"N-TERMINAL PRO BRAIN NATRIURETIC PEPTIDE (NT-proBNP) AS A MARKER FOR RISK STRATIFICATION AND PREDICTION OF FUNCTIONAL OUTCOME IN ACUTE ISCHEMIC STROKE"

By:

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DISSERTATION SUBMITTED TO THE

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DOCTOR OF MEDICINE (M.D.)
IN
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UNDER THE GUIDANCE OF
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Dear Dr. Manoj A G.,

This is with reference to your application seeking financial assistance from the ICMR for MD/MS/DM/MCh dissertation thesis entitled **"N-Terminal Pro Brain Natriuretic Peptide (NT-proBNP) As a Marker for risk Stratification and Prediction of Functional Outcome in Acute Ischemic Stroke"**.

I am glad to inform you that Director General, ICMR, based on the recommendation of Expert Committee, has sanctioned a sum of **₹. 50, 000/- (Fifty thousand only)** for providing an electronic and hard copy of your dissertation thesis to the ICMR. Mandatory requirement to avail this opportunity is to provide us with an undertaking duly forwarded through the guide, to the undersigned, enabling us to release the grant.

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ABSTRACT

BACKGROUND

Stroke is one of the most common life threatening neurological disorders. It is the second leading cause of mortality and disability worldwide. India also has one of the highest case fatality rate for stroke in the world. Large proportions of stroke survivors are left behind with significant residual physical, cognitive and psychological disability. Assessing stroke severity and predicting morbidity and mortality are essential while taking treatment decisions and family counseling.

Recent studies have shown that traditionally used tools like National Institutes of Health Stroke Scale (NIHSS) are not reliable in predicting mortality. There is a need of a biomarker to predict prognosis, studies have shown that Brain natriuretic peptide (BNP) and NT-proBrain natriuretic peptide (NT-proBNP) are elevated in acute ischemic stroke. This study aims to assess the prognostic importance of NT-proBNP in acute ischemic stroke.

OBJECTIVES

1. To measure serum N-TERMINAL PRO BRAIN NATRIURETIC PEPTIDE (NT-proBNP) levels in Acute Ischemic stroke at the time of admission and after 7 days.

2. To measure stroke deficit by National Institutes of Health Stroke Scale (NIHSS) and functional outcome by Barthel index (BI).

3. To correlate NT-proBNP with functional outcome and stroke deficit.

MATERIALS AND METHODS

We prospectively studied 64 consecutive patients presenting with acute ischemic stroke within 24 hours of onset of symptoms and meeting inclusion and exclusion criteria. All the patients underwent laboratory and imaging evaluation and were treated as per standard guidelines, Risk factors were assessed and all patients underwent cardiac evaluation. In

all patients serum NTproBNP was measured on day of admission and on day 7. Stroke severity was assessed by NIHSS on day of admission and functional disability was calculated by Barthel index at 3rd month. Data were entered in MS Excel and appropriate statistical analysis was done using SPSS software. A p calue of <0.05 was considered as significant.

RESULTS

Mean age of presentation was 62.36±12.15 years and 61% were males and 39% were females. Diabetes Mellitus was the most common risk factor. Glasgow Coma Scale (GCS) had significant association with NTproBNP, NIHSS and Barthel Index (p value <0.001) and low GCS on presentation had increased risk of mortality. GCS was significantly lower in individuals who died 8.12±4.13 compared to 13.57±2.465 in survivors. Partial Anterior Circulation Infarct was the most common type of stroke subtype. Total Anterior Circulation Infarct had significant association with NTproBNP level, NIHSS score and BI scores (p value <0.001). Average NIHSS on day of admission was 12.81±7, among deceased it was 20.29±5.882. NIHSS on day of admission is significantly associated with mortality and Barthel Index. NIHSS could predict death but failed to predict functional dependence at 3 months. The median NTproBNP on admission was 776.70±1023.6 pg/ml it was significantly elevated in deceased patients 2014.65±1320.546 pg/ml compared to 328.94±239.353 in survivors. Median NTproBNP measured at day 7 was 223.53±268.39 pg/ml. There was statistically significant decrease in NTproBNP values from admission to day 7(p value <0.001). We demonstrated that NTproBNP is significantly elevated in patients after acute ischemic stroke and is strongly associated with stroke severity (NIHSS) (R^2=0.443; spearman correlation coefficient=0.843, p value <0.001) and functional outcome (BI) (R^2=0.824; spearman correlation coefficient -0.923, p value

<0.001) at 3 months.The average BI score at 3 months was 52.59±32.05 and is strongly associated with NTproBNP, NIHSS and GCS.

On receiver operator characteristic curve (ROC) analysis, at a cut off value of 960 pg/ml Serum NTproBNP had sensitivity and specificity of 94.1% and 97.9% in predicting mortality and a value of 435.1 pg/ml had a sensitivity and specificity of 90% and 81% in predicting disability.

CONCLUSION

Serum NTproBNP is significantly elevated in patients after acute ischemic stroke and is strongly associated with stroke severity and functional outcome at 3 months.

Measuring NTproBNP on day of admission can predict all cause mortality and functional dependence at 3 months after acute ischemic stroke.

KEY WORDS

Acute ischemic stroke, Prognosis, Morbidity, Mortality, functional dependence, NTproBNP, NIHSS, barthel index

LIST OF ABBREVIATIONS USED

NIHSS	➢	NATIONAL INSTITUTES OF HEALTH STROKE SCALE
BI	➢	BARTHEL INDEX
BNP	➢	BRAIN NATRIURETIC PEPTIDE
NTproBNP	➢	N TERMINAL PRO BRAIN NATRIURETIC PEPTIDE
CVA	➢	CEREBROVASCULAR ACCIDENT
TIA	➢	TRANSIENT ISCHEMIC ATTACK
DALY	➢	DISABILITY ADJUSTED LIFE YEARS
TOAST	➢	TRIAL OF ORG10172 IN ACUTE STROKE TREATMENT
OCSP	➢	OXFORDSHIRE COMMUNITY STROKE PROJECT
TACI	➢	TOTAL ANTERIOR CIRCULATION INFARCTS
PACI	➢	PARTIAL ANTERIOR CIRCULATION INFARCTS
POCI	➢	POSTERIOR CIRCULATON INFARCTS
LS	➢	LACUNAR SYNDROMES
ICA	➢	INTERNAL CAROTID ARTERY
ECA	➢	EXTERNAL CAROTID ARTERY
VA	➢	VERTEBRAL ARTERY
ACA	➢	ANTERIOR CEREBRAL ARTERY
MCA	➢	MIDDLE CEREBRAL ARTERY
PCA	➢	POSTERIOR CEREBRAL ARTERY
PICA	➢	POSTERIOR INFERIOR CEREBELLAR ARTERY
MAP	➢	MEAN ARTERIAL PRESSURE
CPR	➢	CARDIOPULMONARY RESUSCITATION
MRI	➢	MAGNETIC RESONANCE IMAGING
CT	➢	COMPUTED TOMOGRAPHY
HTN	➢	HYPERTENSION
DM	➢	DIABETES MELLITUS
CADASIL	➢	CEREBRAL AUTOSOMAL DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY
CARASIL	➢	CEREBRAL AUTOSOMAL RECESSIVE ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY
AF	➢	ATRIAL FIBRILLATION
CNS	➢	CENTRAL NERVOUS SYSTEM
UMN	➢	UPPER MOTOR NEURON
LMN	➢	LOWER MOTOR NEURON
MRA	➢	MEGNETIC RESONANCE ANGIOGRAPHY
CTA	➢	COMPUTED TOMOGRAPHY ANGIOGRAPHY
ASPECTS	➢	ALBERTA STROKE PROGRAMME EARLY COMPUTED TOMOGRAPHY SCORE
CBC	➢	COMPLETE BLOOD COUNT
ECG	➢	ELECTROCARDIOGRAPH

HbA1C	➢	GLYCOSYLATED HEMOGLOBIN
2D ECHO	➢	2 DIMENSIONAL ECHOCARDIOGRAPHY
ASD	➢	ATRIAL SEPTAL DEFECT
IV	➢	INTRA VENOUS
DVT	➢	DEEP VEIN THROMBOSIS
BP	➢	BLOOD PRESSURE
SBP	➢	SYSTOLIC BLOOD PRESSURE
DBP	➢	DIASTOLIC BLOOD PRESSURE
rtPA	➢	RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR
mRS	➢	MODIFIED RANKIN SCORE
FDA	➢	FOOD AND DRUG ADMINISTRATION
AHA	➢	AMERICAN HEART ASSOCIATION
ADL	➢	ACTIVITIES OF DAILY LIVING
SAH	➢	SUBARACHNOID HEMORRHAGE
ESC	➢	EUROPEAN CARDIAC SOCIETY
COPD	➢	CHRONIC OBSTRUCTIVE PULMONARY DISEASE
RBS	➢	RANDOM BLOOD SUGAR
FBS	➢	FASTING BLOOD SUGAR
PPBS	➢	POST PRANDIAL BLOOD SUGAR
SC	➢	SERUM CHOLESEROL
LDL	➢	LOW DENSITY LIPOPROTEIN
TG	➢	TRIGLYCERIDE
HDL	➢	HIGH DENSITY LIPOPROTIEN
RR	➢	RESPIRATORY RATE
GCS	➢	GLASGOW COMA SCALE
HB	➢	HEMOGLOBIN
MCV	➢	MEAN CORPUSCULAR VOLUME
PCV	➢	PACKED CELL VOLUME
ROC	➢	RECEIVER OPERATING CHARACETRISTIC
ANP	➢	ATRIAL NATRIURETIC PEPTIDE
CNP	➢	C TYPE NATRIURETIC PEPTIDE

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INTRODUCTION

Stroke is one of the most common fatal neurological disorders. It is the 2nd leading cause of mortality(1,2) and disability(2,3) worldwide. An estimated 6.17 million people died in 2017 due to stroke(1) and 5 million remained permanently disabled, Over 75 % of death and > 85% of disability adjusted life years were in low and middle income countries(1–4). In India stroke incidence ranged from 105-152/100000 persons / year for the previous 2 decades(5). India also has one of the highest case fatality rate of 42 and 46 % in urban and rural population(5,6).

Stroke has a high incidence and death rate. Huge proportion of survivors is left behind with noticeable residual physical, cognitive and psychological disability. Prediction of outcome after stroke is required to administer post stroke management and to establish an effective continuing care program to reduce the overall burden of stroke. Hence to take treatment decisions and counsel the family there is need to assess stroke severity and predict morbidity and mortality.

Traditionally the most accepted tool for predicting outcome and severity after ischemic stroke is the National Institutes of Health Stroke Scale (NIHSS)(7,8). Recent studies have shown that NIHSS has limited ability to determine the long term outcome and 0 on NIHSS does not rule out stroke(9,10). Barthel Index(11,12) and modified Rankin scale(13,14) are two well accepted functional outcome assessment tools used in stroke survivors but both can’t be used in acute presentation to predict severity. For these reasons there is a need for

an inexpensive, widely available and easily interpreted tool to predict prognosis following stroke.

Studies have shown that B type natriuretic peptide(BNP) is elevated in people with stroke than in normal individuals(15), origin of natriuretic peptides in stroke is still unsettled and there is evidence that suggests BNP is released from hypothalamus in response to cerebral ischemia(16,17). A literature-based meta-analysis study found association between Brain natriuretic peptide (BNP) and N-terminal pro brain natriuretic peptide (NT-proBNP) with death after stroke independent of NIHSS score(18).

Although there are many studies on stroke severity, its management and risk factors, very few studies are available for prediction of outcome following acute ischemic stroke. There is a gap of knowledge in the Indian subcontinent; very few studies are available at present for assessing and prognosticating stroke.

This study aims to assess the prognostic importance of NT-proBNP as a biomarker for risk stratification and prediction of functional outcome in acute ischemic stroke.

OBJECTIVES OF THE STUDY

1. To measure serum N-TERMINAL PRO BRAIN NATRIURETIC PEPTIDE (NT-proBNP) levels in Acute Ischemic stroke at the time of admission and after 7 days.
2. To measure stroke deficit by National Institutes of Health Stroke Scale (NIHSS) and functional outcome by Barthel index (BI).
3. To correlate NT-proBNP with functional outcome and stroke deficit.

REVIEW OF LITERATURE

STROKE

HISTORY

Earliest description of stroke in ancient India is found in Ayurveda where hemiplegia was described as 'Pakshavadha' with detailed clinical presentation and treatment(19). The father of medicine, Hippocrates recognized stroke over 2,400 years ago and called it 'apoplexy' a Greek word meaning "struck down by violence"(20).

Galen (AD 131 to 201) proposed that apoplexy was caused by anything which interfered with flow of vital 'spirit' to the brain he also inferred that hemiplegia was caused by lesion in opposite side of brain(20). The next significant work was done by Vesalius in 1543 with publication of his magnum opus ' De humani corporis fabrica' a set of seven books where he describes structure and functions of brain and its coverings rectifying some of the errors of Galen(21).

During 16th century Ambroise Paré discussed about carotids or soporales calling them 'sleepy arteries' because if they are obstructed or stopped we fall asleep (22). Thomas Willis and Richard Lower during 17th century mentioned about the circle of arteries at the base of the brain(20,23).

In 1658 , The Swiss physician Johann Jacob Wepfer described carotid thrombosis. In his book 'Apoplexia' he describes the carotid and vertebral arteries from their origins to the arterial circle at the base of the brain and noted that patients who died with apoplexy had bleeding in the brain(24). He also describes about examples of completed stroke,

progressing stroke, transient ischemic attack and reversible ischemic neurological deficit in the book ‘Apoplexia’(20,24,25).

In 1909 , in the 7 edition of ‘The Principles and Practice of Medicine’ William Osler describes apoplectic stroke largely due to cerebral hemorrhage , no mention of extracranial occlusive disease is made and in the section dealing with thrombosis and embolism he emphasizes blocking of intracranial vessels(26).

Thromboembolism as a major risk factor and its mechanism was first described by Rudolf Virchow in 1856(27). This was re emphasized by C. Miller Fischer in his 2 articles during 1950s where he found relationship between frequency of disease of the carotid artery in the neck and cerebrovascular insufficiency. He defined the lesion as atherosclerosis and noted partial and complete occlusion and described many syndromes and even suggested a bypass surgery between external carotid and internal carotid above the occlusion(28,29)

There was continued study on cause, symptom and management of apoplexy and in 1927 the apoplexy was divided into categories based on the blood vessel problem and the term ‘ cerebral vascular accident’ (CVA) or stroke was coined and Apoplexy faded from use. Stroke is also referred as a "brain attack" by American stroke association since 1990 to underline its acute nature and the fact that it is caused by a lack of blood supply to the brain as in heart attack, where there is lack of blood flow to heart.

The next major breakthrough occurred in 1995 when the National Institute of Neurological Disorders and Stroke tissue-type Plasminogen activator (NINDS tPA) trial initiated a paradigm shift in treatment of acute ischemic stroke(30). Two major trials in 1997

International Stroke Trial (IST) and Chinese Acute Stroke Trial (CAST) found that aspirin within 48 hours of stroke onset reduced stroke recurrence and mortality (31,32). In 2015, 5 randomized trials showed that endovascular thrombectomy within 6 hours of onset was more efficacious than standard medical treatment in acute ischemic stroke(33) and this time period was extended to 24hrs as recent as 2018 (34).

Even with abundant information on the cause, prevention, risk, and management of stroke there is still lacunae in knowledge to prognosticate stroke.

DEFINITION

STROKE

It is defined as "An abrupt onset of neurologic deficit that is attributable to a focal vascular cause". By definition stroke is a clinical diagnosis and Laboratory studies including imaging are used to support the diagnosis (35).

TRANSIENT ISCHEMIC ATTACK (TIA)

It is defined as acute onset of focal neurological deficit due to focal cerebrovascular disease with full recovery in 24 hours without evidence of brain infarction on imaging (35). TIAs usually last less than 1 hour and long lasting TIA show evidence of acute infarct in imaging.

Many recent studies have shown that 24 hours is too broad period and more than 50% of TIA show injury in MRI so American stroke association define TIA as "a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction" (36) TIA

per se does not cause any lasting injury on the individual but serve as a warning signal for more serious or permanent strokes and risk of developing stroke can be identified by simple ABCD2 score. (37)

Traditionally used terms like Reversible ischemic neurological deficit (RIND) where neurological deficit lasted more than 24 hours but less than 7 days and completed stroke is obsolete and no longer in use(36).

EPIDEMIOLOGY

INCIDENCE AND PREVALANCE

Burden of stroke on the community is best reflected by its incidence. One in four individual over 25 years are at risk of developing stroke , global lifetime risk of stroke above 25 years was around 25% among both men and women in 2016 and the risk was highest in east Asia and central Europe. The risk of developing ischemic stroke is 18.3% and hemorrhagic stroke is 8.2% (38).

There is 100% increase in stroke incidence from 1970-79 to 2000-08 in low and middle income countries including India(39). According to American heart association 4% of all American adults will have had stroke by 2030 (40). In 2016 globally there were 80·1 million prevalent stroke cases, 41·1 million were women and 39·0 million were men and 84·4% of these strokes were ischemic. In 2016 there were around 13·7 million new stroke cases (2).

In different parts of India the crude stroke prevalence ranged from 44.29 to 559/100,000 persons and the cumulative incidence ranged from 105 to 152/100,000 persons/year during the last 2 decades these estimates were much higher than those of high income countries which was reported to be 94/100,000 person-years during 2000-2008 (5).

MORBIDITY AND MORTALITY

Stroke is the most common life threatening neurological disease. It is the second leading cause of death(1,2) and disability(2,3) worldwide. An estimated 6.17 million people died in 2017 due to stroke(1) and 5 million remained permanently disabled, Over 75 % of death and > 85% of disability adjusted life years were in low and middle income countries(1–4).

In 2016, 2·6 million female died due to stroke which was lower than 2·9 million deaths in male. 2.7 million People died due to ischemic stroke which was slightly lesser compared to 2.8 million deaths due to hemorrhagic stroke. There was an increase of Disability Adjusted Life Years (DALYs) from 95.3 million in 1990 to 116.4 million due to stroke; it is the second most common cause of DALYs worldwide. DALYs were lower in women (50·8 million) compared to men (65·6 million). DALYs due to ischemic stroke (51·9 million) was lower than hemorrhagic stroke (64·5 million)(2) .

There is lack of comprehensive data on morbidity and mortality of stroke in India. A systematic review of epidemiological studies of stroke in India found case fatality rate of 42 and 46 % in urban and rural population which is one of the highest in the world (5).

Stroke is a condition with high incidence, mortality and morbidity. Accurate prediction of outcome following stroke is necessary for family counselling, treatment decision and post stroke care.

CLASSIFICATION OF STROKE

Strokes are broadly classified into

1. Arterial stroke
2. Venous stroke

ARTERIAL STROKE

They are further classified into

1. Ischemic stroke (85%)
2. Hemorrhagic stroke(15%)

ISCHEMIC STROKE

It is further subdivided into 2 types

1. Thrombotic stroke
    (1) Large vessel Thrombosis
    (2) Lacunar (small vessel thrombosis
2. Embolic stroke
    (1) Cardiogenic embolisms
    (2) Artery to artery embolism

Embolic strokes are the most common types of strokes.

HEMORRHAGIC STROKE

They can be further classified into

1. Intracerebral hemorrhage
2. Sub arachnoid hemorrhage

The distinction between Ischemic stroke and Hemorrhagic stroke is crucial to decide the treatment modality. Early and appropriate use of thrombolytic therapy is indicated in ischemic stroke but absolutely contraindicated in hemorrhagic stroke.

VENOUS STROKE

It is a rare type of stroke which affects about 5 million people and accounts 0.5% of all strokes and is caused by Dural venous sinuses (like superior sagittal, Lateral and cavernous sinus) obstruction by thrombosis(41).

TOAST CLASSIFICATION (42)

It is a system of classification of ischemic strokes based on etiology developed for the Trial of Org 10172 in Acute Stroke Treatment.

1) Large-artery atherosclerosis
2) Cardioembolism
3) Small-vessel occlusion
4) Stroke of other determined etiology
5) Stroke of undetermined etiology (2 or more causes identified, Negative evaluation, Incomplete evaluation)

This system of classification is widely used by clinicians and researchers as it is easy to use with good interobserver agreement and helps in predicting outcome but doesnot help in making treatment descisions.

OXFORDSHIRE COMMUNITY STROKE PROJECT (OCSP)

CLASSIFICATION(43)

It is a simple, easy clinical classification method used in acute ischemic stroke which predicts the site and size of the infarct on imaging. Some trials have used this classification to predict clinical outcome(44,45).

1) **Total Anterior Circulation Infarcts (TACI)**

   It implies a large cortical stroke in middle or middle and anterior cerebral artery territories. Characterised by

   a) New higher cerebral dysfunction
   b) Homonymous visual field defect
   c) A contra lateral motor and or sensory deficit involving at least 2 out of 3 areas of face , arm or leg.

2) **Partial Anterior Circulation Infarcts (PACI)**

   It implies a cortical stroke in middle or anterior cerebral artery territory.

   Characterised by one of the following

   a) They are characterised by any two of 3 component of TACI
      - New higher cerebral dysfunction
      - Homonymous visual field defect
      - A contra lateral motor and or sensory deficit involving at least 2 out of 3 areas of face , arm or leg
   b) New higher cerebral dysfunction alone
   c) A motor/sensory deficit more restricted than that of TACI

3) **Posterior Circulation Infarct (POCI)**

   Characterised by one of the following

a) Ipsilateral cranial nerve palsy with contralateral motor and or sensory deficit

b) Bilateral motor or sensory deficit

c) Disorder of conjugate eye movement

d) Cerebellar dysfunction without ipsilateral tract involvement

e) Isolated homonymous visual field defects or cortical blindness.

4) Lacunar syndromes

It implies a subcortical stroke due to small vessel disease. Evidence of higher cortical dysfunction or disturbance of consciousness excludes it. It is characterised by

a) Pure motor stroke

b) Pure sensory stroke

c) Ataxic hemiparesis

d) Clumpsy hand – dysarthria syndrome.

PATHOBIOLOGY

Understanding vascular anatomy and its relationships to functional neuroanatomy provide important clues for identifying the cause of symptoms and signs and help guide treatment.

