. Smoking causes vasoconstriction, increases fibrinogen concentration, causes polycythaemia, reduces aggregation of platelets, all these contributes stroke occurrence. There is a dose response relationship, the risk doubling in the heaviest of smokers17. In the Framingham study, cessation of smoking removed the additional risk of stroke within 2 years.

**ALCOHOL:**

High Alcohol Consumption increases the risk of stroke. There is evidence for an association between sudden heavy drinking and the onset of cerebral infarction in young adults. Chronic light alcohol intake is
associated with a decreased risk of stroke. Chronic heavy consumption 180 – 400 g/wk. is associated with an increased risk.

**NIHSS SCORE**

NIHSS scoring was made based on the clinical parameters. In this study, patients with a score of 1-4 were considered as MILD, score 5-15 were considered as MODERATE, score >15 were considered as SEVERE category.

**MRS score**

MRS score of 3,4,5,6 were included under Good Outcome and scores of 1, 2 were considered as Poor outcome.
RESULTS
RESULTS

The study participants were distributed based on their calcium levels such as individuals with low calcium and normal calcium level. Out of 75 participants, 45 (60%) patients presented with ischemic stroke had low serum calcium while 30 (40%) participants had normal level of serum calcium.

![Distribution of study participants based on their calcium levels](chart.png)

**Chart 1: Distribution of study participants based on their calcium levels**

<table>
<thead>
<tr>
<th>Study Subjects</th>
<th>Low Blood Calcium</th>
<th>Normal Blood Calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>45</td>
<td>30</td>
</tr>
<tr>
<td>Percentage</td>
<td>60.00</td>
<td>40.00</td>
</tr>
</tbody>
</table>

**Table 5: Frequency distribution of study participants**
AGE WISE DISTRIBUTION

75 patients diagnosed with acute ischemic stroke were included in the study, of which 45 had low serum calcium and 30 participants had normal serum calcium. Among the participants with low serum calcium, most of the patients were in the age group 61 to 70 years with 55.56% (25) followed by 51-60 years of age with 24.4% (11), 13.3% (6) were in the age group 71-80 years. Least number of patients was noted in the age group 41-50 years with 6.67% (3). No patients were under the age of 40 years had low serum calcium. Among the patients with normal calcium level highest were in the age group 51-60 years with 56.57% (17) followed by the participants in the group 41-50 years with 16.67% (5). 13.3% (4) belong to the age group 61-70 years .13.3% (4) of patients less than 40 years of age also had normal serum calcium while there was no single participant in the age group 71-80 years had normal serum calcium.

Chart 2: showing the age distribution of the participants
Table 6: Frequency distribution of age of the study participants

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>Low Blood Calcium (freq)</th>
<th>Percentage (%)</th>
<th>Normal Blood Calcium (freq)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 40 years</td>
<td>0</td>
<td>0.00</td>
<td>4</td>
<td>13.33</td>
</tr>
<tr>
<td>41-50 years</td>
<td>3</td>
<td>6.67</td>
<td>5</td>
<td>16.67</td>
</tr>
<tr>
<td>51-60 years</td>
<td>11</td>
<td>24.44</td>
<td>17</td>
<td>56.67</td>
</tr>
<tr>
<td>61-70 years</td>
<td>25</td>
<td>55.56</td>
<td>4</td>
<td>13.33</td>
</tr>
<tr>
<td>71-80 years</td>
<td>6</td>
<td>13.33</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>100.00</td>
<td>30</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Table 6: Frequency distribution of age of the study participants

GENDER DISTRIBUTION

Among 45 participants with decreased serum calcium majority were males with 53.3% (24) and females were less comparatively with 46.6% (21). Out of the patients with normal serum calcium majority 83.3% (25) belong to male gender while rest 16.6% (5) belong to female gender.
<table>
<thead>
<tr>
<th>Gender Status</th>
<th>Low Blood Calcium</th>
<th>%</th>
<th>Normal Blood Calcium</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>24</td>
<td>53.33</td>
<td>25</td>
<td>83.33</td>
</tr>
<tr>
<td>Female</td>
<td>21</td>
<td>46.67</td>
<td>5</td>
<td>16.67</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>100.00</td>
<td>30</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Table 7: Frequency distribution of the participants based on gender

