PROGNOSTIC ROLE OF CRP IN ACUTE STROKE

Dissertation submitted to

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY

In partial fulfilment of the regulations

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M.D. GENERAL MEDICINE – [BRANCH - 1]

DEPARTMENT OF GENERAL MEDICINE

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&

M.G.M. GOVERNMENT HOSPITAL,

TIRUCHIRAPALLI

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI

MAY 2020

CERTIFICATE FROM THE DEAN

This is to certify that the dissertation titled **"PROGNOSTIC ROLE OF CRP IN ACUTE STROKE"** is a bonafide research work done by Dr.NIYAS.A under direct supervision and guidance of Prof.Dr.D.NEHRU MD., DMRD., Head of the Department, Department of General Medicine, in partial fulfilment of the requirements for the award of M.D. GENERAL MEDICINE degree of The Tamilnadu Dr. M.G.R. Medical University, to be held in May 2020.

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PLAGIARISM CERTIFICATE

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DECLARATION

I solemnly declare that the dissertation titled **"PROGNOSTIC ROLE OF CRP IN ACUTE STROKE"** is a bonafide and genuine research work done by me at K.A.P.VISWANATHAM GOVT. MEDICAL COLLEGE, TIRUCHIRAPALLI-1 under the guidance and supervision of **Prof.Dr. D. NEHRU M.D., DMRD.** This dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfilment of the requirements for the award of M.D. Degree [Branch-1] in General Medicine.

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ABBREVATIONS

ACA	-	Anterior Cerebral Artery
AHA	-	American Heart Association.
ASA	-	American Stroke Association
ATP	-	Adenosine Triphosphate
BI	-	Barthel ADL index
BMI	-	Body Mass Index
CNSS	-	Canadian Neurological Stroke Scale.
CVA	-	Cerebro Vascular Accident
CBF	-	Cerebral Blood Flow
CHD	-	Coronary Heart Disease
CRP	-	C-Reactive Protein
DVT	-	Deep Vein Thrombosis
DM	-	Diabetes Mellitus
HTN	-	Hypertension
ICH	-	Intracerebral Haemorrhage
mRS	-	Modified Rankin Scale
MCA	-	Middle Cerebral Artery
MI	-	Myocardial Infarction
NIHSS	-	National Institutes of Health Stroke Scale
PCA	-	Posterior Cerebral Artery
PET	-	Positron Emission Tomography
SPECT	-	Single Photon Emission Computed Tomography
SAH	-	Sub Arachnoid Haemorrhage
SBP	-	Systolic Blood Pressure
TIA	-	Transient Ischemic Attack
UTI	-	Urinary Tract Infection

CONTENTS

INTRODUCTION

Cerebrovascular disease is one of the most common and devastating disorder. Stroke is the second most common cause of death in the world. [1] It is one of the most common life threatening and disabling neurologic disease. Cerebrovascular deaths are responsible for approximately 6.15 million deaths per annum globally. Based on various Indian studies, prevalence rate of stroke vary from 40-470/100000 population depending on the region and time of study. Stroke is an important cause of mortality and morbidity in India. [2]

The incidence of cerebrovascular diseases increases with age. As the elderly population grows, the incidence of stroke will increase and also the mortality. This is because strokes are more likely in elderly and disabled patients. Old age is a strong predictor of outcome and mortality after stroke[3]. Among patients who survive stroke chance of recurrence is high. At least 1 in 6 suffers another stroke within next 5 years. Even though the possibility of recurrent CVA is high, its prediction is difficult. Increasing age, cardiovascular co morbidities, atrial fibrillation, hypertension, diabetes mellitus and stroke severity are all associated with death or new vascular events but the sensitivity and specificity of these risk factors are low. Hence, a continued search for predictive markers is of interest.

Pathologically, the two major types of strokes are haemorrhagic and ischemic. The important causes of ischemic stroke are embolic and atherothrombotic. Cardio embolic stroke is due to emboli from the heart

because of rheumatic, ischemic or congenital heart diseases. Atherothrombotic stroke is due to generalized atherosclerosis in the body.

Previous data demonstrate that inflammation plays an important role in the pathophysiology of stroke. Susceptibility of the patients to stroke and further prognosis are influenced by systemic inflammatory processes[4]. Development of stroke is due to longstanding vascular inflammation, plaque rupture, thrombosis and subsequent brain ischemia or infarction. Recent studies show that CRP has a functional role in the inflammatory process. It is well proven that CRP is an acute marker of inflammation and its concentration increases in circulation during inflammatory events. CRP binds to damaged cell membrane and contributes to the inflammatory responses[5]. Elevated blood levels of inflammatory markers are associated with coronary heart disease (CHD) and stroke. C – reactive protein, a peripheral marker of inflammation, has consistently been observed to be related to the risk of cerebrovascular or cardiovascular events. High-sensitivity assays that accurately measure levels of CRP have been recommended for assessing the risk in ischemic stroke patients. CRP increases the activation of the inflammation both invitro and in vivo and get deposited chronically within the brain after ICH[6]. Elevation of CRP during the acute-phase response in intracerebral haemorrhage (ICH) is also associated with the outcomes like death and vascular complications.

Multiple studies demonstrated the role of CRP as a predictive marker for cerebrovascular events. Hence elevated CRP is a predictive marker for future cerebrovascular events but the timing of CRP evaluation in relation to the onset

of the qualifying event has not been determined. Many studies evaluated only the relationship between CRP and mortality instead of functional outcome. Insearch for further clarification we sought to assess CRP level as an early prognostic, marker of functional outcome after stroke.

AIMS AND OBJECTIVES

To evaluate the role of CRP assay within 24 hours of stroke onset as a biomarker for predicting disease severity and short term outcome (within 1 week)

MATERIALS &METHODS

SOURCE OF DATA: This study titled "PROGNOSTIC ROLE OF CRP IN ACUTE STROKE" was done at Mahatma Gandhi Memorial Govt. Hospital attached with KAPV Govt. Medical College Trichy.

PERIOD OF STUDY: This study was conducted from JANUARY 2018-JANUARY 2019.

STUDY DESIGN: DESCRIPTIVE CROSS SECTIONAL STUDY

INCLUSION CRITERIA:

Patients admitted with first ever acute stroke within the first 24 h of onset.

EXCLUSION CRITERIA:

1) More than 24 h after symptoms onset
2) Recent history of traumatic brain injury, ACS, Cerebro-vascular events, autoimmune diseases, liver cell failure and chronic renal failure.

Sample size: 50

ETHICAL COMMITTEE APPROVAL:

Approval was obtained from Institutional Ethical Committee.

CONSENT:

Informed consent was obtained from all the participants and their relatives wherever necessary.

SAMPLE COLLECTION:

This study included patients admitted with first ever acute stroke within first 24 hours of onset admitted to MGMGH, Department of Medicine, Trichy, during the period of January 2018 to January 2019 were included in the study. The diagnosis of stroke was established by history, clinical examination, laboratory investigations and CT scan of brain.

The cases with recent history of traumatic brain injury, acute coronary syndrome, cerebro-vascular events, autoimmune diseases, liver cell failure and chronic renal failure were excluded from the study.

After final selection of the patients, they were subjected to history taking, clinical examination and laboratory investigations according to the proforma which is enclosed Patients included in the study were subjected to neurological evaluation. Assessment of stroke severity at admission was done by National Institute of Health Stroke Scale (NIHSS) and stroke was categorized as mild (NIHSS 0–7), moderate (NIHSS 8–14) or severe (NIHSS >14).

Seven days following the onset of stroke, outcome of patients evaluated using two different scores including modified Rankin Scale (mRS) and Barthel ADL index (BI). Poor outcome was considered to be >2 by mRS score and <95 by BI. End point was assessed for the patient during the hospital stay.

A brain CT scan was done on admission to all patients to differentiate between ischemic and haemorrhagic stroke.

Blood samples were withdrawn on admission for routine laboratory tests and for CRP level assay. Three ml of venous blood was taken through a venipuncture and sent coded by the patient's number to the laboratory. The lab was blinded to the samples. The CRP assay was done using immunoturbidimetry method. Normal reference level of CRP in our laboratory is upto 0. 60mg/L.

NATIONAL INSTITUTES OF HEALTH STOKE SCALE (NIHSS)

PATIENT IMPRINT

Category	Score/Description		Date/Time Initials	Date/Time Initials	Date/Time Initials	Date/Time Initials	Date/Time Initials
1a. Level of Consciousness (Alert, drowsy, etc.)	0 = Alert 1 = Drowsy 2 = Stuporous 3 = Coma						
1b. LOC Questions (Month, age)	0 = Answers both correctly 1 = Answers one correctly 2 = Incorrect						
1c. LOC Commands (Open/close eyes, make fist/let go)	0 = Obeys both correctly 1 = Obeys one correctly 2 = Incorrect						
2. Best Gaze (Eyes open - patient follows examiner's finger or face)	0 = Normal 1 = Partial gaze palsy 2 = Forced deviation						
3. Visual Fields (Introduce visual stimulus/threat to pt's visual field quadrants)	0 = No visual loss 1 = Partial Hemianopia 2 = Complete Hemianopia 3 = Bilateral Hemianopia (Blind)						
4. Facial Paresis (Show teeth, raise eyebrows and squeeze eyes shut)	0 = Normal 1 = Minor 2 = Partial 3 = Complete						
5a. Motor Arm - Left **5b. Motor Arm - Right** (Elevate arm to 90° if patient is sitting, 45° if supine)	0 = No drift 1 = Drift 2 = Can't resist gravity 3 = No effort against gravity 4 = No movement X = Untestable (Joint fusion or limb amp)	Left					
		Right					
6a. Motor Leg - Left **6b. Motor Leg - Right** (Elevate leg 30° with patient supine)	0 = No drift 1 = Drift 2 = Can't resist gravity 3 = No effort against gravity 4 = No movement X = Untestable (Joint fusion or limb amp)	Left					
		Right					
7. Limb Ataxia (Finger-nose, heel down shin)	0 = No ataxia 1 = Present in one limb 2 = Present in two limbs						
8. Sensory (Pin prick to face, arm, trunk, and leg - compare side to side)	0 = Normal 1 = Partial loss 2 = Severe loss						
9. Best Language (Name item, describe a picture and read sentences)	0 = No aphasia 1 = Mild to moderate aphasia 2 = Severe aphasia 3 = Mute						
10. Dysarthria (Evaluate speech clarity by patient repeating listed words)	0 = Normal articulation 1 = Mild to moderate slurring of words 2 = Near to unintelligable or worse X = Intubated or other physical barrier						
11. Extinotion and Inattention (Use information from prior testing to identify neglect or double simultaneous stimuli testing)	0 = No neglect 1 = Partial neglect 2 = Complete neglect						
	TOTAL SCORE						

INITIAL	SIGNATURE	INITIAL	SIGNATURE	INITIAL	SIGNATURE

modified RANKIN SCALE (mRS)

Score	Definition
0	No symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities
3	Moderate disability. Requires some help, but able to walk unassisted
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent
6	Dead

BARTHEL ADL INDEX (BI)

The Barthel Index

Patient name _____ Rater name _____ Date _____

ACTIVITY	SCORE
Feeding	
0 = unable	
5 = needs cutting, spreading butter, etc, or requires modified diet	
10 = independent	_____
Bathing	
0 = dependent	
5 = independent (or in shower)	_____
Grooming	
0 = needs help with personal care	
5 = independent face/hair/teeth/shaving (implements provided)	_____
Dressing	
0 = dependent	
5 = needs help but can do about half unaided	
10 = independent (including buttons, zips, laces, etc)	_____
Bowels	
0 = incontinent (or needs to be given enemas)	
5 = occasional accident	
10 = continent	_____
Bladder	
0 = incontinent, or catheterised and unable to manage alone	
5 = occasional accident	
10 = continent	_____
Toilet use	
0 = dependent	
5 = needs some help, but can do something alone	
10 = independent (on and off, dressing, wiping)	_____
Transfers (bed to chair and back)	
0 = unable, no sitting balance	
5 = major help (one or two people, physical), can sit	
10 = minor help (verbal or physical)	
15 = independent	_____
Mobility (on level surfaces)	
0 = immobile or <50 yards	
5 = wheelchair independent, including corners, >50 yards	
10 = walks with help of one person (verbal or physical) >50 yards	
15 = independent (but may use any aid, eg. stick) >50 yards	_____
Stairs	
0 = unable	
5 = needs help (verbal, physical, carrying aid)	
10 = independent	_____
	Total (0–100)

ANALYSIS OF DATA

Data were collected prospectively and coded prior to analysis using the professional statistical Package for Social Science. (SPSS). The description of data was done in the form of mean (±) SD for quantitative data and frequency and proportion for qualitative data. A correlation study was done and pearson correlation coefficient(r) was used to assess the correlation between variables. r value ranges from -1 to +1. Based on the r values correlation were assessed.

Results were considered significant if p value less than or equal to 0. 05. These analysis were done separately for total stroke patients, ischemic stroke patients, haemorrhagic stroke patients separately.

REVIEW OF LITERATURE

HISTORY OF STROKE:

The history of the study of stroke starts long back. Hippocrates first recognized stroke 2400 years back. It was then called apoplexy. In Greek it means "struck down by violence" [7].Apoplexy was later described by Galen (131 – 200 AD) as sudden loss of sensation and motion all over the body except respiration. Experimental hemiplegia was done by him by sectioning the spinal cord of monkeys. Cause of stroke to be in the brain was considered by Theophilus Protospatharius (630 – 671 AD).

In 1665 Johann JakobWepfer (1620 – 95) who is a Swiss physician advocated that stroke was due to disease in the blood vessels of the brain. He did autopsy and revealed haemorrhage under dura and in ventricles. He thus diagnosed four cases of stroke. He also identified two types of stroke – ischemic and haemorrhagic[8].

Thomas Willis (1621 – 75) described the unique pattern of cerebral blood supply within the circle of arteries. Thus the name of circle of willis originated. He is recognized as the founder of clinical neuroscience[9]. On the basis of autopsy studies Giovanni B. Morgagni (1682 – 1771) classified stroke into infarction and haemorrhage. He contributed much for the early understanding of neuropathology[10]. He postulated the concept that hemiplegia occurs on the side opposite to the lesion in the cerebrum.

Pathology of brain haemorrhage was described by J. Cruveilhier (1719 – 187 4). Jean-André Rochoux (1787–1852) is the author of the first neuropathological and clinical description of cerebral haemorrhage and ischemia. It was based on concepts that underlie current vascular neurology[11]. He also postulated that apoplexy was due to intracerebral haemorrhage. Charcot (1825 – 1895) demonstrated tiny aneurysms within the cerebral arteries. Now they are named after him. One of the common causes of intracerebral haemorrhage is the rupture of these aneurysms.

A detailed report about cerebral venous thrombosis was first given by Minier (1828). First work on cerebral embolism was published by Virchow I (1847).

Joseph Jules Babinski (1857 – 1932) was the person who noted that in certain cases of paralysis, instead of flexing when the sole is stimulated, the toe on the affected side executes extensor movement on the metatarsal. He also pointed out that fanning of the lateral toes can be accompanied by extension of the great toe[12]. This is known as extensor plantar response or Babinski sign. It is diagnostic for upper motor neuron lesion.

Godfrey Hounsfield, an engineer invented the computed tomographic scanner. This was an incomparable contribution to medicine. He had this idea of computed tomography during a weekend ramble in 1967. Atkinson Morley's Hospital in Wimbledon was the first site where scanner was used clinically by James Ambrose in 1971[13]. In 1973 Paul C. Lauterbur published the theory behind MRI. Raymond Damadian reported that tumours and normal tissue can

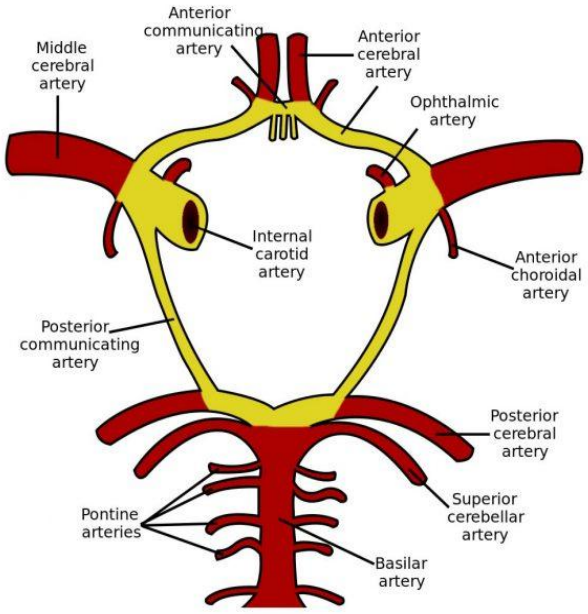
be distinguished by nuclear magnetic resonance ("NMR"). The ability to visualize pathology in the living person has added immensely to the diagnosis, prognosis and study of stroke.

DEFINITION:

A stroke, or cerebrovascular accident, defined as an abrupt onset of a neurologic deficit which is attributable to a focal vascular cause[14]. Thus, the definition of stroke is clinical and investigations including brain imaging are needed to support the diagnosis.

ANATOMY OF CEREBRAL CIRCULATION:

The arterial supply of brain includes internal carotid and vertebral arteries and their branches. The intracranial part of internal carotid artery has three large branches - the ophthalmic artery, the middle cerebral artery and the anterior cerebral artery. The basilar artery is formed by the union of the right and left vertebral arteries at the lower border of the pons. It divides into right and left posterior cerebral arteries at the upper border of pons.



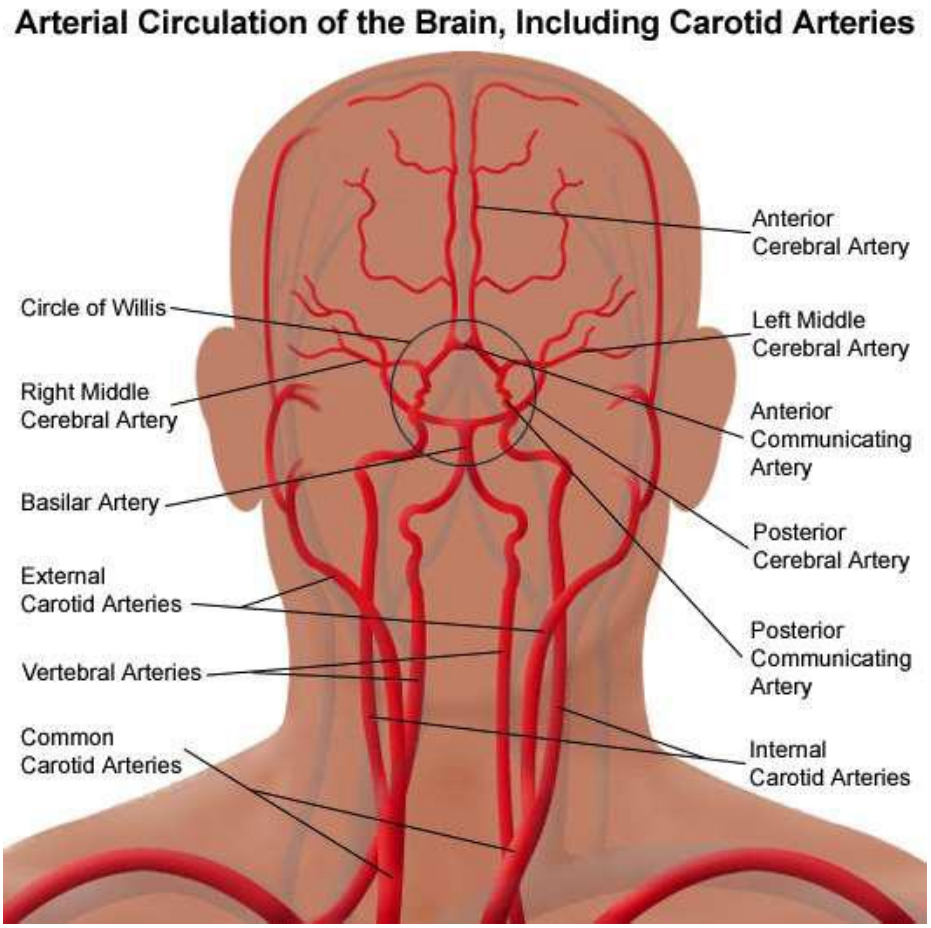
One peculiar feature of cerebral circulation is the presence of a free anastomosis in the form of the circulus arteriosus (circle of Willis). It is formed anteriorly by the anterior communicating artery, posteriorly by the basilar artery as it divides into the right and left posterior cerebral arteries and on each side by the anterior cerebral, internal carotid, posterior communicating and posterior cerebral arteries. It lies in the interpeduncular subarachnoid cisterns. It can equalize the pressure in the arteries of the both sides.