AORTIC ARCH

Paired carotid and vertebral arteries supply the brain. The right subclavian and common carotid artery originates from the brachiocephalic trunk. Right subclavian artery gives rise to right vertebral artery at its proximal part. The left common carotid artery originates directly from the aortic arch. The left subclavian artery arises from the aortic arch distal to the left common carotid artery and also supplies the left vertebral artery (46,47).

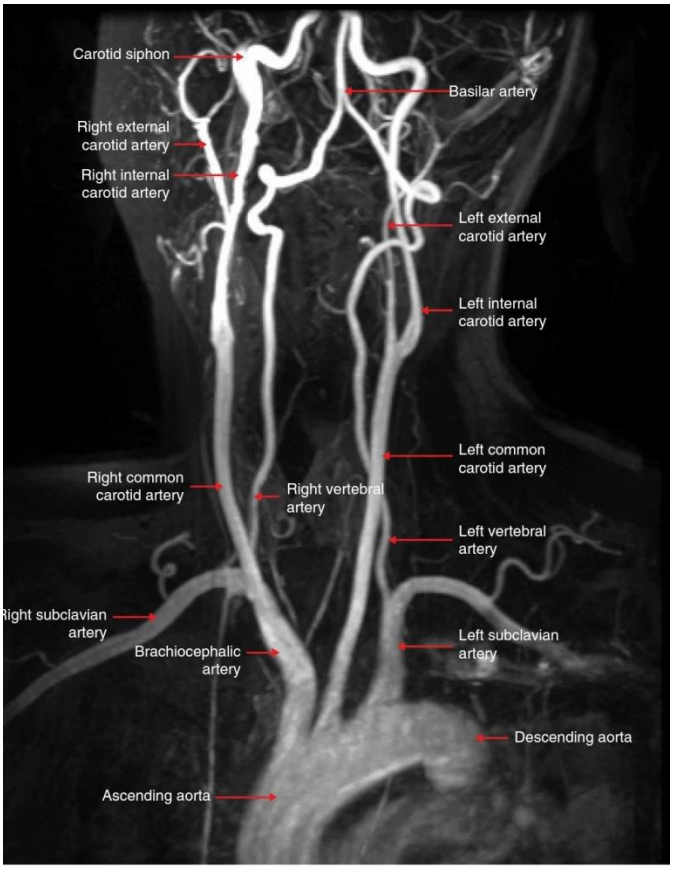


FIGURE 1 : MAGNETIC RESONANCE ANGIOGRAM OF AORTIC ARCH(47)

INTERNAL CAROTID ARTERIES (ICA)

At the level of superior border of thyroid cartilage corresponding to C3 or C4 vertebrae, common carotid arteries divide into internal carotid artery (ICA) and external carotid artery (ECA).

The ICA enters the skull through the carotid canal and passes through the Petrous bone near the inner ear, it then passes above the foramen Lacerum to enter the cavernous sinus and ascends in an S shape before penetrating the Dura and finally dividing into the anterior cerebral artery and middle cerebral artery. Opthalmic artery usually arise from the ICA distal to cavernous sinus(46,47).

EXTERNAL CAROTID ARTERIES (ECA)

The braches of ECA superficial temporal arteries and facial arteries can anastomose with the intracranial circulation through ophthalmic artery branches and this gains significance in proximal internal carotid artery occlusion(46–48).

VERTEBRAL ARTERIES

Vertebral arteries usually arise from the subclavian arteries. They commonly enter transverse process at C6 (V1 segment) and exit at C1 (V2 segment). They turn posteriorly behind the atlantoaxial joint and at the foramen magnum they pass through the dura(V3 segment). Typically at the pontomedullary junction the vertebral arteries join to form a single basilar artery intracanially (V4 segment). Medial branches of vertebral arteries unite to form the anterior spinal artery and lateral branches of vertebral artery supply the dorsolateral medulla, inferior portion of the cerebellum, and vestibular nuclei. Medullary pyramid, inferior olivary nucleus, medial lemniscus, and hypoglossal nerve fibers are supplied by the medial branches. spinothalamic tracts , sympathetic fibers, the sensory nuclei and descending tracts from 5^{th} cranial nerve, fibers from the 9^{th} and 10^{th} cranial nerves are supplied by longer circumferential branches of vertebral and posterior cerebral arteries when they traverse the medulla(44–46).

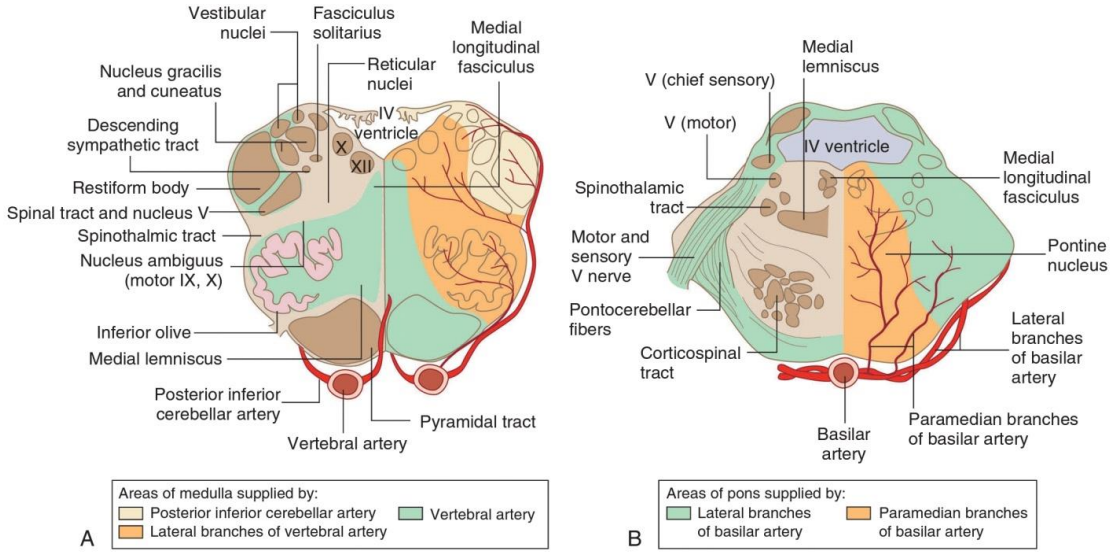


FIGURE 2 : BRAIN STEM BLOOD SUPPLY(47)

(CROSS SECTION OF A: MEDULLA OBLONGATA B: MID PONS REGION)

BASILLAR ARTERY

Dorsal portions of the Pons and midbrain are supplied by small penetrating branches which originate from basilar artery. Mid–basilar artery gives rise to the anterior inferior cerebellar arteries which supply portions of the cerebellar hemispheres, lateral pons; 5th, 7th and 8th cranial nerves and pontine portions of the spinothalamic tracts and sympathetic fibers. The distal basilar artery gives rise to two superior cerebellar arteries at the level of the midbrain which supply dorsal midbrain, including the colliculi and the superior portions of the cerebellar hemispheres and vermis. Paramedian vessels which supply the middle portion of the basis pontis and midline pontine structures, including the corticospinal tracts, medial longitudinal fasciculus, and pontine reticular nuclei arise from basillar artery. Paramedian branches also supply the cerebral peduncles, 3rd cranial nerve and its fibres, and medial portions of the red Nucleus and medial lemniscus. ventrolateral pons and midbrain are supplied by short circumferential branches of basilar artery(44–46).

CIRCLE OF WILLIS

Anterior communicating artery connects the two anterior cerebral arteries. Internal carotid artery is connected with the proximal posterior cerebral artery by the posterior communicating artery. A single patent internal carotid artery or vertebral artery can supply the entire intra cranial circulation but most of individuals have an incomplete circle of willis. Sometimes a single intracranial artery can supply both anterior cerebral arteries and sometimes carotid supply the posterior cerebral artery instead of vertebrobasilar arteries(46,47).

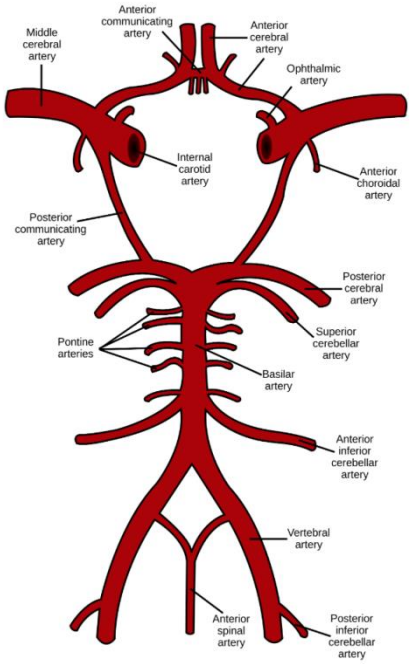


FIGURE 3 : CIRCLE OF WILLIS AND BRANCHES

ANTERIOR CEREBRAL ARTERIES (ACA)

They supply the medial portions of the frontal and parietal lobes. Anterior cerebral artery divides into pericallosal and callosal marginal branches in 50% of individuals. Terminal portion of callosal marginal branch supply the medial cortex between the parietal and occipital lobes.

ACA gives rise to series of lenticulostriate branches. One of the most important branch of ACA is the recurrent artery of Heubner a medial striate artery that supply anterior and inferior portions of the anterior limb of the internal capsule and caudate nucleus, anterior globus pallidus, putamen, hypothalamus, olfactory bulbs and tracts, and uncinate fasciculus(46,47).

ANTERIOR CHOROIDAL ARTERY

It originates from from the supraclinoid internal carotid artery and enters the brain at the choroidal fissure. It supplies the optic tract, anterior hippocampus, amygdala, tail of the caudate nucleus, geniculate body, and inferior portion of the posterior limb of the internal capsule(44–46).

MIDDLE CEREBRAL ARTERY (MCA)

It supplies the major portion of the frontal, parietal, and lateral portions of the temporal lobes. MCA at sylvian fissure bifurcates in 20 to 30% and in 70% individual's trifurcates. Frontal and parietal lobes are supplied by superior division and lateral portion of the temporal lobe is supplied by inferior division. Lateral lenticulostriate and few medial lenticulostriate arteries originate from M1 segment of MCA which is the portion between its origin and distal branches. These striate arteries supply head and body of the caudate nucleus, the putamen, and the globus pallidus , anterior limb of genu, and the superior portions of the posterior limb of the internal capsule(46,47).

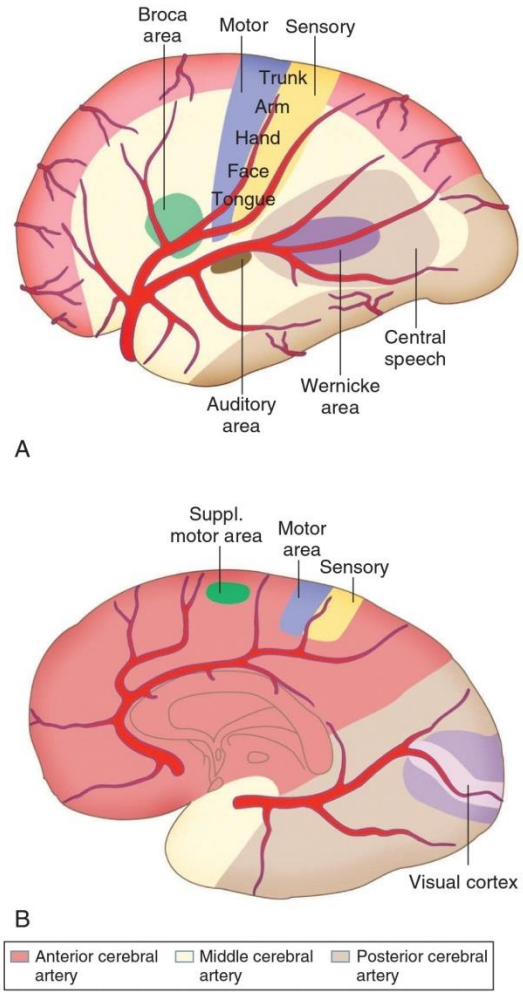


FIGURE 4 : CEREBRAL ARTERY ANATOMY : DISIBUTION OF ANTERIOR , MEDIAL AND POSTERIOR CEREBRAL ARTERY (47).

(A : LATERAL AND B MEDIAL CEEBRAL HEMISPHERE)

POSTERIOR CEREBRAL ARTERY (PCA)

PCA divides into anterior and posterior divison. Inferior and medial portions of the temporal lobe are supplied by the anterior division whereas the occipital lobe and calcarine cortex is supplied by the posterior division. The terminal branches of anterior division anastomose with MCA and posterior division anastomose with MCA and ACA. Thalamus is supplied by small penetrating arteries branches which originate from the proximal portions of both the posterior cerebral artery and the posterior communicating artery .In

few; both the thalami are supplied by a single common artery of ‘Percheron’ originating from PCA. Choroid plexus, posterior thalamus, fornix, and midbrain tectum are supplied by the two posterior choroidal arteries which originate separately from the PCA. The medial portions of the cerebral peduncles, substantia nigra, red nuclei, hippocampus, and posterior hypothalamus are supplied by PCA perforators(46–48).

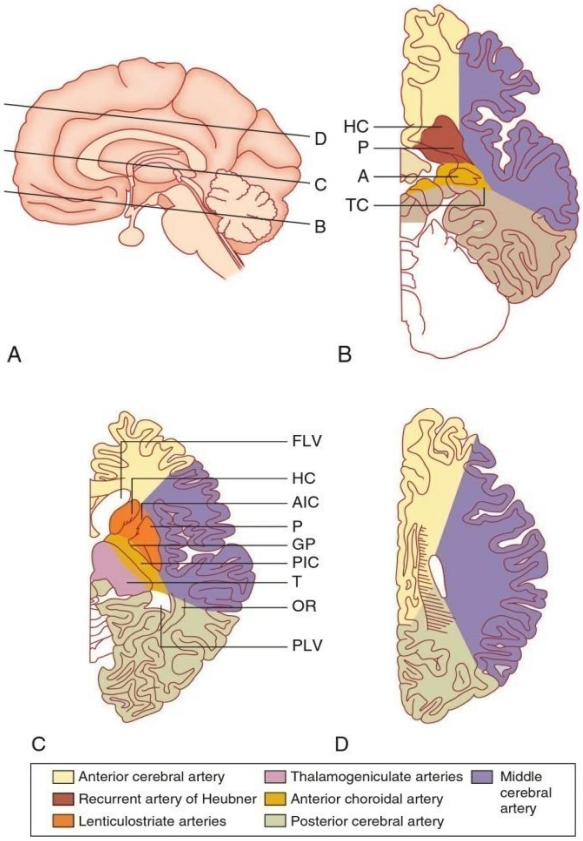


FIGURE 5 : ARTERIAL SUPPLY OF DEEP BRAIN STRUCTURES(47)

A : SAGITTAL VIEW OF BRAIN WITH PLANES PASSING THROUGH VIEW B , C AND D ARE TAKEN.

(HC- head of the caudate nucleus, P- putamen, A- amygdala, TC- tail of the caudate nucleus, FLV- frontal horn of the lateral ventricle, AIC , PIC -anterior and posterior limbs of the internal capsule, GP- globus pallidus, T- thalamus, OR- optic radiations, and PLV- posterior horn of the lateral ventricle)

PHYSIOLOGY

Human brain constitutes only 2% of body weight but consumes 20% of oxygen and receives 14% of cardiac output. Glucose is the main substrate of brain. At rest brain tissue requires 140 μmol of oxygen and 24 μmol of glucose per 100 g of tissue per minute for metabolism. 80% of glucose is used to generate energy and the rest is metabolized to lactate or used for synthetic activities, no glucose is stored in brain(47).

Brain is the most metabolically active tissue of body and very vulnerable to reduction in oxygen or blood supply. Normal cerebral flow range from 50-100 ml/100gram/minute.if there is a decrease in this flow normal brain function is reduced and results in neural injury. Cerebral blood flow remains constant normally and is regulated by various autoregulatory mechanisms. When the mean arterial pressure (MAP) decreases, there is dilation of cerebral arterioles leading to a compensatory decrease in cerebrovascular resistance to maintain a constant cerebral blood flow. If MAP increases, constriction of cerebral arterioles occurs and there is a compensatory increase in cerebrovascular resistance manintaing the cerebral blood flow. At MAP > 150 mm Hg, cerebral arterioles are maximally constricted and cerebral blood flow rises and MAP < 50 mm Hg, cerebral arterioles are maximally dilated resulting in decreased cerebral blood flow(47). Cerebral blood flow is also affected by metabolic factors like hypercapnia which causes cerebral vasodilation and hypocapnia which results in cerebral vasoconstriction. There is a decrease in cerebral blood flow by 2% for every 1 mmHg decline in PCo2. In patients with increased intracranial pressure and threatened herniation, a short period of

hyperventilation can be used as a temporary measure until more definitive treatment can be instituted(47).

PATHOPHISIOLOGY OF ISCHEMIC STROKE

Brain is one of the most metabolically active tissues in body and its functioning is completely dependent on blood and oxygen supply. Clinical symptoms occur when blood flow falls less than 50ml/100gm/min. If cerebral blood flow decreases to 0 it causes brain death within 4-10 minutes, if blood flow falls <16-18 ml/100g/min infarction occurs within 1 hour and <20ml/100g/min results in ischemia without infarction unless prolonged for hours or days(49).

Hypoxic ischemic injury can be focal, diffuse or global. Regions of the hippocampus, cerebellar Purkinje cells, and neocortical layers III, V are highly metabolic and vulnerable to hypoxia and ischemia.

GLOBAL ISCHEMIC INJURY

It occurs in complete cardiovascular collapse as in ventricular fibrillation, asystole, electromechanical disassociation, hypotension and cardiac arrest. In hypotension watershed areas between the arteries like frontal cortex and adjacent subcortical white matter between ACA and MCA, the parieto-occipital cortex and adjacent subcortical white matter between MCA and PCA, and deep hemispheric white matter and centrum semiovale between MCA and lenticulostriate arteries are vulnerable to injury. The duration of cardiac arrest, anoxia, its cause and duration of CPR are related to prognosis after CPR. It might lead to vegetative state when cerebral cortex is irreversibly damaged but the resistant brain stem which controls respiration and cardiovascular regulation is functioning(47).

DIFFUSE HYPOXIC INJURY

It is caused by high altitudes, severe anemia, and pulmonary disease. Symptoms like altered cognition, confusion, impair consciousness, coma can occur which can be irreversible and present when the Pao2 abruptly falls < 40 mm Hg(47).

FOCAL ISCHEMIC INJURY

It is caused by occlusion of artery supplying the brain. Although It can occur from infection, inflammation, metabolic disorders, trauma, and hematologic disorders, the majority of strokes are due to thrombotic or embolic occlusion. If blood flow is restored before significant infarction develops patient may experience only transient symptoms resulting in transient ischemic attack (TIA). Ischemic penumbra is the ischemic but reversible dysfunctional area surrounding infarction which can be seen by perfusion imaging by MRI or CT scan, if there is no change in flow the penumbra will progress to infarction therefore saving the ischemic penumbra is the main goal of revascularisation treatment(49).

Permanent occlusion of a cerebral artery results in necrosis of its supplied neurons, glia, and endothelial cells.

Focal ischemia occurs by 2 pathways

1) **Necrotic pathway** - energy failure of the cell leads to cellular cytoskeletal breakdown
2) **Apoptotic pathway** - cells become programmed to die

Ischemia causes necrosis of neurons due to lack of glucose and oxygen, which results in mitochondrial failure. Failure to produce ATP causes membrane ion pumps to stop functioning and neurons depolarize which raises intracellular calcium level. Cellular

depolarization also leads to release of glutamate from synaptic terminals; excess extracellular glutamate activates postsynaptic glutamate receptors which increases neuronal calcium influx that results in neurotoxicity. Mitochondrial dysfunction and degradation of membrane lipids produce free radicals which cause catalytic destruction of membranes(47,49–51).

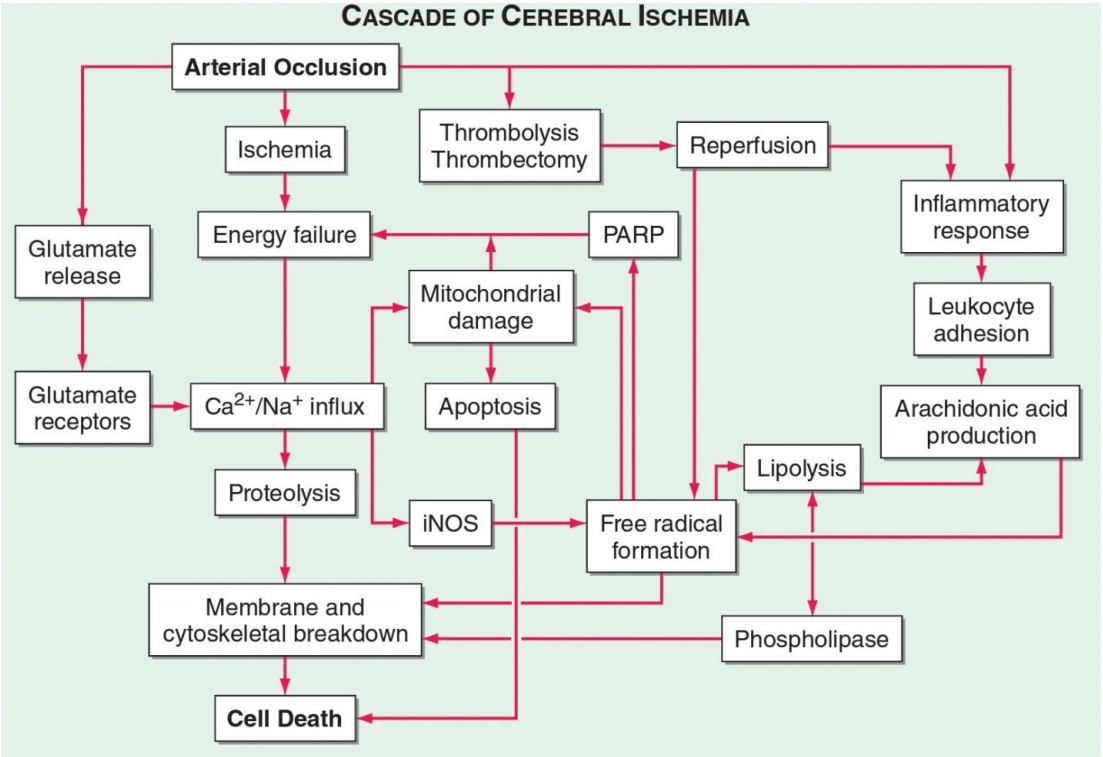


FIGURE 6: CASCADE OF CEREBRAL ISCHEMIA(49)

(iNOS, inducible nitric oxide synthase; PARP, poly-A ribose polymerase.)