**Chart 3: Gender distribution of the participants**

**DISTRIBUTION BASED ON ADDICTIONS**

**Alcoholic habit**

Of all the patients assessed, 44.4% (20) of the patients with low serum calcium were alcoholics while 55.6% (25) participants were non-alcoholic. Equal distribution of alcoholic and non-alcoholic was noted in participants with normal level calcium with 50% (50) each.
Chart 4: Distribution based on alcoholic status

<table>
<thead>
<tr>
<th>Alcoholic status</th>
<th>Low serum calcium</th>
<th>%</th>
<th>Normal serum calcium</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>20</td>
<td>44.4%</td>
<td>15</td>
<td>50%</td>
</tr>
<tr>
<td>No</td>
<td>25</td>
<td>55.6%</td>
<td>15</td>
<td>50%</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>100%</td>
<td>30</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 8: Frequency distribution based on the addiction to alcohol

Smoking habit

Among 45 patients in the low serum calcium category majority 57.8% (26) were non-smokers while 42.2% (19) had the positive history of smoking. 73.3% (22) patients belonging to the group of normal serum calcium was non-smokers while 26.7% (8) was smokers. In both the category majority of the participants are non-smokers.
Chart 5: Distribution based on the habit of smoking

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Low serum calcium</th>
<th>%</th>
<th>Normal serum calcium</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>19</td>
<td>42.2%</td>
<td>8</td>
<td>26.7%</td>
</tr>
<tr>
<td>No</td>
<td>26</td>
<td>57.8%</td>
<td>22</td>
<td>73.3%</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>100%</td>
<td>30</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 9: Frequency distribution based on the addiction to smoking

**DISTRIBUTION BASED ON DIABETIC STATUS**

Among 45 patients who had low serum calcium most of them 53.3% (24) was known diabetic and 46.7% (21) were non-diabetics. Out of 30 participants who had normal blood calcium level 26.7% (8) were diabetic and majority 73.3% was non diabetic.
Chart 6: Distribution based on diabetic status

<table>
<thead>
<tr>
<th>Diabetes Mellitus</th>
<th>Low Blood Calcium</th>
<th>%</th>
<th>Normal Blood Calcium</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>24</td>
<td>53.33</td>
<td>8</td>
<td>26.67</td>
</tr>
<tr>
<td>No</td>
<td>21</td>
<td>46.67</td>
<td>22</td>
<td>73.33</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>100.00</td>
<td>30</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Table 10: Frequency based on diabetic status

HYPERTENSION

Among the study participants, the 45 patients who had low serum calcium level had 57.8% (26) patients with positive history of hypertension while 42.2% (19) were normotensives. Among the patients with calcium within reference range 36.7% (11) were hypertensives and 63.3% (19) had normal blood pressure values.
**Table 11: Frequency distribution based on hypertension status**

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>Low Blood Calcium</th>
<th>%</th>
<th>Normal Blood Calcium</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>26</td>
<td>57.78</td>
<td>11</td>
<td>36.67</td>
</tr>
<tr>
<td>No</td>
<td>19</td>
<td>42.22</td>
<td>19</td>
<td>63.33</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>100.00</td>
<td>30</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**Chart 7: Distribution based on status of the blood pressure**

**SPEECH DISTURBANCE**

Out of 45 patients who had their serum calcium at the low reference range, 95.6% (43) had disturbance in their speech while 56.7% (17) patients with the normal serum calcium level had the similar issue. To the least only 4.44% (2) patients was free from speech disturbance among the low calcium participants whereas 43.3% (13) of normal calcium persons were freed from the disturbance.
Table 12: Frequency distribution of participants based on speech disturbance

<table>
<thead>
<tr>
<th>Speech Disturbance</th>
<th>Low Blood Calcium</th>
<th>%</th>
<th>Normal Blood Calcium</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>43</td>
<td>95.56</td>
<td>17</td>
<td>56.67</td>
</tr>
<tr>
<td>No</td>
<td>2</td>
<td>4.44</td>
<td>13</td>
<td>43.33</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>100.00</td>
<td>30</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Chart 8: Distribution based on the speech disturbance

