CRP IN ACUTE ISCHAEMIC STROKE : PROGNOSTIC IMPLICATIONS

Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfillment of the regulations

for the award of the degree of

M.D. GENERAL MEDICINE (BRANCH - I)

INSTITUTE OF INTERNAL MEDICINE

MADRAS MEDICAL COLLEGE

CHENNAI 600 003

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI

APRIL 2017

CERTIFICATE

This is to certify that the dissertation titled **"CRP IN ACUTE ISCHAEMIC STROKE : PROGNOSTIC IMPLICATIONS"** is a bonafide work done **by Dr.RENJINI RADHAKRISHNAN**, Post graduate student, Institute of Internal Medicine, Madras Medical College, Chennai-03, in partial fulfillment of the University Rules and Regulations for the award of Degree of MD General Medicine (Branch - I), Internal Medicine, under our guidance and supervision, during the academic year 2014 – 2017.

Prof. S.MAYILVAHANAN M.D.,
Director & Professor,
Institute of Internal Medicine,
Madras Medical College &
RGGGH, Chennai – 600003.

Prof.P.VIJAYARAGHAVAN M.D.,
Professor of Medicine,
Institute of Internal Medicine,
Madras Medical College &
RGGGH, Chennai – 600003.

Prof. M.K.MURALITHARAN M.S, M.Ch.,
DEAN,
Madras Medical College &
Rajiv Gandhi Government General Hospital,
Chennai - 600 003.

DECLARATION

I solemnly declare that the dissertation entitled "**CRP IN ACUTE ISCHAEMIC STROKE : PROGNOSTIC IMPLICATIONS"** is done by me at Madras Medical College, Chennai – 3 during April 2016 to September 2016 under the guidance and supervision of **Prof.P.VIJAYARAGHAVAN M.D., & Prof.S.MAYILVAHANAN M.D.,** To be submitted to The Tamilnadu Dr. M.G.R Medical University towards the partial fulfillment of requirements for the award of **M.D. DEGREE IN GENERAL MEDICINE BRANCH – I.**

Place : Chennai – 03

Date :

Dr. RENJINI RADHAKRISHNAN
Post Graduate,
M.D. General Medicine,
Institute of Internal Medicine,
MMC & RGGGH,
Chennai - 600003

ACKNOWLEDGEMENTS

At the outset, I would like to thank **Prof. M.K.MURALITHARAN** M.S., M.Ch., Dean, Madras Medical College, for having permitted me to conduct the study and use the hospital resources in the study.

I express my gratitude to **Prof.S.MAYILVAHANAN, M.D.,** Director and Professor, Institute of Internal Medicine, for his inspiration, advice and guidance in making this work complete.

I am indebted to my chief **Prof.Dr.P.VIJAYARAGHAVAN, M.D.,** Professor, Institute of Internal Medicine for his guidance during the study.

I am extremely thankful to Assistant professors of Medicine **Dr. M. SHARMILA, M.D.,** and **Dr. S.APARNA M.D.,** for guiding me with their corrections and prompt help rendered whenever approached.

In conclusion, I wish to thank all the Professors, assistant Professors and the technical staff in Institute of Internal Medicine for their cooperation in the study.

Last but not the least, I wish to thank all the patients without whom the study would have been impossible.

ABBREVIATIONS

NIHSS	-	National Institute of Health Stroke Scale
MRS	-	Modified Rankin Scale
BI	-	Barthel Index
MCA	-	Middle Cerebral Artery
CT	-	Computed Tomography
MRI	-	Magnetic Resonance Imaging
ICA	-	Internal Carotid Artery
PICA	-	Posterior Inferior Cerebellar Artery
AICA	-	Anterior Inferior Cerebellar Artery
TIA	-	Transient Ischemic Attack
SAH	-	Subarachnoid Hemorrhage
ICH	-	Intra Cerebral Hemorrhage
AF	-	Atrial Fibrillation
CVA	-	Cerebro vascular accident
OCP	-	Oral Contraceptive Pills
PCA	-	Posterior Cerebral Artery
ICT	-	Intracranial Tension
ACA	-	Anterior Cerebral Artery
rtPA	-	Recombinant Tissue Plasminogen Activator
PAN	-	Polyarteritis Nodosa
CRP	-	C Reactive Protein

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INTRODUCTION

Cerebrovascular accident or CVA or stroke forms the major bulk of the burden of the neurological conditions that a physician sees in his day to day practice. There are many synonyms to stroke like CVA or cerebrovascular accident or brain attack etc.

A cerebrovascular accident is defined as an sudden onset of a neurologic deficit due to a focal vascular cause. This can be due to ischaemia or haemorrhage.

Cerebrovascular accident comprises some of the most devastating disorders. There are 15 million people worldwide who suffer a stroke each year. According to the statistics given by World Health Organization (WHO), in people aged more than 60 years cerebrovascular accident is the 2nd leading cause of death and in people aged between 15 to 59 years it is the 5th cause of death. Every year, nearly six million people die from CVA worldover. This summarises the great burden that world faces due to CVA. The problem is even on the rising trend with the world facing a rapid level of rise in the incidence of CVA mainly attributable to the high rise in the level of the contributary risk factors like hypertension, diabetes, obesity, smoking etc.

C-reactive protein (CRP) is an acute phase protein that rises in many conditions of inflammation. High levels of CRP and other inflammatory markers have been found in conditions of atherosclerosis. High levels of CRP have been linked to various vascular events like cerebrovascular accident and myocardial infarction through various studies.

In CARE study high levels of CRP was correlated to recurrent events or even death. Framingham study linked CRP to Tansient ischaemic attack or CVA .Cardiovascular health study found an association between CRP and carotid intima media thickness.

Ischaemic CVA is found to have a higher level of CRP. The pathogenic mechanism behind it is said to be due to the inflammation and tissue damage caused by the ischaemia of brain tissue. Many animal studies show that CRP can cause a secondary damage to brain perhaps by activating complement pathway. However in case of humans we are not sure if this kind of secondary brain damage is caused by CRP or not.

Hence measuring CRP may be of clinical relevance in ischaemic stroke. This test readily available and easily measured in most of the hospitals. Hence I chose this study to determine the prognostic value of CRP measured in acute ischemic stroke for poor functional outcome and death in a sample of patients with acute ischemic stroke.

AIMS AND OBJECTIVES

- To evaluate the role of serum CRP as a biomarker for predicting severity and short term outcome in acute ischaemic stroke.

- To assess the severity of stroke using NIHSS(National Institute of Health Stroke Scale) and outcome using mRS(modified Rankin Scale) and BI(Barthel Index)

REVIEW OF LITERATURE

Cerebrovascular accident is one of the most common neurologic disease encountered in clinical practice. It is defined as sudden occurrence of focal neurological deficit. It is classified broadly into ischaemic and haemorrhagic .ischaemic CVA occurs due to occlusion of blood vessel supplying the brain. Haemorrhagic CVA occurs due to haemorrhage into the brain matter or subarachnoid space or ventricles.

Ischaemic CVA due to blockage of blood supply to the brain causes ischaemia and finally infarction leading to death of neurons . Proper history taking and clinical examination helps to differentiate the two types of cerebrovascular accident. Clinical examination helps to find the region of brain effected.

The usual causes associated with this type of cerebrovascular accident is :-

1) atherothrombosis

2) embolism

However there are many other causes apart from the usual associated with cerebrovascular accident. Another entity associated include Transient Ischaemic Attack(TIA). In this the neurological deficit

will be temporary and patient clinically recovers without any deficit within 24 hours without any imaging evidence.

Haemorrhagic cerebrovascular accident is usually caused by hypertension, coagulopathies, vascular malformations, trauma, haemorrhage into ischaemic area. Subarachnoid haemorrhage is most commonly caused by rupture of aneurysm, rarely by arterio venous malformations.

In case of embolic CVA the deficit is maximum at its onset. Thrombotic CVA evolves slowly. Haemorrhagic CVA may be static or progressive. There may be many variations to this.

The main aims while we evaluate a stroke patient is:-

1) Confirm diagnosis
2) Pathophysiology
3) If acute treatment is needed or not
4) Prevention

Over the years better imaging modality has been an added boon to our diagnosis and management of CVA. However a good understanding of the nervous system and a sound clinical knowledge is a must especially in cases where imaging may not be contributory or in third world countries where the imaging facilities may not be that readily available.

EPIDEMIOLOGY

From the available data[1], in US cerebrovascular accident is the third most common cause of death after heart disease and cancer. [2]Out of 7 lakh cases every year 6 lakh is of ischaemic and 1 lakh is haemorrhagic cerebrovascular accident. This shows that ischaemic CVA is more common than haemorrhagic one.

According to World Health Organisation[3] and other experts cerebrovascular accident claims 6.2 million lives every year. In 2008,17.3 million people died from cerebrovascular diseases which is 30% of global deaths. Of these deaths 7.3 million were due to coronary heart disease and 6.2 million were due to cerebrovascular accidents.

Coming to Indian scenario[4], the updated data in 2012 shows that the rate of cerebrovascular accidents ranges from 84 per 1 lakh to 262 per 1 lakh in rural areas and between 334 per 1 lakh to 424 per 1 lakh in urban areas. However due to various reasons the effective diagnosis and treatment of various modifiable risk factors and the disease , better imaging modalities , intervention techniques have reduced the mortality considerably over many years. But the residual disability still remains a problem and hence the morbidity is still a matter of concern.

RISK FACTORS FOR STROKE

Over 300 risk factors[5] have been identified for cerebrovascular accidents and coronary artery disease. Broadly they can be divided into modifiable and non-modifiable risk factors .

MODIFIABLE RISK FACTORS

- Hypertension
- Atrial fibrillation
- Diabetes mellitus
- Smoking
- Hyperlipidemia
- Obesity
- Stress
- Drugs-OCPs
- Unhealthy diet- low potassium, low fruit and vegetable intake, high saturated fat intake
- Alcohol use
- Hyperhomocysteinemia

NON MODIFIABLE RISK FACTORS

- Advancing age – risk of stroke doubles with every decade after 55 years.
- Family history
- Gender- risk of stroke is higher in men but lifetime risk of stroke is higher in women.
- Ethinicity or race – higher risk in Blacks, some Hispanics, Americans, Chinese and Japanese populations.

CAUSES OF STROKE

1. Atherosclerotic thrombosis
2. Transient ischemic attacks
3. Embolism
4. Hypertensive hemorrhage
5. Ruptured or unruptured saccular aneurysm or AVM
6. Arteritis

a. Meningovascular syphilis, arteritis secondary to pyogenic and tuberculous meningitis, rare infective types (typhus, schistosomiasis, malaria, mucormycosis, etc.)

b. Connective tissue diseases (polyarteritis nodosa, lupus erythematosus), necrotizing arteritis. Wegener arteritis, temporal arteritis, Takayasu disease, granulomatous or giantcell arteritis of the aorta, and giant-cell granulomatous angiitis of cerebral arteries

7. Cerebral thrombophlebitis: secondary to infection of ear, paranasal sinus, face, etc.; with meningitis and subdural empyema; debilitating states, postpartum, postoperative, cardiac failure, hematologic disease (polycythemia, sickle cell disease), and of undetermined cause

8. Hematologic disorders: anticoagulants and thrombolytics, clotting factor disorders, polycythemia, sickle cell disease, thrombotic thrombocytopenic purpura, thrombocytosis, intravascular lymphoma, etc.

9. Trauma and dissection of carotid and basilar arteries

10. Amyloid angiopathy

11. Dissecting aortic aneurysm

12. Complications of arteriography

13. Neurologic migraine with persistent deficit

14. With tentorial, foramen magnum, and subfalcial herniations

15. Miscellaneous types: fibromuscular dysplasia, with local dissection of carotid, middle cerebral, or vertebrobasilar artery, x-irradiation, unexplained middle cerebral infarction in closed head injury, pressure of unruptured saccular aneurysm, complication of oral contraceptives