RISK FACTORS FOR ISCHEMIC STROKE

Modifiable and non modifiable factors increase the risk of stroke (52).

NON MODIFIABLE FACTOR

1) Age
2) Gender
3) Race/ethinicity

4) Family history

5) Genetics

MODIFIABLE RISK FACTORS

1) Arterial hypertension
2) Obesity
3) Cigarette smoking
4) Diabetes mellitus
5) Transient ischemic attacks
6) Physical inactivity
7) Dyslipidemia
8) Asymptomatic carotid bruit/stenosis
9) Cardiac disease
10) Aortic arch atheromatosis
11) Alcohol consumption
12) Increased fibrinogen
13) Elevated homocystine
14) Low serum folate
15) Elevated anticardiolipin antibodies
16) Oral contraceptive use

The INTERSTROKE study, a international case control study in 22 countries found that the 5 risk factors hypertension, current smoking, abdominal obesity, diet, and physical activity accounted for more than 80% global risk of all stroke (53).

AGE

It is the strongest risk factor for stroke. Stroke is a disease of elderly, after the age 55 the incidence of stroke almost doubles for each decade (54). According to global burden of disease study risk of developing of stroke is 25% for individuals more than 25 years , there is a decrease in lifetime risk of stroke among adults after age of 70 reaching incidence of 13.4% among 95 years of age(38).

SEX

The association of sex to stroke risk is dependent on age. Women have the same or high risk as of men of developing stroke at young age but the relative risk is slightly higher for men at older age. Pregnancy, post-partum state and hormonal factors like contraceptives use are the likely cause for higher risk of stroke among women at young age(55). In 2016 out of 80·1 million stroke cases, 41·1 million were women and 39·0 million were men(2) this may be because of the longer life span of women compared to men(54).

RACE/ETHINICITY

The relationship between stroke risk and race is well documented. According to REGARDS study compared to Caucasians, African Americans have a two times high risk of developing stroke, it may be due to high prevalence of other risk factors like hypertension, Diabetes and obesity in them(56). According to global burden of disease study risk of developing stroke is highest in east Asia and central Europe(38).

FAMILY HISTORY

Parental and family history of stroke increases the propensity for stroke. There is a 3 fold increase of stroke in offspring of parents who had a documented stroke by 65 years even after adjusting for other risk factors(57). Other causes of stroke like vascular anomalies, connective tissue disorders, familial hypercholesterolemia which runs in the family increases risk of stroke in offspring.

GENETICS

There is increased stroke risk with expression of genetic variability, there are many mechanisms(55)

1) A Single gene disorders that primarily cause stroke
    a) Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is an autosomal dominant disorder involving NOTCH3 gene and protein, they present with ischemic stroke, leukoencephalopathy, migraine, psychiatric manifestations and dementia.
    b) Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CARASIL) is a autosomal recessive disorder involving HTRA1 gene which codes for HtrA serine peptidase-1 protein which presents with Ischemic stroke, leukoencephalopathy, premature baldness, spondylosis.
    c) Familial amyloid angiopathy and Collagen 4 (COL4A1) mutations are autosomal dominant disorders which cause rupture of cortical vessels causing hemorrhages.

2) Genetic Disorders that include stroke as manifestation

A single gene disorder can cause multisystem disorder where stroke is a manifestation

a) Ehlers Danlos type 4 is a autosomal dominant disorder can lead to arterial dissection
b) Smooth Muscle Alpha-Actin (ACTA2) mutation associated disorders and Marfan syndrome are autosomal dominant disorders involving ACTA2 and fibrillin1 gene which result in ischemic stroke
c) Fabry disease is a X linked disorder involving α-galactosidase Aprotein which can cause ischemic stroke.

d) Mitochondrial encephalopathy with lactic acid and stroke like episodes (MELAS) is a mitochondrial disorder which causes energy failure leading to metabolic stroke, here ischemia does not follow vascular boundaries.
e) Sickle cell anemia is a autosomal recessive disorder which can cause ischemic stroke along with other manifestations.

3) Few common variants of genetic polymorphisms like TSPAN2 , FOXF2 have been associated with stroke risk
4) Genetic causes for other risk factors like hypertension, diabetes mellitus, Atrial fibrillation are also associated with stroke risk.

MODIFIABLE RISK FACTORS

They are very important as early identification and modification of these factors help in preventing stroke.

HYPERTENSION

It is the major risk factor for stroke and the relationship between blood pressure and stroke is well documented(58). 54% of strokes were attributable to hypertension in the INTERSTROKE study(53). Hemorrhagic stroke had higher blood pressure compared to ischemic stroke. Hypertension can lead to stroke by various mechanisms. An increased intraluminal pressure will cause altered function of endothelium and smooth muscle in cerebral arteries which increase permeability over the blood-brain barrier and lead to brain oedema; these can also cause focal thrombi formation and ischaemic lesions. fibrinoid necrosis can lead to local stenosis and blockage causing lacunar infarcts. Intracerebral haemorrhages are caused by degenerated smooth muscle cells

and endothelium. Hypertension also increases the arteriosclerotic process leading to stroke (59).

DIABETES MELLITUS

Diabetics have greater susceptibility to coronary, femoral and cerebral artery atherosclerosis. It is a independent risk factor for stroke with 2 times increased risk and accounting to 20% of stroke mortality(55,60). Duration of diabetes and also pre-diabetes increases the risk of stroke. The risk of stroke increases by 3% with each year of diabetes and becomes 3 times with > 10 years of diabetes mellitus(61).

DYSLIPIDEMIA

The relationship between blood lipids and stroke is complex and much lower compared to coronary artery disease. Elevated total cholesterol has increased risk where as elevated HDL cholesterol has decreased risk for stroke(62,63). There is an inverse relationship between hemorrhagic stroke and total cholesterol. There is a strong association between large artery ischemic stroke and total cholesterol compared to other stroke subtypes(63,64).

OBESITY / SEDENTARY LIFE / DIET

Sedentary life is associated with many disorders including stroke. physical activity reduces risk of diabetes mellitus, hypertension and obesity there by reducing the risk of stroke(55).

There is significant relationship between diet and stroke, diet also increases risk of other conventional risk factors like diabetes, hypertension, dyslipidemia and obesity(65). Salt rich diet increases the risk of hypertension and stroke(66) and whereas low potassium diet decreases the risk of stroke(67). Mediterranean diet, dietary approach to stop hypertension (DASH) diet or diet with increased fruit intake are found to decrease risk of stroke by almost 20%(68).

Obesity increases the risk factors of hypertension and diabetes. Obesity also increase the risk of stroke, abdominal obesity , waist hip ratio is stronger risk factor than body mass index for developing ischemic stroke(53,69).

Metabolic syndrome is a collection of risk factors hypertension, obesity, dyslipodemia and pre diabetes. Risk of stroke doubles in patients with metabolic syndrome.

ALCOHOL CONSUMPTION / SMOKING AND SUBSTANCE ABUSE

Alcohol consumption and stroke risk have a J shaped relation, with 2 -3 drinks per day being protective and heavy drinking increasing the risk of stroke(55,70,71). Alcohol increases the risk of hypertension, dyslipedimea there by increasing risk of stroke. Alcohol has a linear association with hemorrhagic stroke even a small amount of alcohol increases risk of bleed.

Cigarette smoking is a major risk factor for stroke, increasing the risk 2 fold and contributes 15% of all deaths due to stroke(72). Passive smoking is also associated with increased risk of stroke (73). Cocaine, heroin, amphetamines, and ecstasy abuse increases the risk of ischemic and hemorrhagic strokes(74,75).

CARDIAC DISORDERS

Cardiac diseases are a major risk factor for stroke. Heart failure increases the risk of stroke by 2-3 times. 10-24% of stroke patients had heart failure and 9 % of stroke was caused by heart failure(76,77) heart failure is often associated with other risk factors like diabetes, hypertension, dyslipidemia and obesity.

Atrial fibrillation(AF) is one of the important risk factor for stroke, the incidence of stroke due to AF has tripled in past 3 decades(78) one of the proposed mechanism for AF causing stroke is formation of thrombus in atrium resulting in embolisation to cerebral vessels but this model is incomplete as the association between AF and stroke is not convincingly proven(79). The possible mechanism is thromboembolism caused by AF and abnormal systemic and atrial tissue substrate or 'atrial cardiopathy(79)'. There is also evidence that stroke per se causes AF by changes in autonomic tone and post stroke inflammatory state(80,81). Supra ventricular tachycardia also predisposes to stroke. The risk of stroke in patient with AF can be calculated by CHA2DS2-VASc score(82)

Coronary artery disease and stroke have similar risk factors. Coronary artery disease almost tripled the risk of stroke(83) independent of other risk factors. Valvular heart disease like mitral stenosis and mitral regurgitation predispose for development of stroke(84). In patients with left ventricular hypertrophy risk of atherothrombotic stroke was almost 3-4 times(85). Carotid artery bruit and stenosis predisposes to develop stroke.Congenital heart disease like cyanotic heart disease, atrial septal defect, patent foramen ovale increases the risk of cardioembolic stroke(52).

TRANSIENT ISCHEMIC ATTACK (TIA)/ PREVIOUS STROKE

Individual who had previous stroke or a TIA is having a high risk of recurrent stroke, risk following TIA is calculated by ABCD score(37).

HOMOCYSTEINAEMIA

Patients with rare inherited deficiency of cystathionine syntase develop severe homocysteinaemia and homocystinuria and a tendency to develop venous and arterial thrombosis.

ETIOLOGY OF ISCHEMIC STROKE

The clinical features and examination findings often establish the cause of stroke and judicious use of laboratory testing and imaging studies completes the initial evaluation 30% of strokes can remain unexplained despite extensive evaluation(49).

COMMON CAUSES

1) Thrombosis
    a) Lacunar stroke (small vessel)
    b) Large-vessel thrombosis
    c) Dehydration

2) Embolic occlusion
    a) Artery-to-artery
        i) Carotid bifurcation
        ii) Aortic arch
        iii) Arterial dissection

b) Cardioembolic

i) Atrial fibrillation
ii) Mural thrombus
iii) Myocardial infarction
iv) Dilated cardiomyopathy
v) Valvular lesions
vi) Mitral stenosis
vii) Mechanical valve
viii) Bacterial endocarditis

c) Paradoxical embolus

i) Atrial septal defect
ii) Patent foramen ovale

3) Atrial septal aneurysm
4) Spontaneous echo contrast
5) Stimulant drugs: cocaine, amphetamine

UNCOMMON CAUSES

1. Hypercoagulable disorders

A. Protein C deficiency
B. Protein S deficiency
C. Antithrombin III deficiency
D. Antiphospholipid syndrome
E. Factor V Leiden mutation
F. Prothrombin G20210 mutation
G. Systemic malignancy
H. Sickle cell anemia
I. β Thalassemia
J. Polycythemia vera
K. Systemic lupus erythematosus
L. Homocysteinemia
M. Thrombotic thrombocytopenic
N. purpura
O. Disseminated intravascular
P. coagulation
Q. Dysproteinemias
R. Nephrotic syndrome
S. Inflammatory bowel disease
T. Oral contraceptives

2) Venous sinus thrombosis
3) Fibromuscular dysplasia
4) Vasculitis
    a) Systemic vasculitis (PAN, granulomatosis with polyangiitis [Wegener's], Takayasu's, giant cell arteritis)
    b) Primary CNS vasculitis
    c) Meningitis (syphilis, tuberculosis, fungal, bacterial, zoster)
5) Noninflammatory vasculopathy
    a) Reversible vasoconstriction syndrome
    b) Fabry's disease
    c) Angiocentric lymphoma
6) Cardiogenic
    a) Mitral valve calcification
    b) Atrial myxoma
    c) Intracardiac tumor
    d) Marantic endocarditis
    e) Libman-Sacks endocarditis
7) Subarachnoid hemorrhage vasospasm
8) Moyamoya disease
9) Eclampsia

There are 3 major mechanism that cause ischemic stroke

1) Occlusion of an intracranial vessel by an embolus that arises at a distant site (e.g., cardiogenic sources such as atrial fibrillation or artery-to-artery emboli from carotid atherosclerotic plaque), often affecting the large intracranial vessels;

2) In situ thrombosis of an intracranial vessel, typically affecting the small penetrating arteries that arise from the major intracranial arteries;
3) hypoperfusion caused by flow-limiting stenosis of a major extracranial (e.g., internal carotid) or intracranial vessel, often producing "watershed" ischemia.

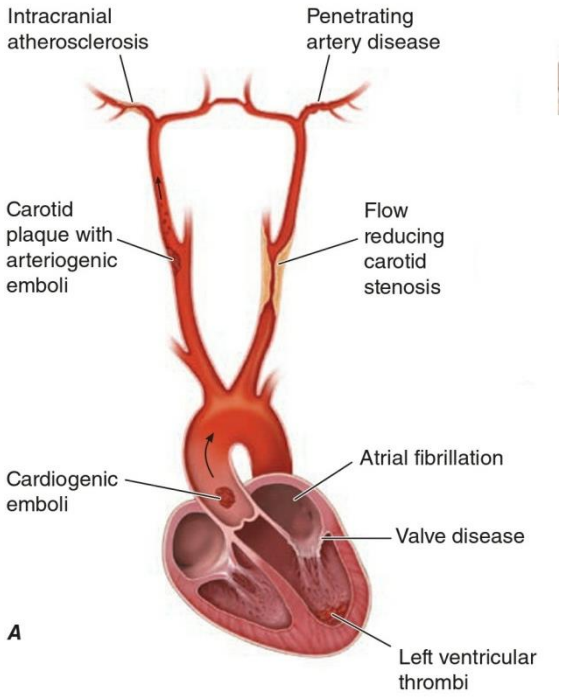


FIGURE 7 : PATHOPHYSIOLOGY OF ISCHEMIC STROKE

CARDIOEMBOLIC STROKE

It is responsible for 20% of all strokes, cardiac disease cause stroke mainly due to embolism of thrombotic material which forms on the atrial or ventricular wall or the left heart valves. They are sudden in onset with maximum neurological deficit at the time of onset with improvement in deficit as time progresses. The most important causes for cardioembolic stroke are non valvular atrial fibrillation, myocardial infarction, prosthetic valves, rheumatic heart disease and ischemic cardiomyopathy. The risk of stroke in patient with AF can be calculated by CHA2DS2-VASc score(82).

When anteroapical ventricular wall is involved Myocardial infarction can cause transmural embolisation leading to stroke.

Paradoxical embolisation occurs when there is right to left shunt due to patent foramen ovale or atrial septal defect. Venous clot, fat and tumor emboli, bacterial endocarditis, IV air, and amniotic fluid emboli can migrate to arterilal circulation causing ischemic stroke. Bacterial endocarditis lead to septic emboli which can cause stroke.

ARTERY-TO-ARTERY EMBOLIC STROKE

Stroke can be caused by emboli from the thrombus formed on atherosclerotic plaque.

CAROTID ATHEROSCLEROSIS

It causes around 10% of all strokes, common carotid bifurcation and proximal internal carotid artery are very vulnerable to atherosclerosis. It can be either symptomatic or asymptomatic. Symptomatic stenosis means that the patient had a stroke or TIA and is associated with a higher risk of subsequent stroke than asymptomatic where stenosis is found during screening.carotid artery disease risk factors are same as that of stroke.
Intracranial atherosclerosis and dissection of internal carotid or vertebral arteries are other causes of artery to artery embolism.

SMALL-VESSEL STROKE

They account for 20% of all strokes and are due to atherothrombotic or lipohyalinotic occlusion of a small artery in brain and are referred to as lacunar stroke, ‘lacunes’ in

Latin means ‘lake’ because at autopsy they look like fluid and the size of infarct range from 3 mm to 2 cm in diameter They can present with pure motor, sensory, ataxic hemiplegia and dysarthria or clumpsy hand symptoms(49).

LESS COMMON CAUSES OF STROKE

Hypercoagulable disorder mainly increases the risk of cerebral venous sinus or cortical vein thrombosis. Various mutations in homocysteine pathway lead to homocysteinemia which cause arterial stroke.

Venous sinus thrombosis can occur as a complication of oral contraceptive use, pregnancy and the postpartum period, inflammatory bowel disease, intracranial infections (meningitis), and dehydration. It is also seen in thrombophilia individuals including antiphospholipid syndrome, polycythemia, sickle cell anemia, proteins C and S deficiencies, factor V Leiden mutation, antithrombin III deficiency, homocysteinemia,cand the prothrombin G20210 mutation(49).
They usually come with headache, seizures and neurological deficits like paraperesis.

In children commonest cause for stroke is Sickle cell anemia. Fibromuscular dysplasia involves the cervical arteries and occurs predominantly in females, there are many rings of segmental narrowing which alternate with dilatation in carotid and vertebral arteries. Temporal (giant cell) arteritis usually affects elderly individuals, where there is subacute granulomatous inflammation of external carotid system especially the temporal arteries with giant cells. carotid or vertebral thrombosis can result from Idiopathic giant cell arteritis involving the great vessels of the aortic arch (Takayasu’s

arteritis). Distal small branches (<2 mm diameter) of the main intracranial arteries are involved in granulomatous (necrorizing) arteritis which can occur along with generalized polyarteritis nodosa or granulomatosis with polyangiitis (Wegener's) causing infarcts in the brain, optic nerve, and spinal cord.

Primary central nervous system vasculitis are extremely rare, they involve small or medium sized vessels and there is no involvement of systemic vasculitis.

Drugs especially amphetamines and cocaine, can cause stroke because of drug induced vasculopathy due to vasospasm or atherosclerosis.

Moyamoya disease involves large intracranial arteries, primarily the distal ICA, the stem of the MCA and ACA. On conventional x-ray angiography, the collateral circulation around the occlusion formed by lenticulostriate arteries appears as "puff of smoke" (Moyamoya in Japanese).

Head injury, seizure, migraine, sympathomimetic drug use, eclampsia, and postpartum period can cause Posterior reversible encephalopathy syndrome (PRES). It involves a hyperperfusion state where blood pressure exceeds the upper limit of cerebral autoregulation resulting in cerebral edema. Patients presents with headache and fluctuating neurologic symptoms and signs, especially visual symptoms. Sometimes cerebral infarction occurs, but usually the clinical and imaging findings reverse completely.

New onset hypertensives can have reversible cerebral vasoconstriction syndrome (RCVS) patient come with sudden, severe headache. These patients can have infarction and hemorrhage.

Multiple small-vessel infarcts within the subcortical white matter can lead to Leukoaraiosis, or periventricular white matter disease. Chronic hypertension causes lipohyalinosis of small penetrating arteries within the white matter.

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), CARASIL (cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy), HERNS (hereditary endotheliopathy, retinopathy, nephropathy, and stroke), Fabrys disease are few genetic disorders causing stroke (49).

CLINICAL MANIFESTATIONS OF ISCHEMIC STROKE

Clinical symptoms, neurological deficit following ischemic stroke depends on the involved artery and underlying cause for stroke.

Embolic stroke usually occurs when individual is active with maximum neurological deficit at onset where as thrombotic stroke occurs early in the morning or during sleep and the deficit progress more slowly in step ladder or stuttering pattern (49,86).

Individuals with ischemic stroke present with history of higher function disorder like altered consciousness, language disturbance, hemineglect or agnosia. Motor symptoms like decreased movements or paralysis, involuntary movements, stiffness or heaviness of limbs. Sensory symptoms like reduced sensation or increased sensation especially in

thalamic strokes. They may also come with cranial nerve involvement like deviation of mouth, slurring of speech in 7^{th} nerve or gaze palsy as in 3^{rd} nerve involvement. They might present with other symptoms like headache, vomiting, blurring of vision, seizure which suggest raised intra cranial pressure and symptoms like palpitation, chest pain and breathlessness give clue towards aetiology of stroke.