The anterior, middle and posterior cerebral arteries give rise to two sets of branches. They are cortical and central. The cortical branches ramify on the surface of the cerebral hemisphere and supply the cortex. Deeper structures of the brain are supplied by the central branches.

BLOOD SUPPLY OF INDIVIDUAL STRUCTURES

Cerebral cortex:

Cerebral cortex is supplied by the cortical branches of anterior, middle and posterior cerebral arteries. The main somatic motor and sensory areas are supplied by the middle cerebral artery except in their uppermost parts (leg areas). They are supplied by the anterior cerebral artery. Posterior cerebral artery supplies the posterior part beyond the calcarinesulcus.



Internal capsule:

Internal capsule is supplied by the central branches of middle cerebral artery, anterior cerebral artery, posterior communicating artery and anterior choroidal artery.

Thalamus:

Central branches of the posterior cerebral artery supplies thalamus.

Cerebellum:

The superior surface of cerebellum is supplied by superior cerebellar branches of basilar artery. Anterior part of inferior surface is supplied by

anterior inferior cerebellar branch of basilar artery and the posterior part is supplied by the posterior inferior cerebellar artery.

Midbrain:

It receives the blood supply from the branches of the posterior cerebral artery.

Pons :

It is supplied by the pontine branches of basilar artery.

Medulla :

It is supplied by the medullary branches of vertebral artery and branches from the posterior inferior cerebellar artery.

Cerebral venous drainage:

Venous drainage from the cerebral hemispheres emerges and thereby forms small venous structures in the pia mater. Larger venous channels can form cerebral veins. They can bridge the subarachnoid space and thereby enters into endothelial-lined sinuses in the dura mater. Small veins from the scalp can communicate with the dural sinus through emissary veins which can perforate the skull. The majority of the cerebral convexities is ultimately drained into superior sagittal sinus. The superior sagittal sinus courses posteriorly back towards the occiput, and there it receives drainage from the straight sinus. The straight sinus itself receives drainage from the inferior sagittal sinus, which courses in the falxcerebri. The inferior margin of the superior sagittal sinus divides into right and left transverse sinus within the tentorium cerebelli, which is again made up of dura mater. Each transverse sinuses curves

downward and backward as sigmoid sinus, which get ultimately drained by each of the internal jugular veins. Venous drainage is asymmetrical most of the times, with the superior sagittal sinus draining into right transverse sinus commonly and the straight sinus into the left transverse sinus.

Cavernous sinus forms an irregular network of venous channels. It lies on either side of the sella turcica and sphenoid sinus. They extends from the superior orbital fissure to the petrous portion of the temporal bone. The cavernous sinus encloses one segment of the internal carotid artery. Each cavernous sinus is connected to each other by basilar venous plexus. Each cavernous sinus drains posteriorly into superior and inferior petrosal sinus. They enter the transverse sinus and bulb of the internal jugular vein.

The lymphatics of the central nervous system continue to be a topic of investigation.

PHYSIOLOGY OF CEREBRAL CIRCULATION

Precise regulation of cerebral blood flow (CBF) is needed for maintenance of constant oxygen and nutrients supply to the brain[15]. The average cerebral blood flow for young adults is 54 ml / 100 g / min. The average adult brain weighs around 1400 g. So the flow for the whole brain is around 756 ml/min. In resting humans, the average blood flow to gray matter is around 69 ml/ 100 g/ min and around 28ml / 100g / min in white matter. There is marked variation in local blood flow with changes in brain activity. In subjects who are awake but at rest, blood flow is more in the frontal and

premotor regions. Blood flow to the left hemisphere is more in right-handed individuals when a verbal task is being performed. Blood flow to the right hemisphere is more when a spatial task is being performed.

Inspite of variation in perfusion pressure, auto regulation maintains the blood flow to the brain at relatively constant levels. Cerebral blood flow is maintained at 50 mL per 100 g of brain tissue per minute, provided cerebral perfusion pressure ranges from 60 to 160 mmHg. There are two components of auto regulation.

1. Myogenic theory :

It is based on the intrinsic contractile process of smooth muscle to stretch. As pressure rises, the blood vessels are distended and the vascular smooth muscle fibers that surround the vessels also contracts. This prevents excess blood flow in the brain and the reverse occurs during fall in blood pressure.

2. Metabolic theory :

When blood flow decreases, vasodilator substances accumulates resulting in the dilatation of vessels. When blood flow increases the reverse occurs. The metabolic changes which produces vasodilatation are decrease in oxygen tension, increase in osmolality and increase in carbon dioxide tension. Lactate and potassium also contributes.

Oxygen consumption by the human brain averages around 3. 5ml / 100g of brain tissue / minute (49ml/min for whole brain) in an adult. This constitutes approximately 20% of the total resting body oxygen consumption. The brain is

very much sensitive to hypoxia. Occlusion of its blood supply can produce unconsciousness within 10 seconds. The vegetative structures in brain stem are even more resistant to hypoxia compared to cerebral cortex. The basal ganglia, thalamus and inferior colliculus are more prone for hypoxic damage. There is a rapid fall in the oxygen utilization and circulation of the brain from childhood to adolescence. There is more gradual and progressive reduction throughout the remaining life span[16].

Glucose is the major ultimate energy source in the brain. Under normal situations, 90% of the energy needed for maintaining ion gradients across the cell membrane and transmitting electric impulses comes from this source. Occlusion of blood supply for few seconds can lead to unconsciousness. This is because neurons lacks glycogen and the energy failure is rapid.

ETIOLOGY OF STROKE:

Stroke is classified into:

i) Ischemic stroke

ii) Intraparenchymal haemorrhage

iii) Subarachanoid haemorrhage

ETIOLOGY OF ISCHEMIC STROKE :

Common causes :

1. **Thrombosis**

- Lacunar stroke (small vessel)

- Large vessel thrombosis
- Dehydration

2. Embolic occlusion

a) Artery to artery

- Carotid bifurcation
- Aortic arch
- Arterial dissection

b) Cardio embolic

- Atrial fibrillation
- Mural thrombus
- Myocardial infarction
- Dilated cardiomyopathy
- Valvular lesions
- Bacterial endocarditis
- Paradoxical embolus
- ASD, patent foramen ovale

Uncommon causes :

- Hyper- coagulable disorders
- Venou sinus thrombosis
- Fibromuscular dysplasia
- Vasculitis
- Subarachanoid haemorrhage vasospasm

Large vessel Thrombosis :

The risk factors are hypertension (relative risk 2-5), diabetes (relative risk 1. 8–6), smoking (relative risk -1. 8) and hyperlipidemia (relative risk 1. 8 – 2. 6).

Lacunar stroke :

Hypertension and age are the principal risk factors.

Cardioembolic stroke :

It constitutes around 20% of all ischemic strokes. It is primarily due to embolism of thrombotic material from the atrial or ventricular wall or left heart valves. The most important causes of cardioembolic stroke are non rheumatic atrial fibrillation, rheumatic heart disease, myocardial infarction, prosthetic valves and ischemic cardiomyopathy[17].

Artery to Artery embolic stroke :

Thrombus which forms on atherosclerotic plaques can embolise to intracranial arteries. The most common source of embolism is from the bifurcation of carotid arteries.

Etiology of haemorrhagic stroke:

- Hypertension
- Cerebral amyloidosis
- Coagulopathies
- Anticoagulant therapy
- Thrombolytic therapy for acute MI or acute ischemic stroke.

- AV malformation, aneurysms, and other vascular malformations (venous and cavernous angiomas)
- Vasculitis
- Intracranial neoplasm
- Subarachanoid haemorrhage (SAH) is due to rupture of saccular or berry aneurysm.

PATHOPHYSIOLOGY OF CEREBRAL ISCHEMIA

Acute occlusion of an intracranial vessel causes decrease in supply of blood to the region of brain where it supplies. The magnitude of flow reduction depends on the collateral blood flow. Thus it depends on individual vascular anatomy and the site where occlusion occurs. Within 4 to 10 minutes death of brain tissue occurs when the blood flow falls to zero. This occurs in the central or core region of ischemic areas which is known as the umbra. Tissue surrounding the core region of infarction is ischemic but reversibly dysfunctional. This is referred to as the ischemic penumbra[18]. The penumbras will eventually infarct if there is no adjustment of blood flow to that area occurs. Reperfusion of that ischemic region is the most effective therapy for acute ischemic stroke

Cellular death occurs through two distinct pathways. First is a necrotic pathway in which cellular cytoskeletal breakdown is rapid due to principally energy failure of the cell. Second is an apoptotic pathway in which cells are programmed to die. Ischemia produces necrosis due to starvation of neurons to

glucose. This inturn results in failure of mitochondria to produce ATP. Without ATP, membrane ion pump fails and neurons depolarize. This allows intracellular calcium to rise. Cellular depolarization can cause glutamate release from synaptic terminals. Excess extracellular glutamate produces neurotoxicity by agonizing postsynaptic glutamate receptors by increasing neuronal calcium influx. Free radicals are produced by degeneration of membrane lipids and mitochondrial dysfunction. Free radicals can cause catalytic destruction of cell membranes which can likely damage other vital functions of cells.

Lesser degrees of ischemia as seen within the ischemic penumbra favours apoptotic cellular death. This causes cells to die days to weeks later. Inspite of extensive clinical study there are no clinically proven strategies which alter these ischemic cascades. Fever can dramatically worsens ischemia. Hyperglycemia (glucose>200 to 300mg/dl) can also worsens ischemia. Presence of hyperthermia increases ischemic mechanisms within the penumbra. This contributes to conversion of the penumbra into an irreversible lesion. So it is reasonable to control fever and prevent hyperglycemia as much as possible.

PATHOPHYSIOLOGY OF HAEMORRHAGIC STROKE:

In intracerebral haemorrhage (ICH), the possible mechanism is due to leakage from small intracerebral arteries which was damaged by chronic hypertension. Other causes includes bleeding disorders, iatrogenic anticoagulation, cerebral amyloidosis and cocaine abuse.

Intracerebral haemorrhage is more seen in certain sites like thalamus, putamen, cerebellum, and brainstem. Surrounding area of intracerebral haemorrhage can be damaged by the mass effect of hematoma. During intracerebral haemorrhage blood accumulates rapidly within the brain parenchyma. This leads to disruption of normal anatomy and increased local pressure[19]

Subarachnoid haemorrhage

Subarachnoid haemorrhage (SAH) can produce multifocal pathologic effects on brain. SAH results in increased intracranial pressure and affects cerebral autoregulation. These effects can be accompanied by acute vasoconstriction, microvascular platelet aggregation, and loss of microvascular perfusion. This can cause profound reduction in blood flow and cerebral ischemia.

CLINICAL FEATURES:

A careful history and neurologic examination often localises the region of brain dysfunction. If this region corresponds to a particular area of arterial distribution, the possible causes for the syndrome can be narrowed.

Stroke syndromes are divided into :

1) Large vessel stroke within the anterior circulation.
2) Large vessel stroke within the posterior circulation and
3) Small vessel disease of either vascular bed.

STROKE WITHIN ANTERIOR CIRCULATION

MIDDLE CEREBRAL ARTERY:

Contralateral hemiplegia, hemianaesthesia, homonymous hemianopia, global aphasia occurs when the dominant hemisphere is involved.

ANTERIOR CEREBRAL ARTERY :

Occlusion of proximal anterior cerebral artery (A1) is usually tolerated well because there is collateral blood flow through the anterior communicating artery and collaterals through the middle and posterior cerebral artery.

Single A2 Segment (distal to anterior communicating artery) occlusion causes :

- Paralysis of opposite foot and leg.
- Paresis of opposite arm.
- Cortical sensory loss over toes, foot and leg.
- Urinary incontinence.
- Abulia

ANTERIOR CHOROIDAL ARTERY:

Contralateral hemiplegia, hemianaesthesia and homonymous hemianopia.

INTERNAL CAROTID ARTERY:

With a competent circle of Willis, occlusions usually go unnoticed. If the thrombus propagates up the internal carotid artery into the MCA or embolises into it, symptoms are similar to proximal MCA occlusion. When the origin of both the ACA and MCA are occluded at the top of the carotid artery,

abulia or stupor occurs along with hemiplegia, hemianaesthesia and aphasia or anosognosia.

STROKE WITHIN POSTERIOR CIRCULATION

POSTERIOR CEREBRAL ARTERY :

a) P1 Syndrome :
   - Third nerve palsy with contralateralhemiplegia (Weber's syndrome)
   - Third nerve palsy with contralateral ataxia (Claude's Syndrome)
   - Contralateral hemiballismus
   - Contralateral hemisensory loss followed by agonizing pain in the affected areas (Thalamic Dejerine –Roussy syndrome).

b) P2 Syndrome :
   - Contralateral homonymous hemianopia with macular sparing.
   - Bilateral infarction in the distal PCAs produces cortical blindness.

VERTEBRAL AND POSTERIOR INFERIOR CEREBELLAR ARTERIES :

a) Lateral medullary syndrome
   - Vertigo, numbness of the ipsilateral face and contralateral limbs, hoarseness, diplopia, dysphagia, dyarthria and ipsilateral Horner's syndrome.

b) Medial medullary syndrome
   - Contralateral hemiparesis of arm and leg sparing face.
   - Contralateral loss of joint position sense and ipsilateral tongue weakness.

LACUNAR STROKE:

Lacunes can be defined as small subcortical infarcts (< 15 mm in diameter). They occurs in the territory of the deep penetrating arteries. A quarter of all ischaemic strokes (one fifth of all strokes) are lacunar stroke. They are small infarcts (2–20 mm in diameter) in the deep cerebral white matter, basal ganglia, or pons. They occurs as a result from the occlusion of a single small perforating artery supplying the subcortical areas of the brain[20].

Specific lacunar syndromes include:

Pure motorhemiparesis	- infarct in posterior limb of internal capsule
Pure sensory stroke	- infarct in ventrolateral thalamus
Ataxic hemiparesis	- infarct in ventral pons or internal capsule.
Dysarthria and clumpsy hand	- infarct in ventral Pons and genu of internal capsule.
Mixed sensorymotor	- Infarct in thalamus and posterior limb of internal capsule

Lacunar infarcts show a paradoxical clinical course. They have a favorable prognosis in the short term, characterized by a low early mortality and reduced functional disability on hospital discharge. They have an increased risk of death, recurrence of stroke and dementia in the mid- and long term.

INVESTIGATIONS:

All routine investigations including complete blood count, ESR, routine urine analysis, blood sugar, blood urea nitrogen, serum creatinine, serum electrolytes, serum lipid profile, prothrombin time, aPTT, chest X- ray and ECG are useful and should be considered in all patients.

IMAGING STUDIES:

1. CT SCAN :

CT scan identifies or excludes haemorrhage as the cause of stroke. Scans obtained in the first several hours after an infarction generally show no abnormality. Infarct may not be seen before 6 hours. CT scan can miss small infarcts in the posterior fossa and on the surface of cortex.

Contrast enhanced CT scan shows contrast enhancement of subacute infarcts. CT angiography shows visualization of cervical and intracranial arteries. Carotid disease and intracranial vascular occlusions are easily identified by this method. After an intravenous bolus of contrast, deficits in brain perfusion which is produced by occlusion of vessels can be demonstrated.

2. MRI :

MRI readily records the extent and location of infarction in all areas of brain including the posterior fossa and cortical surface. Diffusion weighted MRI and FLAIR (fluid – attenuated inversion recovery) are more sensitive for detecting early infarction. Using intravenous gadolinium contrast, MR

perfusion studies can be done. Brain regions showing poor perfusion with no abnormality on diffusion are considered equivalent to the ischemic penumbra. Potential advantage of MR imaging for screening candidates for thrombolytic therapy is that MR may be more sensitive for detecting both acute and chronic brain haemorrhages compared to CT[21.] MR angiography is more sensitive for detecting stenosis of extracranial internal carotid arteries and also large intracranial vessels. MRI with fat saturation helps visualising extra or intracranial arterial dissection.

3. CEREBRAL ANGIOGRAPHY :

Conventional X- ray cerebral angiography is considered to be the 'gold standard' for identifying atherosclerotic narrowing of cerebral arteries. Endovascular techniques can be used to deploy stents within delicate intracranial vessels, to perform balloon angioplasty of stenotic lesions and to correct intracranial aneurysms by embolization. Although its use is investigational in many centers, it may become routine in the near future.

4. ULTRASOUND TECHNIQUES :

Stenosis at the origin of the internal carotid artery can be identified and quantified using USG which combines a B – mode ultrasound image with a Doppler ultrasound assessment of flow velocity. Transcranial Doppler assessment of MCA, ACA and PCA flow and of vertebrobasilar flow is also

useful. Transcranialdoppler does not provide information regarding the pathological nature of the stenosis[22].

5. PERFUSION TECHNIQUES :

Both xenon techniques and PET can quantify cerebral blood flow. Single photon emission computed tomography (SPECT), CT perfusion and MR perfusion techniques detects relative cerebral blood flow.

TREATMENT OF ACUTE ISCHEMIC STROKE

1. ANTIPLATELET AGENTS:

Aspirin is the one of the antiplatelet agent that has been prospectively studied for the treatment of acute ischemic stroke. Use of aspirin within 48 hours of stroke onset reduces risk of stroke recurrence and mortality.

2. THROMBOLYSIS:

The National Institute of Neurological Disorders and stroke (NINDS) recombinant tissue plasminogen activator (rt PA) stroke study showed a well established benefit for iv rt PA in patients who presents with ischemic stroke within 3 hours of onset. In March 2013, the AHA/ASA guidelines revised to expand the window of treatment from 3 hours to 4.5 hours. However, the exact efficacy of intravenous thrombolytics for acute ischemic stroke remains unclear.

3. ANTICOAGULATION:

Current data do not support routine use of anticoagulation in acute ischemic stroke. However, anticoagulation is recommended in some specific clinical situations.