16. Undetermined cause in children and young adults: moyamoya disease and others

PATHOPHYSIOLOGY OF ISCHAEMIC STROKE

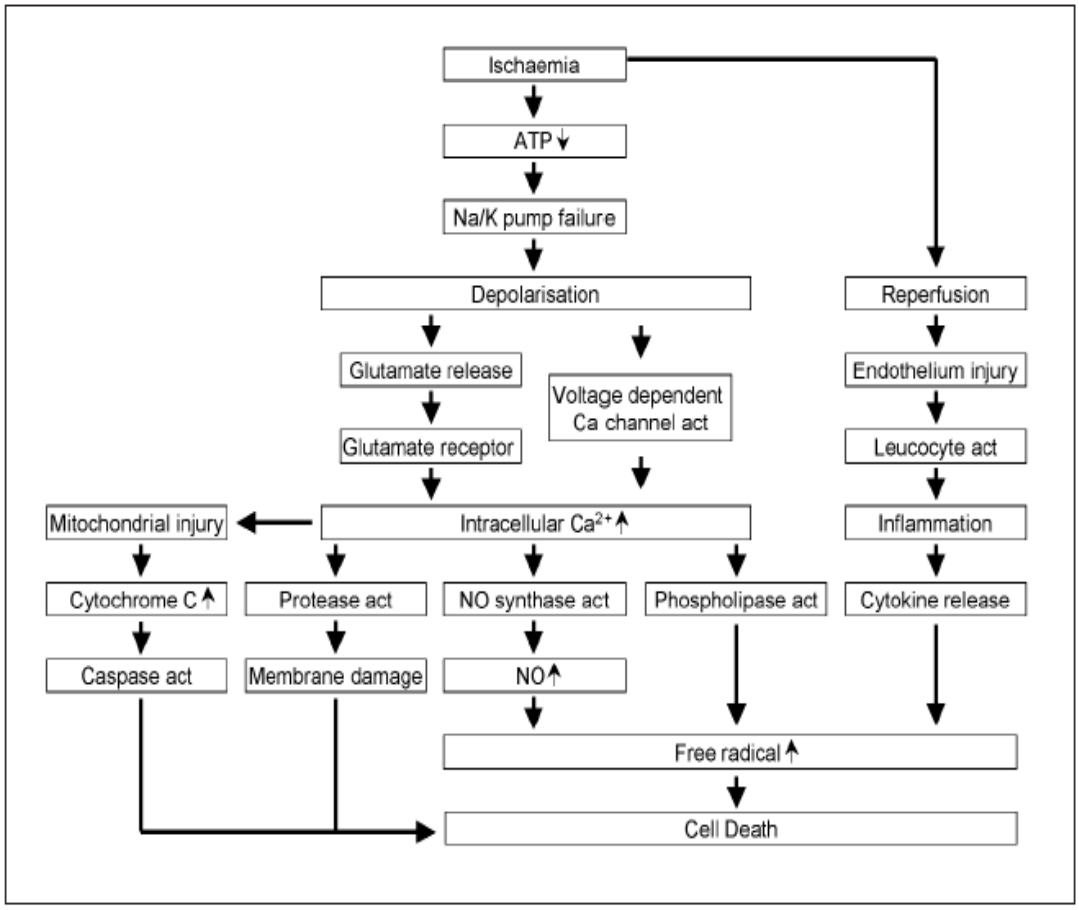
In ischaemic cerebrovascular accident there is occlusion to the blood supply to the brain. The amount of blood flow that is reduced as a result of blockage varies from person to person depending on the vascular anatomy, site of block and blood pressure. [6]When the blood flow to brain is reduced to zero it causes death of brain tissue within 4 to 10 minutes. If the blood flow is reduced to less than 16- 18 ml/ 100 g tissue per minute then infarction occurs in an hour. If less than 20 ml / 100 g tissue per minute then ischaemia occurs without infarction but if its prolonged to

several hours or days then it may lead to infarction. If the blood supply is restored to the brain at the right time, i.e before ishaemia leads to infarction then the patient may experience only transient symptoms. Ischaemic penumbra is a region surrounding infarction which is ischaemic. Hence this region is only reversibly damaged and we aim to restore the blood supply to this area as soon as possible to protect maximum salvageable brain tissue. Ischaemic penumbra can be visualised by imaging modalities like CT or MRI.

Infarction of brain tissue can occur by:-

1) Necrosis – caused by greater degree of ischaemia
2) Apoptosis – caused by lesser degree of ischaemia

   Apoptosis occurs over days to weeks. Both hyperglycemia and hyperthermia have been found to worsen the brain damage. Hence we should avoid both.


Ischaemia
ATP↓
Na/K pump failure
Depolarisation
Reperfusion
Glutamate release
Voltage dependent Ca channel act
Endothelium injury
Glutamate receptor
Leucocyte act
Mitochondrial injury
Intracellular Ca^{2+}↑
Inflammation
Cytochrome C↑
Protease act
NO synthase act
Phospholipase act
Cytokine release
Caspase act
Membrane damage
NO↑
Free radical↑
Cell Death

ETIOLOGY

Most common etiological factors are Atherothrombosis and Embolism.

ATHEROTHROMBOSIS

Half of the cases of thrombotic cerebrovascular accident has a preceding Transient Ischaemic Attack. It has an intermittent progression. Atheromatous plaque usually form at the region of branching or at curves of arteries. Most common sites are :-

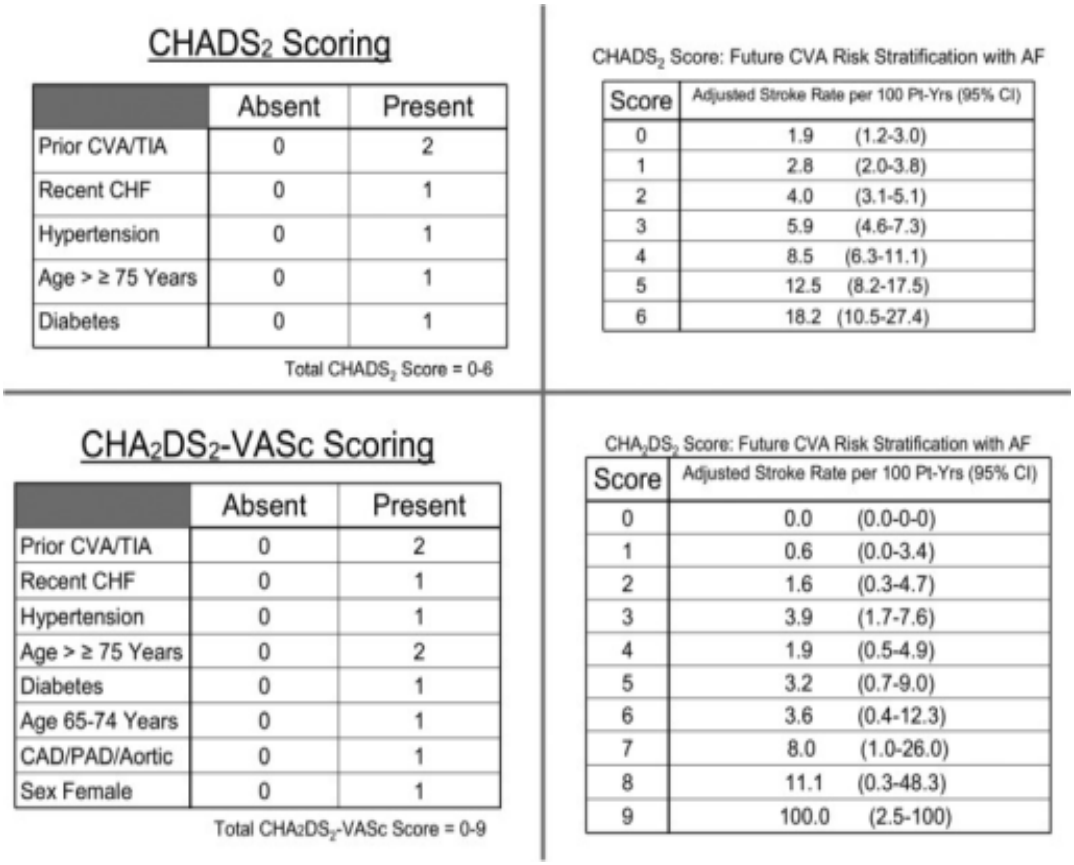
1) Internal carotid artery at its origin
2) Vertebral artery – cervical part and at the junction forming basilar artery
3) Middle cerebral artery – stem or bifurcation
4) Posterior cerebral artery – proximal part
5) Anterior cerebral artery – proximal part

Atheroma may develop in the Common Carotid Artery or Vertebral Artery at its origin from Aorta but it rarely cause symptoms due to adequate collaterals. The atheroma may cause occlusion of the artery and cause symptoms or it may cause an embolism. More than 90% occlusion of lumen of Carotid artery is associated with high incidence of stroke.

EMBOLISM

Embolic cerebrovascular accident develops abruptly usually without Transient Ischaemic Attack. Most frequently it is due to an embolus arising from the heart called cardioembolism. It may also be from another occluded artery like carotid or vertebral artery. It may be a paradoxical embolus or it may be an embolus from vegetation in heart i.e infective endocarditis. Other rare ones may be fat, tumor cells (atrial myxoma), fibrocartilage, air, amniotic fluid. There is no time for collaterals to develop after embolisation, hence symptoms develop depending on the blood vessel occluded.

Framingham Heart Study showed there is 6 times risk for cerebrovascular accident in patients with Atrial fibrillation.[7] Scoring systems like $CHADS_2$ and CHA_2DA_2-VASc have been developed to predict the risk of stroke with atrial fibrillation and to start anticoagulation in such patients.



$CHADS_2$ Scoring

	Absent	Present
Prior CVA/TIA	0	2
Recent CHF	0	1
Hypertension	0	1
Age > ≥ 75 Years	0	1
Diabetes	0	1

Total $CHADS_2$ Score = 0-6

$CHADS_2$ Score: Future CVA Risk Stratification with AF

Score	Adjusted Stroke Rate per 100 Pt-Yrs (95% CI)
0	1.9 (1.2-3.0)
1	2.8 (2.0-3.8)
2	4.0 (3.1-5.1)
3	5.9 (4.6-7.3)
4	8.5 (6.3-11.1)
5	12.5 (8.2-17.5)
6	18.2 (10.5-27.4)

CHA_2DS_2-VASc Scoring

	Absent	Present
Prior CVA/TIA	0	2
Recent CHF	0	1
Hypertension	0	1
Age > ≥ 75 Years	0	2
Diabetes	0	1
Age 65-74 Years	0	1
CAD/PAD/Aortic	0	1
Sex Female	0	1

Total CHA_2DS_2-VASc Score = 0-9

CHA_2DS_2 Score: Future CVA Risk Stratification with AF

Score	Adjusted Stroke Rate per 100 Pt-Yrs (95% CI)
0	0.0 (0.0-0-0)
1	0.6 (0.0-3.4)
2	1.6 (0.3-4.7)
3	3.9 (1.7-7.6)
4	1.9 (0.5-4.9)
5	3.2 (0.7-9.0)
6	3.6 (0.4-12.3)
7	8.0 (1.0-26.0)
8	11.1 (0.3-48.3)
9	100.0 (2.5-100)

TRANSIENT ISCHAEMIC ATTACK

TIA is occurrence of focal neurological deficit temporarily. Patient recovers within 24 hours, and it usually lasts for more than 1 hour. The etiology of TIA is same as that of cerebrovascular accident, i.e embolism or thrombosis. The significance of TIA clinically is because of the fact that it can usually precede stroke. Hence sometimes admitting a patient with TIA may be of use for even thrombolysis at the right time. [8]Studies have shown that 10-15% TIA develop into stroke within 3 months. However most patients with TIA develop stroke within 2 days. Risk scores have been developed to predict the occurrence of stroke after TIA.

Prevention is the goal. Various studies are there that studied the prevention of occurrence of CVA after TIA. Many of these recommend aspirin in combination with clopidogrel.

$ABCD^2$ score	Points
Age > 60 years	1
BP = 140/90 mmHg at initial evaluation	1
Clinical features of the TIA	
Speech disturbance without weakness, or	1
Unilateral weakness	2
Duration of symptoms	
10–59 min, or	1
>60 min	2
Diabetes mellitus in patient's history	1

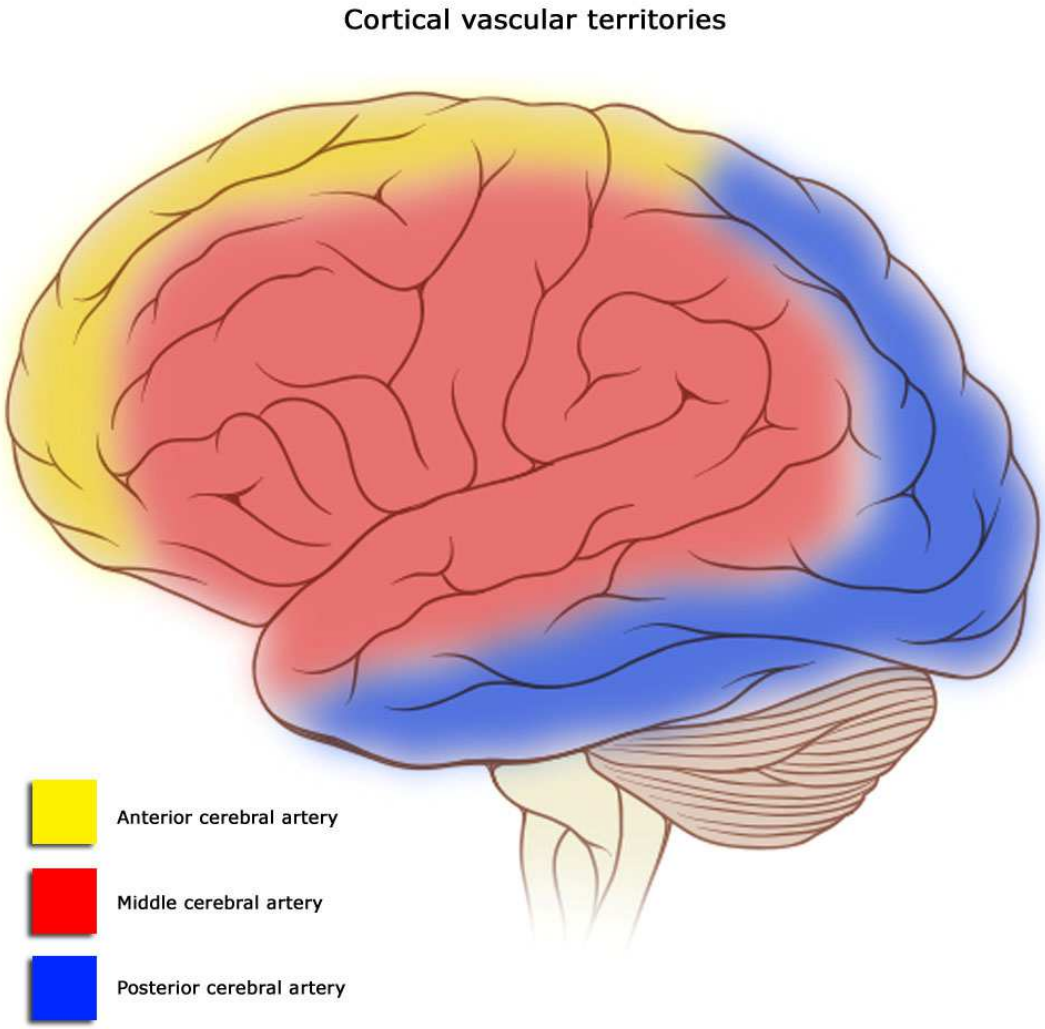
SCORE	**2 DAY RISK FOR STROKE**	**RECURRENCE IN 90 DAYS**
0 TO 3	LOW	1%
4 TO 5	MODERATE	4.1%
6 TO 7	HIGH	8.1%