CORTICAL INFARCT SYNDROMES

1) **Internal carotid artery**
    i) Ipsilateral visual loss
    ii) Ipsilateral middle cerebral artery syndrome
2) **Anterior choroidal artery**
    i) Contralateral hemiparesis
    ii) Contralateral sensory impairment
    iii) Contralateral visual field defect
3) **Anterior cerebral artery**
    i) Contralateral leg > arm paresis
    ii) Contralateral leg > arm sensory deficit
4) **Middle cerebral artery**
    i) Contralateral hemiparesis affecting face and arm > leg
    ii) Contralateral sensory deficit affecting face and arm > leg
    iii) Contralateral visual field defect
    iv) Aphasia (dominant hemisphere)
    v) Contralateral hemispatial neglect (nondominant or dominant hemisphere)
5) **Posterior cerebral artery**

i) Contralateral homonymous hemianopia (or homonymous superior or inferior quadrantanopia)

ii) Contralateral sensory deficits (thalamic involvement)

6) Basilar artery tip

i) Bilateral central visual loss

ii) Confusion

7) Basilar artery

i) Ipsilateral cranial nerve deficit

ii) Contralateral hemiparesis

iii) Contralateral sensory impairment affecting arm and/or leg

iv) Coordination deficit

8) Vertebral artery, posterior inferior cerebellar artery

i) Ipsilateral sensory impairment over the face

ii) Dysphagia

iii) Ipsilateral Horner syndrome

iv) Ataxia

9) Superior cerebellar artery

i) Gait ataxia

ii) Ipsilateral limb ataxia

iii) Variable contralateral limb weakness

BRAIN STEM SYNDROMES

MID BRAIN SYNDROMES

1) Weber Syndrome

Involving 3rd cranial nerve, ventral midbrain and corticospinal tract

a) Ipsilateral 3rd nerve palsy

b) Contralateral hemipaeresis

2) Benedict syndrome

Involving 3rd cranial nerve, ventral midbrain, corticospinal tract and red nucleus

a) Ipsilateral 3rd nerve palsy

b) contralateral hemipaeresis

c) contralateral ataxia and intentional tremors

3) Claude's syndrome

Involving 3rd cranial nerve, dentatorubral fibres and red nucleus

a) Ipsilateral 3rd nerve palsy

b) Contralateral cerebellar ataxia

4) Nothnagels Syndrome

Involving 3rd cranial nerve, superior cerebellar peduncle

a) Ipsilateral 3rd nerve palsy

b) Ipsilateral Cerebellar ataxia

PONTINE STROKE SYNDROME

1) Foville syndrome

Involving 7th cranial nerve, ventral pons, paramedian pontine reticular formation.

a) Ipsilateral 7th nerve palsy

b) Contralateral hemipaeresis

c) Ipsilateral conjugate gaze palsy

2) Millard-Gubler Syndrome

Involving 6th and 7th cranial nerves and ventral pons

a) Ipsilateral LMN 7th nerve

b) Ipsilateral 6th nerve

c) Contralateral hemiparesis

d) +/– contralateral pain/temperature

3) Locked-in Syndrome

Involving ventral pons, basi pontis

Occlusion of basilar artery leads to locked in syndrome where patient is awake and alert but unable to move or communicate except for vertical eye movements.

a) Bilateral LMN 7th nerve

b) Bilateral 6th nerve

c) Quadriplegia

d) +/– bilateral light touch/proprioception

4) Raymond Syndrome

Involving 6th cranial nerve, cortico facial fibres and corticospinal tract

a) Ipsilateral internuclear ophthalmoplegia

b) Contralateral hemiparesis

c) Contralateral UMN 7th nerve

d) Contralateral light touch, proprioception

e) +/– contralateral pain/temperature (with ipsilateral Horner)

5) Marie-Foix syndrome

Involving 7th and 8th cranial nerves, spinothalamic tracts, cerebellar and corticospinal tract

a) contralateral hemiplegia/hemiparesi

b) contralateral loss of pain and temperature sensation

c) ipsilateral limb ataxia

d) ipsilateral facial paralysis

e) ipsilateral hearing loss, vertigo and nystagmus

MEDULLARY STROKE SYNDROMES

1) Medial medullary syndrome (Dejerine syndrome)

involving corticospinal tract, medial leminiscus and 12th nerve

a) Ipsilateral tongue palsy

b) Contralateral hemiparesis

c) Contralateral light touch, proprioception

2) Lateral medullary syndrome (Wallenberg Syndrome)

Involving spinothalamic tract, 5th and 8th nerve nucleus, nucleus ambigus, cerebellum and inferior cerebellar peduncle

a) Ipsilateral facial anesthesia

b) Contralateral pain, temperature

c) Ipsilateral Horner syndrome

d) Ipsilateral IX, X palsy- dysphagia

e) Ipsilateral ataxia (olivocerebellar tract)

DIAGNOSIS

Stroke is a clinical diagnosis. Thorough history, physical and neurological examination diagnoses stroke.

HISTORY

An accurate history should be obtained including the onset of deficit, progression, rapidity of development of symptoms, time of onset and other associated symptoms along with past medical illness, risk factors including smoking, alcohol history and personal history has to be elucidated. History may require inputs from informant as most of the time stroke patient cannot communicate effectively.

PHYSICAL EXAMINATION

General physical examination can give clue regarding etiology, type of stroke.Irregularly irregular pulse suggests atrial fibrillation, absent pulse may suggest takayasu arteritis , pulsus bisferans, collapsing pulse suggest valvular heart disease as risk factor and cause of stroke, where as elevated blood pressure in the setting of sudden onset neurological deficit in the area localisable to thalamus, basal ganglion or Pons suggest hemorrhagic stroke. Signs of atherosclerosis like frank sign, xanthelasma suggest atherothrombotic stroke. A detailed general physical examination has to be done to look for causes of stroke especially in stroke in young patients.

Carotid artery examination is a must in all stroke patients. Absent carotid pulses suggests decreased amplitude of pulse and in-equality between two carotids suggest atherosclerosis, aortic dissection, arteritis or embolus. Carotid bruit suggests partial obstruction of carotid artery or conducted cardiac murmur. Usually bruit develops when the lumen of artery is decreased to <50% of its cross sectional diameter.

A general neurologic examination including evaluations of cognition, language, spatial neglect, cranial nerves, motor function, sensory system, coordination, gait, and reflexes is important both for documenting stroke related deficits and for localising the affected brain area and the severity of the injury.

The National Institutes of Health Stroke Scale is a standardized graded neurologic impairment assessment tool for measuring the severity of the stroke, determining the risks and benefits of management, assessing prognosis, and observing patients objectively over time(86). Other system examination especially cardio vascular system plays a significant role in evaluating stroke. Presence of murmur, third heart sound, and irregular rhythm give clue regarding cardioembolic stroke. Respiratory system examination gives clue regarding infection, tuberculosis, Wegeners as a cause of stroke; also one has to examine respiratory system for complications like aspiration pneumonia. Abdominal system examination may suggest any malignancy, organomegaly giving clue for possible etiology of stroke including autoimmune disorders, coagulopathies, and sickle cell anemia.

NATIONAL INSTITUTES OF HEALTH STROKE SCALE (NIHSS)

National institutes of health stroke scale is a neurological examination tool widely used to evaluate stroke patients on parameters like level of consciousness, language, neglect, visual field loss, motor strength , extra ocular movements, ataxia, dysarthria and sensory loss(8,87). The reliability of NIHSS to predict severity of stroke and outcome is well documented(7). NIHSS is the most frequently used scale in clinical trials and is easily reproducible. Doctors depend upon NIHSS to evaluate acute stroke patients and decide regarding the treatment(88).

NIHSS was first developed by combining several stroke deficit rating scales like Canadian neurological scale, Edinburgh-2 coma scale , Oxbury initial severity scale and university of Cincinatti scale for trial of naloxone in acute stroke sponsored by

National institutes of health(8). This scale was complex and had poor reliability. During NINDS r-Tpa Trial, significant changes were made to it(30). After successful use in NINDS r-Tpa trial NIHSS has become the gold standard for rating stroke severity. Due to critisicm of poor reliability, complexity and not having clear information modifications were made to original NIHSS, 4 questions were dropped from the 15 parameters and non reliable parameters were removed, the score was further validated and found that its reliability increased with video training (89).

The maximum score possible is 31 when compared to 42 of NIHSS. To further increase the reliability modifications to the current NIHSS scale are made and poor reliability items like level of consciousness, facial weakness, ataxia, and dysarthria are removed and sensory system choice was reduced to 2 from 3, mNHISS is identical to NIHSS clinically with fewer items and might be simple to use in clinical trials but no prospective studies are done to validate it(90).

NIHSS is reliable even when used by trained non-neurologists and predict outcome or the presence of large vessel occlusions(91). Not all the symptoms and signs of stroke are considered as deficits in NIHSS, It outweighs deficits in patients with left compared to right brain strokes, with strokes of similar size left sided strokes scored 4 points more than right and for the given NIHSS score the median volume of right sided stroke was much higher than the left (92) also It is highly biased toward deficits due to anterior circulation strokes, posterior circulation stroke deficits receive lesser points compared to anterior deficits(93).

Recent studies have shown that NIHSS is not a reliable and fails to detect stroke, 0 on NIHSS does not mean absence of stroke as found in a study(9). It is also shown that

NIHSS has limitation to predict outcome in chronic stroke and lacks association with impairment and activities of daily living measurements(10).

Even though NIHSS is designed for clinical trials and not advised as bedside tool for clinician day to day practice(94) it is used worldwide as a prognostic tool and to make treatment decisions.

NIHSS system requires training and certification to assure reproducibility across clinical trials, it does not accurately consider patient's coordination; gait impairment; cortical sensory function; distal motor function; memory; or cognition this is done intentionally to achieve reproducibility(95). The rule of NIHSS is to 'score what you see, not what you think' but sometimes in a case of aphasia patient might fail to answer question about orientation and which might be scored as points by non neurologist even though aphasia is the problem not stupor or delirium(95). A recent study found that NIHSS has a very weak correlation with motor dysfunction, functional limitation, and health status measurements and its use in predicting motor outcomes in real life scenarios is not beneficial(96).

Because of these limitations, NIHSS cannot be used to predict prognosis and outcomes of patient with acute ischemic stroke and there is a need of a simple, reliable and easily reproducible tool to prognosticate these patients.

NIHSS ITEM INSTRUCTIONS & SCALE DEFINITIONS (97)

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

INSTRUCTIONS	SCALE DEFINITION	SCORE
1a. **Level of Consciousness:** The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = **Alert**; keenly responsive. 1 = **Not alert**; but arousable by minor stimulation to obey, answer, or respond. 2 = **Not alert**; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.	_____
1b. **LOC Questions**: The patient is asked the month and his/her age. The answer must be correct—there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or nonverbal cues.	0 = **Answers** both questions correctly. 1 = **Answers** one question correctly. 2 = **Answers** neither question correctly.	_____
1c. **LOC Commands:** The patient is asked to open and close the eyes and then to grip and release the nonparetic hand. Substitute another one-step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one, or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = **Performs** both tasks correctly. 1 = **Performs** one task correctly. 2 = **Performs** neither task correctly.	_____
2. **Best Gaze:** Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV, or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, preexisting blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = **Normal**. 1 = **Partial gaze palsy**; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = **Forced deviation**, or total gaze paresis not overcome by the oculocephalic maneuver.	_____
3. **Visual:** Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = **No visual loss**. 1 = **Partial hemianopia**. 2 = **Complete hemianopia**. 3 = **Bilateral hemianopia** (blind including cortical blindness).	_____
4. **Facial Palsy:** Ask—or use pantomime to encourage—the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or noncomprehending patient. If facial trauma/bandages, orotracheal tube, tape, or other physical barriers obscure the face, these should be removed to the extent possible.	0 = **Normal** symmetrical movements. 1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling). 2 = **Partial paralysis** (total or near-total paralysis of lower face). 3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).	_____
5. **Motor Arm**: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the nonparetic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN) and clearly write the explanation for this choice.	0 = **No drift**; limb holds 90 (or 45) degrees for full 10 seconds. 1 = **Drift**; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = **Some effort against gravity**; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity**; limb falls. 4 = **No movement**. UN = **Amputation** or joint fusion, explain: _____ 5a. **Left Arm** 5b. **Right Arm**	_____
6. **Motor Leg:** The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the nonparetic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN) and clearly write the explanation for this choice.	0 = **No drift**; leg holds 30-degree position for full 5 seconds. 1 = **Drift**; leg falls by the end of the 5-second period but does not hit bed. 2 = **Some effort against gravity**; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = **No effort against gravity**; leg falls to bed immediately. 4 = **No movement**. UN = **Amputation** or joint fusion, explain: _____ 6a. **Left Leg** 6b. **Right Leg**	_____

INSTRUCTIONS	SCALE DEFINITION	SCORE
7. **Limb Ataxia**: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN) and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = **Absent**. 1 = **Present in one limb**. 2 = **Present in two limbs**. UN = **Amputation** or joint fusion, explain: _____	_____
8. **Sensory**: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal, and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brain stem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a = 3) are automatically given a 2 on this item.	0 = **Normal**; no sensory loss. 1 = **Mild-to-moderate sensory loss**; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = **Severe to total sensory loss**; patient is not aware of being touched in the face, arm, and leg.	_____
9. **Best Language**: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet, and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a = 3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = **No aphasia**; normal. 1 = **Mild-to-moderate aphasia**; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe aphasia**; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = **Mute, global aphasia**; no usable speech or auditory comprehension.	_____
10. **Dysarthria**: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN) and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = **Normal**. 1 = **Mild-to-moderate dysarthria**; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = **Severe dysarthria**; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = **Intubated** or other physical barrier, explain:_____	_____
11. **Extinction and Inattention (formerly Neglect):** Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosognosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = **No abnormality**. 1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = **Profound hemi-inattention or extinction to more than one modality**; does not recognize own hand or orients to only one side of space.	_____

TABLE 1: NATIONAL INSTITUTE OF HEALTH STROKE SCALE

NIHSS is an ordinal scale, with each possible combination of total score the clinical findings change hence it is useful when changes over time are measured such as increased score suggesting deterioration and decreased suggesting improvement.

INVESTIGATIONS

Stroke is a clinical diagnosis and investigations including imaging of brain are done to support the diagnosis.

BRAIN IMAGING

Once diagnosis of stroke is made imaging of brain is necessary to detect the type of stroke whether it is an ischemic or hemorrhagic stroke. Imaging can also locate the area of injury and rule out stroke mimics like tumour, abscess or subdural hematoma. Both Computed tomography (CT) and Magnetic Resonance Imaging (MRI) plays essential part in assessing patients with ischemic stroke.

Brain CT is widely and rapidly available and provides the information necessary for the treatment of most patients with acute stroke. CT may be normal in patients presenting very early and examination of early CT changes like loss of gray/ white-matter differentiation, sulcal effacement, effacement of the Sylvian fissure, and obscuration of the lentiform nucleus, hypodensity an swelling of insular cortex (insular ribbon sign) in the area of MCA territory is essential. Sometimes the large intracranial vessels appear hyperdense before infarction appears in CT like the dense MCA sign which indicates thrombotic or embolic occlusion of MCA and often predicts a large cortical infarct. Area of infarction appear hypodense in CT whereas area of hemorrhage appear hyperdense. CT is easily available, cheap and rapid gold standard test in the evaluation of stroke but posterior fossa structures cannot be visualised as it is often obscured by artefacts from petrous bones(52,86).

MRI plays a significant role in patients who present with acute stroke and in posterior circulation stroke. MRI is more sensitive in visualising acute ischemic infarct and brain stem, cerebellar structures, but it is not available widely, it is costly and time consuming and patients with metallic implants and devices like cardiac pacemaker, orthopaedic implants cannot undergo MRI. It is superior to CT in acute ischemic stroke because diffusion, perfusion and gradient echo MR sequences can rapidly detect early ischemic

and hemorrhagic lesions and also describe the amount of at-risk tissue (the “ischemic penumbra”). The sensitivity of MRI to differentiate infarct from normal tissue mainly depends on changes in tissue T1 and T2 relaxation times. Magnetic resonance angiography (MRA) is used to generate pictures of arteries to look for stenosis, occlusion or aneurysms and the specificity and sensitivity of MRA can be increased by administrating gadolinium. DW-MRI detects acute cerebral ischemia very early and also differentiates acute from chronic stroke(52,86).

Advanced imaging techniques like multifocal imaging with diffusion/perfusion or perfusion CT and CTA are being used to detect ischemic penumbra(98). Recent study found that diffusion/perfusion mismatches are indicative of brain at risk, still the utility of diffusion/perfusion MRI to select patients for thrombolytic therapy is to be determined(99). There is increasing trend of CT perfusion imaging being used for early diagnosis of stroke along with routine non contrast CT and CT angiography but there is risk of radiation and contrast dye exposure to patients(98).

Alberta Stroke Programme Early CT Score (ASPECTS) is a 10 point CT scan scoring system which has been described for assessing prognosis and identifying patients who are not likely to have good outcomes after IV thrombolysis(100).

LABORATORY INVESTIGATIONS

They help to determine conditions that may mimic, complicate or cause acute ischemic stroke.

A case of suspected ischemic stroke should undergo complete blood count (CBC) and platelet count, blood glucose level, serum electrolytes, renal function tests, lipid analyses, urinalysis, chest x ray and 12-lead ECG. Glycosylated hemoglobin (Hb A1c) in cases of diabetes or suspected diabetes. Laboratory tests for thrombophilia, erythrocyte sedimentation rate, prothrombin time, aPTT and INR and connective tissue disorder, 2D echo are done as and when necessary.

Elevated total count in CBC suggests infection as a cause of stroke, polycethemia can result in increased viscosity causing blockage of vessels leading to stroke, and thrombocytopenia either primary or secondary can lead to platelet thrombi. Deranged PT, aPTT and INR suggest underlying coagulation disorder and they might not be considered for treatment with intravenous recombinant tissue plasminogen activator. Both hypo and hyperglycemia can mimic as stroke. Hyperglycemia is a risk factor and can worsen brain injury during stroke. Deranged renal function test can cause stroke and also interfere with treatment. Dyselectrolytemia can mimick as stroke and also be the cause and effect, stroke per se can cause syndrome of inappropriate anti diuretic hormone secretion (SIADH) leading to hyponatremia. (49,52,86)

CARDIAC EVALUATION OF THE STROKE PATIENT

It plays an important role determining whether emboli have cardiac source and has to be evaluated thoroughly in suspected cases. 12 lead Electrocardiogram (ECG) is the first investigation and may reveal changes like ST elevation in myocardial infarction or irregular rhythm with absent P waves in atrial fibrillation which is the most common cause for embolic stroke. Stroke itself can lead to arrhythmias and cardiac dysfunction.

Acute myocardial infarction can cause stroke by mural thrombi and stroke can also precipitate MI so in suspected cases there is need for cardiac enzymes like troponin I and Brain natriuretic peptide, recent studies have suggested there is elevation of BNP in stroke patients(15).

Non invasive cardiac imaging like two-dimensional echocardiography is used to screen for variety of cardiac conditions like left ventricular hypertrophy, right to left shunts as in ASD, patent foramen ovale, to look for regional wall motion abnormality following myocardial infarction and ventricular dysfunction these disorders can cause stroke.

2D echo can also detect left ventricular thrombi, thrombi which have protruding edge and mobile appearance are more likely to embolise and trans thoracic or transesophageal echo view may be required to evaluate it. Atrial fibrillation cause atrial thrombus due to blood stasis in left atrium or atrial appendage and are not visible in routine 2D echo and trans esophageal echocardiography(TEE) is the gold standard technique to detect cardiac source of emboli. Continuous ECG monitoring is adviced routinely in cases of suspected paroxysmal arrhythmias and 24 hour holter monitoting may also be required in selected cases (52).

OTHER IMAGING TECHNIQUES

Doppler imaging, B-mode scanning, duplex (combined B-mode and Doppler) scanning, and transcranial Doppler (TCD) imaging are adviced in primary screening and rarely used in acute setting.

Cerebral angiography techniques like CT and MR angiography are used in making treatment decision like endovascular therapy.

DIFFERENTIAL DIAGNOSIS OF ACUTE ISCHEMIC STROKE

The hallmark of acute ischemic stroke is the sudden onset of a focal neurologic deficit, usually attributed to an area of brain supplied by a specific artery.

Other neurological conditions which present acutely can mimic stroke

1. Migraine with aura

   Patient can have focal neurologic deficits, including aphasia, visual changes, vertigo, weakness, numbness, and incoordination.

2. Partial seizures

   Patient can have negative symptoms, including aphasia and paresis, and a patient with a postictal Todd paralysis may look like hemiplegic patient.

   Also stroke itself can cause seizures complicating diagnosis.

3. First episode of multiple sclerosis.
4. Mass lesion – Neoplasm and Brain abscess

   They usually have slowly worsening symptoms but can manifest acutely.

5. Metabolic disorders like hypoglycemia or hyperglycemia.
6. Toxin exposures and drug intoxications.
7. Malingering or other psychiatric illness.

TREATMENT OF ACUTE ISCHEMIC STROKE

The main goal of treatment is to prevent further damage or reverse brain injury and improve clinical outcome. After diagnosis of acute ischemic stroke CT brain is done to rule out hemorrhage.

Treatment categories

1) Medical support
2) IV thrombolysis
3) Endovascular revascularization
4) Antithrombotic treatment
5) Neuroprotection
6) Stroke centers and rehabilitation.

MEDICAL SUPPORT

The primary goal is to optimize cerebral perfusion in ischemic penumbra region.

A. Patient's airway, breathing and circulation (ABCs) are assessed and treated;

   Airway support and ventilator assistance are advised to patient who have low consciousness and bulbar stroke that compromises breathing. Saturation has to be maintained > 94%.

B. Care is taken to prevent complication of stroke like infections (pneumonia, skin or urine infections), deep vein thrombosis and pulmonary embolism.

   Infections are treated with antibiotics, subcutaneous heparin can be used as prophylaxis and pneumatic compressive stockings have proven benefit in preventing DVT.

C. Collateral blood flow in brain may be dependent on blood pressure.
   a. Low Blood pressure and hypovolemia has to be corrected to maintain brain perfusion.
   b. If patient has high BP and is a candidate for thrombolysis BP should be carefully lowered to systolic BP < 185mmHg and diastolic < 110mmHg before treatment is initiated

Labetalol and Nicardapine are the drugs recommended to lower BP and BP to be maintained <180/105mmHg for first 24 hours after IV thrombolysis

c. If patient has elevated BP and is not a candidate for IV thrombolysis and BP <220/110mmHG there is no evidence that initaing treatment is of any mortality benefit and for those with pre existing HTN , antihypertensives has to be reinitiatied.

d. If patient has elevated BP and is not a candidate for IV thrombolysis and BP >220/110mmHG, BP has to be lowered by 15% in first 24 hours(101)

D. Fever is detrimental and should be treated with antipyretics and surface cooling, hypothermia is a good neuroprotective agent but its use in acute stroke is not proven and it may increase risk of infection like pneumonia.

E. Serum glucose should be maintained between 60 to 180 mg /dl by using insulin or glucose infusion whenever necessary.

F. IV Mannitol and fluid restriction therapy can be used if patient develops significant edema. Hemicraniectomy is a proven strategy and reduces mortality by 50% and outcome is significantly improved in stroke survivors.

G. Extra care has to be taken in patients with cerebellar stroke as even small edema increases intracranial pressure by obstructing CSF and causing hydrocephalus and compressing brain stem which can cause coma and respiratory arrest which require decompression surgeries.(49,101).

H. Nutrition – enteral diet has to be begun within 1 week of stroke onset, ryles tube feeding in patients with dysphagia and percutaneous gastrostomy tubes for patients who fail to improve is advised(101).

I. Depression screening with structured tool and treatment with antidepressant is recommended by AHA(101).

INTRAVENOUS THROMBOLYSIS

There is clear benefit of intravenous recombinant tissue plasminogen activator(rtPA) in acute ischemic stroke (30) . Administration of rtPA is approved between 3 – 4.5 hours in Europe and Canada where as in USA it is approved only for 0-3 hours.

INDICATIONS

1. Clinical diagnosis of stroke
2. Onset of symptoms to time of drug administration ≤4.5 Hours
3. CT scan showing no hemorrhage or edema of >1/3 of the MCA territory
4. Age 18 ≥ years

CONTRAINDICATION

1. Sustained BP >185/110 mmHg despite treatment
2. Bleeding diathesis
3. Recent head injury or intracerebral hemorrhage
4. Major surgery in preceding 14 days
5. Gastrointestinal bleeding in preceding 21 days
6. Recent myocardial infarction

ADMINISTRATION OF rtPA

1. IV access with two peripheral IV lines (avoid arterial or central line placement)
2. Review eligibility for rtPA.
3. Administer 0.9 mg/kg IV (maximum 90 mg) of IV alteplase as 10% of total dose by bolus over 1 minute, followed by remainder of total dose over 60 minutes.
4. Frequent cuff blood pressure monitoring.
5. No other antithrombotic treatment for 24 hours.