Indications include:

- Conditions with high risk of early cardiogenic rembolization
- Symptomatic dissection of the arteries supplying the brain
- Symptomatic extra or intracranial arteriosclerotic stenosis with crescendo TIAs or if there is early progressive stroke
- Basilar artery occlusion before or after intra-arterial pharmacological or mechanical thrombolysis.
- Known hypercoagulable states
- Cerebral venous sinus thrombosis

4. MEDICAL SUPPORT:

Patients experiencing acute ischemic stroke who are hypertensive but otherwise candidates for thrombolysis do have a specific target blood pressure. This is to limit the risk of haemorrhage in elevated and variable blood pressure. The goal is less than 185 mm / 110 mm Hg before the initiation of IV fibrinolytic therapy. In stroke patients with extreme hypertension (≥220/120 mm Hg) or those not receiving an IV fibrinolytic, a 15% decrease in SBP after initial treatment may be reasonable. This allows some blood-pressure lowering, but not enough to worsen cerebral ischemia. This is termed permissive

hypertension. Cerebral edema is treated with intravenous mannitol and other antiedema measures. Presence of fever in acute stroke has been associated with a poor outcome[23]. It should be treated with antipyretics. Diabetes can worsen the outcome of acute stroke[24]. Serum glucose should be kept at <200 mg/dl. Attention is directed towards preventing the common complications of bedridden patients – infections like pneumonia, UTI, bedsores, DVT and pulmonary embolism.

5. NEUROPROTECTION:

It is the concept which provides a treatment which prolongs brain's tolerance to ischemia[25]. In many studies astrocytes are the prime target. Drugs that block the excitatory amino acid pathways provened to have protection of neurons and glia in animals. Inspite of multiple clinical trials, not yet been proven beneficial in humans. Many researches are ongoing for a safe agent which limits ischemic damage in human stroke.

C- REACTIVE PROTEIN

CRP was discovered by Francis and Tillett in 1930 as a protein reacting with the C- polysaccharide of the cell wall of Streptococcus pneumonia. Avery et al considered C- reactive material as a protein which requires calcium for its reactions with patient's serum. The term acute phase reactant was introduced by him. This is because serum from patients acutely ill with infectious diseases contains the C – reactive protein[26]

CRP is a trace protein in the circulation of healthy people. It has a medium concentration of approximately 1 mg/l. Its concentration can increase hundred fold or more in response to injury, infection or inflammation. Acute phase phenomena can also occur in chronic inflammatory disorders. Raised CRP is seen in smokers, stress, diabetes, obesity, atherosclerosis and elderly. CRP levels are of value in 6 clinical situations like (a) monitoring the response of antibiotics in patients with bacterial infections, (b) in obstetric patients with premature rupture of membranes, rising CRP titre gives early warning of intrauterine infections, (c) to differentiate between active disease and infections in patients with SLE and ulcerative colitis, where level of response to active disease already established, (d)to measure the activity of disease and response to disease-modifying drugs in rheumatoid arthritis, (e) to detect complications of postoperative patients, (f) to differentiate between infection and graft-versus-host-disease in bone marrow transplant patients[27]

STRUCTURE:

CRP is an alpha globulin protein. It has a molecular weight 105500. It has a homopentameric structure. It has Calcium binding specificity for phosphocholine. Expression of CRP is regulated mainly at the transcriptional level. IL-6 is the principal inducer of the gene during the acute phase. The crystal structure of CRP has been determined and the chemical composition of its ligand-binding site was established [28]. CRP is a pattern recognition molecule. It binds to specific molecular configurations that are typically

exposed during cell death or those which are found on the surfaces of pathogens[29]. A cleft on the pentameric face opposite to that of calcium site have an important role[30]. The protein has 187 amino acids in a single polypeptide chain. The amino terminal residue of CRP is pyrrolidine carboxylic acid and the carboxyl terminus is proline. The 2 half-cystine residues at 36 and 78 positions are involved in a disulfide bond[31].

SYNTHESIS :

CRP is produced mainly by hepatocytes in response to interleukin – 1 (IL – 1), interleukin – 6 (IL-6) and tumor necrosis factor (TNF). The formation of CRP by the liver always accompanies enhanced C^{14}-amino acid incorporation into other serum proteins, but the reverse was not always found[32] Some data suggest that it is produced in atherosclerotic lesions, kidney, neurons and alveolar macrophages.

FUNCTION :

Function of CRP is related to its role in innate immune system[33]. The physiological role of CRP is poorly understood. But it has several potentially anti- inflammatory as well as pro- inflammatory effects. Ligand - bound CRP activates the classical complement pathway. It binds to immunoglobulin receptors on immune cells and activates cytokines and complement mediated inflammatory reactions which exacerbates inflammatory ischemic injury. CRP which bounds to a multivalent ligand can efficiently initiates the activity of C3

convertase through the classical pathway. It thus decorate the ligandsurface with opsonic complement fragments[34]. C-reactive protein also induces various inflammatory changes in endothelial and smooth muscle cell, associated with atherosclerosis. It attaches to nuclear components, damaged membranes and apoptotic cells. It also binds to oxidized low – density lipoproteins (LDL) in which phosphorylcholine is the primary phospholipid. The complex of CRP and LDL is opsonized by macrophages. It results in synthesis of foam cells. It induces expression of adhesion molecules E- selectin, vascular cell adhesion molecule – 1(VCAM-1) and intercellular adhesion molecule- 1(ICAM-1) by endothelial cells. It also helps to recruit monocytes by virtue of inducing monocyte chemo attractant protein -1.

CRP binds to both stimulatory receptors, FcγRI and FcγRIIa. It increases phagocytosis and release of inflammatory cytokines. It also binds to the inhibitory receptor, FcγRIIb and blocks activating signals[35]. CRP is associated with endothelial cell dysfunction and progression of atherosclerosis. This could be possibly by decreasing nitric oxide synthesis. CRP is relevant as a distal surrogate marker of various pro-inflammatory cytokines, which can affects endothelial function[36.] It also sensitizes endothelial cells to being destroyed by cytotoxic CD8+ T cells. It also facilitates thrombogenesis through stimulation of tissue factor biosynthesis by macrophages. This shows that high CRP plasma concentrations and the extent of its deposition in the atherosclerotic plaque are results in plaque vulnerability and lead to acute thrombotic events. A proatherogenic role of CRP was also described in

apolipoprotein E- deficient mice recently [37]. It is therefore acceptable that CRP is not only a marker but also involved in the initiation and progression of atherosclerosis.

CRP AND RISK OF VASCULAR DISEASE :

Raised plasma concentration of CRP are associated with atherosclerosis of carotid, coronary or lower limb peripheral arteries. This can also leads to progression of atherosclerotic disease. The earliest studies of CRP and risk of future vascular events were reported in 1996 and 1997. It showed an increased risk of future coronary artery disease and stroke. CRP is an indicator of risk of future cardiovascular events [38]. It is independent of other risk factors like hypercholesterolemia and cigarette smoking in apparently healthy and at- risk populations. Depending on these datas, the CDC and the AHA issued guidelines in 2003 for the use of high – sensitivity CRP (hs-CRP) in clinical practice.

This statement recommends that :

i) An hs – CRP assay is the assay of choice. It should be performed in metabolically stable persons with no obvious infectious or inflammatory diseases.

ii) The results should be expressed in mg/l. There should be 2 assays, 2 weeks apart which represents the inflammatory status better.

iii) The adult population should be stratified in 3 groups : Lower risk : < 1mg/l, average risk: 1 – 3 mg/l, high risk : > 3 mg/l.

iv) Persons at high risk have 2-fold increased risk of future cardiovascular disease compared to low risk.

v) Persons with moderate risk (10% to 20% risk of coronary heart disease in 10 years) benefits from measurement of CRP in addition to traditional cardiovascular risk factors.

CRP IN STROKE:

The data on CRP in coronary heart disease are strong and persuasive. But questions were raised regarding extensive use of CRP testing in cerebrovascular disease without analysis of the need of specific studies in this area. Inspite of the view of atherosclerosis as a single disease, the risk factor profiles of stroke and MI clearly varies in lot of aspects. Stroke and CHD affect different patient populations (older age more in stroke). There is only a partial overlap in the pathogenesis (atherothrombosis is the first but not the only cause of stroke). Stroke and CHD have different risk factor profiles (raised cholesterol levels are stronger risk factors in CHD, whereas arterial hypertension is more important in stroke). So it is not possible to transfer concepts which are valid for CHD directly to stroke. There is a correlation of CRP concentration with either the extent of cerebral infarction caused by the incident stroke or the presence of secondary complications of stroke at the time of sampling like infection, underlying malignancy, or deep vein thrombosis. All of these can cause elevation of CRP and other inflammatory mediators[39]. Elevated CRP is a direct response to the extent of cerebral injury. As an

inflammatory marker, it is possible that high CRP is associated with underlying processes which cause a more severe stroke[40]. There is a role and relationship between haemorrhagic stroke and inflammation also. High levels of CRP are also seen among individuals with risk for future cerebro or cardiovascular event. Elevated CRP also predicts the outcome of the patients[41]. Researchers have now proposed that assessment of CRP levels provides a useful method to assess cerebrovascular risk which improves treatment decisions and patient outcomes.

PRIMARY PREVENTION OF STROKE: THE ROLE OF CRP IN STROKE RISK ASSESSMENT:

Several studies demonstrated that a single, non – fasting measurement of CRP in apparently healthy individuals can predicts future fatal and non – fatal cerebrovascular events. The relationship between a patient's baseline concentration of CRP and future cerebrovascular risk has been consistent in various studies. In most cases, this has been proven to be independent of major risk factors -age, smoking, BP and diabetes. Various studies showed secondary preventive therapies such as statin drugs and aspirin depends on the individual patient's baseline CRP[42]. However analysis from these studies provides information about relative risks only. We know little or nothing about predictive values and absolute risk for cerebrovascular disease. Lack of information on the absolute risk and the cost of screening strategies indicates the need for further studies.

SECONDARY PREVENTION OF STROKE: THE ROLE OF CRP IN THE RISK ASSESSMENT OF RECURRENT VASCULAR EVENTS:

Multiple studies demonstrate that CRP concentrations in stroke patients predict outcome or new vascular events independently of age, stroke severity and other conventional prognostic factors. Higher levels of CRP have been associated with large infarcts. Further, knowledge of inflammatory status helps in deciding the management status-aggressive or conservative. However, the data are less consistent for the in-hospital prognostic stratification. Plasma CRP production increases markedly over 48 hours to 72 hours following spontaneous intracerebral haemorrhage. It is also related to the outcome[43.] High concentrations of CRP in the acute phase reflects the extent of cerebral tissue injury, inflammatory disease or inflammatory disease.

Some of the major studies regarding CRP and outcome of ischemic stroke are detailed below.

Muir et al (1999) conducted a study to examine the relationship between CRP and outcome in acute ischemic stroke[44]. This was a subgroup analysis. It is a prospective observational study done University Hospital Acute Stroke Unit with a population of 2, 60, 000 people. Survival time and cause of death for upto 4 years after the index stroke was determined and related to CRP concentrations within 72 hours of stroke. 283 patients admitted to the stroke unit during 1992-93 were studied. A total of 228 patients had ischemic stroke. CRP was measured within 72 hours of stroke. Median follow up period was for 959 days. The mean CRP value was 10. 1 mg/l. Patients were divided into 2

groups on the basis of a CRP concentration above or below the mean. Mean CRP in the low CRP group was 4. 2 mg/L and in the high CRP group was 33. 9 mg/L. Patients with CRP above the mean were older (p=0. 01). They had more severe strokes as judged by NIHSS and lower total cholesterol levels. A higher proportion of patients with CRP above the mean had definite infarcts which are identified on CT scan.

In both groups, cardiovascular events were the most common cause of death. A higher proportion of patients with CRP concentration above the mean died of cardiovascular causes although this was not statistically significant. The median survival time for those dying of myocardial infarction was 40 days in the high CRP group. Median survival for patients died of stroke was 32. 5 days in the low CRP group and 47 days in the high CRP group. So the study conclusion was that CRP concentration is an independent predictor of survival after ischemic stroke.

Di Napoli et al (2001) conducted a study for assessing the prognostic values of CRP at admission and discharge with 1- year outcome[45]. 193 patients with first-ever ischemic stroke were studied - 128 in a derivation set and 65 in a validation set. CRP was measured within 24 hours after first ischemic stroke, within 48 to 72 hours and at the time of hospital discharge. The Canadian Neurologic Stroke Scale (CNSS) and Barthel index (BI) were used to assess stroke severity and disability respectively. They were followed up regularly as outpatients for 1 year. During the follow up period, new vascular events were also monitored. The primary end point was the combination of death of any

cause and any new vascular event like TIA, recurrent stroke, unstable angina or MI whichever comes first. In the derivation set, the median CRP value within 24 hours, between 48 – 72 hours and at time of hospital discharge was 1. 5 mg/L, 1 mg/L and 0. 6 mg/L respectively (normal value <0. 5 mg/dl). The level of CRP changed between admission and discharge (p=0. 0002). No difference was found in the length of hospital stay between the different patterns of CRP.

A cut off point of 1. 5 mg/dL for CRP at discharge provided optimum sensitivity for adverse outcome, based on the receiver operator curves. The patients were divided into 2 groups (CRP < 1. 5 and CRP > 1. 5 mg/L). High CRP at admission was associated with more severe neurological deficit and disability at admission as judged by the CNSS score and BI respectively. CRP levels above normal (>0. 5 mg/dl) at entry were significantly associated with larger infarcts. At discharge, higher CRP values were also associated with larger infarcts.

At the end of 1 year of follow up, 40 patients had a primary end point. 20 patients died, 16 had vascular causes. 20 patients experienced a new vascular event (TIA in 1year, MI in 3, recurrent stroke in 7 and occurrence of unstable angina requiring new admission to hospital is 9). The functional status was significantly worse in the subgroup of patients with CRP levels at discharge >1. 5 mg/dl; only 3 patients were functionally dependent at 1 year. The occurrence of combined end point at 1 year follow up was related to CRP level at admission and discharge. CRP level at hospital discharge showed the strongest

independent association with the combined end point at 1 year. These results were confirmed in the validation set.

Di Napoli et al (2002) performed a study to assess the usefulness of markers of inflammation as predictors of cardiovascular events in ischemic stroke patients[46]. They analyzed levels of CRP, fibrinogen and D- dimer within the first 24 hours after stroke onset in 473 first-ever ischemic stroke patients. Study also assessed the cumulative survival curves free of cardiovascular events in relation to the level of each of these markers.

In the study, the median age of the population was 74 years and 42% had > 3 associated atherogenic risk factors. Approximately 39% had a previous diagnosis of CHD and 25% had atrial fibrillation on admission to the hospital. The median CRP, fibrinogen and D- dimer values within 24 hours were 12 mg/L, 4. 55 mg/L and 692 mg/L respectively.

All patients received secondary preventive treatment with aspirin, ticlopidine or warfarin and control of recognized vascular risk factors. After 1 month, 65 patients had a cardiovascular event. After 1 year, 139 patients had a cardiovascular event and 6 died of nonvascular causes. During the entire 2 year follow up period, 182 patients had a cardiovascular event or died of nonvascular causes. Of these 46 experienced a recurrent stroke and 58 had a cardiac event. At the end of follow up 281 were functionally dependent and 104 patients were functionally independent. 149 of them resided in nursing homes or needed assistance to live in homes. For CRP, the levels cut off were <5, 5-33 and >33 mg/L. The median CRP level was significantly higher at

enrollment among patients who had a cardiovascular event than in patients who survived free of cardiovascular events and in patients who died of cardiovascular causes during follow up. The median CRP level at enrollment was also higher among patients who died of nonvascular causes than among those who survived. Higher median levels of CRP were also significant predictors of recurrent stroke and cardiac event. Patients with the highest levels of CRP at enrollment had a significantly higher probability of a primary end point during the entire follow up period. The difference was more evident in the first months after stroke.

Patients in the highest tertiles of D-dimer, fibrinogen and CRP had an excess risk of new cardiovascular events respectively compared to patients in the lowest tertile. The patients in the highest tertile of CRP had 4 times the risk of a new cardiovascular event. Risk was independent of D-dimer and fibrinogen levels. Thus, the conclusion was that elevated levels of CRP more than that of D-dimer and fibrinogen are related to the risk of new cardiovascular events after ischemic stroke.

Winbeck et al (2002) investigated the impact of early serial CRP measurement in ischemic stroke on long – term outcome[47]. 127 patients who had a first ischemic stroke within 12 hours after symptom onset were examined. Serial CRP measurements were done at admission (CRP1), within 24 hours (CRP2) and within 48 hours (CRP3). MRI of the brain was performed and infarct volume was determined. The patients were followed up for a period of 1 year. The end point was the combination of death due to any cause and any

new nonfatal vascular event such as recurrent stroke, unstable angina, or MI. The Barthel Index and the modified Rankin scale were used to assess functional disability and were evaluated at admission and during follow up. A Barthel adl Index score >85 was defined as favourable and functionally independent. Patients were divided according to the modified Rankin scale into the following categories independent in terms of day to day activities and with a good outcome (score 0 to2) and dependent or dead (score 3 to 6).

Of the total 127 patients studied, the medium initial Barthel index score was 55 and the median Ranking scale score was 4 at admission. After 1 year of follow up, 62% of the patients were functionally independent (BI score >85). CRP concentration >0.5 mg/dl was defined as pathologically increased. The CRP concentration increased significantly during the first 48 hours after the onset of symptoms. The mean CRP level at admission was 0.86 mg/dl. The patients were further subdivided into patients above and below the CRP concentration. The mean CRP increased significantly from the first to the third measurement. In 32 patients, the peak CRP level was not reached within 96 hours after stroke onset. Both subgroups were comparable regarding several clinical and laboratory parameters, including the incidence of other known cardiovascular risk factors.

As calculated from the MRI, the mean lesion volume was 33.4ml. An increased CRP was significantly associated with a larger initial MRI lesion volume only for the third CRP measurement neither for the first nor for the second CRP measurement. During follow up 24 patients had a primary end

point. 10 patients died. 14 patients experienced a new vascular event (TIA n=3; recurrent stroke n=9; unstable angina n=2). Patients with increased CRP 2 levels had a significantly lower follow up BI score. Accordingly, the incidence of dependency (BI score <85) after 1 year tended to be increased in the group of patients with CRP 2 levels >0.86 mg/l. Death was significantly more often observed in patients with CRP 2 levels>0. 86 mg/dl. There was a significantly higher rate of end point events in patient with a CRP 2 >0.86 mg/dl after symptom onset. CRP1 and CRP 3 were not significantly related to end point events.

Thus this study concluded that CRP level measured within 12 hours after symptom onset of an acute ischemic stroke is not independently related to long term prognosis. In contrast, a CRP increase between 12 and 24 hrs after symptom onset predicts an unfavorable outcome and it is associated with an increased incidence of cerebrovascular or cardiovascular events.

Di Napoli et at (2001) studied about the 1 year prognostic influences of fibrinogen and CRP levels on outcome in ischemic stroke patients[48]. A total 0f 128 patients with first ischemic stroke were included in the study. Fibrinogen and CRP were determined within 24 hours after stroke and related to 1 year outcome. The stroke severity and disability was assessed by the CNSS and BI scores respectively. The primary end point was the same as in the previous studies.

Among 128 patients, there were 53 men and 75 women. CT was performed in 113 patients and MRI or both in all remaining patients. The CRP

values within 24 hours were 13 mg/L. 33 patients had normal CRP level on admission. The mean fibrinogen level was 4. 76g/l.