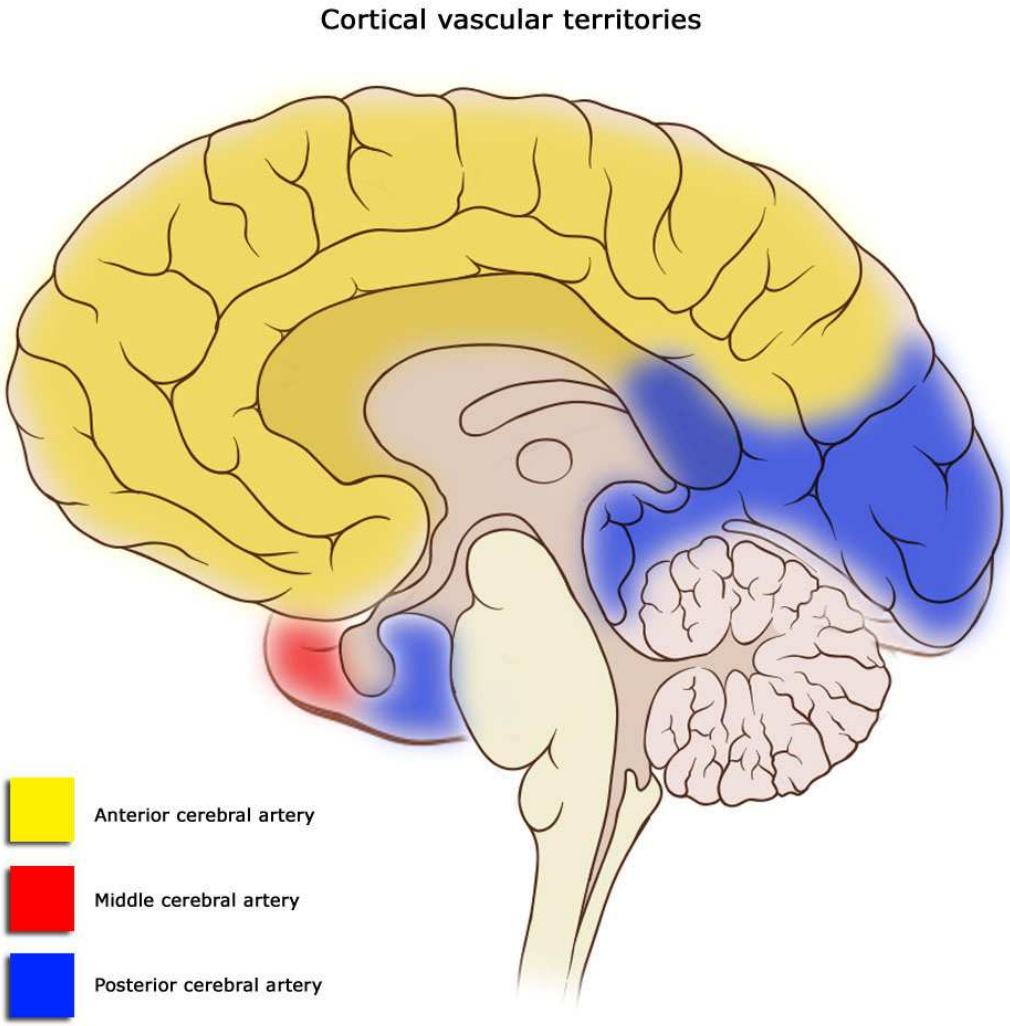
STROKE SYNDROMES

A careful and precise understanding of the blood supply of the brain may help to delineate the area of occlusion in cerebrovascular accident.

SYNDROME	ANATOMY INVOLVED	MAJOR SYMPTOMS	VESSELS INVOLVED	ETIOLOGY
Left MCA	Left frontal/parietal cortex and subcortical structures	Aphasia, right visual field cut, right motor/sensory deficits; face > arm > leg weakness; left gaze preference	Left MCA or major branch; could also be left ICA or siphon	Emboli from heart or proximal lesion; intrinsic atherothrombosis
Right MCA	Right frontal/parietal cortex and subcortical structures	Neglect syndrome, agnosia, apraxia, left motor/sensory deficits, visual field deficit; right gaze preference	Right MCA or major branch; right ICA or siphon	Same as left MCA
Left ACA	Left frontal and parasagittal areas	Speech disturbance, behavioral changes, leg > arm weakness	Left ACA	Intrinsic atherothrombosis, embolic
Right ACA	Right frontal and parasagittal areas	Behavioral changes, leg > arm weakness	Right ACA	Same as left ACA
Brainstem	Pons, midbrain, medulla, cerebellum	Ophthalmoplegia, bilateral motor deficits, ataxia/dysmetria; nausea/vomiting/vertigo, coma/altered mentation	Basilar artery	Intrinsic atherothrombosis, embolism from heart or proximal vessel
PCA	Upper midbrain, occipital cortex/subcortex, thalamus, medial temporal lobes	Visual field cut, motor/sensory loss, seizures, gaze problems; 3rd nerve deficits	Posterior cerebral artery, thalamic perforators	Embolism from proximal lesion, intrinsic atherothrombosis

ACA, anterior cerebral artery; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.


Cortical vascular territories
Anterior cerebral artery
Middle cerebral artery
Posterior cerebral artery


Cortical vascular territories
Anterior cerebral artery
Middle cerebral artery
Posterior cerebral artery

STROKE SEVERITY

Stroke can be assessed using NIHSS[9] (National Institute of Health Stroke Scale). It divides the stroke into mild moderate and severe based on the scores obtained.

MILD	–	NIHSS 0 TO 7
MODERATE	–	NIHSS 8 TO 14
SEVERE	–	NIHSS MORE THAN 14

NIHSS

1. **Level of consciousness**
   0 alert
   1 drowsy
   2 stuporous
   3 coma
2. **LOC questions (month, age)**
   0 both correct
   1 one correct
   2 incorrect
3. **LOC commands (close eyes, make a fist)**
   0 both correct
   1 one correct
   2 incorrect
4. **Best gaze**
   0 normal
   1 partial gaze palsy
   2 forced deviation
5. **Visual fields**
   0 no visual loss
   1 partial hemi
   2 complete hemi
   3 bilateral hemi
6. **Facial palsy**
   0 normal
   1 minor
   2 partial
   3 complete

7-10. **Motor (L/R arm + leg)**
   0 no drift
   1 drift
   2 can't resist gravity
   3 no effort against gravity
   4 no movement
   UN amputation/joint fusion
11. **Limb ataxia (Finger-Nose, Heel-Knee-Shin)**
   0 absent
   1 present in 1 limb
   2 present in 2 limbs
12. **Sensation (pinprick)**
   0 normal
   1 partial loss
   2 severe loss
13. **Best language**
   0 no aphasia
   1 mild-mod aphasia
   2 severe aphasia
   3 mute
14. **Dysarthria**
   0 none
   1 mild-mod
   2 near to unintelligible or worse
   UN intubated/barrier
15. **Extinction and inattention**
   0 no neglect
   1 partial neglect
   2 complete neglect

OUTCOME

Various scoring systems are available for the measurement of outcome in cerebrovascular accident. Many such scores[10] are used for study and research purpose as they help to quantify patients disability and morbidity for better understanding of the outcomes. Examples of such scoring systems include – Modified Rankin score (MRS) and Barthel Index (BI). A score of more than 2 in MRS and less than 95 in BI are generally considered poor.

MODIFIED RANKIN SCORE

SCORE	DESCRIPTION
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Barthel Index Activity	Score
FEEDING 0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent	
BATHING 0 = dependent 5 = independent (or in shower)	
GROOMING 0 = needs to 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 catheterized 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	

IMAGING

CT BRAIN

It helps to immediately differentiate ischaemic CVA from Haemorrhagic one. The biggest advantage is that it can be done immediately at great speed and is readily available in government hospitals too in our country. This is also a very cost effective imaging modality available for cerebrovascular accident. Hence it is the imaging modality of choice in stroke. However the problem with this technique is that infarct may not be visible in CT film during the first few hours after the event. It usually takes 24 to 48 hours to be visible in the film. Posterior circulation ischaemic may be missed due to bony artifice. Another disadvantage of the imaging is the hazard of being exposed to harmful X Ray radiations.

Contrast enhanced CT is another option available. It helps to delineate the venous structures of brain better. Hence it may be of good use in diagnosing cortical venous thrombosis.

CT angiography is also of use. It helps to visualise arterial structure. Hence we can directly see the region of blood vessel that is blocked. By correlating with the vascular blood supply of brain we will

know the area of brain that is infarcted. This may be use in finding the ischaemic penumbra and salvaging it.

MRI BRAIN

This is a more precise and better imaging modality compared to CT. The images produced are of better quality and clarity. Even minor abnormalities and infarcts, hemorrhages are easily picked up. Diffusion weighted imaging and Fluid attenuated inversion recovery (FLAIR) are very sensitive to pick up very early abnormalities.

MR angiography is very useful one to detect the abnormalities of cerebral blood vessels like occlusion or aneurysms.

Iron Sensitive Imaging (ISI) is sensitive for detecting microbleeds.

However the disadvantage of MRI is that it is not that readily available in all hospitals, it is time consuming hence cannot be done on an emergency basis. If the patient is unstable then it may not be possible to do an MRI urgently. If patients have claustrophobia then it may not be possible to do an MRI. Most importantly MRI is a very costly imaging modality and in a country like our it may not be afforded by all patients.

CEREBRAL ANGIOGRAPHY

X Ray angiography is the gold standard technique to detect cerebral atherosclerosis and other abnormalities like vasospasm, aneurysm, etc. however nowadays this modality is rarely used as we have CT angiography and MR angiography, which are less cumbersome and provides better image.

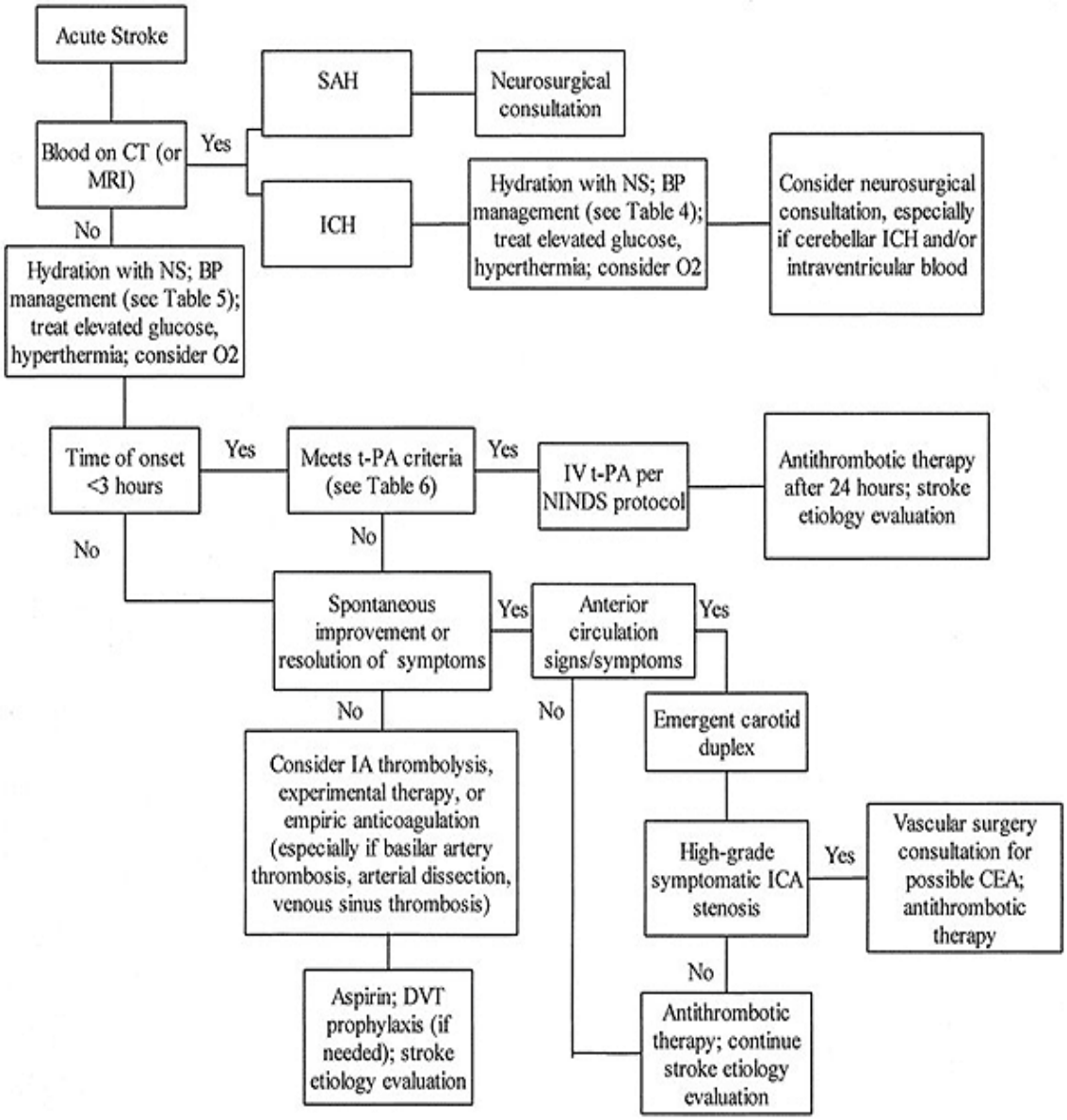
ULTRASOUND TECHNIQUES

Duplex ultrasound can detect flow velocity. Transcranial Doppler may of use in assessing the blood flow in cerebral blood vessels, it may aid in thrombolysis too. It also helps to visualize the origin of carotid artery and its caliber which may be of use in intervention.