DISTRIBUTION BASED ON THE NIHSS SCORE

Out of the 45 participants who presented with low levels of calcium majority of them (48.89%, 22) reported with severe stroke with NIHSS score 21-41 followed by 31.1% (14) with moderate to severe type of stroke NIHSS score 16-20, 17.8% (8) had score in the range 5-15, that is moderate stroke and at the least 2.22% (1) had minor stroke with score
ranging from 1 – 4 while majority 43.3% (13) patients with normal serum calcium had the score 1-4 which represents minor stroke followed by 36.7% (11) with moderate stroke of score 5-15 and 20% (6) were in the moderate to severe category with score 16-20. None of the participants with normal serum calcium had severe form of stroke.

Table 13: Frequency distribution based on NIHSS Score

<table>
<thead>
<tr>
<th>National Institute of Health Stroke Scale</th>
<th>Low Blood Calcium</th>
<th>%</th>
<th>Normal Blood Calcium</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor Stroke (1-4)</td>
<td>1</td>
<td>2.22</td>
<td>13</td>
<td>43.3</td>
</tr>
<tr>
<td>Moderate Stroke (5-15)</td>
<td>8</td>
<td>17.7</td>
<td>11</td>
<td>36.6</td>
</tr>
<tr>
<td>Moderate to severe stroke (16-20)</td>
<td>14</td>
<td>31.1</td>
<td>6</td>
<td>20.0</td>
</tr>
<tr>
<td>Severe Stroke (21-41)</td>
<td>22</td>
<td>48.8</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>100.00</td>
<td>30</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Modified Rankin scale

Among 45 patients who had low serum calcium majority, 97.8% (44) had poor outcome of the disease while 80% (24) with normal calcium level had comparatively poor outcome. Only 2.22% (1) patient with low blood calcium had good prognosis whereas 20% (6) with normal calcium had good prognosis, which is comparatively higher.

Table 14: Frequency distribution based on MRS

<table>
<thead>
<tr>
<th>Modified Rankin Scale</th>
<th>Low Blood Calcium</th>
<th>%</th>
<th>Normal Blood Calcium</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good Outcome</td>
<td>1</td>
<td>2.22</td>
<td>6</td>
<td>20.00</td>
</tr>
<tr>
<td>Poor Outcome</td>
<td>44</td>
<td>97.78</td>
<td>24</td>
<td>80.00</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>100.00</td>
<td>30</td>
<td>100.00</td>
</tr>
</tbody>
</table>
When analysing the age distribution between the participants with the low and normal calcium level, the trend was noted in which higher age presentation was noted in low serum calcium group with the mean value 63.62 and Standard deviation 7.26 whereas in participants with normal calcium level the mean was 53.1% with standard deviation 8.53. The increased difference in mean age of the patients participated was statistically significant (P-value <0.05).

**Table 15: Association of Age distribution with the calcium levels**

<table>
<thead>
<tr>
<th>Age Distribution</th>
<th>Low Blood Calcium</th>
<th>Normal Blood Calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td>63.62</td>
<td>53.10</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>7.26</td>
<td>8.53</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Unpaired t Test</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
When gender status has been analysed, it was found that the lower male gender presentation was observed in low calcium with 53.3% compared to normal serum calcium group participants with 83.3%. The increased difference in percentage of male patients between low calcium group and normal calcium group (30 percentage points, 36% lower) was found to be statistically significant (p <0.05).

**Table 16: Association of Gender with the calcium levels**

<table>
<thead>
<tr>
<th>Gender Status</th>
<th>Low Blood Calcium (%)</th>
<th>Normal Blood Calcium (%)</th>
<th>P value Chi Squared Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>24(53.33)</td>
<td>25(83.33)</td>
<td>0.0071</td>
</tr>
<tr>
<td>Female</td>
<td>21(46.67)</td>
<td>5(16.67)</td>
<td></td>
</tr>
</tbody>
</table>

A trend of lower alcoholics presentation observed in low blood calcium group compared to normal blood calcium group was found to be statistically insignificant (p >0.05), when the alcohol intake was analysed with the study groups.
**Table 17: Association of status of alcohol with the calcium levels**

<table>
<thead>
<tr>
<th>Alcoholic</th>
<th>Low Blood Calcium</th>
<th>Normal Blood Calcium</th>
<th>P value Chi Squared Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20(44.44)</td>
<td>15(50.00)</td>
<td>0.6373</td>
</tr>
<tr>
<td>No</td>
<td>25(55.56)</td>
<td>15(50.00)</td>
<td></td>
</tr>
</tbody>
</table>

A trend of low smokers presentation observed in normal blood calcium group compared to low blood calcium group was found to be statistically insignificant (p >0.05) when statistical analysis done using chi squared test.