40 patients (31. 3%) had a primary end point within 1 year of stroke onset. 18 were men and 22 were women. 32 (80%) were older than 70 years. 20 patients died. The mean fibrinogen level was significantly higher in patients who had a primary end point during the follow up period. The patients were classified into tertiles based on fibrinogen levels with cut off limits of <3.78, 3. 78 to 6.17 and >6. 17

A significantly higher median level of CRP was found in patients who had a primary end point during the follow up period. Stratification of the patients into tertiles on the basis of CRP (<5, 5-33 and >33 mg/L) revealed an increased probability of death or new vascular event in patients with increased CRP levels.

A risk of death or new vascular event was significantly associated with increased CRP level and stroke severity on CNSS. An increased fibrinogen level was an independent risk factor for the primary end point. The conclusion was that increased levels of CRP are associated with a worse outcome in patients with ischemic stroke. The increased risk associated with elevated CRP levels is independent of the prognostic influence of fibrinogen.

Di Napoli et al (2003) studied the association between blood pressure and CRP levels in acute ischemic stroke[49]. In a prospective observational study 535 first – ever ischemic stroke patients were included. They studied the association between blood pressure and baseline concentration of CRP within 24 hours

after stroke onset. As per the study it was found that increased SBP was significantly associated with elevated levels of circulating CRP in ischemic stroke patients. These findings support a possible role of acute hypertension after stroke as an inflammatory stimulus which contributes to ischemic brain inflammation.

Hamidon BB et al (2004) conducted a study - prognostic value of CRP values in a first ever ischemic stroke at 1 month[50]. All ischemic stroke patients who were admitted to Hospital University Kebangsaan Malaysia (HUKM). Study duration was between May 2002 and July 2002. CRP levels were taken within 72 hours after an acute ischemic stroke. The functional disability was assessed using the BI after 1 month of stroke. During the study period 84 patients were admitted to HUKM with the diagnosis of ischemic stroke. Study concluded that elevated CRP levels are associated with poorer functional outcome and they predicts a large infarct size.

Guo Y et al (2003) conducted a study for understanding association between serum CRP and prognosis of ischemic stroke. 121 patients with ischemic stroke were included in the study. Serum levels of CRP were measured within 72 hours of the event. All patients were clinically examined and imaging done with CT/MRI and carotid duplex ultrasound scanning.

Leukocyte count and serum blood glucose level at admission were significantly higher in the group with abnormal serum levels of CRP than those with normal CRP. Incidence of territory infarction was also significantly higher than that of lacunar infarction. Occurrence of carotid plaques was higher in the

former than that in the latter. Neurological deficit was also higher in the former than in the later. Severe prognosis was also found in the former than the latter. The conclusion was that CRP was an important prognostic marker for stroke and carotid plaque.

Massotti et al (2005) assessed the role of CRP on short and long – term prognosis in 75 years old and over elderly patients[51]. They retrospectively evaluated CRP values performed within 12 hours for hospital admission. A total of 196 elderly patients discharged with the diagnosis of acute ischemic stroke were included in the study. Relationship between CRP values and short-term prognosis [30 days mortality, length of hospitalization and physical disability measured by modified Rankin Scale and long – term prognosis (12 month mortality and rehospitalization)] were studied.

Mean value of CRP were significantly higher in patients with cardioembolic stroke compared with atherothrombotic large vessel and lacunar stroke. Length of hospitalization and physical disability score rose with increasing values of CRP for all subtypes of stroke. Higher CRP values were associated with the 12 month rehospitalization for cerebrovascular events. So, it as concluded that elevation of CRP at admission could represent a negative prognostic index in elderly patients with ischemic stroke, especially for short-term prognosis.

Kocer A et al(2005) undertook a study with the aim of evaluating serum hs CRP levels in ischemic stroke patients and in a control group[52]. A total of 47 patients with ischemic stroke and 26 control subjects were recruited. Blood

samples from stroke patients were obtained between 12-24 hours after the stroke. The mean serum levels of hs CRP were found to be significantly higher in patients than controls. Study concluded that elevated serum hs CRP levels may be an indicator of fatal outcome in first-time stroke patients.

Rallidis LS et al (2005) examined the short- term prognostic value on mortality of C-reactive protein (CRP), interleukin-6 (IL-6) and serum amyloid A (SAA) in patients with ischemic stroke[53]. Study includes 203 patients. Patients with atrial fibrillation or evidence of inflammatory or malignant disease were excluded. The diagnosis was confirmed with a computed tomography or MRI of the brain within 24 hours of admission. CRP, IL-6 and SAA were determined within 12 hours of admission. 14 patients died during hospitalization. Serum concentrations of CRP, IL-6, SAA were significantly higher in patients who died compared with those who survived. For one unit increase in CRP there was an 14% higher risk of dying during hospitalisation. Conclusion was that in hospital mortality in ischemic stroke is associated with an exacerbation of inflammatory response like elevated of IL-6, CRP and SAA.

Arevalo – Lorido JC et al (2005) studied the prognostic importance of CRP in the acute phase of ischemic stroke patients[54]. 117 patients within 48 hr. after index ischemic stroke were included. CRP levels were obtained at this time. A brain CT or MRI was performed. Patients were divided according to the outcome into the following categories: TIA, favorable stroke and non – favorable stroke. 32 patients were classified as TIA, 31 as favorable stroke and

54 as non- favorable stroke. They concluded that increased levels of CRP in the non- favorable stroke category was related with neurological and functional disabilities and with radiological findings predominantly when CRP levels were greater than 3.6 mg/dl.

Montaner J et al(2006) studied whether CRP measured before tissue plasmonogen activator (tPA) treatment can guide stroke thrombolysis[55]. A total of 151 patients with an ischemic stroke involving the middle cerebral artery who received tPA administration and CRP gene polymorphism was assessed. Functional outcome was evaluated after 3 month by modified Rankin scale (mRS). Patients with history of previous stroke, hypertension or atrial fibrillation had higher levels of CRP. CRP was higher in patients who died after thromboysis than in survivors. A correlation between CRP and mRS was found. CRP polymorphisms were not related to neurologic outcome. CRP and age were the only baseline mortality predictors. Hence, the conclusion was that admission CRP predicts mortality among tPA- treated stroke patients. Early recanalization does not ameliorate the negative prognostic impact of increased CRP.

WHEN SHOULD PLASMA CRP BE SAMPLED AFTER STROKE ?

In patients with acute stroke, plasma CRP concentrations are elevated early and remain elevated above control values for few months after index stroke. The CRP concentration is persistently increased after stroke. The extent to which elevation occurs depends on the inflammatory response to stroke as

opposed to the underlying atherosclerosis has not been established. Discharge concentrations closely reflects the baseline inflammatory activity. A case can be made for assessment of CRP concentration at admission, at discharge, at 1 to 3 months and again at further intervals. This is because highest risk of future events is present in patients with persistently elevated CRP.

RESULTS & STATISTICS

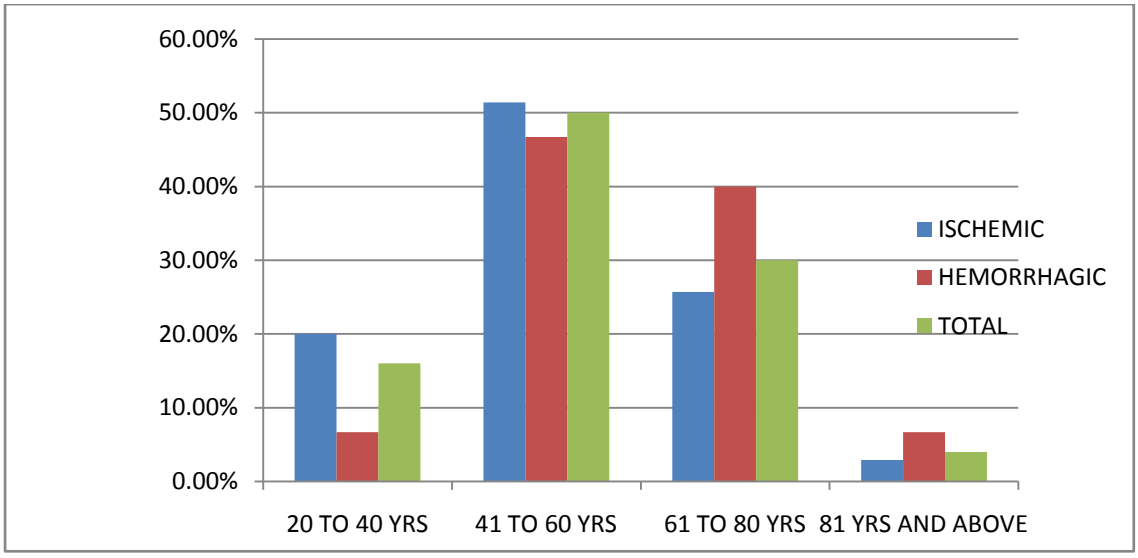
TABLE 1: Age distribution of patients

AGE	ISCHEMIC		HAEMORRHAGIC		TOTAL	
	N	%	N	%	N	%
20 TO 40 YRS	7	20.0%	1	6.7%	8	16.0%
41 TO 60 YRS	18	51.4%	7	46.7%	25	50.0%
61 TO 80 YRS	9	25.7%	6	40.0%	15	30.0%
81 YRS & ABOVE	1	2.9%	1	6.7%	2	4.0%

Min:28, Max:90,

Mean:57. 48, SD:14. 867

GRAPH 1: Age distribution of patients

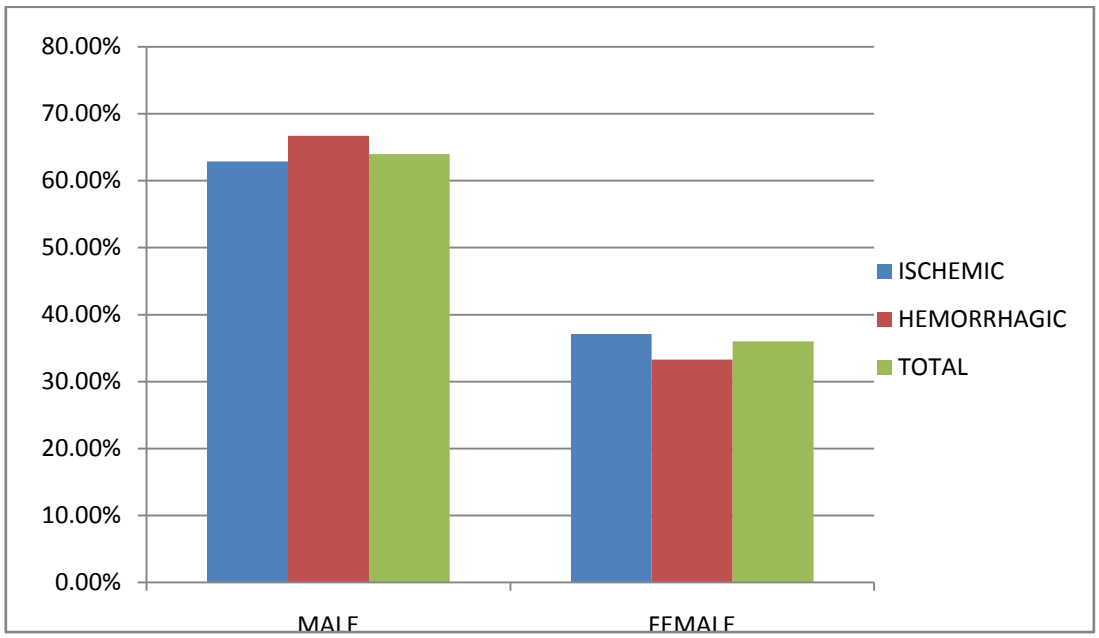


In this study a total of 50 patients were studied. They were divided into four age groups. 16 percentage comes between 20-40 years, 50 percentage between 41 -60 years, 30 percentage between 60 -80 years and 4 percentage above 80 years. Minimum age is 28 years and maximum is 90 years. Mean age group is 57.48 years with standard deviation of 14.867. In both ischemic and haemorrhagic group more people comes in the age group of 41-60 years.

TABLE 2: Sex wise Distribution in Patients

SEX	ISCHEMIC		HAEMORRHAGIC		TOTAL	
	N	%	N	%	N	%
MALE	22	62.9%	10	66.7%	32	64%
FEMALE	13	37.1%	5	33 3%	18	36%

GRAPH 2: Sex wise distribution of patients

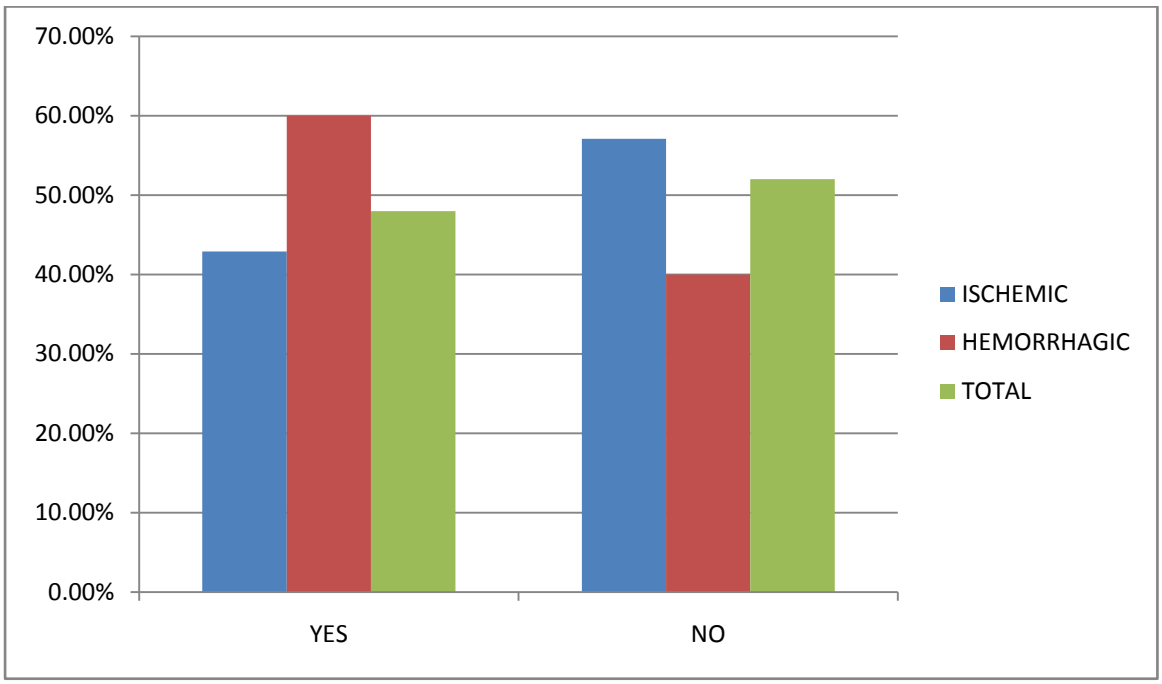


In the total study group 64% were males and 36% females. In the ischemic group 62.9%were males and 37. 1% were females. In haemorrhagic group 66.7% were males and 33.3% were females

TABLE 3: Distribution of hypertension in patients

HTN	ISCHEMIC		HAEMORRHAGIC		TOTAL	
	N	%	N	%	N	%
YES	15	42.9%	9	60.0%	24	48%
NO	20	57.1%	6	40.0%	26	52%

GRAPH 3: Distribution of hypertension in patients

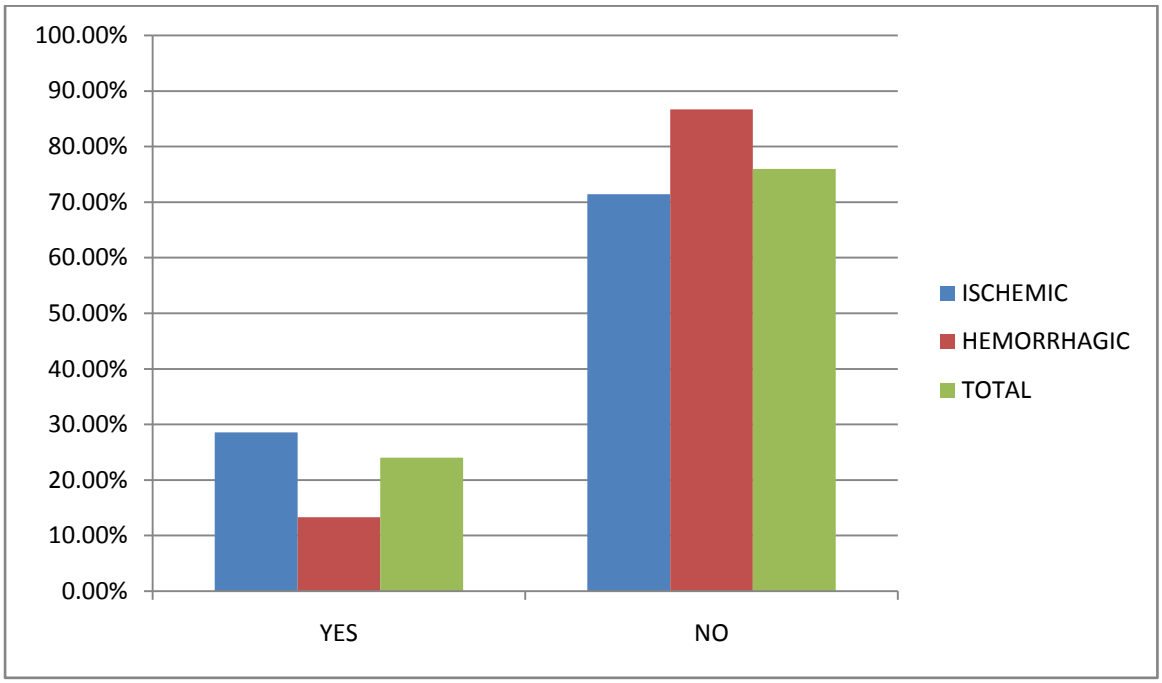


In the study group 48% of patients had hypertension and 52% were non hypertensives. In ischemic group 42.9% were hypertensive and 57.1% were non hypertensive. In haemorrhagic group 60% were hypertensive and 40% were non hypertensives.

TABLE 4: Distribution of diabetes mellitus in patients

DM	ISCHEMIC		HAEMORRHAGIC		TOTAL	
	N	%	N	%	N	%
YES	10	28.6%	2	13.3%	12	24%
NO	25	71.4%	13	86.7%	38	76%

GRAPH 4: Distribution of diabetes mellitus in patients



In the study group 24% were diabetic and 76% were non diabetic. In the ischemic group 28.6% were diabetic and 71.4% were non diabetic. In the haemorrhagic group 13. 3% were diabetic and 86.7% were non diabetic. In the both the groups non diabetic patients were more.