PERFUSION TECHNIQUES

Xenon CT and PET scan may be used. However both are costly techniques which is currently in use only for research purposes. Single photon emission computerized tomography (SPECT) , MR perfusion techniques may also be used to assess perfusion.

TREATMENT


Acute Stroke
Blood on CT (or MRI)
Yes
SAH
Neurosurgical consultation
ICH
Hydration with NS; BP management (see Table 4); treat elevated glucose, hyperthermia; consider O2
Consider neurosurgical consultation, especially if cerebellar ICH and/or intraventricular blood
No
Hydration with NS; BP management (see Table 5); treat elevated glucose, hyperthermia; consider O2
Time of onset <3 hours
Yes
Meets t-PA criteria (see Table 6)
Yes
IV t-PA per NINDS protocol
Antithrombotic therapy after 24 hours; stroke etiology evaluation
No
No
Spontaneous improvement or resolution of symptoms
Yes
Anterior circulation signs/symptoms
Yes
No
No
Emergent carotid duplex
Consider IA thrombolysis, experimental therapy, or empiric anticoagulation (especially if basilar artery thrombosis, arterial dissection, venous sinus thrombosis)
High-grade symptomatic ICA stenosis
Yes
Vascular surgery consultation for possible CEA; antithrombotic therapy
No
Aspirin; DVT prophylaxis (if needed); stroke etiology evaluation
Antithrombotic therapy; continue stroke etiology evaluation

APPROACH TO A STROKE PATIENT

The first and foremost step in the management would be to stabilize the patient as in any other condition. Make sure that the Airway , Breathing and Circulation (ABC) is maintained. Once the patient is stable we have to proceed with CT brain to differentiate between ischaemic and haemorrhagic stroke.

SUPPORTIVE MEASURES

The basic goal is to maintain as much as cerebral blood flow as possible especially to the salvageable ischaemic penumbra. We usually maintain the blood pressure at higher level as the rise in blood pressure after ischaemic stroke is actually a protective mechanism of the brain to maintain the cerebral blood flow. By non judicious use of antihypertensives we may be duing more harm to the brain. Hence[11] antihypertensives is to be used only if there is malignant hypertension or myocardial infarction or if the patient has BP more than 185/110 mm Hg and planned for thrombolysis. According to guidelines antihypertensive sto be used only if BP is more than 220/130 mm Hg. Avoid hyperthermia , maintain[12] blood glucose level below 180 mg/dl. If cerebral oedema is present then [13] antioedema measures like intravenous mannitol and

furosemide may be needed. Sometimes craniotomy may be needed if there is severe raised intracranial tension.

THROMBOLYSIS

The golden period upto which intravenous thrombolysis can be done is still a matter of debate. In our hospital the [14]golden period is upto 4.5 hours.

Inclusion

- Age >18 yr
- Ischemic stroke by clinical assessment
- Persistent neurologic deficit beyond an isolated sensory deficit or ataxia
- Cranial computed tomography negative for hemorrhage
- Initiation of treatment within 3 hours after symptom onset

Exclusion

- Treatment initiated >3 hours after symptom onset
- Neurologic deficit that is rapidly improving based on history or observation
- CT scan shows major early infarct signs (eg, substantial edema, mass effect, midline shift)
- Patient taking oral anticoagulants or with PT >15 seconds (INR > 1.7)
- Patient receiving heparin within the preceding 48 hours who has a prolonged PTT
- Platelet count $<100{,}000/mm^3$
- Pretreatment systolic blood pressure >185 mm Hg or diastolic pressure >110 mm Hg or if aggressive treatment is required to reduce blood pressure to the specified limits before thrombolytic therapy
- Prior stroke or any serious head trauma in the preceding 3 months
- Major surgery within the preceding 21 days
- Prior intracerebral hemorrhage
- Gastrointestinal or urinary tract hemorrhage within the preceding 14 days
- Seizure at the onset of stroke
- Symptoms suggestive of SAH
- Arterial puncture at a noncompressible site within the previous 7 days

ENDOVASCULAR REVASCULARISATION

Many a times intravascular thrombolysis may not be sufficient if the clot is very big. Hence studies have been conducted to find better methods. Mechanical thrombus removing devices and intra-arterial thrombolysis have all been tried but these facilities are not available in all centres. [15] Intra-arterial thrombolysis has not shown much benefit than intravenous therapy.

ANTITHROMBOTIC AGENTS

ANTIPLATELETS-

Aspirin has shown benefit in stroke. No other antiplatelets have shown much of a benefit.

ANTICOAGULANTS-

Many studies show there is no much benefit, both long and short term , for anticoagulation in acute ischaemic CVA. Heparin may be used in case the patient has atrial fibrillation, in embolic stroke, cortical vein thrombosis, and for prevention of DVT in chronic bedridden patients.

NEUROPROTECTION

Several animal studies have shown benefit by using[16] neuroprotective agents. However in humans perhaps because the body and mechanisms are more complex it has failed to show any much benefit. Most of these neuroprotective agents are ones that try to protect the ischaemic neurons in brain and decrease the excitatory neurotransmitters in brain.

REHABILITATION

Most of the stroke patients are left with residual disability. Hence physical, occupational, psychological , speech therapy and rehabilitation is needed and is of utmost importance.

PREVENTION OF STROKE

Control of hypertension:-

Reduction of both systolic and diastolic blood pressure is of value in reducing the risk of stroke.risk[17] of CVA increased by 46% for every 7.5 mm Hg increase in diastolic blood pressure. On an average reduction of blood pressure by 5.8 mm Hg decreased the risk of CVA by 42%. Though in the earlier times it was thought that only diastolic blood

pressure is important in stroke prevention but later it was proved that both systolic and diastolic are important. Usually a BP less than 130/80 mm Hg is targeted for CVA prevention.

Cessation of smoking:-

Studies have shown that there is increased risk of stroke if the patient smokes. The risk rises as the number of cigarettes smoked increases. [18]Once a patient stops smoking for 5 years the risk of CVA is same as a person who has not smoked at all. This is strikingly similar to the coronary artery disease and smoking association.

Increased physical activity:-

Exercise is of proven benefit in stroke. It aids in reducing body weight, control of high blood pressure, blood glucose and hyperlipidemia. Many studies have shown an increased incidence of stroke associated with physical inactivity. Even moderate level of activity may be beneficial. Hence as physicians we must encourage our patients for weight reduction and increased physical activity, exercise to be included in daily routine.

Anticoagulation

As mentioned earlier atrial fibrillation increases the risk of stroke by nearly 5 times. It is also observed that the patients with atrial fibrillation are at increased risk of recurrent stroke. Hence such patients with[19] atrial fibrillation must be placed on life long anticoagulation with warfarin and the target of PT INR must be between 2 to 3.

Antiplatelets

After an episode of stroke or transient ischaemic attack the patient must take Aspirin for further prevention. Other drugs like [20]Clopidogrel and Ticlopidine have shown benefit. But these are not used much in clinical practice.

Surgery

Carotid stenosis correction by surgical endarterectomy was studied in various studies. It was found to be beneficial in patients with symptomatic[21] stenosis more than 70%. But the benefit of surgery in patients without any symptoms still remains a matter of debate and controversy. Other surgical options studied includeballoon angioplasty

with stenting and bypass surgery. However practically these methods are rarely used.

Lipid lowering agents

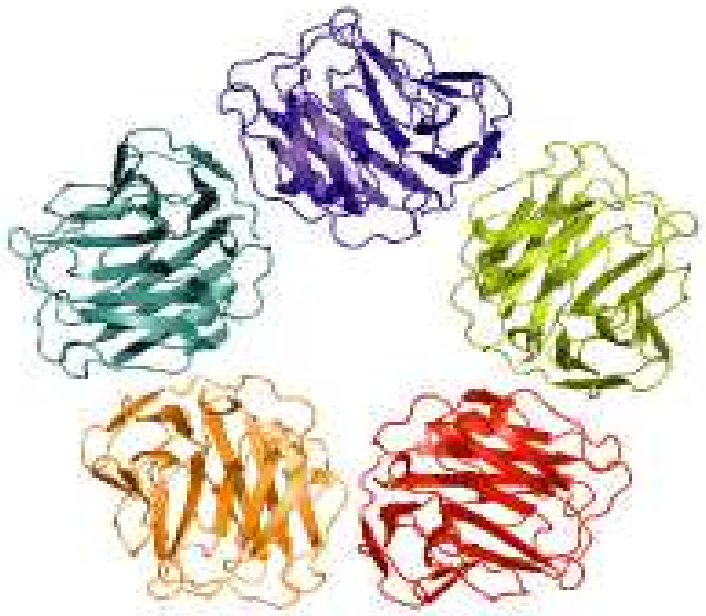
Studies have shown beneficial role for statin use in prevention of stroke. Hence statins are routinely prescribed after the occurrence of CVA. It is found to stabilize the atherosclerotic plaque, exert beneficial effects on clotting and improve endothelial function. Thus very useful for the purpose.

Folic acid

High homocystein levels have been linked both to increased risk of stroke as well as myocardial infarction. Addition of folic acid is found to reduce homocystein levels and thus exert beneficial effect for stroke prevention.

All these measures should be given due consideration and applied in daily clinical practice especially to those patients with high risk of stroke. Our aim should always be prevention is better than cure especially when it comes to CVA where the morbidity and mortality is considerably high.

C REACTIVE PROTEIN



C reactive protein is an acute phase protein that is produced in the liver. As the picture shows it is a pentameric structure and is ring shaped. It has a molecular weight of 115 kDa. Since it is an acute phase reactant it increases in the blood in response to inflammation. It is named so because it was first identified during acute inflammation in response to pneumococcal infection and it reacted with the c carbohydrate antigen of the organism. Initially it was thought to be a pathogenic substance produced in the body in response conditions like malignancy, however this concept was later changed. Nowadays it is viewed as a marker of inflammation.

CRP causes activation of various complement proteins and thus play a role in inflammatory response of body. It usually rises after 2 hours of inflammation and peaks in 48 hours. It has a half life of 18 hours. Various studies have been conducted to study the role of C reactive protein in the diagnosis and prognosis of various diseases.

The value of less than 10 mg/ dl may be taken as normal for CRP. Earlier we had assay that used to measure CRP but later on better laboratory techniques have made to detect even very low level of crp i.e even in the normal range called hs CRP or highly sensitive CRP. So nowadays we have assays to measure hs CRP. The normal range of hs CRP is less than 3 mg/ dl ; that can again be divided into less than 1mg / dl ; 1 – 3 mg / dl ; >3 mg / dl depending on the cardiac risk associated with the elevation of hs CRP.

As already mentioned CRP is an important biomarker of inflammation. Atherosclerosis is a state of chronic inflammation ; hence it a may be associated with elevated CRP. Thus CRP can be an important predictor of vascular events.

Most cases of acute ischaemic stroke may be associated with an elevated CRP. The[22] rise in CRP following acute ischaemic CVA is due to the inflammation and tissue damage associated with it. There are various studies that tried to find the association between CRP and CVA.

All of them found that an increased level of CRP is associated with poor outcome in ischaemic cerebrovascular accident be it short or long term. Some studies even showed that higher CRP values even point towards a risk of recurrence of CVA. Hence practically we can use CRP for prognosticative purpose for our patients. Some studies also found that there is no much correlation between CRP and haemorrhagic cerebrovascular accident[23].

MATERIALS AND METHODS

The study was conducted at the department of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai 600003.

ETHICAL COMMITTEE APPROVAL

Obtained

PATIENT CONSENT

Obtained

DURATION OF STUDY

6 months

STUDY DESIGN

Observational study

SAMPLE SIZE

100 patients

INCLUSION CRITERIA

Patients

- 18-60 years
- Diagnosed as first episode of Acute ischaemic stroke admitted in medical wards .

EXCLUSION CRITERIA

- Pregnant women
- Haemorrhagic stroke
- Cortical venous thrombosis
- Recurrent stroke
- Traumatic brain injury
- Autoimmune diseases
- Recent acute coronary syndrome
- Chronic renal failure
- Liver cell failue
- Infectious diseases

DATA COLLECTION AND METHODOLOGY

Patients are subjected to detailed history taking and clinical examination.

Patients admitted with acute ischaemic stroke - selected for clinical study as per inclusion / exclusion criteria are subjected to routine blood investigations like complete hemogram, renal function tests, serum electrolytes, liver function test, S.CRP, CT Brain. Detailed history taking and clinical examination will be done. Patients with acute ischaemic stroke will be analysed for following factors

- Age
- sex
- diabetic or hypertensive
- dyslipidemia
- history of smoking
- onset and duration of weakness

Stroke will be categorized as mild,moderate and severe using National Institute of Health Stroke Scale(NIHSS).Patients will be followed up for outcome at the time of discharge using modified Rankin

Scale(mRS) and Barthel Index(BI) .Poor outcome considered to be >2mRS score and <95 BI.Serum CRP will be correlated with severity and outcome.

STATISTICAL ANALYSIS

The results are analysed using SPSS software version 20. Association between variables were analysed using chi-square test. The primary association expected was C reactive protein and severity of stroke. Hence both were compared and also with the outcome of stroke at discharge.