6. For decline in neurologic status or uncontrolled blood pressure, stop infusion give cryoprecipitate, and reimage brain emergently.
7. Avoid urethral catheterization for ≥2 hours.

ENDOVASCULAR REVASCULARIZATION

Ischemic strokes which involve large vessels like Middle Cerbebral Artery, Internal Carotid and Basilar artery have poor prognosis and high risk of mortality and morbidity, they have high clot volume and IV rtPA alone fails to open up the occlusion so intraarterial thrombolytics were used to increase the chance of clot lysis and decrease systemic bleeding complication, PROCAT II trial found significant improvement in outcome for intraarterial prourokinase even upto 6 hours after onset in MCA strokes(102). Intraarteial thrombolysis is not approved by FDA many studies suggest it can be considered when mechanical thrombectomy fails (49)

In patients who have contraindication or failed IV thrombolysis, Endovascular mechanical thrombectomy has been tried as adjuvant or alternate treatment. The HERMES meta analysis study which included the 5 studies MR CLEAN, ESCAPE, REVASCAT, SWIFT PRME and EXTEND IA found that mechanical thrombectomy within 6 hours of stroke after large vessel occlusion improved the outcome and the number needed to treat to decrease disability by 1 point in modified rankin score was 2.6(33). The DAWN and DEFUSE 3 trials have reported good clinical outcome in patients undergoing mechanical thrombectomy with 24 and 12 hours of onset of stroke respectively (34,103). If the patient has good collaterals in CT or MRI perfusion imaging patient can be treated with mechanical thrombectomy for upto 24 hours(49,101).

Patient who meets following criteria should undergo mechanical thrombectomy with stent retriever(101).

1. Pre stoke mRS score 0-1
2. Internal carotid artery or Middle Cerebral artery (M1 Segment) occlusion
3. Age > 18 years
4. NIHSS score > 6
5. ASPECTS >6
6. Management can be started (groin puncture) within 6 hours of onset of symptoms

ANTITHROMBOTIC TREATMENT

Platelet Inhibition

Aspirin is the only drug proven to effective in treatment of acute ischemic stroke. The 2 trials IST and CAST where aspirin was given 300mg/ day and 160 mg/ day respectively reduced mortality and stroke recurrence(31,32). American heart association recommends initial Aspirin dose of 325mg (101).

ANTICOAGULATION

There is no clear benefit of anticoagulation following acute ischemic stroke, routine use of heparin or other anticoagulants are not recommended and have shown high risk of hemorrhage(101).

NEUROPROTECTION

Even though many drugs have shown positive results in animal studies in prolonging brain’s tolerance to ischemia, no neuroprotectors have been approved by FDA in

treatment of ischemic stroke. There is no benefit of either pharmacological or non pharmacological treatments according to AHA (101).

Hypothermia is beneficial neuroprotective agent after cardiac arrest but studies have failed to prove its efficacy in acute ischemic stroke and patients are prone to develop pneumonia which impacts stroke outcome(49,52).

STROKE CENTERS AND REHABILITATION

Many centres have a dedicated stroke team which provide emergency services round the clock like medical management, IV thrombolysis or thrombectomy in cases of acute ischemic stroke.

Studies have proven the benefit of stroke centres in improving neurological recovery and decreasing mortality(49,52).

Rehabilitation of stroke patients includes early physical, occupational and speech therapies. Patient and family are educated about the neurological deficit and complications of stroke and its prevention are explained including prevention of DVT, back care to prevent bed sores, physiotherapy to prevent contractures, bowel and bladder care to prevent infections. The aim of rehabilitation is to increase recovery by giving a safe, progressive regimen(49).

POST STROKE ASSESMENT

In spite of advances in early diagnosis and treatment of acute ischemic stroke many patients experience some functional disability or mortality following stroke. ‘To be able

to walk again' is the goal of patients after stroke; many studies have been done to asses stroke outcome.

Morbidity following stroke has many modalities like impairment (sign of underlying pathology), disability (functional result of impairment) and handicap (social impact of disease).

Stroke is a difficult case to study because of its highly variable clinical presentation, variety of causes and the patients who survive have disability which is highly variable. The traditional neurological examination is suited for only description of a single patient and cannot be used in large scale trial descriptions hence many impairment scales were developed which involved scoring different modalities of neurological examination and adding the scores to get the neurological condition of the patient.

Stroke is the second most common cause of disability worldwide efficacy of its treatment is usually described by measuring disability, ie, functional assessment. Barthel Index (BI) and modified Rankin score (mRS) are two of the most extensively used functional assessment scales which measure basic activities of daily living (ADL), these are the tasks the individual has to perform to achieve functional independence. Barthel index measures performance where as Rankin score measures independence(104,105).

BARTHEL INDEX

It was first developed in 1965(11) by modifying 'Maryland disability index' which was used in Baltimore's chronic disease hospitals to measure recovery(104,106). Barthel index had 10 tasks which the patient had to perform like feeding, grooming, care of

bowel and bladder, dressing, bathing, getting up from bed and climbing stairs and scores were given with 5 points increment and minimum score is 0 and maximum being 100 which tells that patient is completely independent. It was modified by Collin et al who scored increments in 1 point and maximum score of 20 was used and also found that asking a trained nurse or relative of patient is as reliable as direct examination(107).

Barhel index has been used extensively in many disorders like spinal cord injuries, burns, rheumatoid arthritis, elderly patients and also in cardiac disorders(104,108). It has been proven to be reliable after stroke(109). There are other modified Barthel scores with truncated and expanded versions depending on the disorder and need of the study and the BI has been found reliable and validated for stroke and is the most commonly used scales for stroke to asses ADL(104).

Barthel index was originally described by interview and distant observation, this still remains the standard. BI should be graded only on what the patient does and not on what the examiner thinks patient can do. There is no recognized training course for Barthel index unlike NIHSS.

BI is a scale used to measure physical dependence and cannot be used to measure to evaluate speech, cognition or mood of the patient. Change in BI over a set period of time can be a better predictor of clinical intervention than measuring a single time and it is more sensitive to change in scores than other scales used in stroke the limitation of Barthel index is that it is not sensitive at extremes of ability because of 'floor effect' and 'ceiling effect'(104) and making it less useful in minor or severe stroke but these effects are not seen in modified Rankin scale. The worst outcome after stroke is death but unlike mRS there is no scoring to represent mortality.

Criteria to classify patients based on Barthel Index vary widely and the cut-off values are chosen arbitrarily and not validated. It is an ordinal scale and many studies have dichotomized it and it has been suggested that at score of < 40 patient is completely dependent, at score >60 patient becomes independent for personal care like feeding, bowel and bladder continence but still need assistance and at score > 85 patients are reasonably independent with minimal aid. The landmark trials NINDS and ECASS II have taken score of >95 as minimal or no disability to define good or favourable outcome(104,105) but this approach has been criticised as inefficient, as a patient with minimal disability can make good recovery and score >85 and have no impact on trial where as another patient with major disability can recover substantially but have a score of less than 85, hence analytical methods that measure changes are considered.

Because of its easiness to perform, simplicity, fastness it is one of the most widely used scale to measure outcome following stroke.

THE BARTHEL INDEX SCORING(110)

Barthel Index Scoring Form

Patient Name: _____ Rater Name:_____ Date:_____

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

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; for example, stick) > 50 yards

STAIRS
0 = unable
5 = needs help (verbal, physical, carrying aid)
10 = independent

TOTAL SCORE= _____

TABLE 2: BARTHEL INDEX(110)

N-TERMINAL PRO BRAIN NATRIURETIC PEPTIDE (NTproBNP) IN STROKE

NATRIURETIC HORMONES

These are structurally related peptides which act by endocrine or paracrine fashion to reduce extracellular fluid volume and blood pressure by stimulation of renal sodium excretion.

3 group of compounds are recognised (17)

1. Natriuretic peptide (Atrial Natriuretic Peptide(ANP), Brain Natriuretic Peptide (BNP) and C- type Natriuretic Peptide (CNP))
2. Guanylin peptides (GP)
3. Endogenous cardiac steroids(CS) (ouabain, digoxin, and marinobufagenin)

Along with maintaining homeostasis it has been found that they have neurotransmission or neuromodulation action in brain.

NATRIURETIC PEPTIDES

Atrial Natriuretic Peptide(ANP) was the first to be discovered by De Bold and his co-workers in 1981, they found that injecting atrial muscle extracts to rats caused natriuresis and diuresis(111). Over the course of few years B-type natriuretic peptide was found in porcine brain which was similar in structure to ANP and had similar functions and it was named Brain natriuretic Peptide (112). Similarly C type natriuretic peptide was found in porcine brain which was similar to ANP and BNP structurally and functionally(113).

ANP is released from atria due to stretching of atria and BNP is also released from atrium but its main role is in ventricles and is released due to volume overload causing stretching of cardiac walls(114). CNP is released from endothelium and lacks the strong natriuretic and diuretic effect of ANP and BNP. Fast gene expression with new synthesis of BNP is the mechanism of BNP secretion, very less amount of it is stored in granules whereas ANP is stored in granules and can be released immediately after stimulation(115).

N-terminalpro Brain Natriuretic Peptide(NTproBNP)

Even though BNP was discovered in porcine brain it was found that it is released from cardiac myocytes, along with increased wall stress, neurohormonal activation and hypoxia or ischemia stimulates BNP release. There are evidence that suggest BNP is

also released in hypothalamus and other brain structures(16,116) it may be released due to cerebral ischemia(15).

It is encoded by gene NPPB and released as 134 amino acid preprohormone (preproBNP). It is cleaved into 108 amino acid prohormone (proBNP) and a 26 amino acid single peptide. proBNP is stored intracellulary and is eventually cleaved into 32 amino acid BNP and 76 amino acid

N –terminal proBNP (NTproBNP) at arginine 123 and serine 103 by a specific convertase like furin/corin (117).

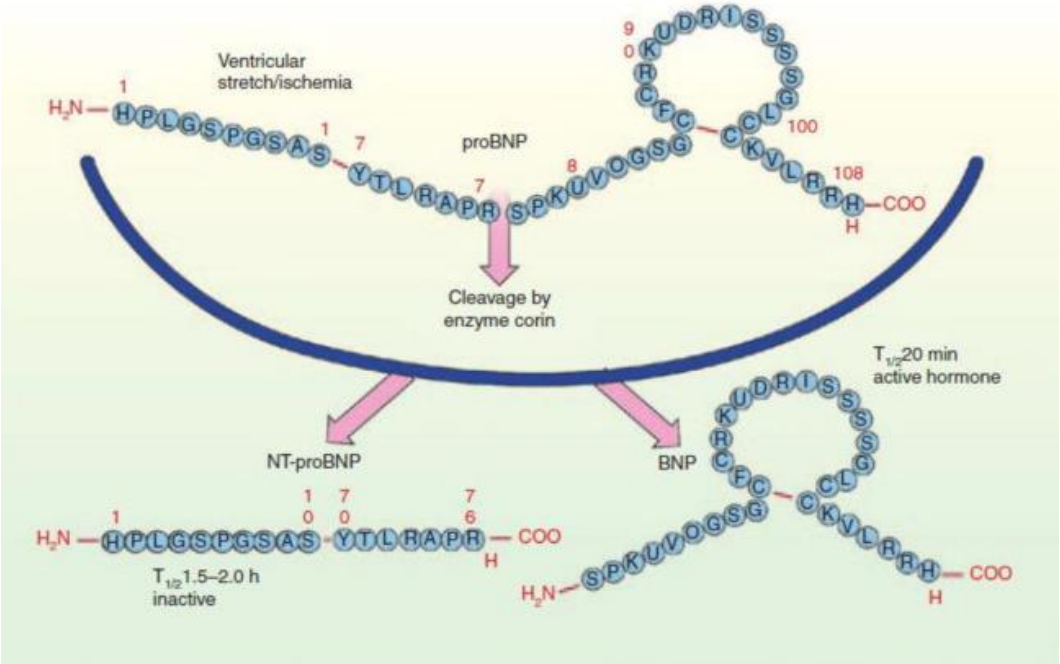


FIGURE 8: SYNTHESIS OF NTproBNP (17).

BNP and NT proBNP are released in equal proportion. BNP elimination is based on receptor mediation and metabolism and enzymatic proteolytic degradation by endopeptidase in kidneys where as NT pro BNP elimination is poorly understood. NT proBNP is dependent on kidney function for its elimination than BNP. NT pro BNP is inactive moiety which is larger and has longer half life (120 minutes) compared to the active BNP which has a shorter half life of 20 minutes therefore NT proBNP is

concentration is atleast 6 times higher than BNP(115). It is more stable during sampling, freezing and long term storage when compared to BNP hence NT proBNP estimation is preferred over BNP in various clinical trials.

Number of physiological paracrine and autocrine effects has been found in addition to 88ieresis and vasodilator action of BNP like

- Central and peripheral sympathetic nervous system suppression
- Renin angiotensin aldosterone system(RAAS) suppression
- Vascular smooth muscle growth inhibition and anti fibrotic action on cardiac muscle
- Peripheral vascular resistance reduction
- Increased endothelial permeability.

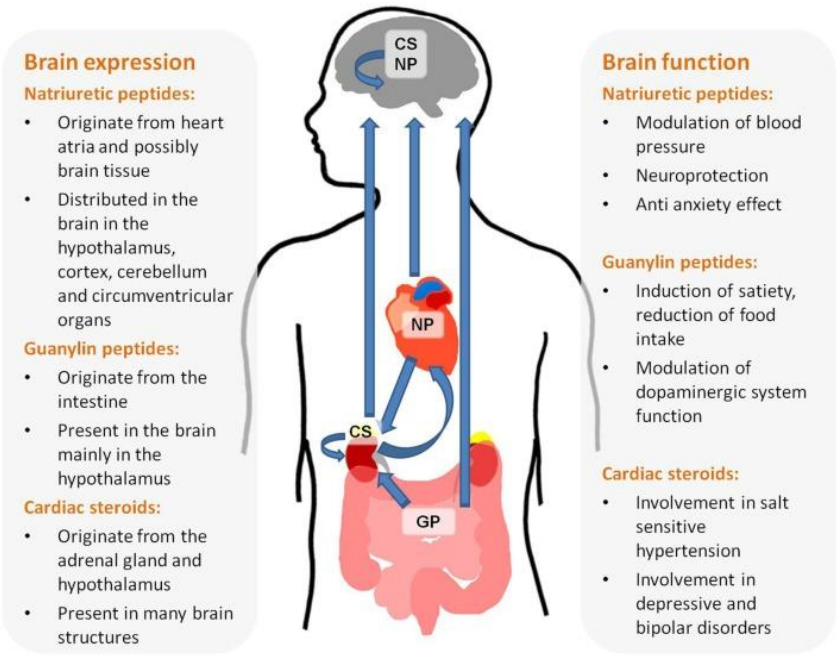


FIGURE 9: ORIGIN, DISTRIBUTION AND FUNCTIONS OF NATRIURETIC HORMONES(17)

Medical conditions where NT-proBNP can be elevated are (115,116)

1. Cardiac conditions – heart failure, left ventricular systolic or diastolic dysfunction, myocardial infarction and acute coronary syndromes, hypertensive heart disease, hypertrophic cardiomyopathy, dilated cardiomyopathy, Atrial fibrillation and other arrhythmias, Valvular and other structural heart disease.
2. Acute kidney injury and chronic kidney disease
3. Severe anaemia(118)
4. Respiratory disorders like severe chronic obstructive pulmonary disease (COPD), pneumonia, Adult respiratory distress syndrome (ARDS) and pulmonary embolism
5. Older age and female sex (119)
6. Cirrhosis of Liver
7. Hyperthyroidism
8. Sepsis
9. chemotherapy

Conditions where NT proBNP levels are decreased

1. Obesity(120)
2. Flash pulmonary edema
3. pericardial constriction

Many studies have proven that Ischemic stroke is associated with elevated NTproBNP levels(15,121–123). In the study conducted by jensen et al where they measured daily NTproBNP following stroke for 5 days they found that NTproBNP was maximum a day after stroke and started declining after that (123) the reasons postulated for elevated levels of NTproBNP in these studies were that higher proportion of cardiac failure,

kidney failure and patients in atrial fibrillation were included in the studies and all these factors might play a role in causing increased natriuretic peptide levels.

NTproBNP is found to be markedly elevated in patients with acute ischemic stroke and the value of NTproBNP is as high as or even higher than NTproBNP levels found in acute myocardial infarction even when acute coronary events were ruled out. These suggest that in ischemic strokes NTproBNP is released directly from ventricles or from extra cardiac sites like brain or vessel wall(15). One of the proposed mechanisms for elevated NT proBNP levels is the neurohormonal and inflammatory response following acute stress reaction due to acute ischemic stroke(124).

One of the mechanisms hypothesised for elevation of NTproBNP in hemorrhagic strokes like subarachnoid haemorrhage is the hyponatremia associated natriuresis following stroke and it has also been speculated that increased levels of noradrenaline in SAH patients may increase BNP release(125).

The most clinically relevant use of BNP and NTproBNP is in diagnosis of heart failure, American heart association(AHA) and European cardiac society (ECS) both recommended BNP or NTproBNp levels for diagnosis, predicting prognosis and severity of disease in their guidelines(126,127). ESC recommends NTproBNP level of 125pg/ml as cut-off value to rule out heart failure but a value of <300pg/ml is generally considered to rule out heart failure. Similarly studies have been done to predict prognosis and mortality in acute ischemic stroke by estimation of NTproBNP levels(15).

Estimation of NTproBNP to predict the risk of developing stroke has been tried. In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study cohort it was found that in those who had no prior stroke high levels of NTproBNP was associated with increased risk of stroke(128) The APEX trial sub study also came to similar conclusion where they found that in hospitalised patients NTproBNP was associated with increased risk of stroke at 77days(129). A study based on Biomarkers for Cardiovascular Risk Assessment in Europe-Consortium (BiomarCaRE consortium) found that in Europeans free from stroke high NTproBNP levels were associated with increased risk of both hemorrhagic and ischemic stroke independent of other risk factors(130) these studies did not distinct between cardiac and non cardiac causes of stroke.

There is evidence that in patient with sickle cell anemia elevated NTproBNP levels are associated with increased risk of death and stroke. In the study Machado et al found that NTproBNP of >160pg/ml was associated with increased risk of mortality and stroke(131).In a study done in Spain It was found that irrespective of cause TIA, NTproBNP of >800pg/ml can be used to predict stroke following TIA (132).

In a systematic review of blood biomarkers for diagnosing acute ischemic stroke Monbailliu et al analyzed 42 articles and examined 25 biomarkers and found that BNP and S100B can be used to diagnose ischemic stroke especially by less experienced medical workers and it also can be used to differentiate stroke from stroke mimics and hemorrhagic strokes and in conditions where CT brain may be normal i.e. when patients presents within 3 hours of onset and MRI is not available or contraindicated BNP can

be used to diagnose stroke and take treatment decision like administering IV thrombolysis(133).

In a similar systematic review Pandey et al examined 26 articles and various biomarkers to differentiate ischemic stroke subtypes and found only BNP and D-dimer had clinical use. Though they did not recommend any biomarkers they suggested BNP was optimal for diagnosing and differentiating acute ischemic stroke(134).

NTproBNP has also been extensively studied to detect and predict prognosis in cardioembolic stroke. Researchers from the Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE) trial found that NTproBNP was elevated in patients with persistent or permanent atrial fibrillation and it had a significant association with risk and mortality of stroke(135).

In a meta analysis study involving 6 studies based on NTproBNP and 10 studies of BNP to detect cardioembolic stroke it was found that BNP was sensitive whereas NTproBNP was specific in distinguishing cardiaoembolic and non cardioembolic stroke in patients with acute ischemic stroke(136).

Studies have shown that NTproBNP levels are highest within 2 days after stroke and start declining after that and estimation of NTproBNP before 72 hours of stroke has a high accuracy of diagnosing cardioembolic stroke , even in cryptogenic stroke which can occur after an episode of paroxysmal atrial fibrillation like in occult AF there is elevation of NTproBNP(137). In a study done in Austria it was found that NTproBNP of > 505pg/ml distinguished cardiogenic from other causes of stroke and detected occult

AF and AF related stroke(138) in a similar study in China they proposed that physician should consider cardiogenic strokes in patient with NTproBNP > 501.2 pg/ml(139).

It has also been shown that elevated NTproBNP levels predict prognosis and 6 month mortality in cases of cardioembolic stroke(140) .Many recent studies have validated the use of NTproBNP in detecting cardioembolic stroke due to atrial fibrillation and other cardiac causes (141,142) In our study care was taken to rule out cardioembolic stroke and occult AF.

NTproBNP AND MORTALITY AFTER STROKE

Studies have shown that NTproBNP can predict poor outcome following stroke and they were better predictors of prognosis compared to neurological deficit measurement. The prevalent theory is that high natriuretic peptide levels indicate activation of neuroendocrine system and reflects hemodynamic dysfunction and increased death in patients with acute cardiac disorders. Mechanism of association between high NTproBNP levels and mortality after stroke in patients without cardiac illness is still not clear, one of the proposed reason for elevated NTproBNP is severity of brain injury and it is possible to surmise that high NTproBNP levels in acute ischemic stroke reflect intensity of brain injury and there by the risk of mortality after stroke(15).

Neuropeptides also play a role in modulation of autonomic control of heart, NTproBNP is found to increase parasympathetic vagal neurotransmission and elevated levels of peptides can stimulate Cardiac pacemakers directly suggesting that autonomic

disturbance can increase the risk of mortality in patients with high levels of natriuretuc peptides and the autonomic dysfunction can predict mortality in long term(143,144)

Natriuretic peptides are also involved in forming atherosclerotic plaques in coronary vessels and higher Natriuretic peptide values are associated with increased severity of coronary artery diseases(145). This suggest that atherosclerosis due to high natriuretic peptide values may be the reason for poor outcome(15).