TABLE 5 : Distribution of Dyslipidemia in Patients

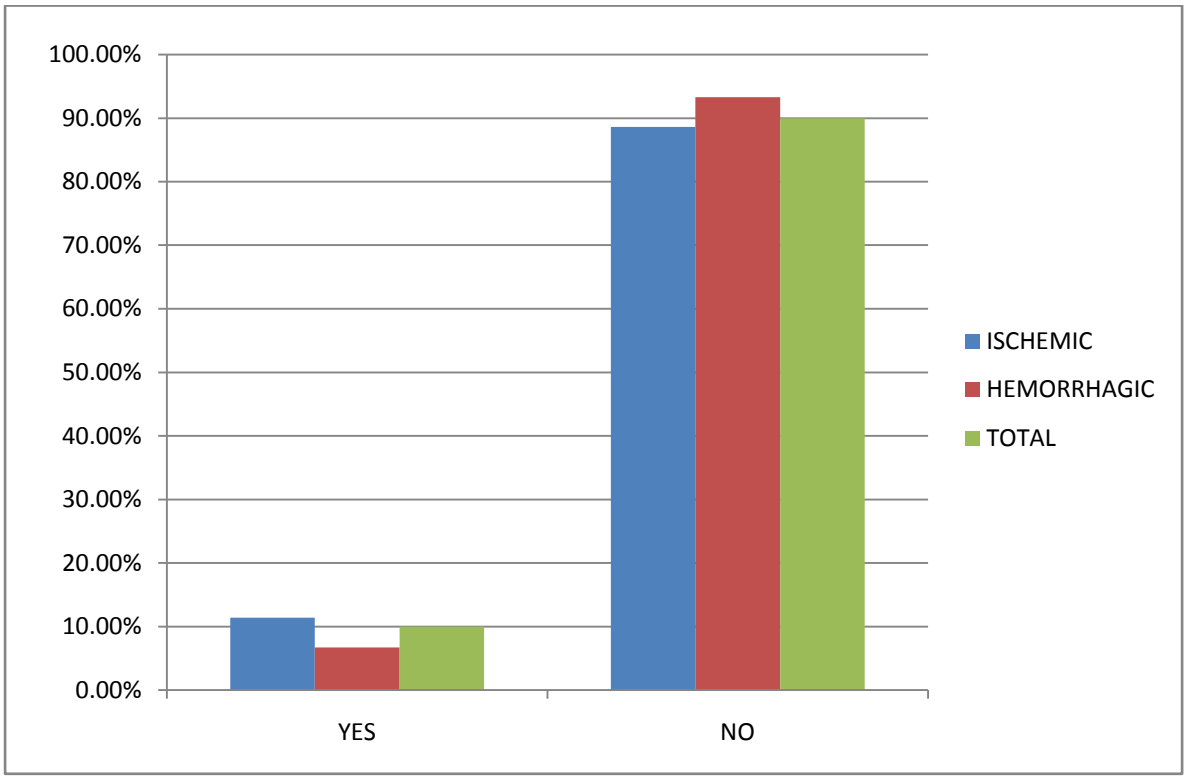
DLP	ISCHEMIC		HAEMORRHAGIC		TOTAL	
	N	%	N	%	N	%
YES	-	-	-	-	-	-
NO	35	100%	15	100.0%	50	100%

In the study none of the patients had dyslipidemia

TABLE 6: Distribution of CAD in patients

CAD	ISCHEMIC		HAEMORRHAGIC		TOTAL	
	N	%	N	%	N	%
YES	4	11.4%	1	6.7%	5	10%
NO	31	88.6%	14	93.3%	45	90%

GRAPH 5: Distribution of CAD in patients

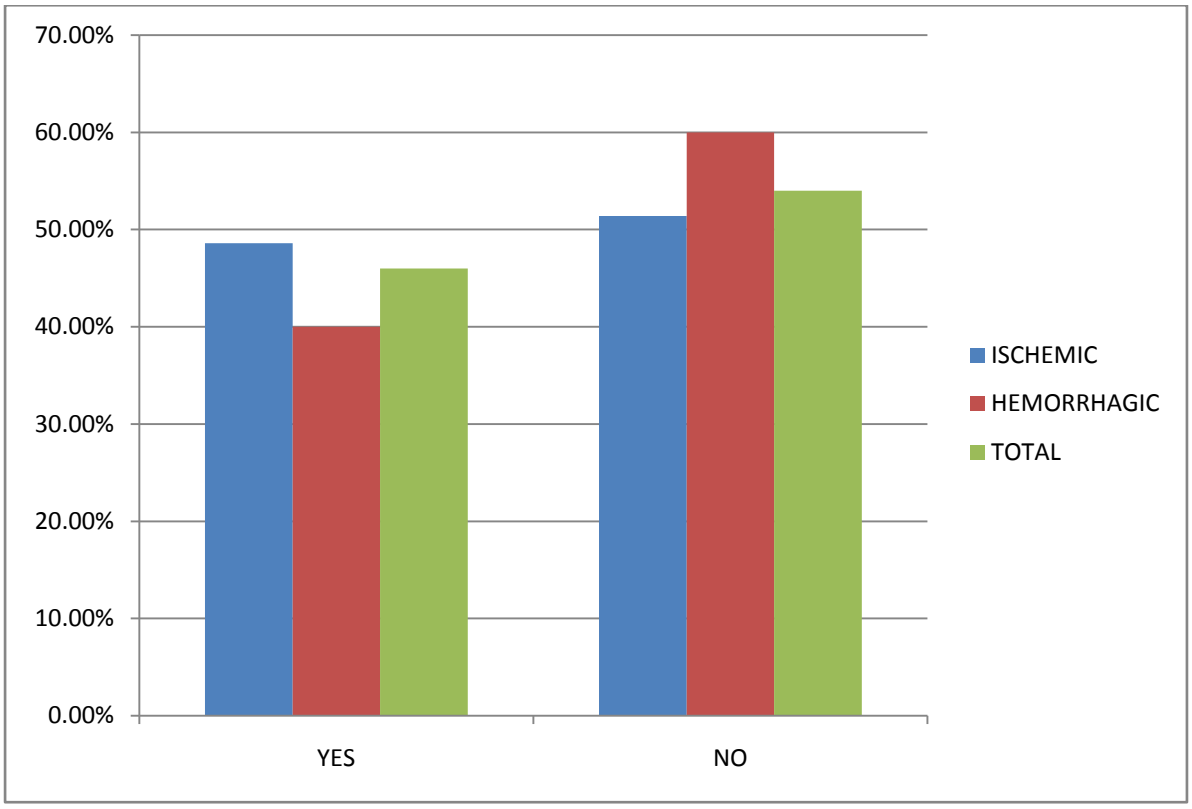


In the total study group 10% had coronary artery disease and 90% had no coronary artery disease. In the ischemic group 11. 4% had CAD and 88.6% patients had no CAD. In haemorrhagic group 6.7% had coronary artery disease and 93.3% have no coronary artery disease

TABLE 7: Distribution of patients having no risk

NR	ISCHEMIC		HAEMORRHAGIC		TOTAL	
	N	%	N	%	N	%
YES	17	48.6%	6	40.0%	23	46.0%
NO	18	51.4%	9	60.0%	27	54.0%

GRAPH 6: Distribution of patients having no risk



In the whole study group 54%have some risk factors and 46% have no risk factors. In the ischemic group 51.4% have any of the risk factors and 48.6 have no risk factors. In the haemorrhagic group 60% have any of the risk factors and 40% have no risk factors.

Table 8: Distribution of AF in patients

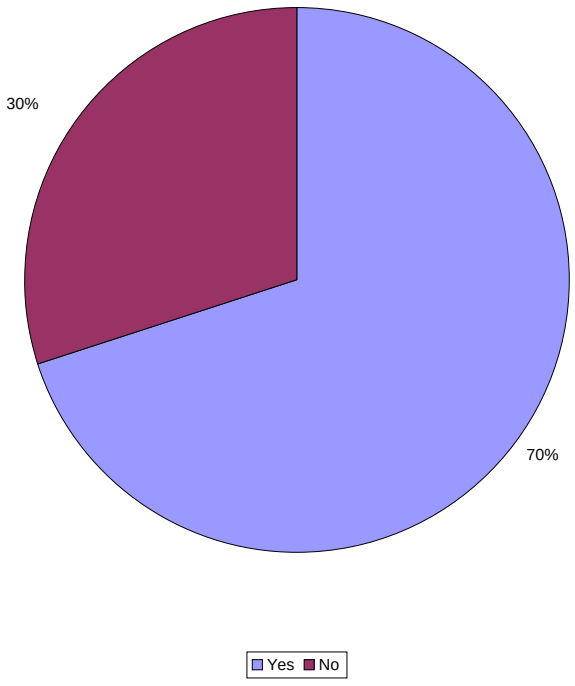
AF	ISCHEMIC		HAEMORRHAGIC		TOTAL	
	N	%	N	%	N	%
YES	-	-	-	-	-	-
NO	35	100%	15	100.0%	50	100%

In the study group none of the patients had atrial fibrillation.

TABLE 9: Distribution of Ischemic stroke patients

Particulars	No. of respondents	Percentage
Yes	35	70.0
No	15	30.0
Total	50	100.0

Pie diagram 1: Distribution of ischemic stroke patients

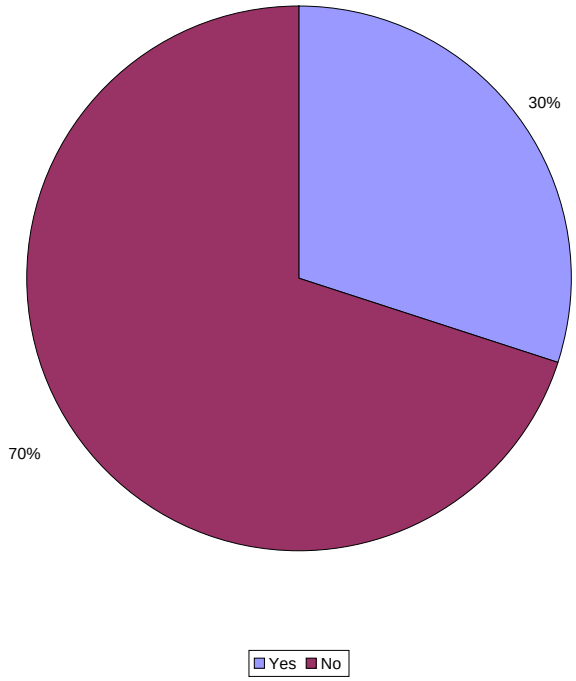


In the total study group 70 % were ischemic stroke patients.

TABLE 10: Distribution of haemorrhagic stroke patients

Particulars	No. of respondents	Percentage
Yes	15	30.0
No	35	70.0
Total	50	100.0

Pie chart 2: Distribution of haemorrhagic stroke patients

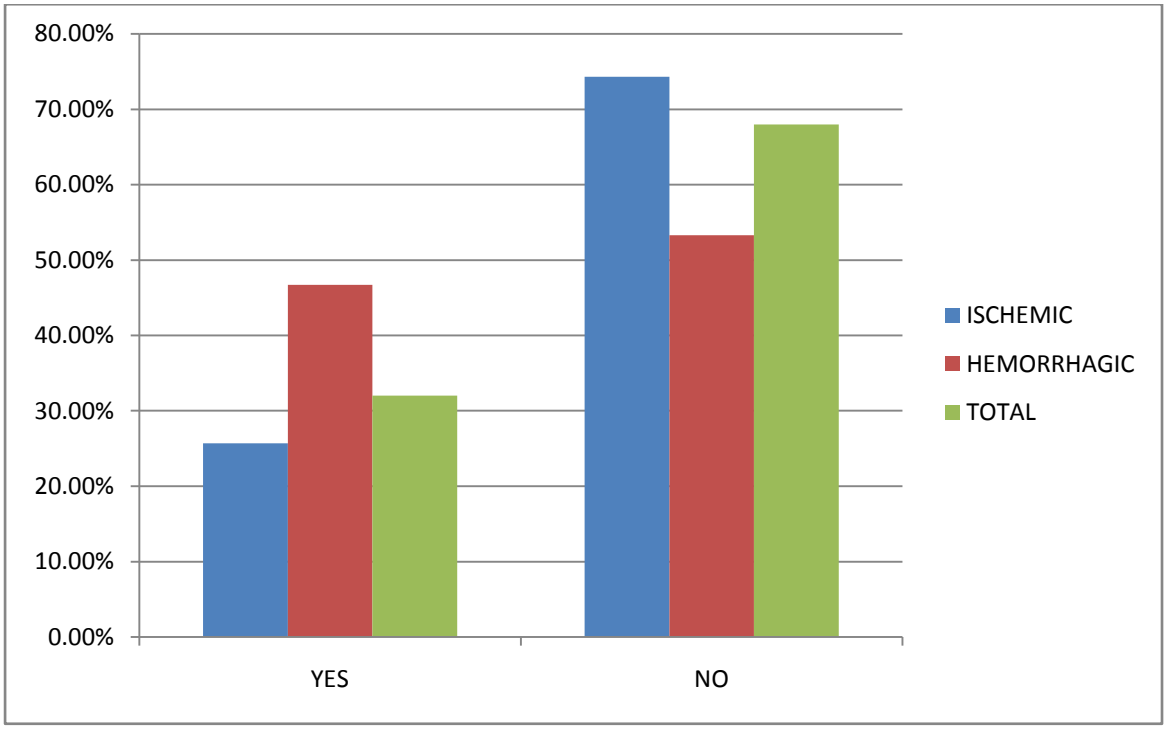


In the total study group 30% were haemorrhagic stroke patients

TABLE 11: Distribution of LVH in patients

LVH	ISCHEMIC		HAEMORRHAGIC		TOTAL	
	N	%	N	%	N	%
YES	9	25.7%	7	46.7%	16	32%
NO	26	74.3%	8	53.3%	34	68%

GRAPH 7: Distribution of LVH in patients.

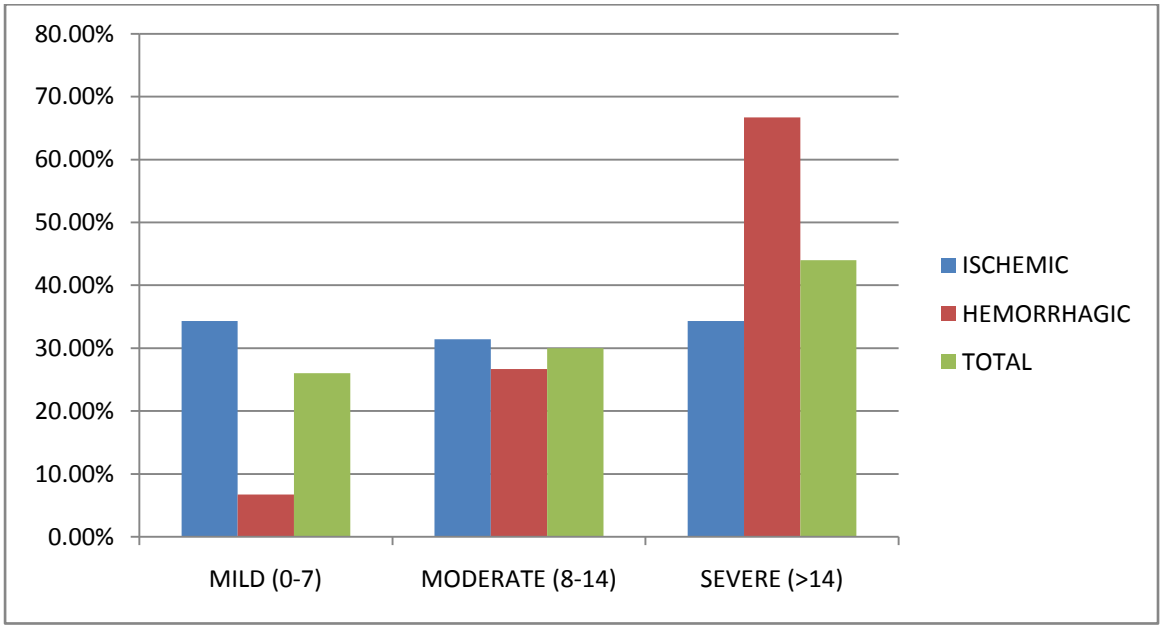


In the study group 68% had no LVH and 32% of patients had LVH. 46.7% had LVH in haemorrhagic group compared to 25.7% in ischemic group.

TABLE 12: NIHSS levels in patients

NIHSS	ISCHEMIC		HAEMORRHAGIC		TOTAL	
	N	%	N	%	N	%
MILD (0-7)	12	34.3%	1	6.7%	13	26.0%
MODERATE (8-14)	11	31.4%	4	26.7%	15	30.0%
SEVERE (>14)	12	34.3%	10	66.7%	22	44.0%

GRAPH 8:NIHSS levels in patients

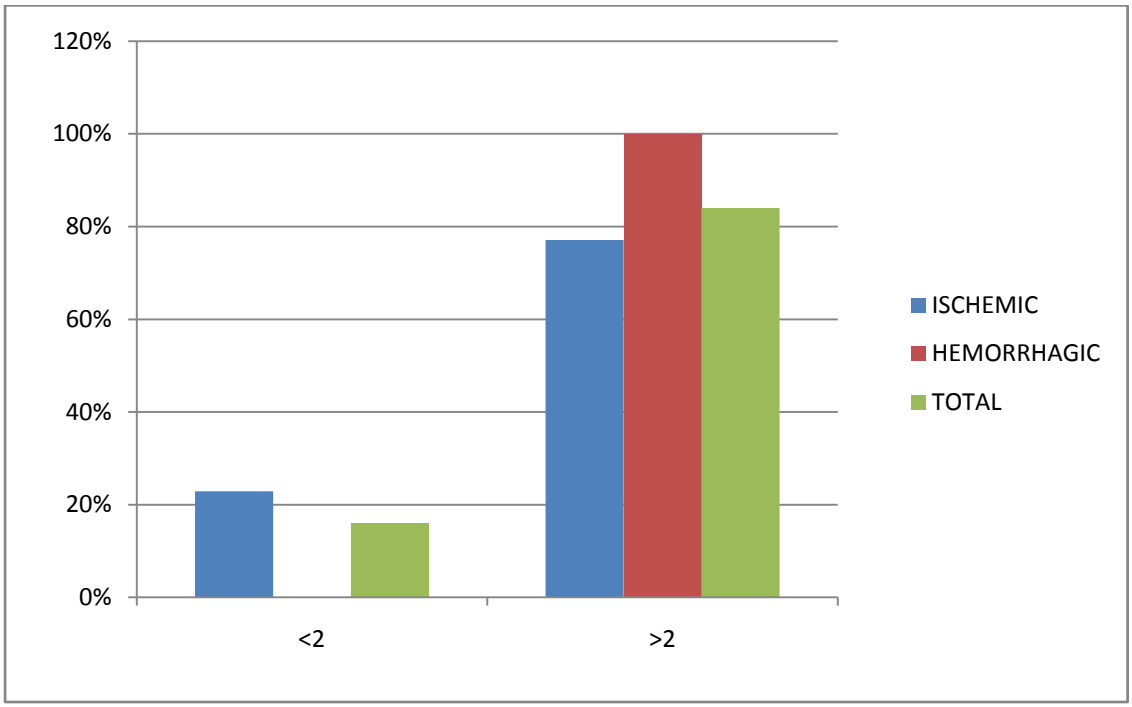


In the study group 3 groups of NIHSS scoring were used-mild moderate, severe. Out of this 26% comes in the mild group, 30% comes in the moderate group and 44% comes in the severe group. In ischemic group both mild and severe group had 34.3% patients. Moderate group has less number of patients. In haemorrhagic group more number of patients comes in the severe group.