Statistical significance is assumed with a p value of less than 0.005

SPONSORSHIP

No

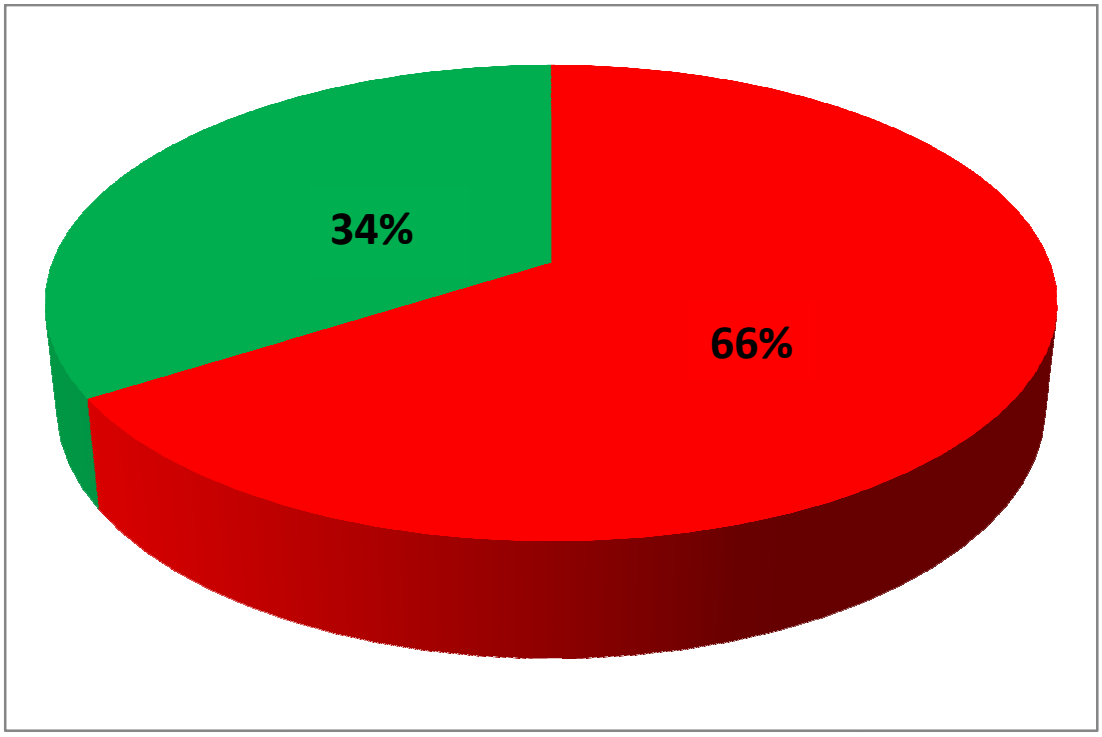
CONFLICT OF INTEREST

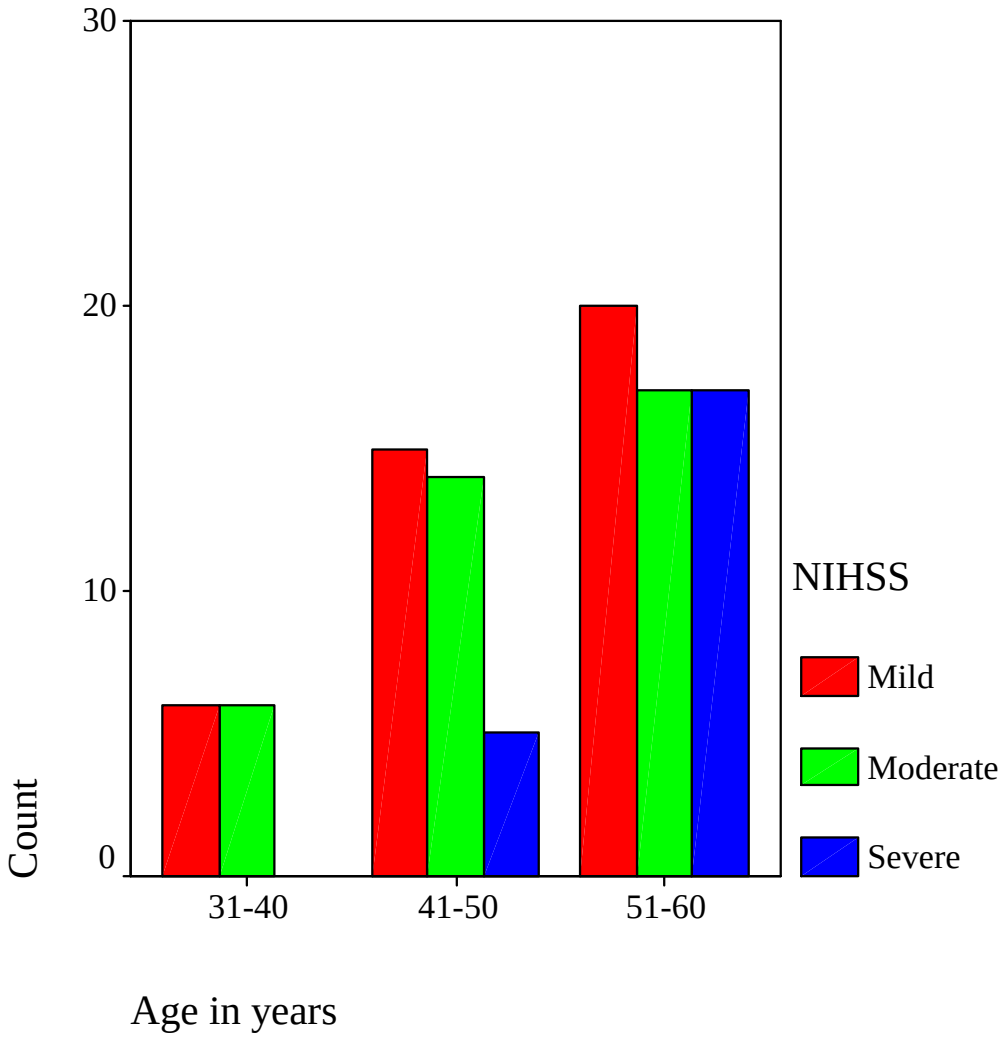
None

OBSERVATION AND RESULTS

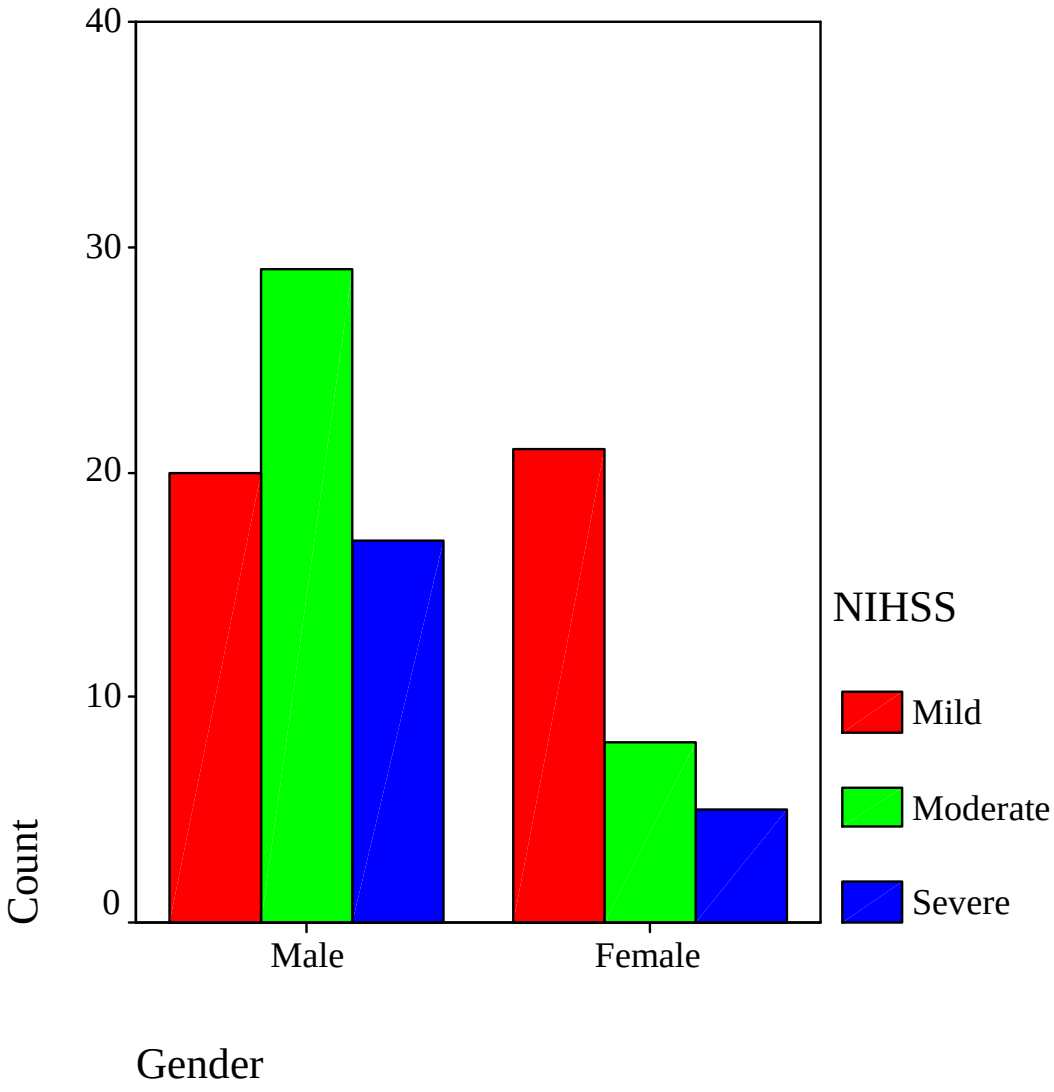
PATIENTS		NIHSS			Total
		Mild	Moderate	Severe	
Male	Count	20	29	17	66
	% within Gender	30.3%	43.9%	25.8%	100.0%
	% within NIHSS	48.8%	78.4%	77.3%	66.0%
Female	Count	21	8	5	34
	% within Gender	61.8%	23.5%	14.7%	100.0%
	% within NIHSS	51.2%	21.6%	22.7%	34.0%
Total	Count	41	37	22	100
	% within Gender	41.0%	37.0%	22.0%	100.0%
	% within NIHSS	100.0%	100.0%	100.0%	100.0%

SEX DISTRIBUTION





As the age of the patient increases the severity of stroke increases as observed in the study.



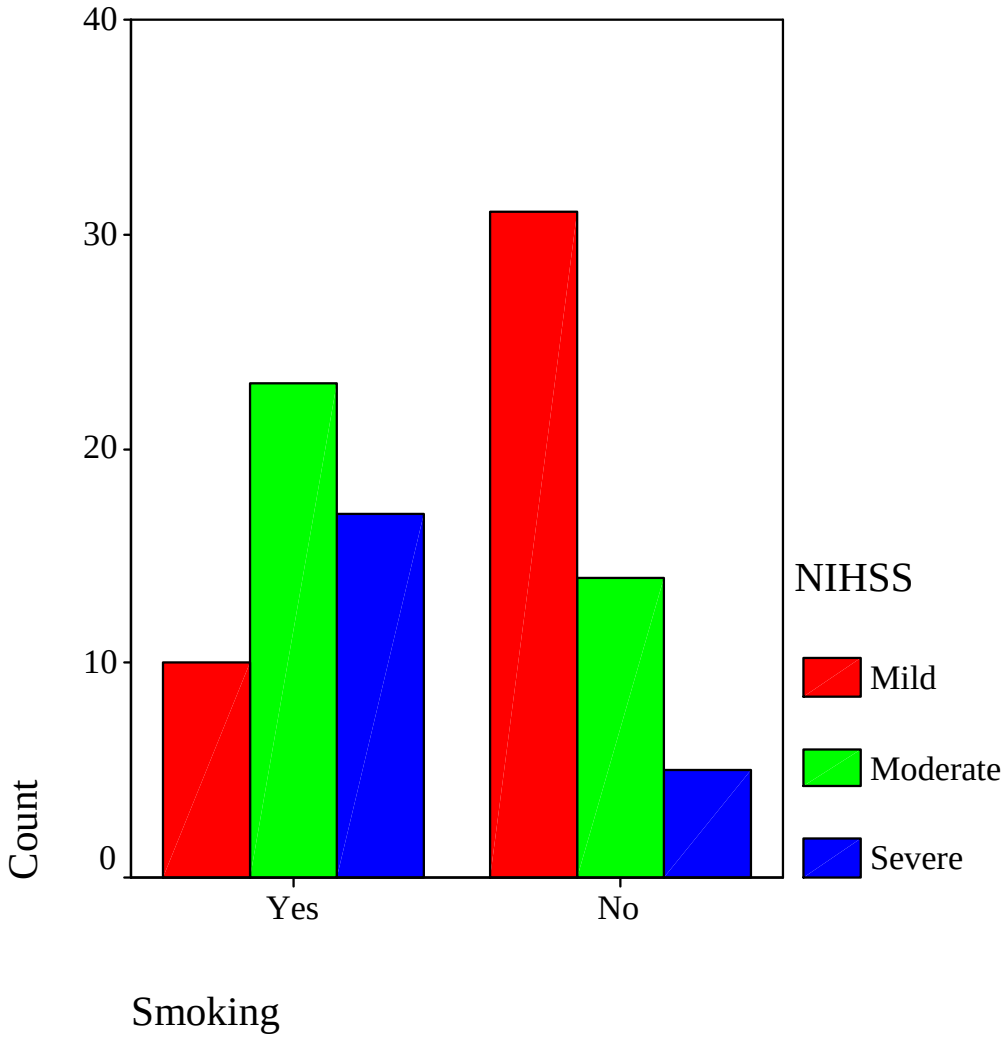
In our study most of the patients were male. Males were found to have severe stroke compared to females.