**Table 18: Association of smoking status with the calcium levels**

<table>
<thead>
<tr>
<th>Smoking</th>
<th>Low Blood Calcium</th>
<th>Normal Blood Calcium</th>
<th>P value Chi Squared Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19 42.22</td>
<td>8 26.67</td>
<td>0.1688</td>
</tr>
<tr>
<td>No</td>
<td>26 57.78</td>
<td>22 73.33</td>
<td></td>
</tr>
</tbody>
</table>

When statistically analysing diabetes mellitus status between the study groups, a trend of higher diabetes mellitus presentation was observed in low blood calcium group (53.33%) compared to normal
blood calcium group (26.67%). The increased difference in percentage of diabetes mellitus patients between low calcium group and normal calcium group (26.67 percentage points, 50% higher) was found to be statistically significant (p <0.05).

When statistically analysing diabetes mellitus status between the study groups, a trend of higher diabetes mellitus presentation was observed in low blood calcium group (53.33%) compared to normal blood calcium group (26.67%). The increased difference in percentage of diabetes mellitus patients between low calcium group and normal calcium group (26.67 percentage points, 50% higher) was found to be statistically significant (p <0.05).

Table 19: Association of diabetic status with the calcium levels

<table>
<thead>
<tr>
<th>Diabetes mellitus</th>
<th>Low Blood Calcium</th>
<th>%</th>
<th>Normal Blood Calcium</th>
<th>%</th>
<th>P value Chi Squared Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>24</td>
<td>53.3</td>
<td>8</td>
<td>26.6</td>
<td>0.0224</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td></td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>21</td>
<td>46.6</td>
<td>22</td>
<td>73.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
<td></td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

On analysing hypertension status between the study groups, a trend of higher hypertensives presentation observed in low blood calcium
group compared to normal blood calcium group was found to be statistically insignificant (p >0.05).

**Table 20: Association of hypertension status with the calcium levels**

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>Low Blood Calcium</th>
<th>%</th>
<th>Normal Blood Calcium</th>
<th>%</th>
<th>P value Chi Squared Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>26</td>
<td>57.78</td>
<td>11</td>
<td>36.67</td>
<td>0.0728</td>
</tr>
<tr>
<td>No</td>
<td>19</td>
<td>42.22</td>
<td>19</td>
<td>63.33</td>
<td></td>
</tr>
</tbody>
</table>

When statistically analysing NIHSS score status between the study groups, a trend of higher NIHSS score presentation (Severe Stroke category (21-41)) was observed in low blood calcium group (48.89%) compared to normal blood calcium group (0.00%). The increased difference in percentage of NIHSS score (Severe Stroke category (21-41)) presentation between low calcium group and normal calcium group (48.89 percentage points, 95% higher) was found to be statistically significant (p <0.05).
Table 21: Association of NIHSS with the calcium levels

<table>
<thead>
<tr>
<th>NIHSS</th>
<th>Low Blood Calcium</th>
<th>%</th>
<th>Normal Blood Calcium</th>
<th>%</th>
<th>P value Chi Squared Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor Stroke (1-4)</td>
<td>1</td>
<td>2.22</td>
<td>13</td>
<td>43.33</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Moderate Stroke (5-15)</td>
<td>8</td>
<td>17.78</td>
<td>11</td>
<td>36.67</td>
<td></td>
</tr>
<tr>
<td>Moderate to severe stroke (16-20)</td>
<td>14</td>
<td>31.11</td>
<td>6</td>
<td>20.00</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Severe Stroke (21-41)</td>
<td>22</td>
<td>48.89</td>
<td>0</td>
<td>0.00</td>
<td></td>
</tr>
</tbody>
</table>