TABLE 13:mRS levels in patients

mRS	ISCHEMIC		HAEMORRHAGIC		TOTAL	
	N	%	N	%	N	%
<2	8	22.9%	0	0%	8	16%
>2	27	77.1%%	15	100%	42	84%

GRAPH 9: mRS levels in patients



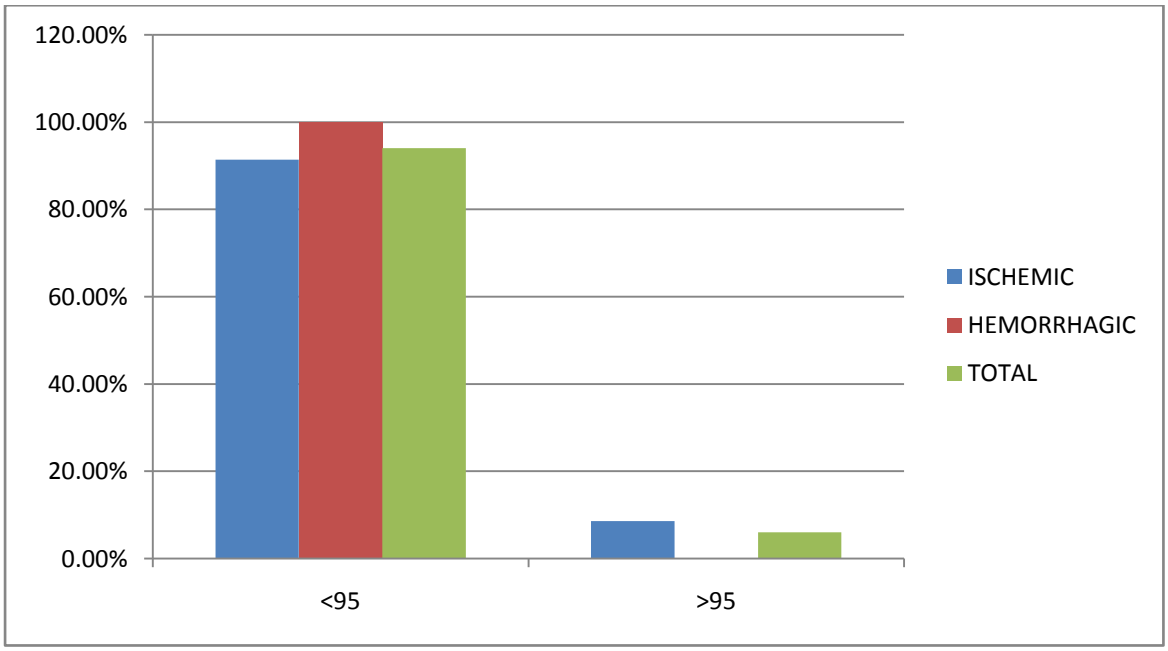
In the study group 84% had mRS more than 2 and 16% less than 2. In both ischemic and haemorrhagic group more number of patients had mrs>2

Barthel ADL index

TABLE 14:BI levels in patients

BI	ISCHEMIC		HAEMORRHAGIC		TOTAL	
	N	%	N	%	N	%
<95	32	91.4%	15	100%	47	94. 0%
>95	3	8.6%	0	0%	3	6. 0%

GRAPH 10 : BI levels in patients

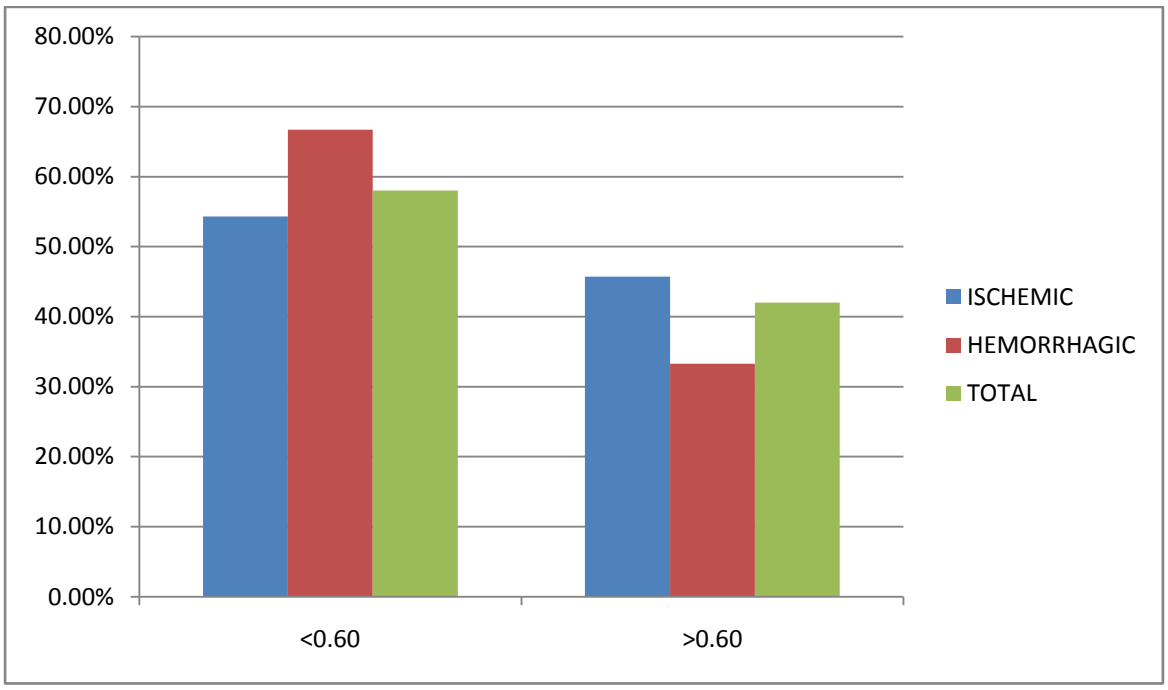


In the study group 94% had BI less than 95 and 6% had more than 95. In ischemic group majority of patients had BI less than 95. In haemorrhagic group all the patients had BI less than 95.

TABLE 15:Distribution of CRP in patients

CRP	ISCHEMIC		HAEMORRHAGIC		TOTAL	
	N	%	N	%	N	%
<0. 60	19	54.30%	10	66.7%	29	58.0%
>0. 60	16	45.70%	5	33.3%	21	42.0%

GRAPH 11: Distribution of CRP in patients.

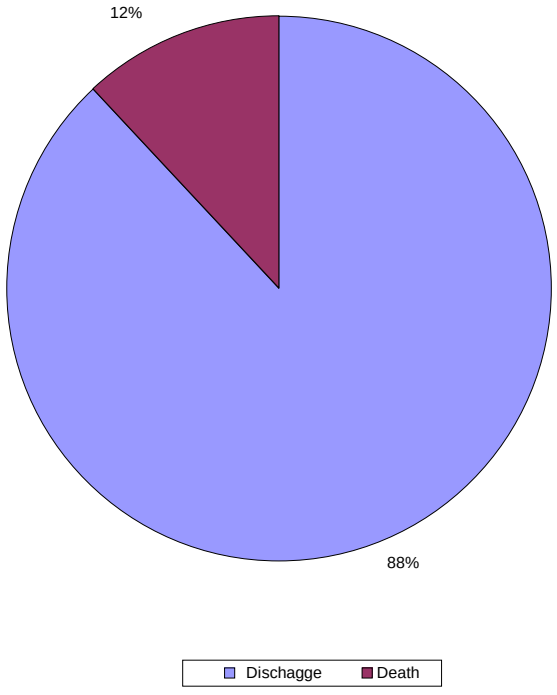


42% of the patients in the study group had CRP values more than 0.60 and 58% had CRP less than 0.60mg/l. In both groups more number of patients had CRP less than 0.60mg/l.

TABLE 16: Distribution of END POINT

Particulars	No. of Respondents	Percentage
Discharge	44	88.0
Death	6	12.0
Total	50	100.0

PIE CHART 3: Distribution of End point



Out of the total study group 88% were discharged and 12% died during the hospital stay.

DESCRIPTIVE STATISTICS:

Frequencies

Statistics						
		Age	**NIHSS**	**MRS**	**BI**	**CRP**
N	Valid	50	50	50	50	50
	Missing	0	0	0	0	0
Mean		57.48	15. 20	3.92	39.50	1.65496
Median		60.00	12.00	4.00	32.50	.33300
Std. Deviation		14.867	10.566	1.122	32.186	3.361796
Minimum		28	1	1	0	.001
Maximum		90	36	5	125	14.700

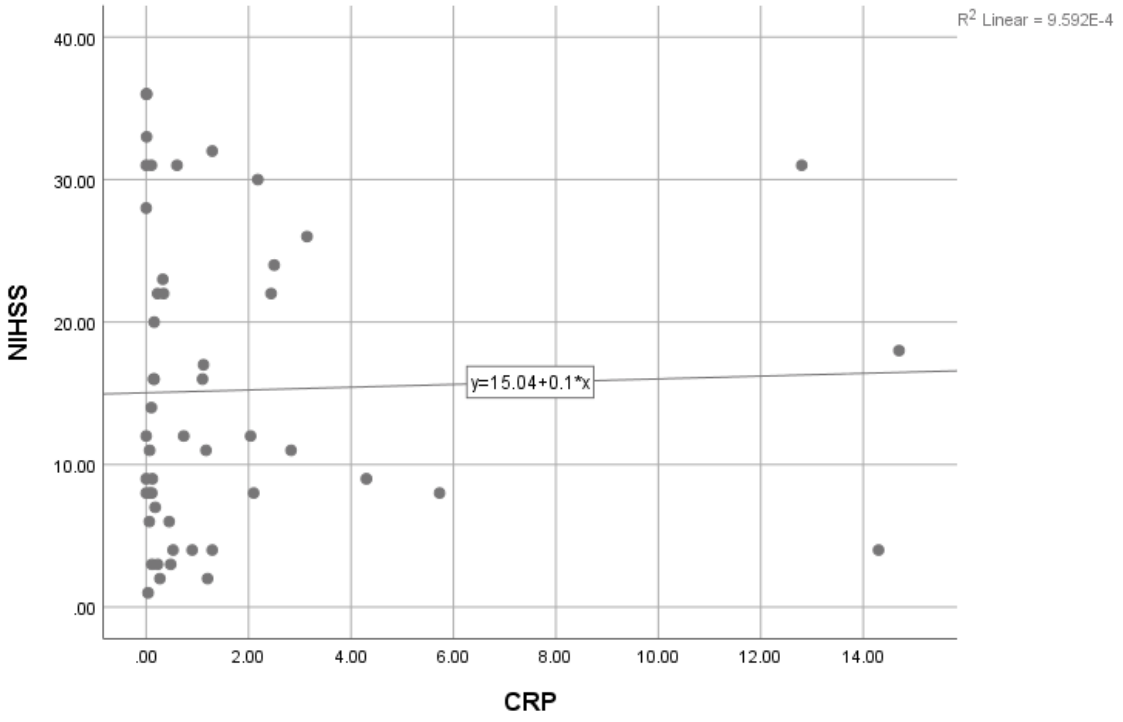
Various parameters like age, NIHSS, Modified rankin scale, Barthel adl index and CRP were analysed. Mean age group was 57.48 and standard deviation of 14.867. Mean NIHSS value was 15.20 and standard deviation of 10.566. Mean mRS was 3.92 with a standard deviation of 1.122. Mean BI level was 39.50 with a standard deviation of 32.186. Mean CRP level was 1.655 with a standard deviation of 3.362.

CORRELATION STUDY

1. TOTAL STROKE PATIENTS:

a) NIHSS and CRP

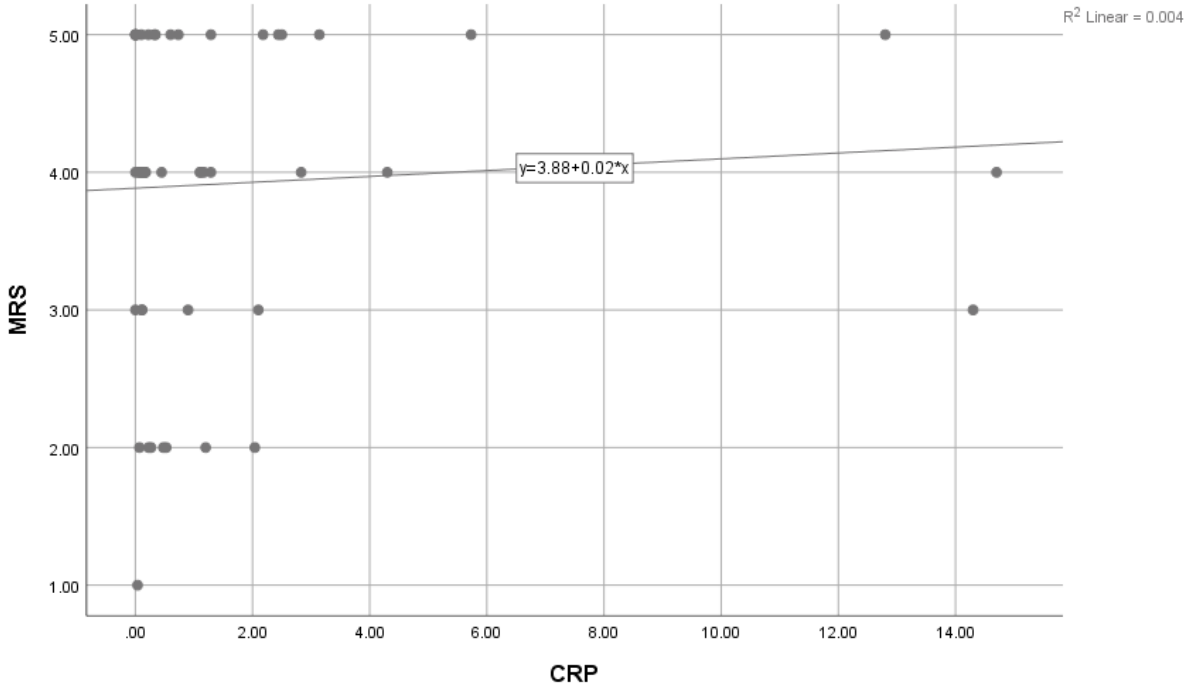
		NIHSS	CRP
NIHSS	Pearson Correlation	1	. 031
	Sig. (2-tailed)		. 831
	N	50	50
CRP	Pearson Correlation	. 031	1
	Sig. (2-tailed)	. 831	
	N	50	50



Results showed there is a r value of 0.031. But p value comes to 0.831 which is more than 0.05. So it is not statistically significant.

b) mRS and CRP

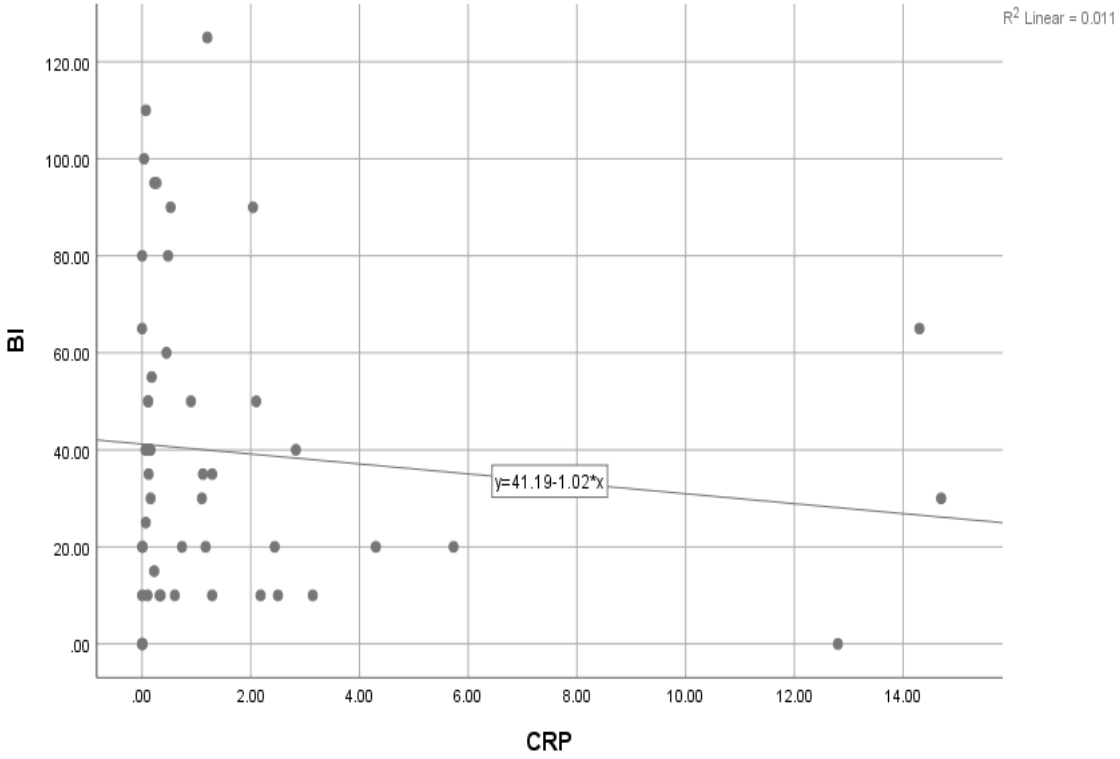
		mRS	CRP
mRS	Pearson Correlation	1	.064
	Sig. (2-tailed)		.660
	N	50	50
CRP	Pearson Correlation	.064	1
	Sig. (2-tailed)	.660	
	N	50	50



Results showed that there was an r value of 0.064. But it is not statistically significant since its p value is 0.660 which is more than 0.05

c) BI and CRP

		BI	CRP
BI	Pearson Correlation	1	-.107
	Sig. (2-tailed)		.460
	N	50	50
CRP	Pearson Correlation	-.107	1
	Sig. (2-tailed)	.460	
	N	50	50



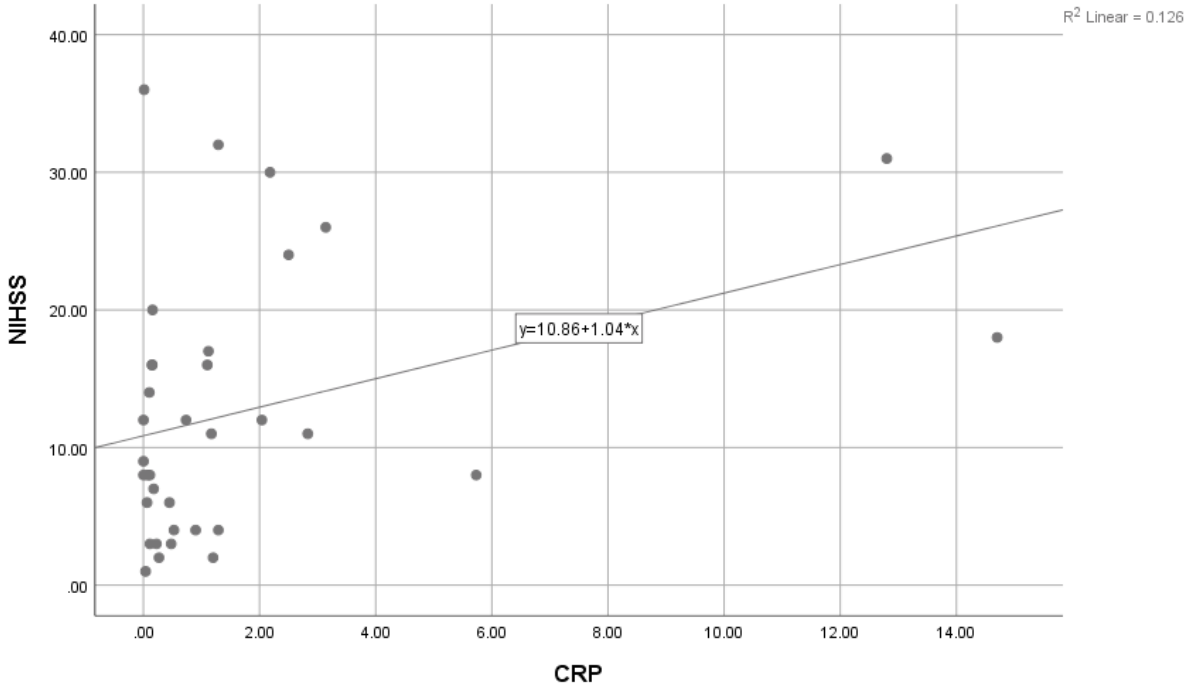
Results showed that r value comes to -0.107. It is not statistically significant since the p value is more than 0.05