SMOKING AND STROKE

			NIHSS			Total
			Mild	Moderate	Severe	
Smoking	Yes	Count	10	23	17	50
		% within Smoking	20.0%	46.0%	34.0%	100.0%
		% within NIHSS	24.4%	62.2%	77.3%	50.0%
	No	Count	31	14	5	50
		% within Smoking	62.0%	28.0%	10.0%	100.0%

		% within NIHSS	75.6%	37.8%	22.7%	50.0%
Total		Count	41	37	22	100
		% within Smoking	41.0%	37.0%	22.0%	100.0%
		% within NIHSS	100.0%	100.0%	100.0%	100.0%

Most of the patients who had not smoked developed mild stroke compared to the patients who had smoked. P value was less than 0.001 hence statistically significant.

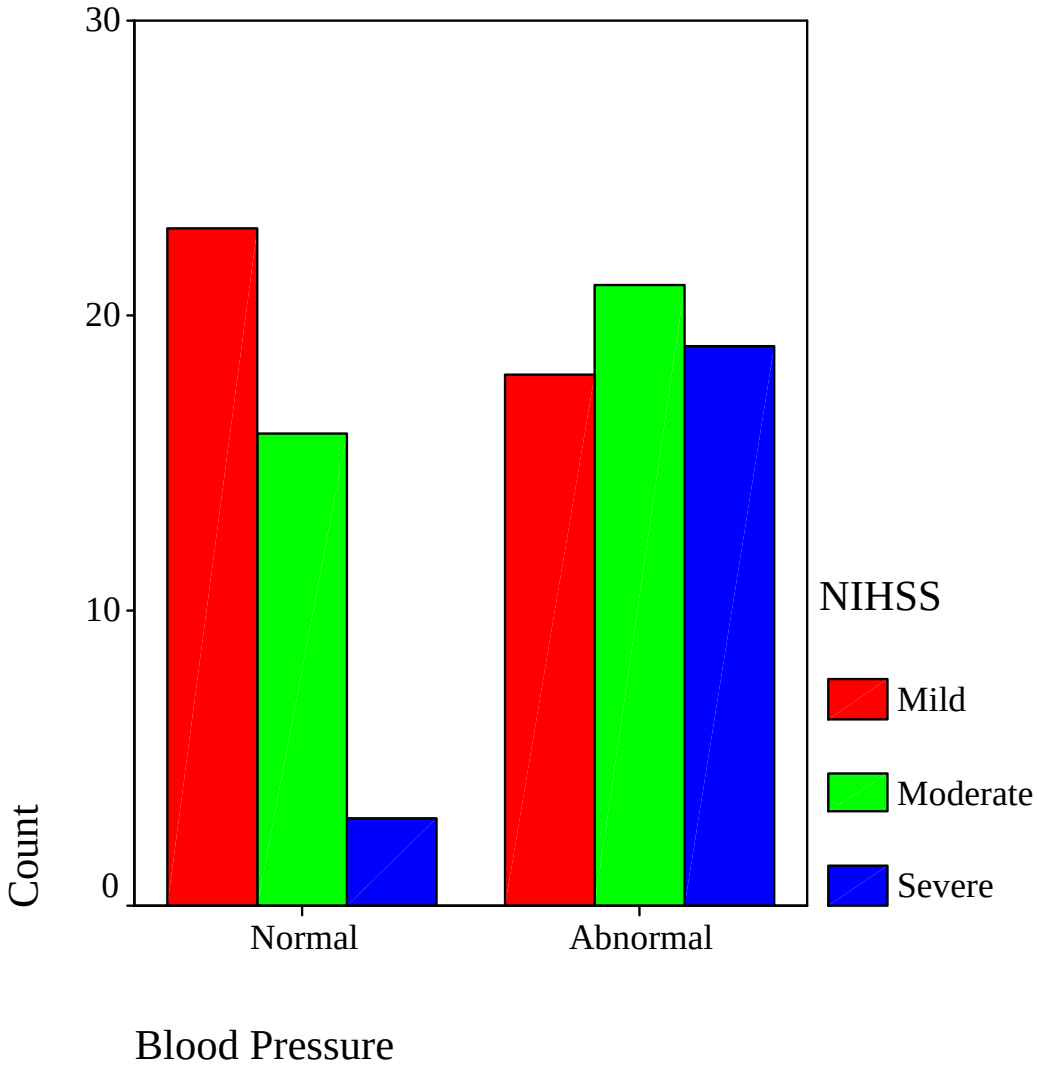

40
30
20
10
0
Count
Yes
No
Smoking
NIHSS
Mild
Moderate
Severe

BLOOD PRESSURE AND STROKE

Blood Pressure			NIHSS			Total	P value
			Mild	Moderate	Severe		
	Normal	Count	23	16	3	42	0.002
		% within Blood Pressure	54.8%	38.1%	7.1%	100.0%	
		% within NIHSS	56.1%	43.2%	13.6%	42.0%	
	Abnormal	Count	18	21	19	58	

		% within Blood Pressure	31.0%	36.2%	32.8%	100.0%	
		% within NIHSS	43.9%	56.8%	86.4%	58.0%	
Total		Count	41	37	22	100	
		% within Blood Pressure	41.0%	37.0%	22.0%	100.0%	
		% within NIHSS	100.0%	100.0%	100.0%	100.0%	

Most of the patients who developed stroke were hypertensive.

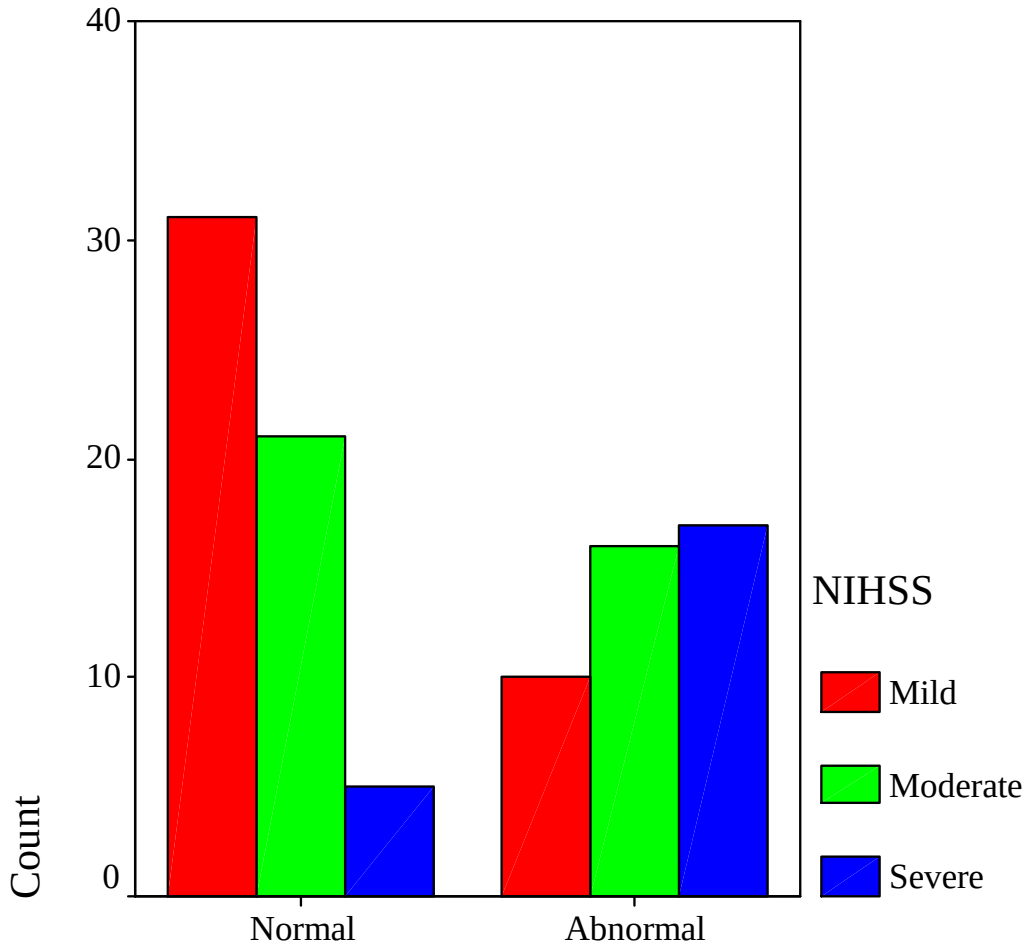

30
20
10
0
Count
Normal
Abnormal
Blood Pressure
NIHSS
Mild
Moderate
Severe

STROKE AND RANDOM BLOOD SUGAR

Random blood sugar			NIHSS			Total	P value
			Mild	Moderate	Severe		
	Normal	Count	31	21	5	57	
		% within Random blood sugar	54.4%	36.8%	8.8%	100.0%	Less than 0.001
		% within NIHSS	75.6%	56.8%	22.7%	57.0%	
	Abnormal	Count	10	16	17	43	

		% within Random blood sugar	23.3%	37.2%	39.5%	100.0%	
		% within NIHSS	24.4%	43.2%	77.3%	43.0%	
Total		Count	41	37	22	100	
		% within Random blood sugar	41.0%	37.0%	22.0%	100.0%	
		% within NIHSS	100.0%	100.0%	100.0%	100.0%	

Patients with elevated random blood sugar suffered severe stroke.



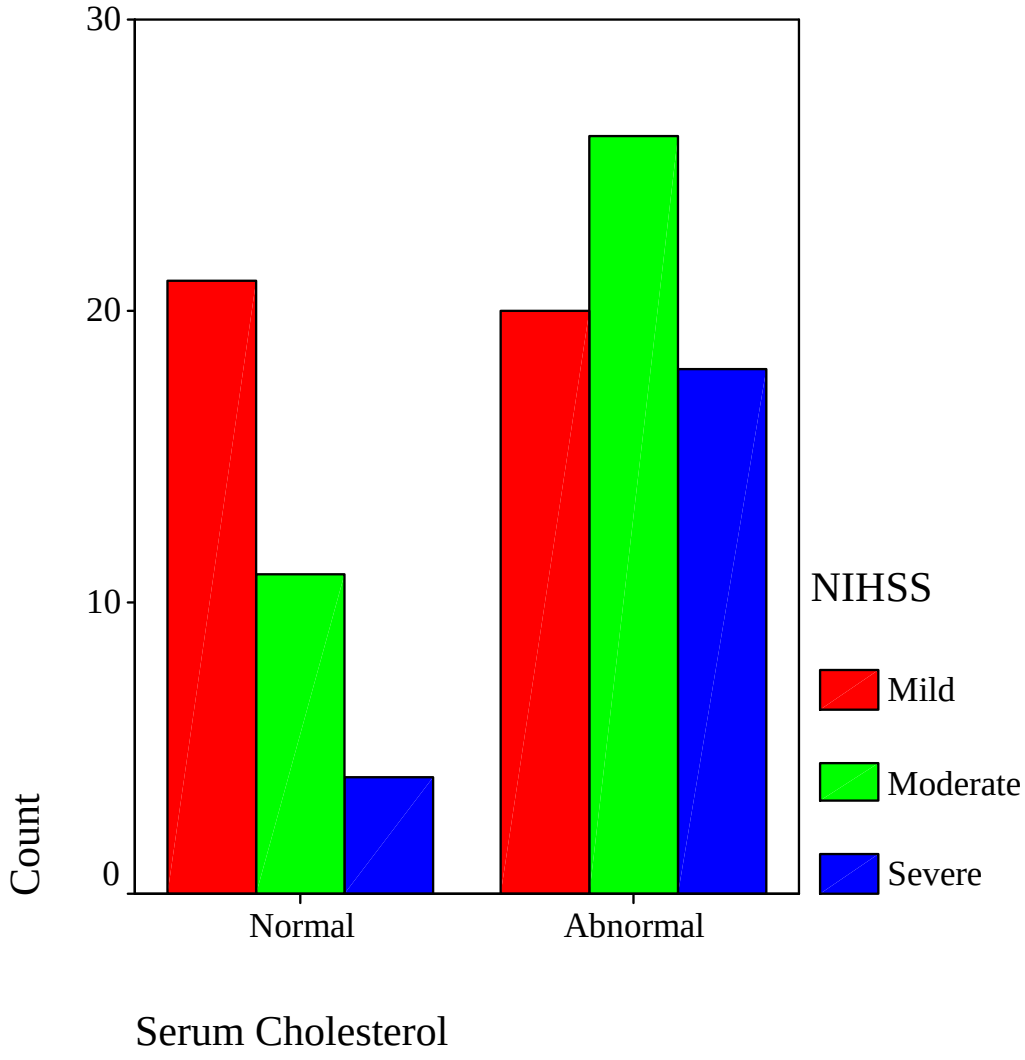
Random blood sugar

STROKE AND SERUM CHOLESTEROL

Serum Cholesterol		NIHSS			Total	P value
		Mild	Moderate	Severe		
Normal	Count	21	11	4	36	
	% within Serum Cholesterol	58.3%	30.6%	11.1%	100.0%	0.019
	% within NIHSS	51.2%	29.7%	18.2%	36.0%	
Abnormal	Count	20	26	18	64	

	% within Serum Cholesterol	31.3%	40.6%	28.1%	100.0%	
	% within NIHSS	48.8%	70.3%	81.8%	64.0%	
Total	Count	41	37	22	100	
	% within Serum Cholesterol	41.0%	37.0%	22.0%	100.0%	
	% within NIHSS	100.0%	100.0%	100.0%	100.0%	

Most (64%) of the patients who developed stroke had high serum cholesterol.


30
20
10
0
Count
Normal
Abnormal
Serum Cholesterol
NIHSS
Mild
Moderate
Severe

STROKE AND C REACTIVE PROTEIN

	Gender	N	Mean	Std. Deviation	Std. Error Mean	P value
CRP	Male	66	45.50	33.266	4.095	0.02
	Female	34	29.44	32.697	5.608	

In our study males had an average higher CRP value compared to females with ischaemic stroke.