When analysing Modified Rankin score status between the study groups, a trend of higher poor outcome status was observed in low blood calcium group (97.78%) compared to normal blood calcium group (80.00%). The increased difference in percentage of poor outcome status as per MRS between low calcium group and normal calcium group (17.78 percentage points, 18% higher) was found to be statistically significant (p <0.05).
Table 22: Association of MRS with the calcium levels

<table>
<thead>
<tr>
<th>Modified Rankin Scale</th>
<th>Low Blood Calcium</th>
<th>%</th>
<th>Normal Blood Calcium</th>
<th>%</th>
<th>P value Chi-Squared Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good Outcome</td>
<td>1</td>
<td>2.22</td>
<td>6</td>
<td>20.0</td>
<td>0.0102</td>
</tr>
<tr>
<td>Poor Outcome</td>
<td>44</td>
<td>97.7</td>
<td>24</td>
<td>80.0</td>
<td>0</td>
</tr>
</tbody>
</table>

Calcium vs NIHSS

While evaluating the relationship between blood calcium levels and NIHSS scores, a positive correlation was observed with a Pearson’s coefficient of 0.32. It was statistically significant with a p-value of 0.0058 according to ANOVA test.

Chart 11: Calcium vs NIHSS

Calcium Vs NIHSS

\[ y = 2.7868x - 4.6058 \]

\[ R^2 = 0.0993 \]
Table 23: Correlation analysis –calcium vs NIHSS

<table>
<thead>
<tr>
<th>Correlation Analysis - Calcium Vs NIHSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson’s R</td>
</tr>
<tr>
<td>R Square</td>
</tr>
<tr>
<td>P value</td>
</tr>
<tr>
<td>ANOVA</td>
</tr>
</tbody>
</table>

In our study blood calcium levels almost matched NIHSS scores steadily in a linear fashion. The rate of increase predicted was 2.79 NIHSS score points for every 1 gm/dl increase in blood calcium levels.

**Calcium vs MRS**

While evaluating the relationship between blood calcium levels and MRS scores, a positive correlation was observed with a Pearson’s coefficient of 0.38. It was statistically significant with a p-value of 0.0008 according to ANOVA test.
In our study blood calcium levels almost matched MRS scores steadily in a linear fashion. The rate of increase predicted was 0.49 MRS score points for every 1 gm/dl increase in blood calcium levels.
SUMMARY

Majority of the study subjects in low blood calcium group were distributed in 61-70 years age group (n=25, 55.56%) and 51-60 years age group in normal blood calcium group (n=17, 56.66%) (p= <0.0001, unpaired t test). The trend of higher age presentation was observed in low blood calcium group (63.62) compared to normal blood calcium group (53.10). The increased difference in mean age of patients between low calcium group and normal calcium group (10.52 mean years, 17% higher) was found to be statistically significant (p <0.05).

Most of the study subjects in low blood calcium group most of them were males (n=24, 53.33%) and same in normal blood calcium group (n=25, 83.33%)( p= 0.0071, chi squared test), a trend of lower male gender presentation was observed in low blood calcium group (53.33%) compared to normal blood calcium group (83.33%). The increased difference in percentage of male patients between low calcium group and normal calcium group (30 percentage points, 36% lower) was found to be statistically significant (p <0.05).