In a Finland study 51 patients were followed up to 4 years after ischemic stroke and it was found that plasma natriuretic peptide levels were same as that of in patients with acute myocardial infarction and it predicted mortality after stroke(15). This study sample size was small and cardiac and renal conditions which might interfere with peptide values were not excluded in the study and no comment was made on functional outcome in survivors.

Tomita et al studied plasma BNP levels independent of cardiac disease in acute ischemic stroke and correlated BNP with severity of stroke, they found that BNP was elevated in stroke and correlated with NIHSS scores and infarct volume and suggested that plasma BNP levels can be used in assessing severity of stroke but they did not asses the functional outcome after stroke and no comments on mortality were made(146).
Etgen et al studied prognostic value of cardiac troponin T, troponin I and NTproBNP in patients with acute ischemic stroke who had no evidence of myocardial injury. They found that NTproBNP was elevated in more than 2/3 patients and toponin I and T were elevated in less than 10% of patients. Patients were followed up to 90 days and functional assessment was done by NIHSS, Barthel index or Rankin score through

telephone or in person interview they found that NTproBNP had significant influence in univariate analysis but multivariate regression analysis did not show any significant association between NTproBNP and outcome the reason postulated for lack of significance was that the reference level used for NTproBNP was that of cardiac failure and the reference range in acute ischemic stroke might not be the same as that in heart failure(147).

In a Meta analysis study, association between BNP/NTproBNP with all cause mortality after stroke was examined. They included 16 articles and found that BNP/NTproBNP values were 255.78pg/ml more in people who died and concluded that natriuretic peptides are associated with mortality after stroke even after normalisation of secerity by NIHSS, age and gender. In this study cardiac disease and other causes like sepsis, pulmonary disorders which might increase NTproBNP were also considered and no distinction between ischemic and hemorrhagic strokes was made, it was also found that BNP/NTproBNP was elevated significantly in subarcanoid hemorrhage similar to other studies (148).

In a study done in Tokyo it was found that Plasma BNP levels were significantly correlated with coronary vessel diseases, atrial fibrillation, cardioembolism and outcome in stroke. BNP values were elevated in patients with large infarcts, high modified Rankin Scale (mRS) scores, and high CHADS2 scores. (125).

Jensen et al in their study done in Denmark on long term prognosis after stroke found that NTproBNP measured at 6 months following ischemic stroke was associated with mortality and they proposed that NTproBNP could be used as marker for predicting long term prognosis but they did not take into consideration cardiac and other causes

which might cause elevation of peptides and also no comment on functional outcome was made in the study(149).

In a study done in China, Chen et al assessed the prognostic importance of combined value of NIHSS and NTproBNP levels in acute ischemic patients and found that high NTproBNP level i.e. >1583.50 pg/ml and NIHSS score of >12.5 had very high in hospital mortality than those with low values but here heart failure and atrial fibrillation patients were also included which might cause elevated NTproBNP levels. NTproBNP values were much higher than previous studies (150).

Very few studies have been done in India to assess the prognostic importance of BNP/NTproBNP in stroke. Naveen et al studied the importance of NTproBNP in short term prognosis in stroke patients and found that log NTproBNP was higher in patients who died compared to survivors. They proposed that plasma log NTproBNP can be used a biological marker in predicting in hospital mortality. They only looked into short term mortality and no comments were made regarding functional outcome or long term mortality(151).

In another study done in South India Menon et al investigated the prognostic importance of BNP in ischemic stroke and found that elevated BNP levels predicted poor functional outcome as assessed by Barthel index at 3 months and proposed its use in predicting outcome after stroke but here only patients with evidence of ischemic heart disease were ruled out and no comments were made about other cardiac causes like structural or valvular heart disease, atrial fibrillation and cardiomyopathies which could elevate BNP values(124).

In an American retrospective study Gupta et al studied prognostic ability of BNP in those who were given IV thrombolysis after stroke and found no association between BNP and bad prognosis. Here cardiogenic cause of strokes were not excluded (152).

In a recent study done in Sikkim Dey et al correlated BNP with 7th day outcome after stroke and found that even though BNP was elevated in ischemic stroke compared to hemorrhagic stroke it was a poor predictor of outcome at 7 days(153).

Different studies have used different methods for analysing NTproBNP levels and there is no clear cut off level of NTproBNP, Most of the studies have not excluded other causes of elevated NTproBNP levels and functional and long term mortality was assesed only in few studies.

Even though there are recent advances in diagnosing and managing acute stroke there is paucity of knowledge regarding its prognosis. Stroke is a debilitating disease and 2nd commonest cause of death and disability. There is a need for biomarker which is easily available, cheap, validated and fast to stratify stroke patients. The aim of this study is to examine the role of NTproBNP as a prognostic biomarker in clinical practice.

MATERIALS AND METHODS

SOURCE OF DATA

Patients admitted with history and clinical features suggestive of acute ischemic stroke admitted at R.L. Jalappa Hospital and Research Centre, a tertiary care hospital, Tamaka, Kolar.

Prospective observational study from JULY 2018 to SEPTEMBER 2019.

SAMPLE SIZE

Average sample size based on the mean difference in BI scores reported with average variance estimate of 18.5 in a study of Menon B et al(124) with 80% power and 95% confidence interval with an effect size of 7 points increase in BI score. The estimated sample size is 57.

INCLUSION CRITERIA:

- Patients > 18 years of age with acute ischemic stroke presenting within 24 hours of onset of symptoms.

EXCLUSION CRITERIA:

- Age > 80 years
- Previous history of stroke
- Head injury
- Intracerebral bleed or hemorrhagic stroke
- Renal disorders
- H/o seizure
- Anemia (hemoglobin < 10gm %)
- Severe COPD with corpulmonale
- Patients with any evidence of heart failure, left ventricular systolic or diastolic dysfunction, myocardial infarction and acute coronary syndromes, hypertensive heart disease, hypertrophic cardiomyopathy, dilated cardiomyopathy, Atrial fibrillation and other arrhythmias, Valvular and other structural heart disease.
- Sepsis

- Pregnant females

METHOD OF COLLECTION OF DATA

All patients with features suggestive of acute ischemic stroke presenting within 24 hours of onset to outpatient and inpatient department of General Medicine department, R.L Jalappa Hospital and research centre, Tamaka , Kolar were screened and patients who met the inclusion and exclusion criteria were recruited and followed up for three months.

Written and Informed consent were taken from all patients or responsible next of kin patient attendant. Acute ischemic stroke was diagnosed clinically and CT Brain or MRI Brain was done to confirm the diagnosis and rule out hemorrhagic stroke

Detailed history was taken and a thorough clinical examination including detailed neurological examination was done in all patients and data collected were entered into the proforma. Signs of atherosclerosis like xanthelasma, arcus senalis, thickened vessels and History of risk factors for stroke like hypertension, diabetes, smoking, alcohol and tobacco chewing were obtained. Patients with history of cardiac disorders, seizure, renal and liver diseases were excluded from the study. Based on history and examination patients were also classified into groups according to Oxfordshire community stroke project classification as total anterior circulation stroke, partial anterior circulation stroke, lacunar stroke and posterior circulation stroke.

Venous blood was collected in EDTA vacutainers for hemotological and in clot activated vacutainers for biochemical analysis. Routine investigations like complete blood count, blood urea, serum creatinine, serum electrolytes, random blood sugar,

fasting and post prandial sugars, glycated Hba1c and lipid profile were done in all patients by using standard techniques. A RBS value of >200mg/dl with symptoms, FBS of > 126mg/dl, PPBS of >200 mg/dl or HbA1c of > 6.5 % was considered as diabetic. Patients with blood urea > 60mg/dl, serum creatinine > 1.5mg/dl and haemoglobin < 10 gm% were excluded from the study. Patients with serum cholesterol > 200mg/dl, LDL > 130mg/dl , triglyceride > 150mg/dl and HDL cholesterol < 40mg/dl were considered dyslipidemic.

All patients underwent standard 12 lead Electrocardiogram and standard 2D echocardiography and patients who had structural or valvular changes, ischemic changes, arrhythmias or atrial fibrillation were excluded from the study. Chest x ray was done in all patients. Carotid Doppler was done in 53 patients and patients were classified based on stenosis into low grade (1-49%), moderate grade (50-69%) and high grade (70-99%). None of the patients presented within window period and all patients received standard medical therapy.

Stroke deficit was calculated by National institutes of health stroke scale (NIHSS) on the day of admission, at 7th day on the day of discharge and at end of one and 3rd month. Patients were classified into groups based on NIHSS score.

GROUP	NIHSS SCORE	DESCRIPTION
1	0	NO STROKE
2	1-4	MINOR STROKE
3	5-15	MODERATE STROKE
4	16-20	MODERATE/SEVERE STROKE

5	21-42	SEVERE STROKE

TABLE 3: NIHSS GROUP

Stroke disability and functional outcome was measured using Barthel Index (BI) on 7th day, at time of discharge and at end of 1 months and 3 months following stroke. They were classified into group based on BI scores.

GROUP	BARTHEL INDEX	DESCRIPTION
1	<40	DEPENDENT
2	40-85	SLIGHTLY INDEPENDENT
3	>85	INDEPENDENT

TABLE 4: BARTHEL INDEX GROUP

2ml of venous blood sample was collected in EDTA vacutainers from all the patients at time of presentation and 7 days after stroke. Blood was immediately centrifuged and serum sample was stored in EDTA vacutainers at -20^0 Celsius and serum assay of NTproBNP was carried out by NTpro BNP fast test kit using AGAPPE - MISPA REVO immunofluorscence quantitative analyser by fluorescence immunochromatography.

Principle of test- The test uses anti- human NTproBNP monoclonal antibody conjugated with fluorescence latex and an anti human NTproBNP polyclonal antibody coated on test line.

Total duration of assay is 10 minutes and measuring range <100-35000 pg/ml and for heart failure value < 300 pg/dl is considered normal based on 97.5th percentile concentration in normal individuals.

FIGURE 10: MISPA REVO IMMUNOFLUORESCENCE QUANTITATIVE ANALYSER

STATISTICAL ANALYSIS

Data which was collected on predesigned Proforma was entered into Microsoft Excel software and analysed by SSPS (statistical package of social sciences) software version 20. Descriptive statistics were performed by computing frequencies and Quantitative variables were expressed as mean± standard deviation. Correlation of NIHSS, NTproBNP and Barthel index was studied using spearman correlation coefficient. Chi square tests, independent sample t test and one way analysis of variance (ANOVA) were used when necessary. Receiver operating characteristic (ROC) was used to get optimal cut off values for NTproBNP and NIHSS for predicting mortality and functional outcome. A P value of less than 0.05 was considered as significant.

CT BRAIN IMAGES:

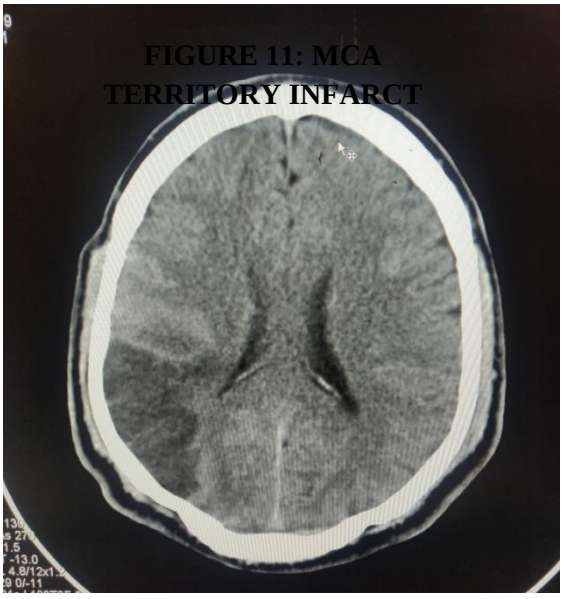


FIGURE 11: MCA TERRITORY INFARCT

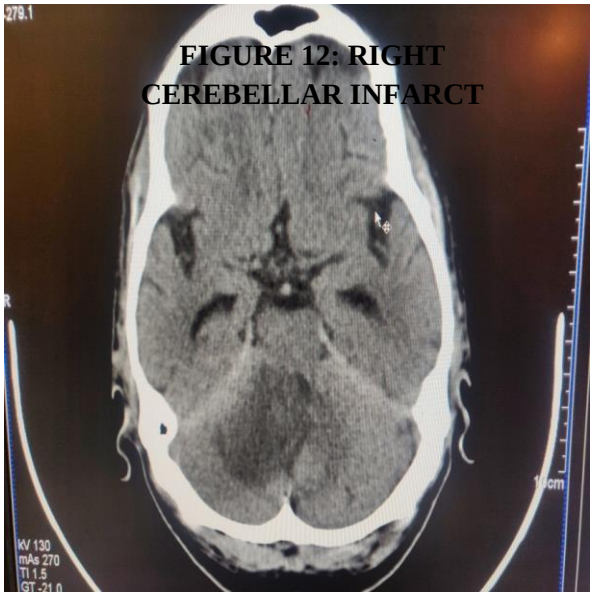


FIGURE 12: RIGHT CEREBELLAR INFARCT

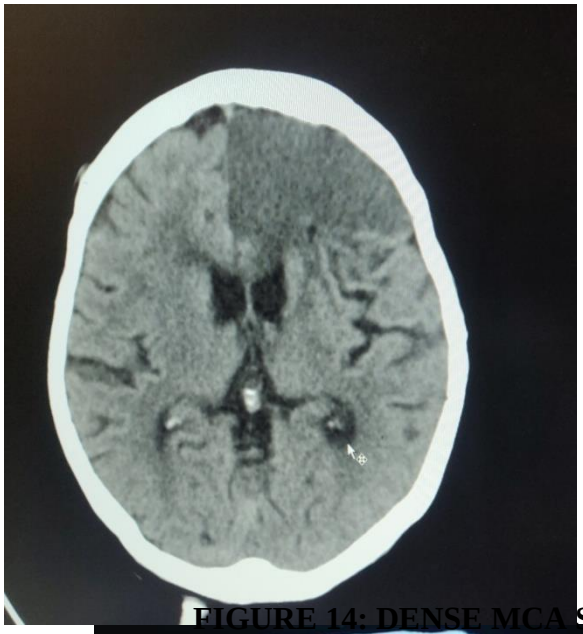
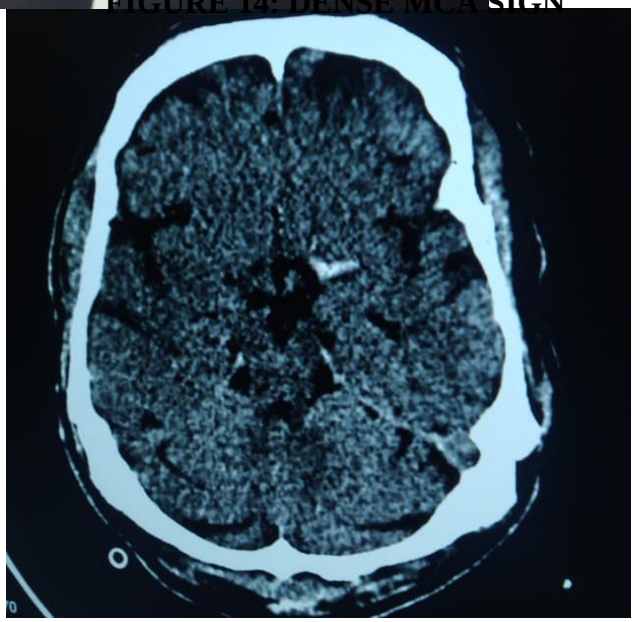


FIGURE 14: DENSE MCA SIGN

13: ACA
INFARCT



RESULTS

During the study period 75 patients with acute ischemic stroke were recruited and 11 patients were lost to follow up and total 64 patients were included in the study.

AGE DISTRIBUTION

Study subjects were in the age group of 18-80 years with average age of 62.36±12.15 years. The youngest was 40 years and eldest was 80 years old. 54.7% of cases were in between 61-80 years. None of the cases were less than 40 years in our study. The average age in males was 61.10±11.89 years and females were 64.32±12.54 years. Even though females were older it was not significant statistically (P value 0.305).

AGE GROUP (YEARS)	FREQUENCY	PERCENTAGE
18-39	0	0
40-60	29	45.3
61-80	35	54.7
TOTAL	64	100

TABLE 5: AGE GROUP DISTRIBUTION

SEX DISTRIBUTION

Among the 64 patients studied 39 (61%) were Male and 25 (39%) were Female. Ischemic stroke was more common in males compared to females.

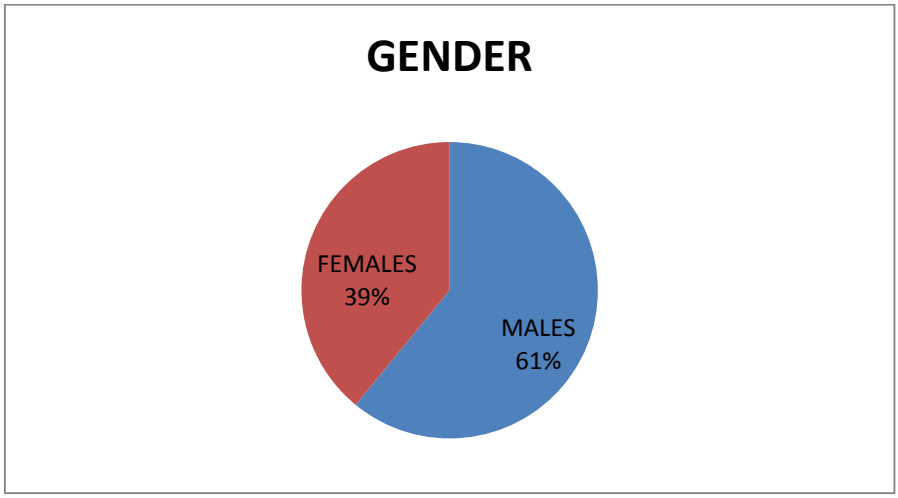


FIGURE 15: PIE CHART REPRESTING GENDER DISTRIBUTION

CLINICAL FEATURES

In this study, the most common presenting complaint was acute onset weakness of one half of the body (hemipaeresis) or a single limb (monopaeresis) in 40 patients (62.5%) followed by loss of consciousness in 14 patients (21.8%), giddiness in 10 patients (15.62%) speech disturbance in 14 patients (35.9% - slurring of speech in 9 patients (14.06%) and loss of speech in 5 (7.8%)), vomiting in 8(12.5%), altered sensorium in 5 patients (7.8%), headache in 4 (6.25%) patients, deviation of angle of mouth in 3(4.68%) and sensory disturbance in 1 (1.5%)patient.

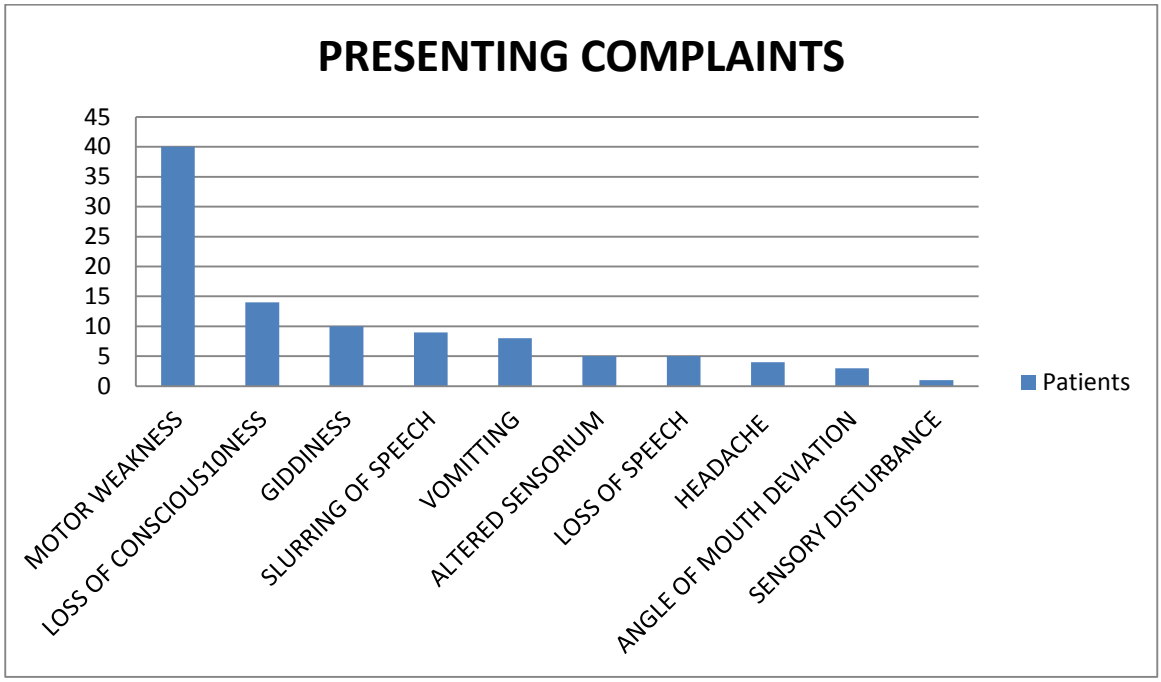


FIGURE 16: BAR GRAPH REPRESENTING PRESENTING COMPLAINTS

RISK FACTORS

In the study 34 patients (53.1%) were hypertensive, 36 patients (56.3%) were diabetic, 26 (40.6%) patients were dyslipidemic, 26 (40.6%) patients were smoker, 8 (12.5%) were alcoholic and 4 (6.3%) patients had history of tobacco chewing.