	Smoking	N	Mean	Std. Deviation	Std. Error Mean	P value
CRP	Yes	50	54.24	34.352	4.858	Less than 0.001
	No	50	25.84	26.730	3.780	

In our study those who smoked had a higher CRP value compared to non smokers with ischaemic stroke.

	Random blood sugar	N	Mean	Std. Deviation	Std. Error Mean	P value

	Blood Pressure	N	Mean	Std. Deviation	Std. Error Mean	P value
CRP	Normal	42	29.10	26.319	4.061	0.003
	Abnormal	58	47.97	36.497	4.792	

In our study higher CRP values were found in hypertensive patients with stroke.

CRP	Normal	57	29.46	28.821	3.817	Less than 0.001
	Abnormal	43	54.07	35.062	5.347	

In our study stroke patients with abnormal random blood sugar had higher mean CRP values.

	Serum Cholesterol	N	Mean	Std. Deviation	Std. Error Mean	P value
CRP	Normal	36	32.69	31.548	5.258	0.002
	Abnormal	64	44.17	34.533	4.317	

In our study stroke patients with abnormal serum cholesterol had higher mean CRP values.

	MRS	N	Mean	Std. Deviation	Std. Error Mean	P value
CRP	Good	39	8.85	2.651	.425	Less than 0.001
	Poor	61	59.98	29.017	3.715	

	BI	N	Mean	Std. Deviation	Std. Error Mean	P value
CRP	Good	31	8.13	2.232	.401	Less than 0.001
	Poor	69	54.38	31.412	3.782	

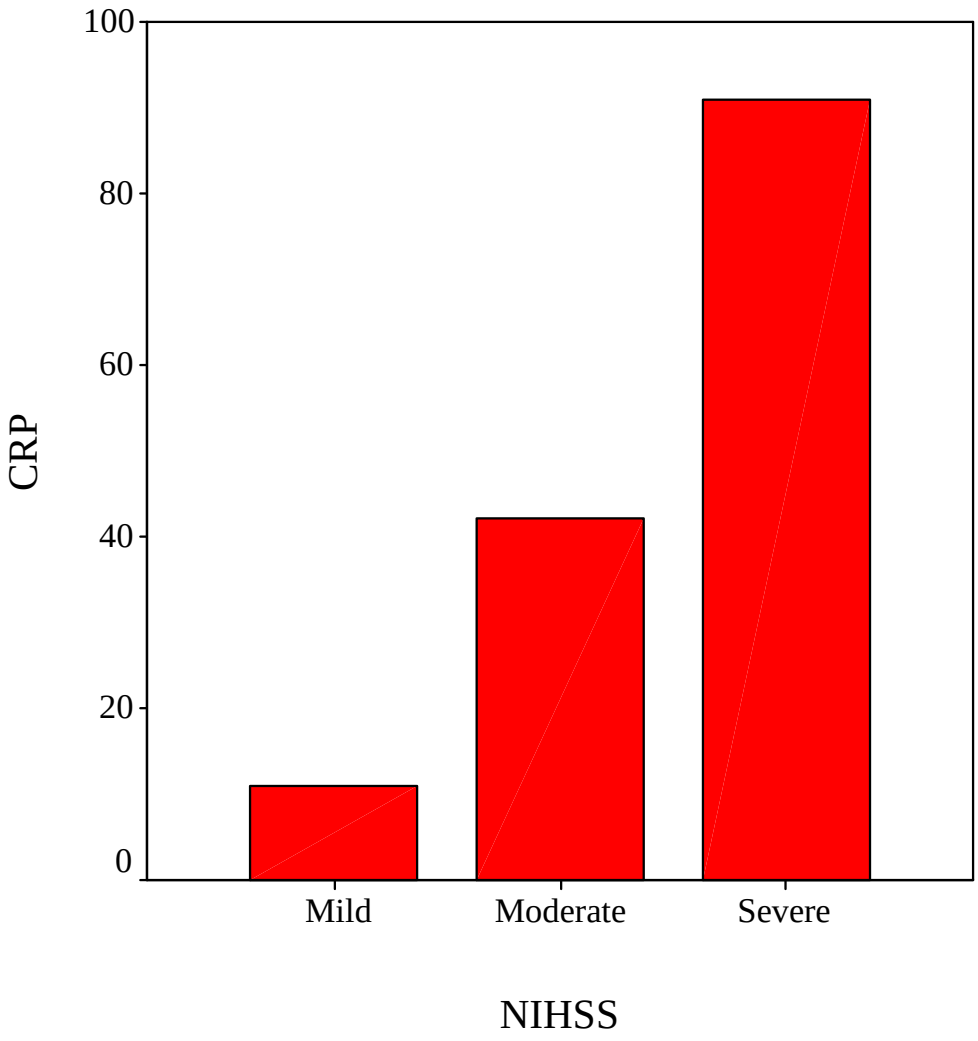
From the study it was found that stroke patients with a mean CRP of 8.85 had a good prognosis according to modifies rankin score. Those patients with a mean CRP of 59.98 had poor prognosis. Similar outcome was obtained using barthel index ; where the mean CRP was 8.13 for good prognosis and 54.38 for bad prognosis.

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Mild	41	10.85	10.355	1.617	7.59	14.12	5	70
Moderate	37	42.19	17.211	2.829	36.45	47.93	18	72
Severe	22	90.82	17.215	3.670	83.19	98.45	60	118
Total	100	40.04	33.784	3.378	33.34	46.74	5	118

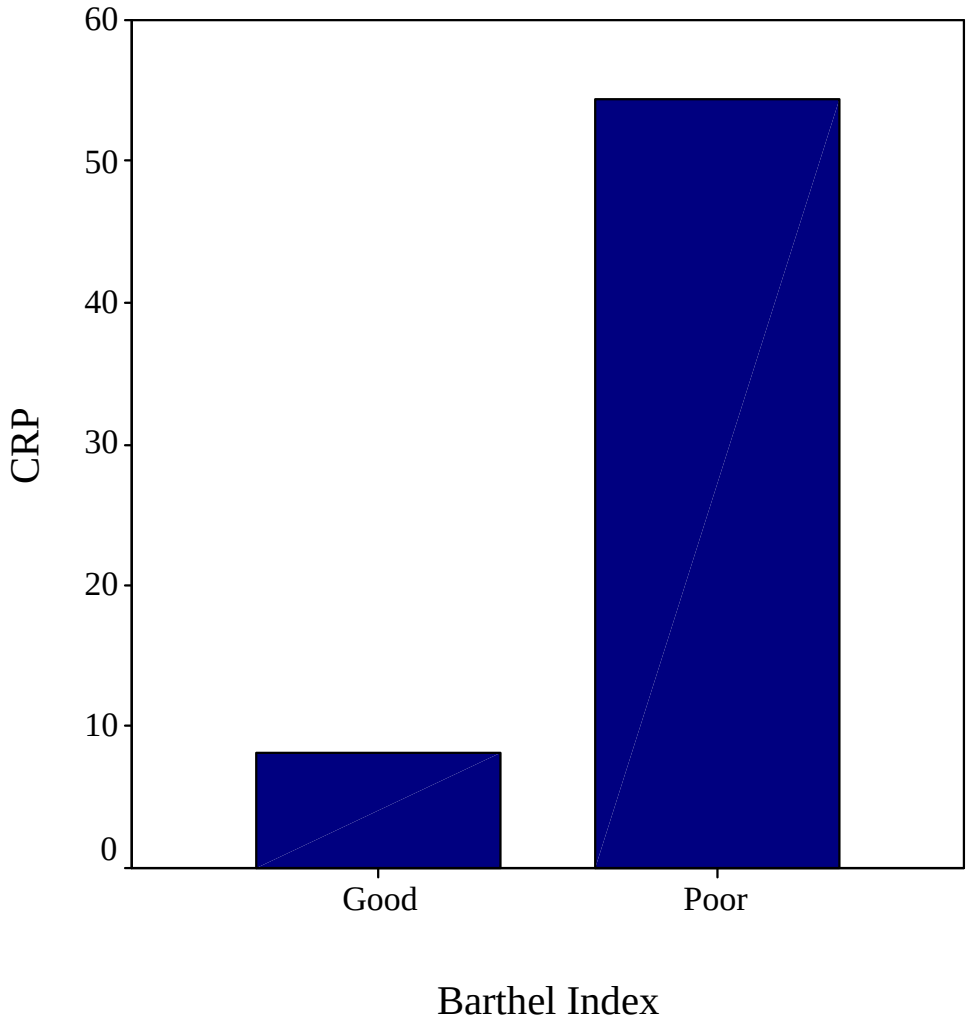
The study showed that the mean CRP values for mild stroke was 10.85 ; moderate stroke 42.19 ; and for severe stroke was 90.82. Thus higher the CRP values more severe the stroke.this was found to be statistically significant using ANOVA , P value being less than 0.001

Age	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
31-40	12	29.42	21.707	6.266	15.62	43.21	7	63
41-50	34	34.38	31.546	5.410	23.38	45.39	6	104
51-60	54	45.96	36.507	4.968	36.00	55.93	5	118
Total	100	40.04	33.784	3.378	33.34	46.74	5	118

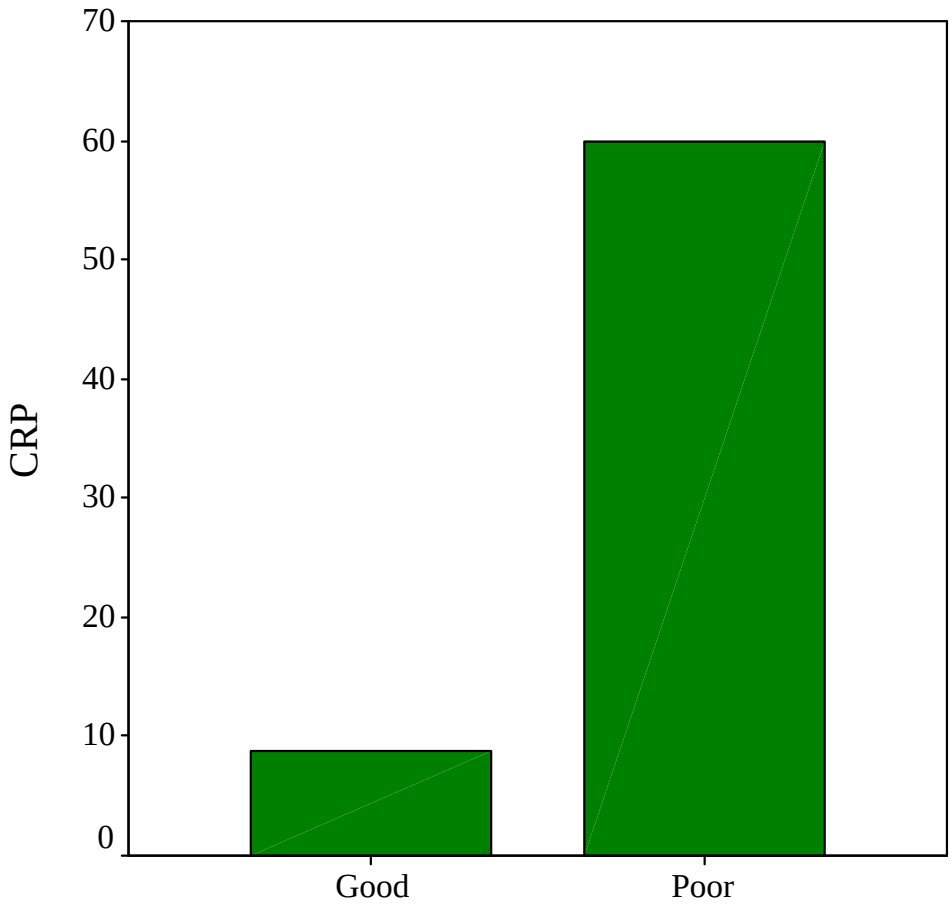
The study showed a higher value of CRP in older age group patients with stroke. The p value was 0.002 and statistically significant.



This chart clearly shows that stroke patients with higher values of CRP had more severe stroke according to NIHSS.



This chart shows that stroke patients with higher CRP values had poorer outcome compared to those with lower values of CRP.



This chart shows that stroke patients with higher values of CRP had poorer outcome than with lower values of CRP according to modified rankin score.

		CRP
Age in years	Pearson Correlation	.210(*)
	Sig. (2-tailed)	.036
	N	100
SBP	Pearson Correlation	.359(**)
	Sig. (2-tailed)	.000
	N	100
DBP	Pearson Correlation	.193
	Sig. (2-tailed)	.055
	N	100
Random blood sugar	Pearson Correlation	.418(**)
	Sig. (2-tailed)	.000
	N	100
Serum Cholesterol	Pearson Correlation	.236(*)
	Sig. (2-tailed)	.018

	N	100
NIHSS	Pearson Correlation	.916(**)
	Sig. (2-tailed)	.000
	N	100
MRS	Pearson Correlation	.861(**)
	Sig. (2-tailed)	.000
	N	100
BI	Pearson Correlation	-.922(**)
	Sig. (2-tailed)	.000
	N	100

Descriptive statistics

	N	Minimum	Maximum	Mean	Std. Deviation
Age in years	100	32	60	51.21	7.568
SBP	100	110	184	142.28	23.960
DBP	100	70	100	84.70	7.714
Random blood sugar	100	112	300	198.82	57.944
Serum Cholesterol	100	112	280	215.82	47.555
CRP	100	5	118	40.04	33.784
NIHSS	100	1	20	10.18	4.883
MRS	100	1	5	3.11	1.442
BI	100	30	100	73.90	23.832
Valid N (listwise)	100				

This summarises the various variables used in the study and their ranges.