Majority of the study subjects in low blood calcium group were non alcoholics (n=25, 55.56%) and equal distribution in normal blood calcium group (n=15, 50.00%)( p= 0.6373, chi squared test). When alcohol intake status between the study groups analysed, a trend of lower alcoholics
presentation observed in low blood calcium group compared to normal blood calcium group was found to be statistically insignificant (p > 0.05). Majority of the study subjects in low blood calcium group were non-smokers (n=26, 57.78%) and same in normal blood calcium group (n=22, 73.33%) (p = 0.1688, chi squared test). When statistically analysing smoking status between the study groups, a trend of higher smokers presentation observed in low blood calcium group compared to normal blood calcium group was found to be statistically insignificant (p > 0.05). Majority of the study subjects in low blood calcium group had diabetes mellitus (n=24, 53.33%) and non-diabetics in normal blood calcium group (n=22, 73.33%) (p = 0.0224, chi squared test). When statistically analysing diabetes mellitus status between the study groups, a trend of higher diabetes mellitus presentation was observed in low blood calcium group (53.33%) compared to normal blood calcium group (26.67%). The increased difference in percentage of diabetes mellitus patients between low calcium group and normal calcium group (26.67 percentage points, 50% higher) was found to be statistically significant (p < 0.05). Among the study subjects in low blood calcium group were hypertensives (n=26, 57.78%) and normotensives in normal blood calcium group (n=19, 63.33%) (p = 0.0728, chi squared test). When analysing hypertension status between the study groups, a trend of higher hypertensives presentation observed in low blood calcium group compared to normal
blood calcium group was found to be statistically insignificant (p >0.05). Majority of the study subjects in low blood calcium group had speech disturbance (n=43, 95.56%) and same in normal blood calcium group (n=17, 56.67%) (p= <0.0001, chi squared test). When statistically analysing speech disturbance status between the study groups, a trend of higher speech disturbance presentation was observed in low blood calcium group (95.56%) compared to normal blood calcium group (56.67%). The increased difference in percentage of speech disturbance presentation between low calcium group and normal calcium group (38.89 percentage points, 41% higher) was found to be statistically significant (p <0.05). Majority of the study subjects in low blood calcium group had NIHSS score between 21-41 (n=22, 48.89%) and NIHSS score between 1-4 in normal blood calcium group (n=13, 43.33%) (p= <0.0001, chi squared test). When statistically analysing NIHSS score status between the study groups, a trend of higher NIHSS score presentation (Severe Stroke category (21-41)) was observed in low blood calcium group (48.89%) compared to normal blood calcium group (0.00%). The increased difference in percentage of NIHSS score (Severe Stroke category (21-41)) presentation between low calcium group and normal calcium group (48.89 percentage points, 95% higher) was found to be statistically significant (p <0.05). Majority of the study subjects in low blood calcium group had poor outcome as per MRS (n=44, 97.78%) and
same in normal blood calcium group (n=24, 80.00%) (p= 0.0102, chi squared test). When statistically analysing modified Rankin score status between the study groups, a trend of higher poor outcome status was observed in low blood calcium group (97.78%) compared to normal blood calcium group (80.00%). The increased difference in percentage of poor outcome status as per MRS between low calcium group and normal calcium group (17.78 percentage points, 18% higher) was found to be statistically significant (p <0.05).
DISCUSSION

In our study, majority of the participants (60%) had low levels of serum calcium than participants with normal calcium range. The normal corrected calcium value taken, range from 8.6 to 10.2, where the level less than 8.6 is considered to be low and more than 10.2 is considered as high calcium level. With this corrected calcium range as base the distribution of participants were done. Each group has been compared with the demographic factors such as age and gender along with the personal habits such as alcohol and smoking and also with the diabetic and hypertension status of the participants. Finally the calcium levels are compared with the NIHSS and the MRS. From all these it is found that majority of the study population were in the age group 61 to 70 years with 55.56% and the male gender was high among the study participants with 53.2%. Most of the participants with low calcium level were non-alcoholic whereas equal distribution was found among the patients with normal calcium values. Regarding smoking habit more number of study subjects belongs to low calcium group were non-smokers. 53.3% were diabetic among the low calcium group and 26.75% had positive history of diabetes mellitus among the normal serum calcium group. Most of the participants in the group of decreased calcium were found to be hypertensive compared to the participants in the category of normal blood
calcium. Significant association was noted between the age distribution and the level of calcium with p-value <0.001, gender with p-value 0.007, diabetes mellitus with p-value 0.022. No significant association between smoking, alcohol and the status of the blood pressure. Significant association was seen when NIHSS is compared with the calcium and the significance also noted when calcium is compared with MRS, with p-value <0.0001 and 0.0102 respectively. ANOVA test was done which also elicited significant association between the calcium and NIHSS.

Similar to our study, the study conducted by Guven H, Cililier AE, et., al.. in their study titled “Association of serum calcium levels with clinical severity of acute ischemic stroke” inferred that NIHSS scores were higher in the patients with decreased calcium levels with p-value <0.05.