2. ISCHEMIC STROKE PATIENTS

a) NIHSS and CRP

Correlations

		NIHSS	CRP
NIHSS	Pearson Correlation	1	. 354*
	Sig. (2-tailed)		. 037
	N	35	35
CRP	Pearson Correlation	. 354*	1
	Sig. (2-tailed)	. 037	
	N	35	35

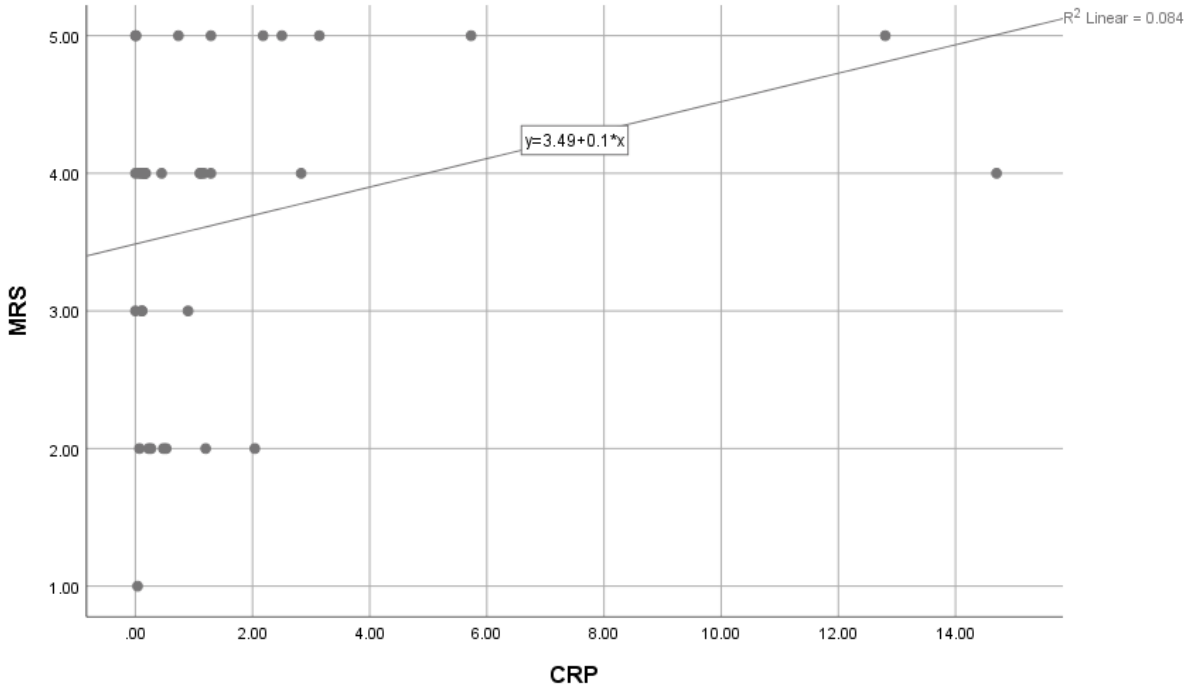


Results showed that r value is 0.354. p value came to 0.037. Since p value is less than 0.05, it is statistically significant and positively correlated.

b) **mRS and CRP**

Correlations

		mRS	CRP
mRS	Pearson Correlation	1	.290
	Sig. (2-tailed)		.091
	N	35	35
CRP	Pearson Correlation	.290	1
	Sig. (2-tailed)	. 091	
	N	35	35

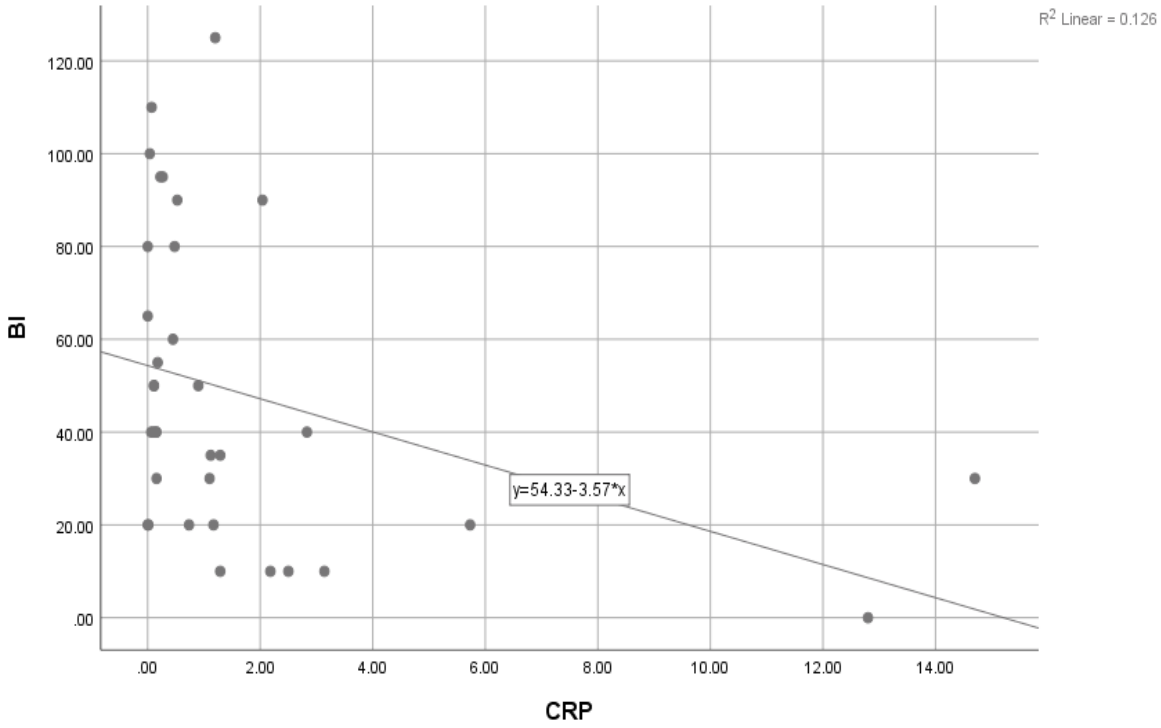


Results showed that r value is 0.290. p value is 0.091. Here p value is more than 0.05, so it is not statistically significant

c) **BI and CRP**

Correlations

		BI	CRP
BI	Pearson Correlation	1	-. 355*
	Sig. (2-tailed)		. 036
	N	35	35
CRP	Pearson Correlation	-.355*	1
	Sig. (2-tailed)	.036	
	N	35	35



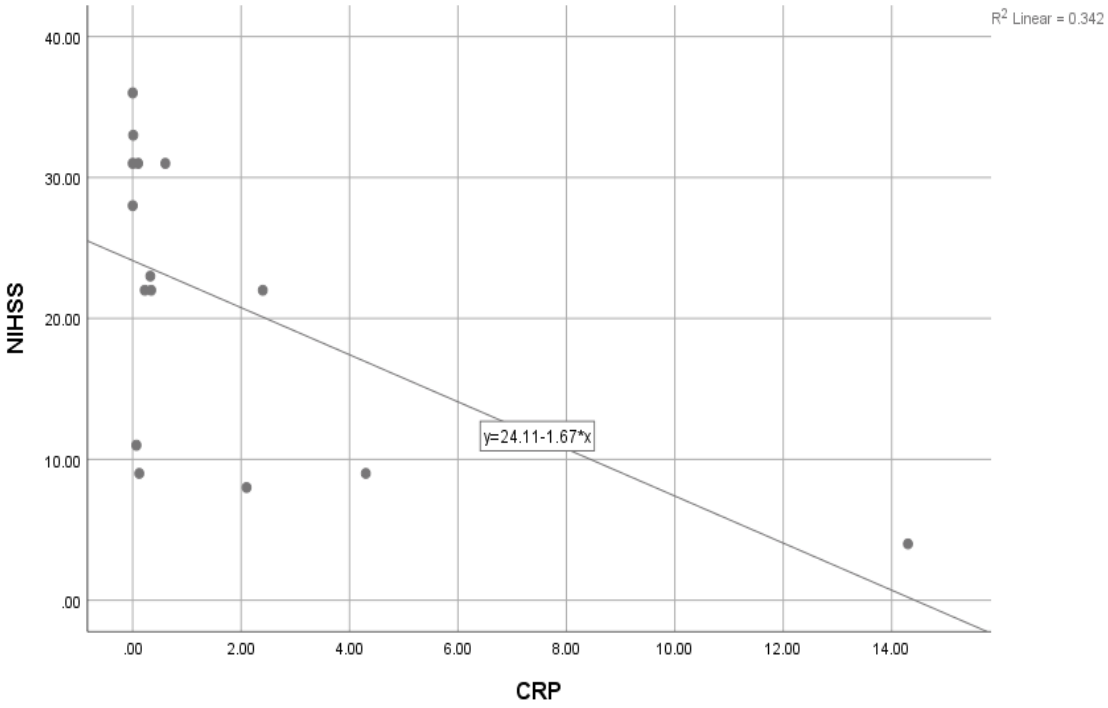
Results showed that r value is -0.355. p value is 0.036 which is less than 0. 05. Hence it is negatively correlated and statistically significant.

3. HAEMORRHAGIC STROKE PATIENTS

a)NIHSS AND CRP

Correlations

		NIHSS	CRP
NIHSS	Pearson Correlation	1	-.585*
	Sig. (2-tailed)		.022
	N	15	15
CRP	Pearson Correlation	-.585*	1
	Sig. (2-tailed)	.022	
	N	15	15

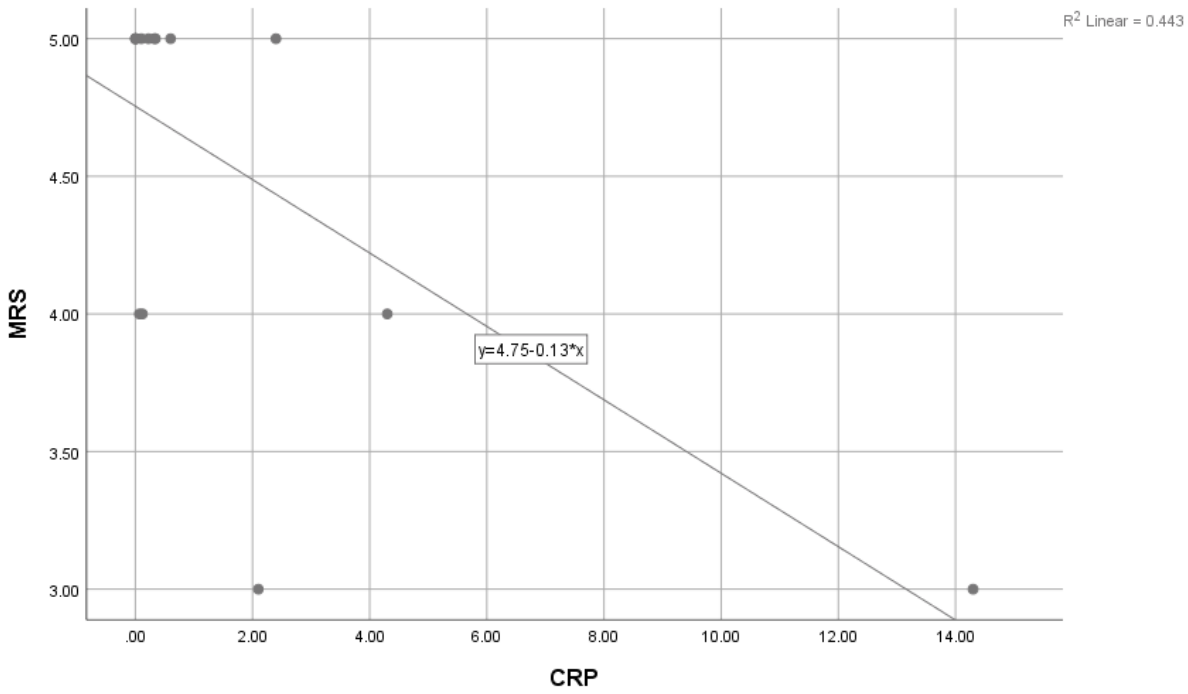


Results showed that r value is -0.585 and p value is 0.022. So results came as negatively correlated and statistically significant.

b) mRS and CRP

Correlations

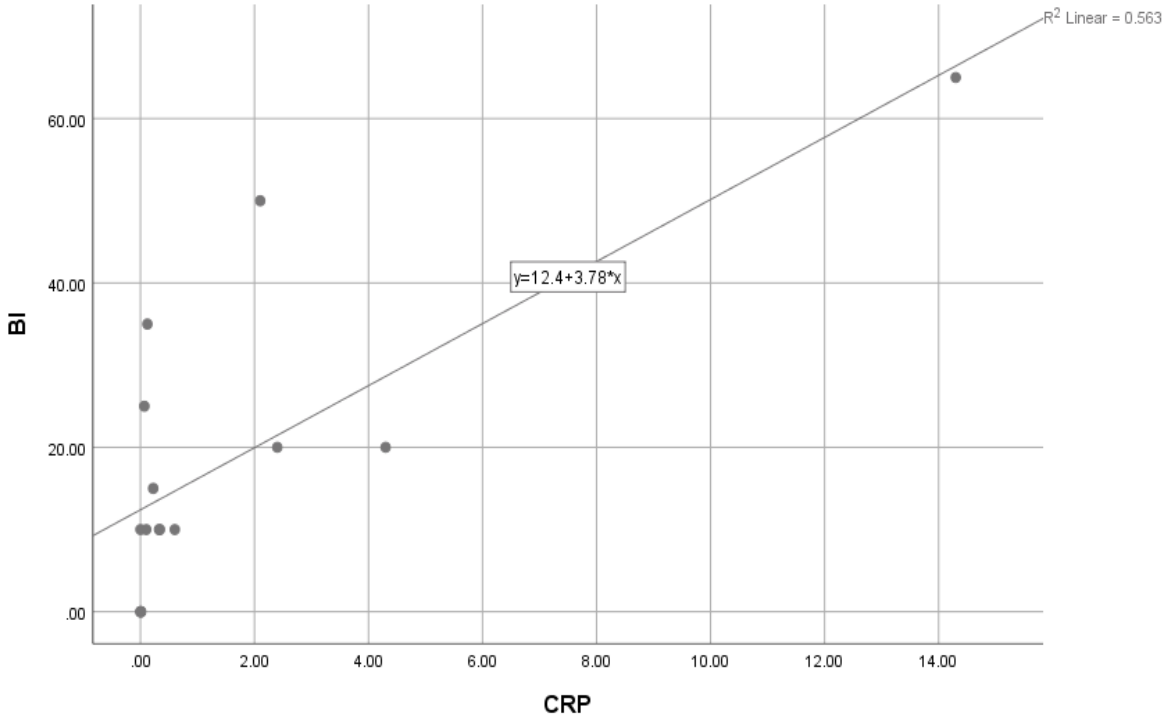
		mRS	CRP
mRS	Pearson Correlation	1	-.665**
	Sig. (2-tailed)		.007
	N	15	15
CRP	Pearson Correlation	-.665**	1
	Sig. (2-tailed)	.007	
	N	15	15



Here the r value came to -0.665. p value is 0.007. It is negatively correlated. It is statistically significant.

c)BI and CRP

		BI	CRP
BI	Pearson Correlation	1	.750**
	Sig. (2-tailed)		.001
	N	15	15
CRP	Pearson Correlation	.750**	1
	Sig. (2-tailed)	.001	
	N	15	15



Results showed that r value is 0.750. p value is 0.001. So it is positively correlated and statistically significant.

DISCUSSION

Stroke is one of the leading cause of disability in developing and developed countries. The CRP typically increases within 6 hours of the initiation of inflammation. Inflammation is central for initiation, development and for the rupture of atherosclerotic plaques. The recruitment of immune cells like macrophages and T-cells into the atherosclerotic plaques leads to the secretion of multiple inflammatory mediators - cytokines, free radicals and proteases. It finally promotes plaque rupture and thrombosis. Brain damage, either ischemic or haemorrhagic stimulates the mobilization and migration of immune cells like neutrophils and macrophages, into brain. They induces systemic inflammatory response. We intended to assess the value of early serum CRP level on admission as a biomarker for predicting the severity of stroke and short term outcome for patients admitted with stroke.

In this study total 50 patients were studied. They were divided into four groups. 16 percentage comes between 20-40 years, 50 percentage between 41 - 60 years, 30 percentage between 60 -80 years and 4 percentage above 80 years. Minimum age is 28 years and maximum 90 years. Mean age group is 57. 48 years.

In the present study males predominates females. Of the total 64% were males and 36% were females. This correlates with study of Mishra et al, 1967 (Males-72.8%, Female-27.2%).Other studies of stroke which shows males were more includes Haberman et al, Rose et al (1987), Framingham study and Gupta et al. Male to female ratio in this study is 1.7:1.

Other studies:

STUDY	**RATIO**
1) Gupta et al, 1965	1. 6:1
2) Kurtzke J and Kurland et al, 1970	1. 3:1
3) Rohtak Study (WHO), 1987	1. 6:1
4) Colombo Study (WHO) 1987	1. 29:1
5) Venkataraman et al, 1997	1. 4:1

In this study 48% were hypertensives and 52% were non hypertensives. Percentage of hypertensives in haemorrhagic group were more compared to ischemic group. In this study group 76% were non diabetic and 24% were diabetic. This was similar to study conducted by winbeck et al (2002)- 29% were diabetic. In ischemic group 28.6% patients were diabetic and in haemorrhagic group 13.3% patients were diabetic. In both ischemic and haemorrhagic group non diabetics were more. In this study group non of them were dyslipidemic.

In this study group 10% have coronary artery disease and 90% have no coronary artery disease. In ischemic group 11.4%had history of CAD and in haemorrhagic group it was 6.7%.

Comparison with previous studies:

	Di Napoli ‘01	Winbeck’02	Present study
Hypertension	71.9%	70%	48%
Diabetes	40.6%	29%	24 %
Dyslipidemia	41.4%	42%	0%
CAD	40.6%	27%	10%

In the study group 54% have some risk factors and 46% have no risk factors. In the present study group none of the patients have atrial fibrillation. 70% were ischemic group and 30% were haemorrhagic group. 68% of patients had no LVH and 32% of patients had LVH. 46.7% had LVH in haemorrhagic group compared to 25.7% in ischemic group. In the NIHSS scoring 26% comes in the mild group, 30% comes in the moderate group and 44% comes in the severe group. Mean NIHSS value was 15.20. More patients comes under the severe group. In this study group 84% had mrs>2 and 16% had mrs <2. Mean mRS was 3.92. So 84% patients had poor outcome compared to 16% seven days after stroke.

In the study group 94% had BI less than 95 and 6% had more than 95. BI level was 39. 50. So 94% had poor outcome based on BI index. 58% of patients had CRP level less than 0.60mg/l and 42% had CRP level more than 0.60mg/l. Mean CRP level was 1.655. Of the total study group 88% were discharged and 12% died during the hospital stay.