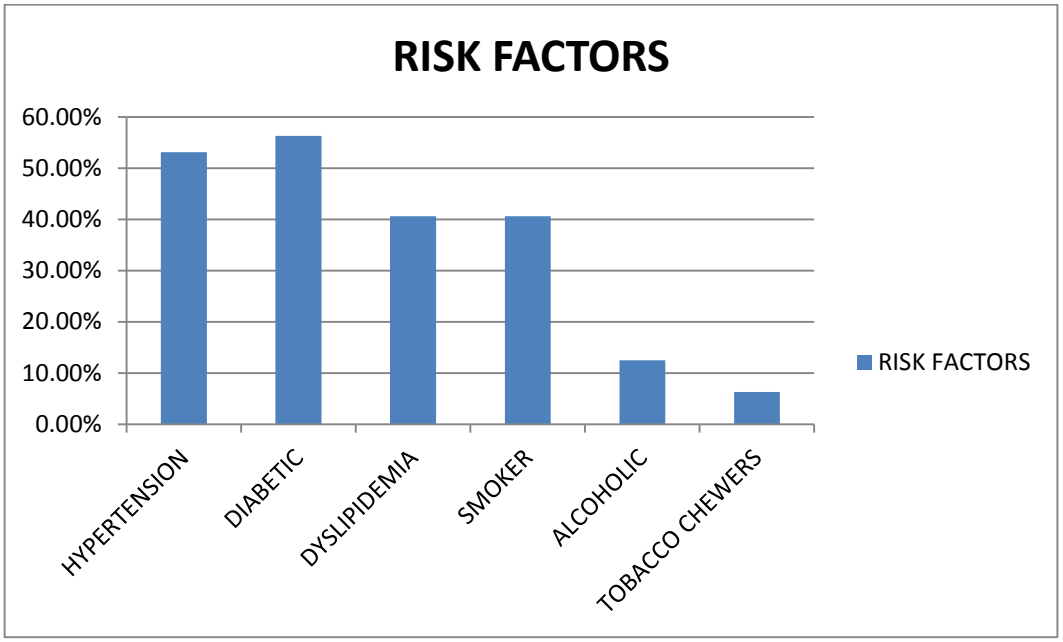


FIGURE 17: BAR GRAPH REPRESENTING RISK FACTORS

In our study, out of 64 patients 34 (53.1%) had signs of atherosclerosis like thickened peripheral vessels and arcus senalis. 2 patients had clubbing .The average duration of hospital stay was 8.11±5.17 days. The average GRBS at presentation was 178mg/dl, average systolic blood pressure was 145.94±27.06 mmHg and diastolic blood pressure was 86.56±12.11 mmHg. The average pulse rate was 90.34±12.04 beats/min and respiratory rate was 19.06±3.5 cycles/minute and saturation at room air was 95.45±2.36 %. All patients were afebrile at presentation.

VITALS	MEAN	SD
PULSE	90.34	12.045
SBP	145.94	27.064
DBP	86.56	12.113
TEMPERATURE	97.64	.651
RR	19.06	3.598
SPO2	95.45	2.363
GRBS	178.00	99.661
GCS	12.13	3.832

TABLE 6: VITALS

Cardiovascular, respiratory and abdominal system examinations were normal. The average Glasgow coma scale at presentation was 12.13±3.832. 12 patients had a GCS score of <8(severe altered sensorium), 12 patients scored in between 9-12(Moderate altered sensorium) and 40 patients had GCS of >13 (mild altered sensorium).

GCS	PERCENTAGE	NO OF PATIENTS
MILD (>13)	62.5%	40
MODERATE (9-12)	18.75 %	12
SEVERE (<8)	18.75%	12
TOTAL	100%	64

TABLE 7: GCS CLASSIFICAION

28 patients were either unconscious, drowsy or had altered sensorium at time of presentation. 2 patients had aphasia on examination. 17 patients had upper motor

neuron facial nerve palsy. 7 patients had conjugate gaze palsy. 4 patients had nystagmus. Dysarthria was present in one patient and one patient had hemianopia. 29 patients were hemiplegic and 20 had hemipaeresis or mono paeresis. Power could not be assessed in 10 patients. 9 patients had spasticity, 3 patients had hypotonia and the rest of patients had normal tone. 2 patients had sensory disturbance, 11 patients had cerebellar dysfunction like impaired dysdiodokinesia, impaired finger-finger or finger nose test and impaired knee heel or tandem walking and in 20 patients sensory examination and cerebellar examination could not be completed because of altered sensorium.

All patients had normal 12 lead ECG with No ST T changes or arrhythmias. 2D echocardiography and chest x ray were normal in all patients. Hematological and biochemical laboratory tests were done and mean and standard deviation calculated. 4 Patients had hyperkalemia and 27 patients had hyponatremia. Patients with deranged renal function and low haemoglobin were excluded from the study.

BIOCHEMICAL PARAMETERS	MEAN	SD
HB (gm%)	13.42	1.956
PCV (%)	39.19	5.904
MCV (fl)	81.20	7.769
TOTAL COUNTS(Thousand/mm^3)	13.42	5.270
PLATELETS (Thousand/mm^3)	268.77	93.188
BLOOD UREA (mg/dl)	31.09	10.194
SERUM CREATININE (mg/dl)	0.83	0.380
SODIUM (meq/L)	134.70	5.436

POTASSIUM (meq/L)	4.11	0.911
RBS (mg/dl)	153.20	86.015
FBS (mg/dl)	155.23	102.447
PPBS (mg/dl)	196.64	101.526
HBA1C	8.28	2.989
SERUM CHOLESTEROL (mg/dl)	183.09	43.338
TRI GLYCERIDES(mg/dl)	138.08	53.799
HDL CHOLESTROL(mg/dl)	41.30	10.191
LDL CHOLESTEROL(mg/dl)	112.30	38.155

TABLE 8: BIOCHEMICAL PARAMETERS

Carotid Doppler was done in 53 patients. 16 patients had normal study. Atherosclerotic changes were present in rest of the patients. 2 patients had atherosclerotic changes of vertebral artery. Increased intimal thickness was seen in 29 patients. 11 patients had plaques in internal carotid artery. Patients were grouped into low, moderate or high grade based on percentage of stenosis.

GRADE	STENOSIS	NUMBER OF PATIENTS
LOW	<50%	19
MODERATE	50-69%	6
HIGH	>70%	12

TABLE 9: CAROTID DOPPLER CLASSIFICATION

CT or MRI brain was done in all patients to confirm the diagnosis of stroke and rule out hemorrhagic stroke. Lacunar strokes were present in 2 patients. 12 patients had cerebellar involvement, 3 patients had hyperdense MCA. Imaging showed involvement of middle cerebral arteries (MCA) in 47 (73.4%), posterior cerebral arteries (PCA) in 13(20.3%), anterior cerebral arteries (ACA) in 11(17.2%), posterior inferior cerebellar artery (PICA) in 3 (4.7%) and vertebral artery (VA) in 1 (1.6%) 112Patient.

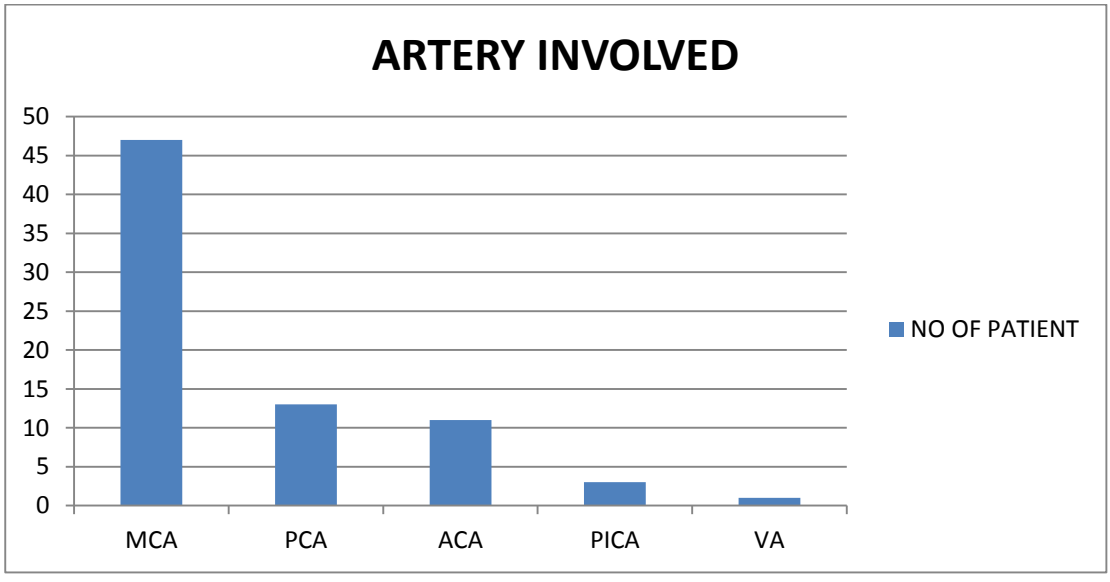


FIGURE 18: BAR GRAPH REPRESENTING ARTERIAL TERRITORY INVOLVED

Patients were also classified as per Oxfordshire Community Stroke Project(OCSP). Total Anterior Circulation Infarcts (TACI) were seen in 20 (31.3%) patients, 26 (40.6%) had Partial Anterior Circulation Infarcts (PACI), Posterior Circulation Infarct (POCI) was seen in 11 (17.2%) and Lacunar syndromes (LS) in 7 (10.9%) patients.

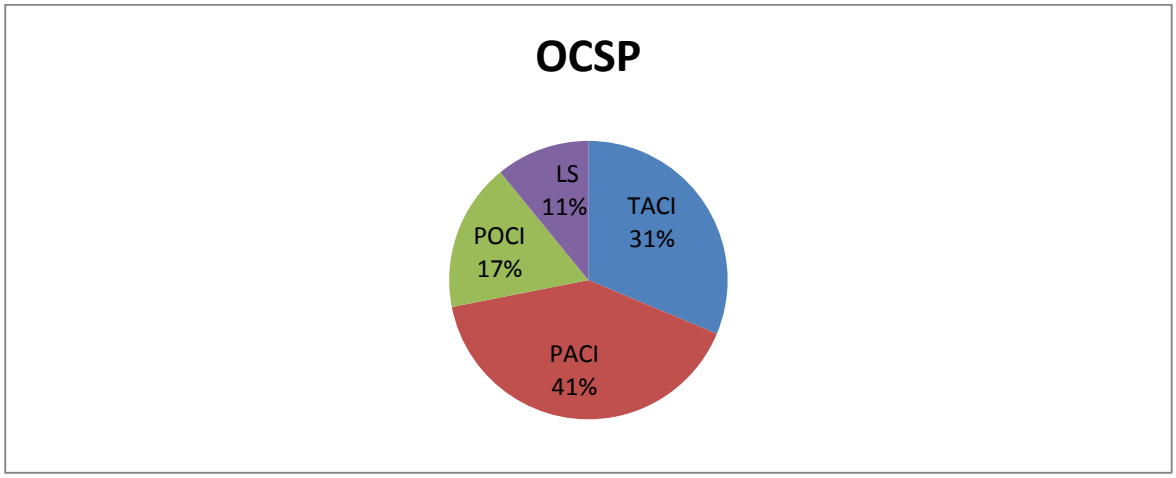


FIGURE 19: PIE CHART REPRESENTING OCSP CLASSIFICATION

STROKE	FREQUENCY	PERCENTAGE
TACI	20	31.3
PACI	26	40.6
POCI	11	17.2
LACUNAR INFARCTS	7	10.9
TOTAL	64	100

TABLE 10: OSCP STROKE CLASSIFICATION

Average NIHSS measured on the day of admission was 12.81±7, on day 7 was 11.07±6, at the time of discharge was 10.55±5.7, at end of 1st month was 8.84±5.47 and NIHSS was 7.21±5.09 at 3rd month after stroke. The highest value of NIHSS on day of admission was 30 and lowest was 2.

NIHSS SCORE AT ADMISSION	NO OF PATIENTS	PERCENTAGE
0	0	0
1-4	9	14.06
5-15	34	53.12
16-20	13	20.3
21-42	8	12.5

TABLE 11: NIHSS SCORE AT ADMISSION

The average NIHSS score at admission in males was 13.92±6.99 and in females 11.08±6.79. Gender and NIHSS was correlated and there was no significance (P value 0.075)

GENDER * NIHSS at admission								
		NIHSS_GROUP				Total		
		1 – 4	5 - 15	15 – 20	21 – 42		Chi square value	P value
GENDER	F	2	18	2	3	25	6.89	0.075
	M	7	16	11	5	39		
Total		9	34	13	8	64		

TABLE 12: GENDER AND NIHSS CROSS TABULATION

NIHSS and age was cross tabulated and there was no significance (P value 0.57)

AGE GROUP * NIHSS at admission								
		NIHSS_GROUP				Total		
		1 – 4	5 – 15	15 – 20	21 - 42		Chi square	P value
AGE GROUP	40 to 60	5	17	4	3	29	1.98	0.57
	60 to 80	4	17	9	5	35		
Total		9	34	13	8	64		

TABLE 13: AGE GROUP AND NIHSS CROSS TABULATION

NIHSS values on day of admission were correlated with stroke subtypes according to OCSP. It was highest in total anterior circulation stroke 19.95±5 and lowest in Posterior circulation infarct 3.64±1.69 which was statistically significant (F value 50.994, P value <0.001).

OCSP	Frequency	NIHSS at Day 0	
		Mean	Standard deviation
TACI	20	19.95	5
PACI	26	12.88	3.5
LS	7	6.57	3.15
POCI	11	3.64	1.69

TABLE 14: OCSP CLASSIFICATION AND NIHSS AT ADMISSION

Average NTproBNP measured on the day of admission was 776.70±1023.6 pg/ml and at day 7 was 223.53±268.39 pg/ml. Paired sample t test was done between the 2 values and there was statistically significant difference in the mean value of NTproBNP at time of admission and at Day 7 (p value <0.001). Suggesting that there is significant decrease of NTproBNP values on day 7 compared to admission value.

		Mean difference	t value	P value
NTproBNP	NTproBNP at D0	495.48	6.09	<0.001
	NTproBNP at D7			

TABLE 15: NTproBNP ON ADMISSION AND AT DAY 7

NTproBNP values on day of admission were correlated with stroke subtypes according to OCSP. It was highest in total anterior circulation stroke 1650.40±1406.38 pg/ml and lowest in lacunar strokes 184.86±162.349 pg/ml. It was statistically significant (F value 10.71, P value <0.001).

OCSP	Frequency	Mean	Standard Deviation
TACI	20	1650.40	1406.384
PACI	26	492.00	390.554
LS	7	184.86	162.349
POCI	11	237.73	379.346

TABLE 16: OCSP CLASSIFICATION AND NTproBNP ON ADMISSION

The highest NTproBNP value on day of admission was 5520 pg/ml and the lowest was 50pg/ml. The highest value on day 7 was 957pg/ml and lowest 50pg/ml. The average NTproBNP on day of admission in males was 891.28±966.84 pg/ml and in females 597.96±1103.7 pg/ml which was not significant statistically (p value 0.26). Average NTproBNP between age 40-60 was 657.76±798.5 pg/ml and between 61-80 years was 875.26±1180.4 pg/ml which was not significant statistically (p value 0.40). There was no co relation between age and NTproBNP in our study r^2 0.136 and p value 0.2809.

Average Barthel Index (BI) measured on the day of admission was 19.21±33.04, on day 7 was 29±33.61, at the time of discharge was 31.78±32.77, at end of 1st month was 44.80±33.37 and was 59.68±28.86 at 3rd month after stroke. The highest value of barthel index at end of 3rd month was 100 and lowest was 5. Many patients had 0 Barthel index at time of admission because of floor effect and as patient were bed ridden.

BARTHEL INDEX	FREQUENCY	PERCENTAGE
<40	10	21.28
40-85	24	51.06
>85	13	27.66
Total	47	100

TABLE 17: BARTHEL INDEX AT 3 MONTHS

The average BI score at 3 months in males was 52.59±32.05 and in females 69.25±21.04 which was statistically significant with p value 0.04. Gender and BI was correlated and there was significance (P value 0.05) suggesting that females had better outcome following stroke.

GENDER * Barthel_Index at 3 months							
		Barthel_group			Total		
		<40	>85	40 - 85		Chi square	P value
GENDER	F	1	6	13	20	5.78	0.05
	M	9	7	11	27		
Total		10	13	24	47		

TABLE 18: GENDER AND BI CROSS TABULATION

BI and age was cross tabulated and there was no significance (P value 0.89)

AGE GROUP * Barthel Index at 3 months							
		Barthel_group			Total		
		<40	>85	40 to 85		Chi square	P value
AGE GROUP	40 to 60	5	7	11	23	0.22	0.89
	60 to 80	5	6	13	24		
Total		10	13	24	47		

TABLE 19: AGE GROUP AND BI CROSS TABULATION

Barthel Index values on day of admission were correlated with stroke subtypes according to OCSP. It was highest in posterior circulation infarct 90.5±13 and lowest in total anterior circulation infarct 21.25±20.13. It was statistically significant (F value 25.774, P value <0.001).

OSCP	Frequency	BI at 3 months	
		Mean	Standard deviation
TACI	8	21.25	20.13
PACI	22	53.64	18.33
LS	7	78.57	19.30
POCI	10	90.5	13

TABLE 20: OCSP CLASSIFICATION AND BI AT 3 MONTHS

There were 17 deaths in the study. 8 patients died within 7 days of hospitalisation. 5 patients died by the end of one month and 4 died by the end of 3rd month following stroke. 12 males and 5 females died in the study there was no association between death and gender (p value 0.34)

GENDER * Death Cross tabulation						
		Alive	Dead	TOTAL	Chi square	P value
GENDER	F	20	5	25	0.946	0.34
	M	27	12	39		
Total		47	17	64		

TABLE 21: GENDER AND DEATH CROSS TABULATION

Average age of survivors is 61.34±12.046 and non survivors is 65.18±12.286 which was not statistically significant (p value 0.26). 6 patients in age group 40-60 and 11 patients in age group 60-80 died in the study and there was no significant association between death and age in the study (p value 0.33)

AGE GROUP* Death Cross tabulation						
		Alive	Dead	TOTAL	Chi square	P value
AGE GROUP	40 to 60	23	6	29	0.938	0.33
	60 to 80	24	11	35		
Total		47	17	64		

TABLE 22: AGE GROUP AND DEATH CROSS TABULATION

OSCP stroke classification was correlated with death and significant association was found with total anterior circulation infarct and death (p value 0.001). 12 patients of TACI, 4 patients of PACI and 1 patient with posterior circulation infarct died.

OCSP * Death Cross tabulation						
		Alive	Dead	TOTAL	Chi square	P value
OCSP	TACI	8	12	20		
	PACI	22	4	26	17.38	0.001
	LS	7	0	7		
	POCI	10	1	11		
Total		47	17	64		

TABLE 23: OCSP CLASSIFICATION AND DEATH CROSS TABULATION

NTproBNP on admission was correlated with NIHSS on admission and Barthel Index on 3rd month. There was a positive correlation between NIHSS and NTproBNP (R^2=0.443; spearman correlation coefficient=0.843, p value <0.001). suggesting higher the NTproBNP value on day of admission higher the NIHSS score (higher the stroke deficit)

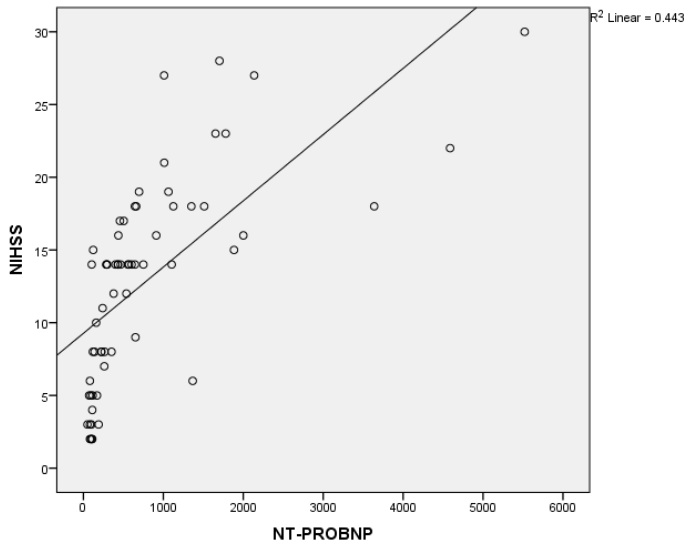


FIGURE 20: SCATTER DIAGRAM SHOWING POSITIVE CORELATION BETWEEN NTproBNP and NIHSS

There was negative correlation between Barthel Index at 3 month and NTproBNP (R^2=0.824; spearman correlation coefficient -0.923, p value <0.001) suggesting higher the NTproBNP value on admission lower the Barthel Index score (more functional disability) at 3 months.

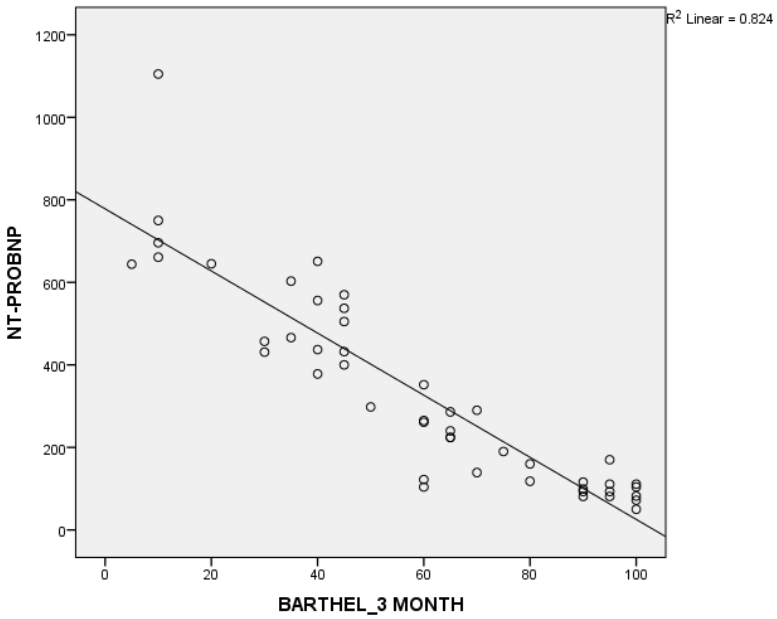


FIGURE 21: SCATTER DIAGRAM SHOWING NEGATIVE CORELATION BETWEEN NTproBNP AND BARTHEL INDEX

There was no statistically significant correlation between NTproBNP at day 7 and Barthel index at 3 months.

There was negative correlation between Barthel Index at 3 month and NIHSS at admission (R^2=0.770; spearman correlation coefficient -0.86, p value <0.001) suggesting higher the NIHSS value lower the Barthel Index score (more functional disability) at 3 months.