Similarly, the study conducted by Meghna Borah, Sriparna Dhār, et., al titled “Association of serum calcium levels with infarct size in acute ischemic stroke :observation from Northeast India”, concluded that calcium can be used as a prognostic indicator in ischemic stroke based on its significant association between calcium level and the size of the ischemic stroke.

Similar finding also noted in the study titled “low adjusted serum calcium level as a predictor of poor outcome in patients with acute
ischemic stroke” inferred that calcium level is an important predictor of outcome of stroke based on the statistically significant association between the variable with p-value <0.001.

In the study conducted by Abha Gupta, Umesh Dubay, et al. titles “Correlation of serum calcium levels with severity and functional outcome in acute ischemic stroke patients” stated that patients with high calcium had significantly less severity of the stroke and during follow up after 7 days the prognosis is better in patients with high calcium compared to the lower levels of calcium, which was statistically significant(p-value 0.01).

Muhammed Ishfaq, Fahim Ullah, et al. Conducted a study titled “correlation of serum calcium with severity of acute ischemic stroke” inferred that lower serum calcium is associated with more severe clinical finding at the onset of stroke and proved the significance with the help of Bivariate analysis and Pearson’s correlation coefficient was significant (p-value 0.005).
CONCLUSION

Age of the study subjects is normally distributed across the intervention groups and has an effect on prognosis in patients with acute ischemic stroke. Low blood calcium levels occurred in patients with age > 60 years consistently compared to patients with age < 60 years among ischemic stroke patients. Gender of the study subjects is normally distributed across the intervention groups has an effect on prognosis in patients with acute ischemic stroke. Low blood calcium levels occurred in female patients consistently compared to male patients among ischemic stroke patients. Alcohol intake status of the study subjects is normally distributed across the intervention groups has no effect on prognosis in patients with acute ischemic stroke. Smoking status of the study subjects is normally distributed across the intervention groups has no effect on prognosis in patients with acute ischemic stroke. Diabetes mellitus presentation among study subjects is normally distributed across the intervention groups has an effect on prognosis in patients with acute ischemic stroke. Low blood calcium levels occurred in diabetes mellitus patients consistently compared to non-diabetes mellitus patients among ischemic stroke patients. Hypertension status of the study subjects is normally distributed across the intervention groups has no effect on prognosis in patients with acute ischemic stroke. NIHSS score
presentation among study subjects is normally distributed across the intervention groups has an effect on prognosis in patients with acute ischemic stroke. Low blood calcium levels occurred in patients with NIHSS score (Severe Stroke category (21-41)) consistently compared to patients with NIHSS score (Minor Stroke category (1-4)) among ischemic stroke patients. Modified Rankin score presentation among study subjects is normally distributed across the intervention groups has an effect on prognosis in patients with acute ischemic stroke. Low blood calcium levels occurred in patients with poor outcome status as per MRS consistently compared to patients with good outcome status as per MRS among ischemic stroke patients. We conclude that blood calcium measurement can be an important additional parameter for predicting poor prognosis and recovery in ischemic stroke patients.

From all these, We can conclude that:

Alcohol intake, smoking, hypertension, hemiplegia side and facial nerve involvement had no statistically significant role to play on blood calcium levels in ischaemic stroke patients. Ischemic stroke patients with low blood calcium levels had bad prognosis. Female Ischemic stroke patients aged >60 years with low blood calcium levels and comorbid conditions like diabetes mellitus had grave prognosis.
LIMITATIONS:

Our study has a major limitation of small sample size, and no data was collected on ionized calcium which is a physiological active component of calcium. In addition to this limitation, the serum calcium is measured during admission irrespective of stroke onset time interval. Patients with unrecognized malignancy and with hypo parathyroid disorders also have a low calcium level which leads to misconception of the outcome.

RECOMMENDATIONS:

Serum calcium levels may reflect the severity of ischemic injury. Further trials will be required to clarify the mechanism of this effect and to assess the role of serum calcium level as a prognostic variable and of calcium modulation as part of a strategy for prevention of stroke. We also suggest further research on the relationship between adjusted serum calcium levels with the outcome of acute ischemic stroke patients with consideration for the aforementioned weaknesses.
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