Patients were categorized into mild stroke (NIHSS 0–7), moderate (NIHSS 8–14), or severe stroke (NIHSS >14). Outcome of patient was

measured by mRS and BI seven days after stroke onset. Poor outcome was defined by mRS > 2 orBI <95. Using pearson correlation studies all the three scores-NIHSS, mrs, BI were invidually correlated with CRP levels in total stroke patients, ischemic and haemorrhagic group separately also. In total stroke patients correlation of NIHSS, mRs, BI individually with CRP were not statistically significant. In ischemic group alone correlation with NIHSS and CRP is positively correlated and statistically significant.

In the same group BI and CRP is negatively correlated and statistically significant. But correlation between mrs and CRP is not statistically significant. In haemorrhagic stroke group patients all the three scores were correlating insignificantly. So in ischemic stroke patients elevated NIHSS score is positively correlated with the CRP levels. So stroke severity at admission correlates well with the CRP levels for ischemic stroke patients. Admission CRP levels were negatively correlated with BI in ischemic stroke patients. So CRP levels at admission can predict the poor outcome. Studies done by Admas jr HP et al, Johnston KC et al, Henon H et al and Dhamoon MS etal also showed importance of using NIHSS in stroke patients for predicting the outcome. A study done by chang KC et al in ischemic stroke patients found that admission stroke severity measured by NIHSS score as one of the strongest predictor of 3-month mortality

In our study serum CRP level, measured within 24 h of onset of stroke, was significantly correlated with severity of disease and outcome in ischemic stroke patients. Similar to this study Di Napoli M et al. found that CRP levels

were increased in the first 24 hours following stroke. Studies done by Pepys MB et al showed that CRP itself can cause secondary brain damage after focal cerebral ischemia. It occurs through a complement-mediated exacerbation of tissue injury. Di Napoli M et al also found that an association exists between elevated CRP and outcome in haemorrhagic stroke patients. They showed an association also exists with hematoma size and intracerebral haemorrhage.

But in our study showed no association between CRP levels and outcome in haemorhhagic stroke patients. Aronowski J et al in their studies came to conclusion that spontaneous intracerebral haemorrhage was seen to precipitate a complex cascade of cerebral and systemic inflammatory response. Emsley H etal in their study came to a conclusion that in acute ischemic stroke the response of CRP appears to be stimulated quite rapidly.

In this present study also results showed that serum CRP can be considered as a predictor for severity and short term outcome for ischemic stroke patients and not for haemorrhagic stroke patients. This was similar to the study conducted by shoaeb et al.

CONCLUSION

1) Mean age group of stroke patients in this study is 57. 48.
2) Males were predominant in this study.
3) Non hypertensives were more in ischemic group and hypertensives were more in haemorrhagic group
4) Non diabetics were more in this study.
5) None of the patients had dyslipidemia
6) Majority of patients had no coronary artery disease.
7) Majority of stroke patients in this study had some risk factors
8) None of the patients had AF.
9) Of the total stroke patients ischemic group were more.
10) Majority of patients had no LVH
11) Majority of patients comes in the severe NIHSS group.
12) Both modified Rankin scale and Barthel ADL index scoring showed most of the patients had poor outcome.
13) Majority of patients had a CRP below the cut off value of 0. 6mg/l.
14) CRP levels are not correlating with NIHSS, mRS, BI levels for predicting severity and outcome in total study group of stroke patients.
15) CRP levels are correlating with NIHSS levels for predicting the severity of ischemic stroke patients and not for haemorrhagic group patients.
16) CRP levels are not correlating with mRS levels for predicting the outcome in stroke patients.

17)15)CRP levels are correlating with BI levels for predicting outcome in ischemic stroke patients and not for haemorrhagic group patients

So in this study final conclusion is that CRP levels at admission can predict the severity of stroke in ischemic stroke patients. It can also predict the outcome using BI in ischemic stroke patients. In haemorhhagic stroke patients CRP levels are not useful for predicting stroke severity and outcome.

LIMITATIONS

1) Sample size of this study is limited.
2) Total number of patients in each group were not equal.
3) Though the use of high sensitivity CRP is more sensitive than regular CRP, however, we thought to evaluate the commonly present, readily available marker in our country as a prognostic marker for cerebrovascular accidents.
4) Use of multiple CRP measurements rather than single CRP measurements as in our study could have been more informative to assess the later stages of the stroke. However in our study we aimed at assessing the early predictive value of the biomarker.

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ANNEXURES

DATA COLLECTION PROFORMA

Serial No :

Name of the Patient :

Address :

Age :

Sex :

IP NO :

Date of admission :

Date of discharge/death :

Presenting complaints :

a) Onset :

b)Duration :

c)Associated complaints:

Past H/O:

DM :

HTN :

Dyslipidemia :

CAD :

Renal disease :

Liver Disease :

CVA :

Other comorbidities :

Personal History :

Smoking :

Alcohol :

Other addictions:

Socio-economic status : Poor/ middle class/ rich

Food habits : vegetarian/ non vegetarian

Occupation :

Menstrual history:

Family History :

DM/HTN/CAD/Stroke:

Treatment History :

Antihypertensives /hypolipidemics/antiplatelets/ Antidiabetics

Other medications:

General examination :

Weight :

Height :

BMI :

Pallor: Icterus: Cyanosis : Clubbing:

Lymphadenopathy: Pedal edema:

Neurocutaneous markers:

Pulse :

Rate :

Rhythm: Regular / Irregular

Peripheral pulses:

BP:

Temperature :

Respiration :

CNS EXAMINATION:

Higher mental function:

Handedness/Consciousness/orientation/Emotional state:

Speech/Memory/Intelligence:

CRANIAL NRVE EXAMINATION:

Cranial Nerve	RIGHT	LEFT
Olfactory		
Optic		
Oculomotor,trochlear,abducens		
Trigeminal		
Facial		
Vestibulocochlear		
Glossopharyngeal		
Vagus		
Accessory		
Hypoglossal		

MOTOR

	UPPER LIMB		**LOWER LIMB**	
	RIGHT	**LEFT**	**RIGHT**	**LEFT**
Bulk Tone Power – Proximal Distal Reflexes Biceps Supinator Triceps Knee Ankle Plantar Cremasteric Abdominal				

SENSORY :

	UPPER LIMB		LOWER LIMB	
	RIGHT	**LEFT**	**RIGHT**	**LEFT**
Touch Pain Temperature Position Vibration				

Cortical sensation:

Neck rigidity:

Kernig's sign:

Skull & spine:

Peripheral nerves:

Other systems examination:

Cardiovascular system:

Respiratory system:

Gastro intestinal system:

Musculoskeletal system:

Investigations :

Complete Blood count:

Urine Routine :

RBS:

FBS:

PPBS :

Fasting Lipid profile:

Renal function test:

Liver function test:

CRP at admission:

ECG :

Chest Xray:

Echocardiogram:

CT scan brain :

Others:

Atrial fibrillation:

Left ventricular Hypertrophy:

NIHSS:

Modified Rankin scale:

Barthel ADL INDEX:

FINAL DIAGNOSIS:

TYPE OF LESION:

Infarct :

Hemorrhage :

TREATMENT GIVEN:

Medical

Surgical

END POINT:

Discharge:

Death:

Signature of the Invigilator **Signature of the Patient/Guardian**

PATIENT CONSENT FORM

TITLE OF THE STUDY: PROGNOSTIC ROLE OF CRP IN ACUTE STROKE

Study Centre: Mahatma Gandhi Memorial Government Hospital, Trichy.

Patient's Name: **Age/Sex:**

Parent/Guardian's Name:

Address:

- ☐ The details of the study have been provided to me in writing and explained to me in my own language. I confirm that I have understood the above study and had the opportunity to ask questions about A STUDY ON PROGNOSTIC ROLE OF CRP IN ACUTE STROKE.
- ☐ I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without affecting the medical care that will normally be provided by the hospital.
- ☐ I understand that the doctor involved in the study does not require my permission, to monitor and assess me for various medical parameters
- ☐ I agree not to restrict the use of any data or results that arise from this study, provided such a use is only for scientific purpose(s).

- ☐ I give my consent for the study and it was explained to me that this study methods does not alter any standard management for this disease and is in no way will be affecting the patients health as mentioned in the patient information sheet.
- ☐ I consent wholeheartedly after understanding that the study is taken up for the benefit for me

Signature/Thumb impression of the patient

Date:

Place: Tiruchirappalli

Signature of the investigator

PATIENT INFORMATION SHEET

Name	:
Age	:
Sex	:
Education	:
Occupation	:
Duration of Illness	:
Informant	:
Relationship with the patient	:

I ----------

---------- is willing to include my particulars about ---------- in the study titled PROGNOSTIC ROLE OF CRP IN ACUTE STROKE .

SIGNATURE

ETHICS COMMITTEE CLEARANCE CERTIFICATE

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TIRUCHIRAPALLI -1
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LAW PERSON
Mr.R.Ravindran, ML
Rtd. District Judge

SOCIAL WORKER
Mrs.Kalavathy,
Vice President, Exnora

Lay person.
Tmt.R.Rajeswari

This is to certify that the project work titled Prognostic role of CRP in acute stroke - in patients admitting to MGMGH attached to K.A.P.V.Govt. Medical College, Tiruchirapalli proposed by Dr.A. Niyas, First Year part of fulfillment of M.D/M.S course in the subject of General Medicine for the year 2017-2020 by The Tamilnadu Dr.MGR Medical University has been cleared by the ethics committee.

CHAIRMAN,
Institutional Ethics Committee
K.A.P.Viswanatham Govt. Medical
College, Tiruchirapalli -1

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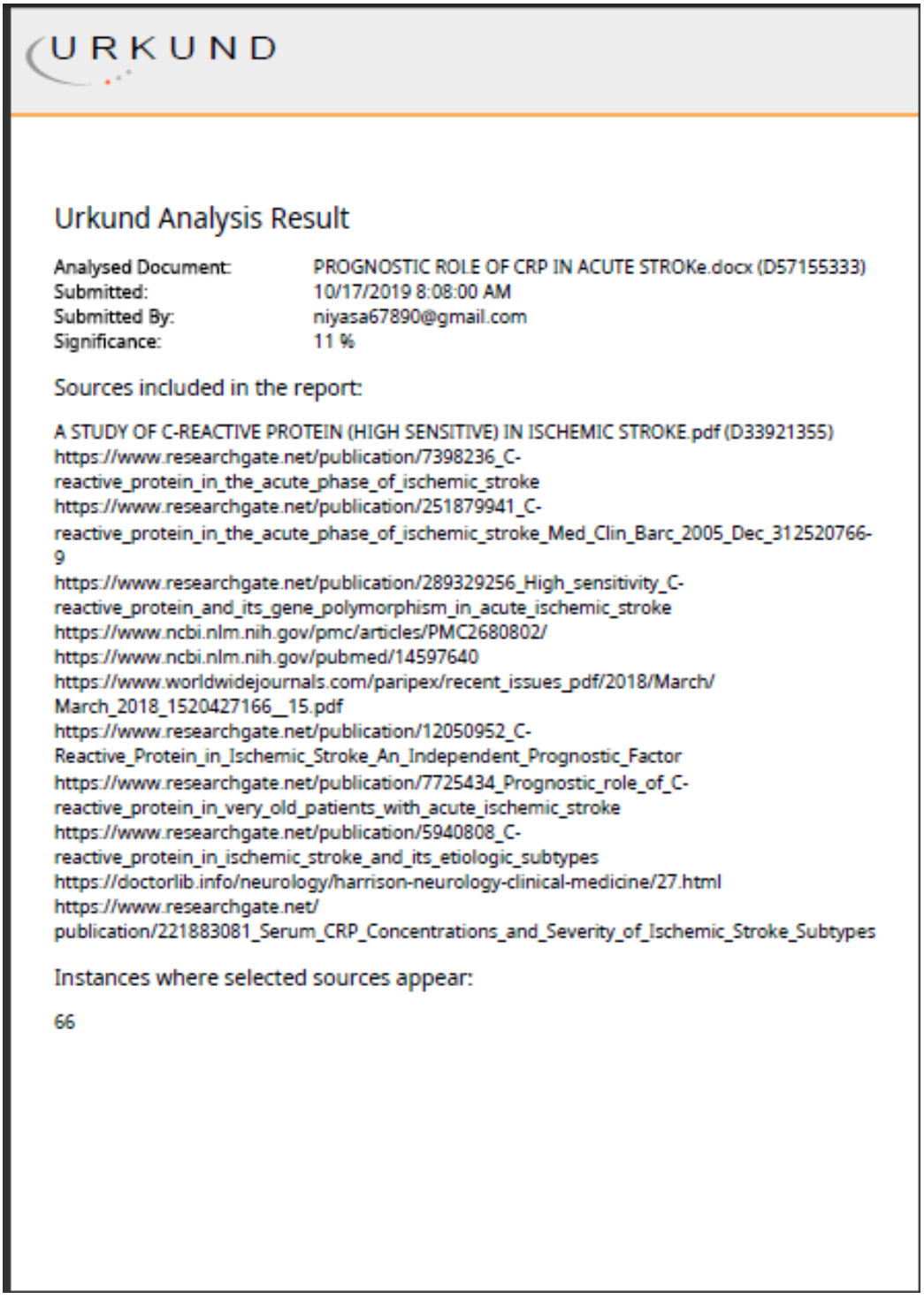

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MASTER CHART

S. No.	Name	Age	sex	HTN	DM	DLP	CAD	NR	AF	ISCHEMIC	HMG	LVH	NIHSS	MRS	BI	CRP	END POINT
1	KUMAR	30	M	N	N	N	N	Y	N	Y	N	N	18	4	30	14.7	DIS
2	RAJKUMAR	38	M	Y	Y	N	Y	N	N	Y	N	Y	31	5	0	12.8	DEATH
3	KRISHNAN	60	M	N	N	N	N	Y	N	Y	N	N	20	4	30	0.157	DIS
4	Elangovan	57	M	N	N	N	N	Y	N	N	Y	N	31	5	0	0.001	DIS
5	Pappathy	80	F	Y	N	N	N	N	N	N	Y	Y	33	5	0	0.01	DIS
6	Periyasamy	70	M	N	N	N	N	Y	N	N	Y	N	9	4	20	4.3	DIS
7	Andi	50	M	Y	N	N	N	N	N	N	Y	N	4	3	65	14.3	DIS
8	Chinnammal	60	F	Y	Y	N	N	N	N	Y	N	Y	6	4	60	0.449	DIS
9	LAKSHMI	45	F	N	N	N	N	Y	N	Y	N	N	7	4	55	0.177	DIS
10	Maheswari	35	F	N	N	N	N	Y	N	Y	N	N	8	2	110	0.07	DIS
11	PAPPATHY	70	F	N	N	N	N	Y	N	Y	N	N	11	4	20	1.17	DIS
12	GOVINDAN	50	M	N	N	N	N	Y	N	Y	N	N	16	4	30	1.1	DIS
13	RAMAR	60	M	Y	Y	N	Y	N	N	N	Y	Y	11	4	25	0.0678	DIS
14	PALANIMANICKAM	90	M	N	Y	N	N	N	N	Y	N	N	9	4	65	0.001	DIS
15	BASHA	60	M	N	Y	N	N	N	N	Y	N	N	2	2	95	0.268	DIS
16	ABDUL RAHUMAN	52	M	N	N	N	N	Y	N	Y	N	N	16	4	40	0.15	DEATH
17	AROCKIYASAMY	62	M	Y	N	N	N	N	N	N	Y	Y	22	5	10	0.341	DIS
18	NALLUSAMY	53	M	N	N	N	N	Y	N	Y	N	N	11	4	40	2.83	DIS
19	SIVA	47	M	Y	Y	N	N	N	N	N	Y	Y	23	5	10	0.325	DIS
20	MUTHUKANNU	75	F	Y	N	N	Y	N	N	Y	N	N	3	2	95	0.225	DIS
21	Chinnammal	85	F	Y	N	N	N	N	N	N	Y	Y	22	5	15	0.223	DIS
22	THYAGARAJAN	75	M	Y	N	N	N	N	N	N	Y	Y	36	5	10	0.001	DIS
23	VARATHARAJAN	28	M	N	N	N	N	Y	N	Y	N	N	12	3	80	0.001	DIS
24	XAVIER	41	M	N	N	N	N	Y	N	Y	N	N	1	1	100	0.038	DIS
25	SUBRAMANI	70	M	Y	N	N	N	N	N	Y	N	Y	3	2	80	0.478	DIS
26	ASOKAN	40	M	Y	N	N	N	N	N	Y	N	Y	12	5	20	0.734	DIS
27	THANGAVEL	70	M	Y	Y	N	N	N	N	Y	N	Y	26	5	10	3.14	DIS
28	Palaniyammal	55	F	Y	Y	N	Y	N	N	Y	N	Y	14	4	40	0.102	DIS
29	vijayalekshmi	67	F	N	N	N	Y	N	N	Y	N	N	4	3	50	0.899	DIS
30	PALANIVEL	60	M	Y	N	N	N	N	N	Y	N	N	8	5	20	0.001	DIS
31	GOVINDHRAJ	55	M	N	N	N	N	Y	N	Y	N	N	32	5	10	1.29	DIS
32	ALAGAMMAL	57	F	Y	N	N	N	N	N	N	Y	N	22	5	20	2.44	DIS
33	Sarada	55	F	Y	Y	N	N	N	N	Y	N	Y	8	5	20	5.73	DIS
34	SARASU	75	F	Y	N	N	N	N	N	Y	N	N	4	4	35	1.29	DIS
35	Akhilambal	75	F	N	N	N	N	Y	N	Y	N	N	8	3	50	0.112	DIS

36	LAKSHMI	60	F	N	N	N	N	Y	N	N	Y	N	28	5	0	0.001	DIS
37	Arun	40	M	N	N	N	N	Y	N	Y	N	N	12	2	90	2.04	DIS
38	varadarajan	80	M	N	N	N	N	Y	N	N	Y	N	31	5	10	0.101	DIS
39	veeramani	50	M	Y	N	N	N	N	N	Y	N	N	6	4	40	0.0624	DIS
40	selvaraj	60	M	N	N	N	N	Y	N	Y	N	N	36	5	20	0.012	DEATH
41	kamatchi	60	F	Y	Y	N	N	N	N	Y	N	Y	30	5	10	2.18	DEATH
42	Natarajan	49	M	Y	N	N	N	N	N	N	Y	Y	9	4	35	0.121	DIS
43	Nallammal	70	F	N	N	N	N	Y	N	N	Y	N	8	3	50	2.1	DIS
44	Susheela	65	F	Y	Y	N	N	N	N	Y	N	Y	4	2	90	0.526	DIS
45	Raju	63	M	Y	Y	N	N	N	N	Y	N	N	17	4	35	1.12	DIS
46	Anand	28	M	N	N	N	N	Y	N	Y	N	N	24	5	10	2.5	DEATH
47	Muhammed ibrahim	60	M	N	N	N	N	Y	N	Y	N	N	3	3	50	0.112	DIS
48	Dhanam	57	F	Y	N	N	N	N	N	Y	N	N	2	2	125	1.2	DIS
49	varatharajan	28	M	N	N	N	N	Y	N	N	Y	N	31	5	10	0.602	DIS
50	settu	52	M	N	N	N	N	Y	N	Y	N	N	16	4	40	0.15	DEATH

HTN : HYPERTENSION

NR : NO RISK

DIS : DISCHARGE

CAD : CORONARY ARTERY DISEASE

HMG : HAEMORRHAGIC

LVH : LEFT VENTRICULAR HYPERTROPHY

DM : DIABETES MELLITUS

AF : ATRIAL FIBRILLATION

DLP : DYSLIPIDEMIA