DISCUSSION

An observational study was conducted at The Institute of Internal Medicine at Madras Medical College and Rajiv Gandhi Government General Hospital , Chennai 600003 for a period of 6 months.

100 patients admitted with acute ischaemic stroke were selected for the study. These patients were assessed at the time of admission by a detailed history taking giving due importance to smoking history, comorbidities like diabetes, hypertension, dyslipidemia etc. A thorough clinical examination was done for the patients which included general examination, vitals, neurological examination and other system examination. Patients were then categorised into mild, moderate and severe using the clinical National Institute of Health Stroke Scale (NIHSS). Routine blood investigations like complete haemogram , renal function test, liver function test were done. Apart from these lipid profile, random blood sugar, C reactive protein, and CT brain were done. Patients blood reports were followed up and then after a week at the time of discharge of the patients they were again clinically assessed for the outcome using Modified Rankin Score (MRS) and Barthel Index (BI).

The results obtained were analysed using various statistical tests like chi-square , ANOVA and p value were obtained.

In a study conducted by M.A Shoeb, M .A Shehata et al 50 patients with new onset acute ischaemic stroke were included. They were assessed clinically and graded into mild moderate and severe according to NIHSS score. Blood samples were sent for routine investigations and CRP. Outcome was assessed after a week using Modified Rankin Score and Barthel Index. They found out that serum CRP was indicative of stroke severity and correlated with the prognosis of stroke as the p value was less than 0.001 indicating it to be statistically very significant.

After analysing the various variables of our study many observations were made. Our study had more number of males , 66% males and 34% females. More percent of males were found to have severe stroke compared to females probably because many of the males were smokers and smoking is a risk factor for stroke. Correlation of age and stroke showed that severe stroke occurred in older age group compared to younger patients. Severe stroke patients were found to be hypertensive and they also had elevated blood sugar and serum cholesterol values. All these correlations had a p value less than 0.05 and hence statistically significant. Study also showed that smokers, hypertensive, diabetic and patients with dyslipidemia had higher mean CRP values. This was also found to be statistically significant. The mean CRP values for mild stroke was found to be 10.85 mg / dl, moderate was

42.19 mg / dl , severe was 90.82 mg / dl. The p value was less than 0.001. Higher crp values had severe stroke. Outcome measured by Modified Rankin Score showed that a CRP values less than 8.85 mg/ dl had good prognosis. Using Barthel Index CRP values less than 8.13 mg / dl had good prognosis. Both the correlations were statistically highly significant as P value were less than 0.001.

LIMITATIONS OF THE STUDY

- A multicentric and larger study may be needed to prove the correlation.

- There may be variations in the various methods of measurements of CRP from one laboratory to other.

CONCLUSION

- A higher value of C reactive protein is a predictor of severe disease.

- A higher values of C reactive protein on admission is a predictor of poor prognosis for stroke.

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"CRP IN ACUTE ISCHAEMIC STROKE: Prognostic Implications"

PROFORMA

Name: Age/Sex:

Address: Occupation:

SYMPTOMS:

Weakness of upper and lower limbs

Slurring of speech

PAST HISTORY:

DM	
HTN	
DYSLIPIDEMIA	
CAD	
CKD	
CLD	

PERSONAL HISTORY:

SMOKING

ALCOHOL

GENERAL EXAMINATION:

GCS	

VITAL SIGNS:

PR-

BP-

RR-

TEMP-

SYSTEMIC EXAMINATION:

CVS:

RS:

ABDOMEN:

CNS:

	RIGHT	**LEFT**
HIGHER MENTAL FUNCTIONS		
CRANIAL NERVES Olfactory Optic Oculomotor Trochlear Abducent		

Trigemenal Facial Vestibulocochlear Glossopharyngeal Vagus Spinal accessory Hypoglossal		
MOTOR		
BULK:UL LL		
TONE:UL LL		
POWER:UL LL		
REFLEX:UL LL		
PLANTAR		

SENSORY EXAMINATION:

CEREBELLAR SIGNS:

SIGNS OF MENINGEAL IRRITATION:

INVESTIGATIONS

COMPLETE HEMOGRAM

RFT

SERUM ELECROLYTES

LFT

ECG

SERUM CRP

CT BRAIN

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.Renjini Radhakrishnan
Post Graduate in M.D. General Medicine
Madras Medical College
Chennai 600 003

Dear Dr.Renjini Radhakrishnan,

The Institutional Ethics Committee has considered your request and approved your study titled **"CRP IN ACUTE ISCHAEMIC STROKE: Prognostic Implications " - NO.10032016.**

The following members of Ethics Committee were present in the meeting hold on **01.03.2016** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.R.Vimala,MD.,Dean,MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.B.Vasanthi,MD.,Inst.of Pharmacology,MMC,Ch-3	: Member
5.Prof.P.Raghumani,MS, Dept.of Surgery,RGGGH,Ch-3	: Member
6.Dr.Baby Vasumathi, Director, Inst. of O&G,Ch-8	: Member
7.Prof.M.Saraswathi,MD.,Director, Inst.of Path,MMC,Ch-3:	Member
8.Prof.Srinivasagalu,Director,Inst.of Int.Med.,MMC,Ch-3	: Member
9.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
10.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
11.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

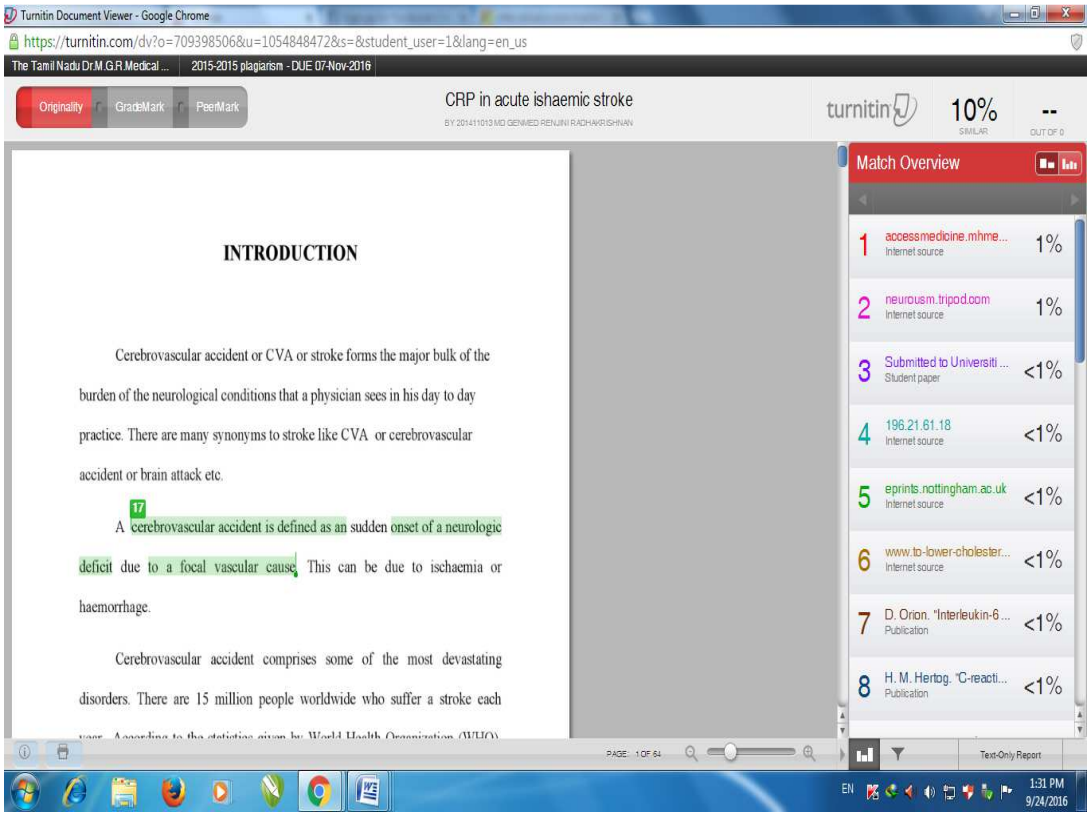
We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE.
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

TURNITIN PLAGIARISM SCREENSHOT



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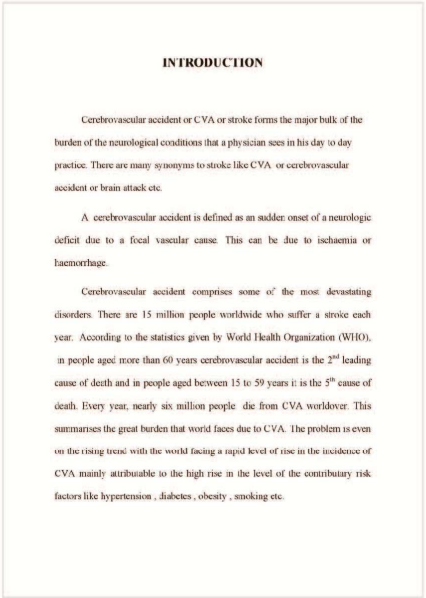

INTRODUCTION

Cerebrovascular accident or CVA or stroke forms the major bulk of the burden of the neurological conditions that a physician sees in his day to day practice. There are many synonyms to stroke like CVA or cerebrovascular accident or brain attack etc.

A cerebrovascular accident is defined as an sudden onset of a neurologic deficit due to a focal vascular cause. This can be due to ischaemia or haemorrhage.

Cerebrovascular accident comprises some of the most devastating disorders. There are 15 million people worldwide who suffer a stroke each year. According to the statistics given by World Health Organization (WHO), in people aged more than 60 years cerebrovascular accident is the 2nd leading cause of death and in people aged between 15 to 59 years it is the 5th cause of death. Every year, nearly six million people die from CVA worldover. This summarises the great burden that world faces due to CVA. The problem is even on the rising trend with the world facing a rapid level of rise in the incidence of CVA mainly attributable to the high rise in the level of the contributary risk factors like hypertension , diabetes , obesity , smoking etc.

INFORMATION SHEET

We are conducting a study on **"CRP IN ACUTE ISCHAEMIC STROKE : PROGNOSTIC IMPLICATIONS"** among patients admitted in EMERGENCY MEDICINE DEPARTMENT in Rajiv Gandhi Government General Hospital, Chennai and for that your specimen may be valuable to us.

The purpose of this study is to assess the ROLE OF C REACTIVE PROTEIN IN PREDICTING THE SEVERITY AND OUTCOME IN ACUTE ISCHEMIC STROKE PATIENTS.

We are selecting certain cases and if you are found eligible, we may be using your blood samples to do certain tests which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment

Signature of Investigator Signature of Participant

Date:

ஆராய்ச்சி தகவல் தாள்

சென்னை ராஜீவ் காந்தி அரசு பொது மருத்துவமனைக்கு வரும் நோயாளிகளில் பக்கவாதத்தில் சி ரியாக்டிவ் புரதத்தின் கனிப்பு திறன் அதன் தொடர்பு பற்றிய ஆய்வு நடைபெறுகிறது.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். அதனால் தங்களது நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்பு ஏற்படாது என்பதையும் தெரிவித்துக்கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின்போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதை தெரிவித்துக்கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின்பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளையும் நோயின் தன்மை பற்றியும் ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின்போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

நோயாளியின் உறவினர்/ காப்பாளர் கையொப்பம்

PATIENT CONSENT FORM

Study Detail	:	"**CRP IN ACUTE ISCHAEMIC STROKE : PROGNOSTIC IMPLICATIONS**"
Study Centre	:	Rajiv Gandhi Government General Hospital, Chennai.
Patient's Name	:	
Patient's Age	:	
Identification Number	:	

Patient may check (√) these boxes

a) I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ❑

b) I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ❑

c) I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ❑

d) I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ❑

e) I hereby consent to participate in this study. ❑

f) I hereby give permission to undergo detailed clinical examination and blood investigations as required. ❑

SIGNATURE OF INVESTIGATOR
SIGNATURE/THUMB IMPRESSION

STUDY INVESTIGATOR'S NAME:

DR.RENJINI RADHAKRISHNAN

PATIENT'S NAME AND ADDRESS:

ஆய்வு பற்றிய சுய ஒப்புதல் படிவம்

ஆய்வின் தலைப்பு

பக்கவாதத்தில் சி ரியாக்டிவ் புரதத்தின் கனிப்பு திறன் அதன் தொடர்பு

ஆய்வு நிலையம் : சென்னை மருத்துவக் கல்லூரி மற்றும் ராஜீவ் காந்தி அரசு பொது மருத்துவமனை, சென்னை - 3.

பங்கு பெறுவரின் பெயர் : உறவுமுறை:

பங்குபெறுபவரின் எண் :

பங்குபெறுபவர் இதனை (✓) குறிக்கவும்

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக்கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கின்றேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன், இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிக்கிறேன். ☐

இந்த ஆய்வில் எனக்கு மருத்துவபரிசோதனை, இரத்தப் பரிசோதனை, சிறுநீர் பரிசோதனை, ஊடுகதிர்படம், இதய மின்துடிப்பு வரைவி மற்றும் நுண்கதிர் வயிறு பரிசோதனை செய்து கொள்ள முழு மனதுடன் நான் சம்மதிக்கிறேன். ☐

பங்கேற்பவரின் கையொப்பம் ..... இடம்..... தேதி.....

கட்டைவிரல் ரேகை:

நோயாளியின் உறவினர்/ காப்பாளர் கையொப்பம் ..... இடம்..... தேதி.....

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

ஆய்வாளரின் கையொப்பம் ..... இடம்..... தேதி.....

ஆய்வாளரின் பெயர் .....

KEY TO MASTER CHART

BP	-	Blood Pressure
RBS	-	Random Blood Sugar
CRP	-	C Reactive Protein
NIHSS	-	National Institute of Health Stroke Scale
MRS	-	Modified Rankin Score
BI	-	Barthel Index