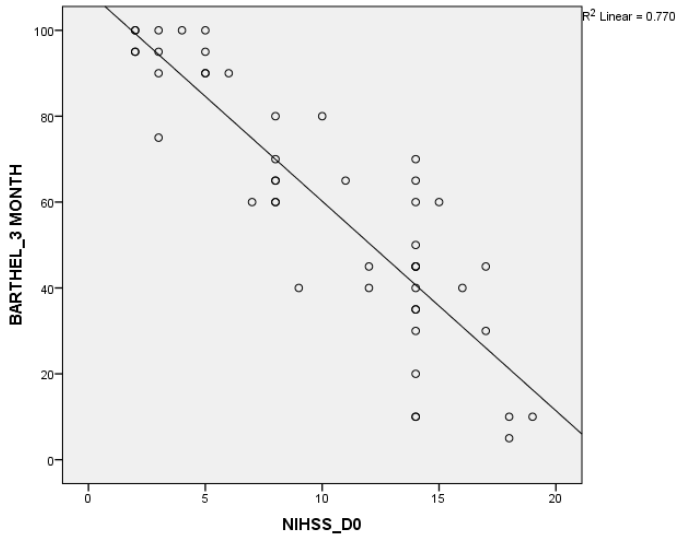


FIGURE 22: SCATTER DIAGRAM SHOWING NEGATIVE CORELATION BETWEEN BI AND NIHSS

Receiver operating characteristic (ROC) of NT PROBNP at Day 0 in predicting death (P value <0.001, area under the curve 0.995, 95% confidence interval 0.984 to 1.000) The cut off value calculated is 960pg/ml with sensitivity = 94.1 % and specificity = 97.9 %

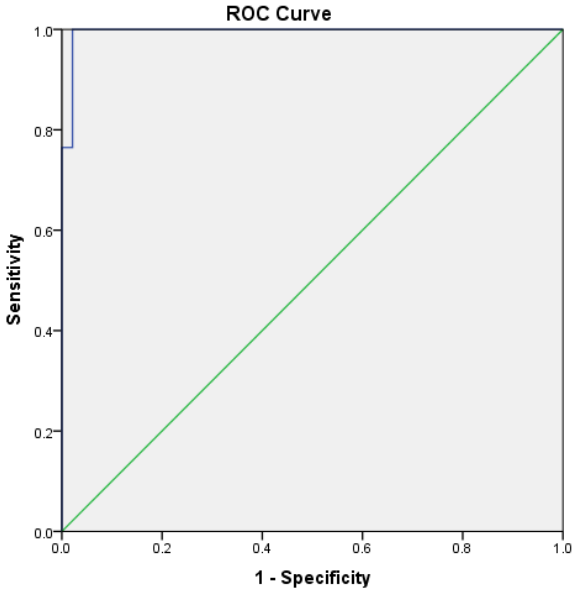


FIGURE 23: ROC CURVE OF NTproBNP IN PREDICTING DEATH

Receiver operating characteristic (ROC) of NT PROBNP at Day 0 in predicting dependency (P value <0.001, area under the curve 0.946, 95% confidence interval 0.884 to 1.000). The cut off value calculated is 431.5 with sensitivity = 90.0 % and specificity = 81 %

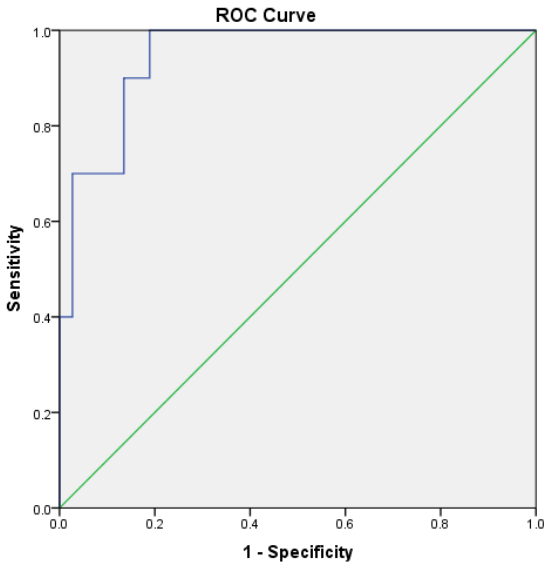


FIGURE 24: ROC CURVE OF NTproBNP IN PREDICTING DEPENDENCY

Receiver operating characteristic (ROC) of NIHSS at Day 0 in predicting death (P value <0.001, area under the curve 0.926, 95% confidence interval 0.841 to 1.000). The cut off value calculated is 14.5 with sensitivity = 94.1% and specificity = 86%

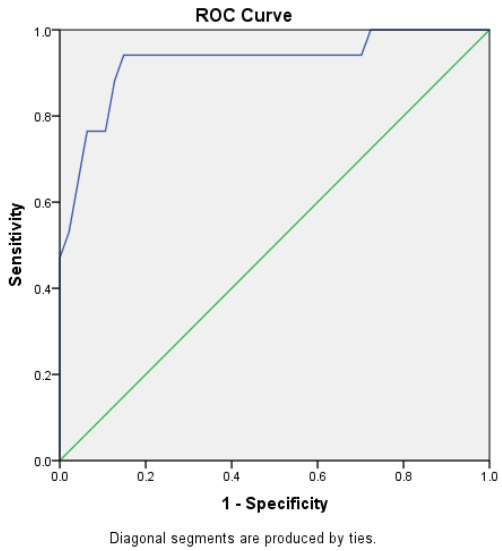


FIGURE 25: ROC CURVE OF NIHSS IN PREDICTING DEATH

Area under the ROC curve above 0.8 indicates fairly good prediction. Area under the ROC curve for both NIHSS and NTproBNP on admission is almost similar with 0.926 and 0.995 suggesting they can predict mortality. The sensitivity for both NIHSS and NTproBNP was 94.1% but NTproBNP had a higher specificity of 97.9% compared to 86% of NIHSS;

Area under the ROC curve for NTproBNP was 0.946 in predicting dependency at 3 months with sensitivity of 90% and specificity of 81% and NIHSS failed to predict dependency hence NTproBNP is better predictor of mortality and functional disability compared to NIHSS.

RISK FACTORS CORRELATION

We correlated sex with NTproBNP and NIHSS on day of admission and Barthel Index at 3rd month and found that there was no significant association between sex and NIHSS and NTproBNP but females had better outcome compared to men at 3rd month (p value 0.04)

	Male		Female		P value
	Mean	SD	Mean	SD	
NIHSS at Day 0	13.92	6.99	11.08	6.79	0.11
NT-PROBNP at Day 0	891.28	966.84	597.96	1103.7	0.26
Barthel index at 3 months	52.59	32.05	69.25	21.04	0.04

TABLE 24: GENDER WITH NTproBNP, NIHSSS and BI CORRELATION

We correlated age with NTproBNP and NIHSS on day of admission and Barthel Index at 3rd month and found that there was no significant association between age and NIHSS , NTproBNP and Barthel index.

	Age group – 40 to 60		Age group 61 to 80		P value
	Mean	SD	Mean	SD	
NIHSS at Day 0	12.1	7.07	13.4	6.9	0.46
NT-PROBNP at Day 0	657.76	798.5	875.26	1180.4	0.40
Barthel index at 3 months	61.96	29.2	57.5	28.9	0.60

TABLE 25: AGE WITH NTproBNP, NIHSSS and BI CORRELATION

We correlated hypertension and normotensive with NTproBNP and NIHSS on day of admission and Barthel Index at 3rd month and found that there was no significant association.

	Hypertension		Normotensive		P value
	Mean	SD	Mean	SD	
NIHSS at Day 0	11.68	7.08	14.1	6.8	0.16
NT-PROBNP at Day 0	593.41	750	984.43	1245.7	0.12
Barthel index at 3 months	63.7	26.7	54.25	31.34	0.27

TABLE 26: HYPERTENSION WITH NTproBNP, NIHSSS and BI CORRELATION

We correlated diabetics and non diabetics with NTproBNP and NIHSS on day of admission and Barthel Index at 3rd month and found that there was no significant association.

	Diabetic		Non diabetic		P value
	Mean	SD	Mean	SD	
NIHSS at Day 0	12.64	7.04	13.04	7.06	0.22
NT-PROBNP at Day 0	579.56	550.64	1030.18	1390.13	0.08
Barthel index at 3 months	57.5	28.96	62.89	29.59	0.53

TABLE 27: DIABETES WITH NTproBNP, NIHSSS and BI CORRELATION

We correlated smokers and non smokers with NTproBNP and NIHSS on day of admission and Barthel Index at 3rd month and found that there was significant association between non smokers and Barthel index (P value <0.001) suggesting non smokers had a better outcome than smokers.

	Smoker		Non smoker		P value
	Mean	SD	Mean	SD	
NIHSS at Day 0	15.73	5.9	10.82	7.09	0.005
NT-PROBNP at Day 0	1009.65	807.16	617.32	1131.3	0.13
Barthel index at 3 months	40.94	23.89	69.35	26.6	0.001

TABLE 28: SMOKING WITH NTproBNP, NIHSSS and BI CORRELATION

We correlated alcoholics and non alcoholics with NTproBNP and NIHSS on day of admission and Barthel Index at 3rd month and found that there was no significant association.

	Alcoholic		Non alcoholic		P value
	Mean	SD	Mean	SD	
NIHSS at Day 0	14.63	7.24	12.55	6.93	0.43
NT-PROBNP at Day 0	664.75	494.30	792.7	1080.3	0.74
Barthel index at 3 months	48.33	30.76	61.34	28.59	0.30

TABLE 29: ALCOHOL WITH NTproBNP, NIHSSS and BI CORRELATION

We correlated dislipidemics and normal with NTproBNP and NIHSS on day of admission and Barthel Index at 3rd month and found that there was no significant association.

	Dyslipidemia		NO Dyslipidemia		P value
	Mean	SD	Mean	SD	
NIHSS at Day 0	13.58	8.1	12.29	6.19	0.47
NT-PROBNP at Day 0	869.58	1111.86	713.16	968.24	0.55
Barthel index at 3 months	64.38	30.32	57.26	28.28	0.42

TABLE 30: DYSLIPIDEMIA WITH NTproBNP, NIHSSS and BI CORRELATION

We correlated admission Blood Pressure, GRBS , HbA1C and GCS with NTproBNP and NIHSS on day of admission and Barthel Index at 3rd month. There was significant association only with GCS .

		Spearman Correlation Co-efficient	P value
GRBS	NT-PROBNP at Day 0	0.058	0.64
	NIHSS score at Day 0	0.103	0.48
	Barthel Index at 3 months	-0.308	0.035

TABLE 31: GRBS WITH NTproBNP, NIHSSS and BI CORRELATION

SYSTOLIC BLOOD PRESSURE

		Spearman Correlation Co-efficient	P value
SBP	NT-PROBNP at Day 0	-0.049	0.70
	NIHSS score at Day 0	-0.145	0.25
	Barthel Index at 3 months	0.125	0.40

TABLE 32: SBP WITH NTproBNP, NIHSSS and BI CORRELATION

DIASTOLIC BLOOD PRESSURE

		Spearman Correlation Co-efficient	P value
DBP	NT-PROBNP at Day 0	-0.046	0.71
	NIHSS score at Day 0	-0.17	0.17
	Barthel Index at 3 months	0.12	0.41

TABLE 33: DBP WITH NTproBNP, NIHSSS and BI CORRELATION

HbA1C

		Spearman Correlation Co-efficient	P value
HbA1C	NT-PROBNP at Day 0	-0.076	0.54
	NIHSS score at Day 0	-0.032	0.8
	Barthel Index at 3 months	0.006	0.96

TABLE 34: HbA1C WITH NTproBNP, NIHSSS and BI CORRELATION

There was significant association between GCS on presentation and NTproBNP and NIHSS on day of admission and Barthel Index at 3rd month

		Spearman Correlation Co-efficient	P value
GCS	NT-PROBNP at Day 0	-0.695	<0.001
	NIHSS score at Day 0	-0.76	<0.001
	Barthel Index at 3 months	0.464	<0.001

TABLE 35: GCS WITH NTproBNP, NIHSSS and BI CORRELATION

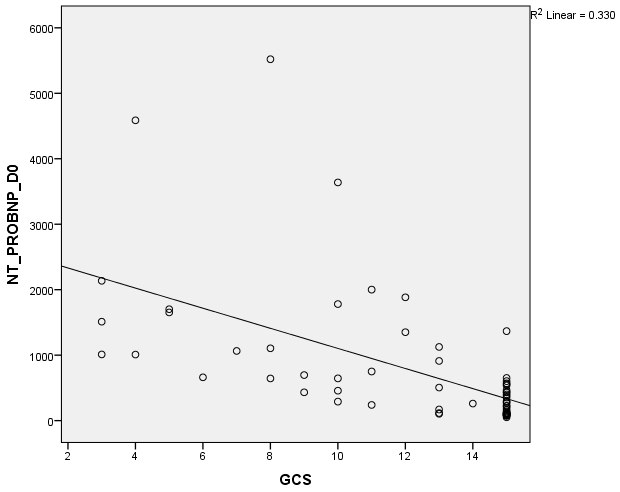


FIGURE 26: SCATTER DIAGRAM SHOWING NEGATIVE CORELATION BETWEEN NTproBNP and GCS

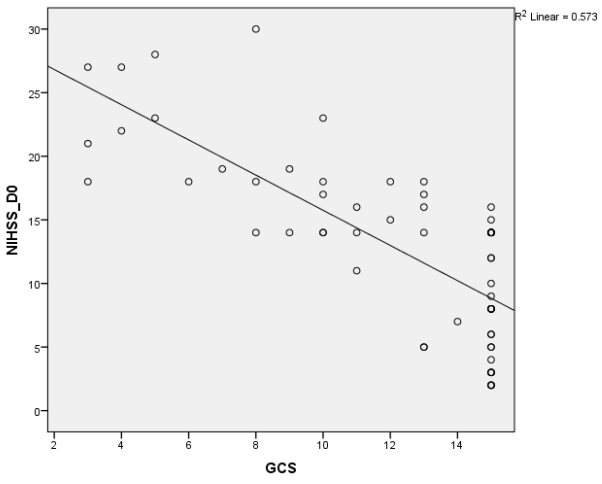


FIGURE 27: SCATTER DIAGRAM SHOWING NEGATIVE CORELATION BETWEEN NIHSS and GCS

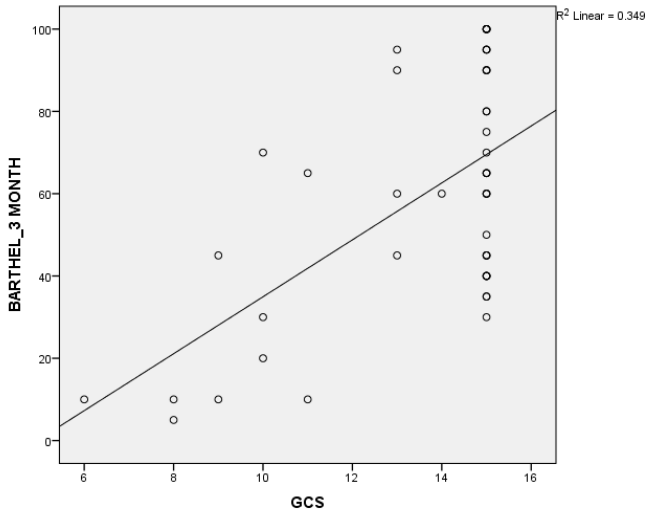


FIGURE 28: SCATTER DIAGRAM SHOWING POSITIVE CORELATION BETWEEN BI and GCS

We compared clinical and laboratory parameters among alive and dead patients. There was significant relationship between death and GCS, NIHSS and NTproBNP on day of admission and NTproBNP at day 7 p value < 0.001

CLINICAL AND LABORAT0RY PATAMETERS					
	status	N	Mean	SD	P value
SBP	Alive	47	145.11	28.120	0.68
	Dead	17	148.24	24.555	
DBP	Alive	47	86.60	13.396	0.97
	Dead	17	86.47	7.859	
GRBS	Alive	47	182.64	100.266	0.54
	Dead	17	165.18	99.836	
HBA1C	Alive	47	8.36	2.900	0.72
	Dead	17	8.06	3.307	

GCS	Alive	47	13.57	2.465	<0.001
	Dead	17	8.12	4.136	
RBS	Alive	47	159.19	91.406	0.35
	Dead	17	136.65	68.664	
FBS	Alive	47	155.72	89.329	0.95
	Dead	17	153.88	135.578	
PPBS	Alive	47	195.34	97.657	0.86
	Dead	17	200.24	114.667	
SERUM CHOLESTEROL	Alive	47	178.02	38.190	0.12
	Dead	17	197.12	54.015	
TG	Alive	47	130.74	51.570	0.069
	Dead	17	158.35	56.176	
HDL	Alive	47	41.30	10.089	0.99
	Dead	17	41.29	10.786	
LDL	Alive	47	108.72	33.585	0.21
	Dead	17	122.18	48.458	
NIHSS_D0	Alive	47	10.11	5.189	<0.001
	Dead	17	20.29	5.882	
NT_PROBNP_D0	Alive	47	328.94	239.353	<0.001
	Dead	17	2014.65	1320.546	
NT_PROBNP_D7	Alive	47	287.64	223.5	<0.001
	Dead	9	794.58	852.62	

TABLE 36: COMPARISION OF CLINICAL AND LABORATORY PARAMETERS AMONG ALIVE AND DEAD PATIENTS.

DISCUSSION

Presently as there are no validated biomarkers to predict prognosis of stroke, we examined the easily available, cheap and rapidly measurable NTproBNP as a prognostic indicator in acute ischemic stroke.

All patients with history suggestive of stroke who presented to R.L.Jalappa hospital and research centre-- were screened and 75 patients who met inclusion and exclusion criteria were recruited and followed up for 3 months. 11 patients were loss to follow up and a total of 64 patients were studied.

Mean age of presentation was 62.36±12.15 years and 61% were males and 39% were females in our study and 54% were aged between 60-80 years. The average age in males was 61.10±11.89 years and females were 64.32±12.54 years similar to study by Dey et al where average age in male patients was 62±13.92 years and in female 64.38±17.53 years (153). Stroke incidence was more common in age group 60-80 years and more common in males compared to females and females had late presentation compared to males.

	PRESENT STUDY	CHEN ET AL(150)	NAVEEN ET AL(151)
AGE	62.36±12.15	71.5±9.8 years	54±13.5 years
MALES	61 %	56.6 %	66.2%
FEMALES	39%	43.4%	33.8%

TABLE 37: AGE AND GENDER COMPARISON

There was no statistical significance between age and sex with mortality, NIHSS score and NTproBNP. There was no co relation between age and NTproBNP in our study (r^2 0.136 and p value 0.2809), similar to study by Naveen et al but Menon et al found a positive relation between BNP and age in their study (124,151). There was a significant relationship between gender and outcome in our study females had better Barthel Index at 3rd month (p value 0.04) compared to males.

Acute onset motor weakness was the commonest presenting feature in our study and clinical features were compared to prevalence study done by Yew and Cheng.

CLINICAL FEATURES	PRESENT STUDY	YEW AND CHENG ET AL (154)
MOTOR WEAKNESS	62.5%	63% IN ARMS+ 54% IN LEGS
LOSS OF CONSCIOUSNESS	21.8%	-
SPEECH DISTURBANCE	35.9%	55%
VOMITTING	12.5%	-
ALTERED SENSORIUM	7.8%	-
HEADACHE	6.25%	14%
FACIAL WEAKNESS	4.08%	23%
SENSORY SYMPTOMS	1.5%	20% IN ARMS+17% IN LEGS
GIDDINESS	15.62%	13%
EXAMINATION		
HEMIPLEGIA/HEMIPAERESIS	45.3%	69.61%

DYSARTHRIA	1.5%	5%
FACIAL PALSY	26.5%	45%
GAZE PALSY	10.9%	27%
VISUAL DISTURBANCE	1.5%	24%
NYSTAGMUS	6.25%	-

TABLE 38: CLINICAL FEATURES COMPARISON

The most common risk factor for stroke in our study was diabetes (56.3%) compared to studies by Naveen et al and Menon et al where hypertension was most common with 65% and 70% respectively (124,151). 54% were hypertensive in study by Jenson et al similar to present study.

RISK FACTORS	PRESENT STUDY	NAVEEN et al(151)	MENON et al (124)	Jenson et al(149)
DIABETES MELLITUS	56.3%	28%	31%	11%
HYPERTENSION	53.1%	65%	70%	54%
SMOKING	40.6%	46%	44%	52%
DYSLIPIDEMIA	40.6%	29%	-	-
ALCOHOL	12.5%	-	29%	-
TOBACCO CHEWING	6.37%	-	-	-

TABLE 39: RISK FACTORS COMPARISON

We correlated risk factors with NTproBNP, NIHSS at admission and BI at 3rd month and found no significance except that Non smokers had significantly better BI score at 3rd month compared to smokers (p value <0.001), suggesting non smokers having a better functional outcome than smokers. In our study dyslipidemia did not have any significant association with mortality compared to a study by Naveen et al where hyperlipidemia had higher proportion of mortality(151).

Severity of altered sensorium as per GCS at presentation was compared with study by Naveen et al. 62.5% of patients had mild altered sensorium in our study compared to 20% by Naveen et al and in their study 47% had severe altered sensorium where as only 18.75% had severe altered sensorium in our study.

GCS	PRESENT STUDY	NAVEEN et al(151)
MILD (>13)	62.5%	20%
MODERATE (9-12)	18.75 %	33%
SEVERE (<8)	18.75%	47%

TABLE 40: GCS COMPARISON

We correlated GCS with NTproBNP and NIHSS on admission and Barthel Index at 3rd month there was significant (P value <0.001) positive correlation between BI and GCS (spearman coefficient 0.464) and negative correlation between GCS and NTproBNP (spearman coefficient= -0.69) and NIHSS (spearman coefficient =-0.76) this was similar to study by Naveen et al where they found significant correlation between GCS and NTproBNP and NIHSS (p value <0.001)(151) suggesting that low GCS at presentation had high mortality risk and poor outcome.

Average Blood Pressure at admission was systolic blood pressure -145.94±27.06 mmHg and diastolic blood pressure - 86.56±12.11 mmHg and it ranged between 110/70 to 180/110 in study by Menon et al(124) and it was around SBP 160±20 mmHg and DBP 88±15 mmHg in large artery atherosclerosis(LAA) and SBP 155±22 and DBP 88±15 mmHg in small artery occlusion (SAO) in study by Tomita et al. Heart rate on admission was 90.34±12.04 beats/min compared to 74±13 in LAA and 70±14 beats/min in SAO in study conducted by Tomita et al(146). The average GRBS at presentation was 178±99.66 mg/dl. There was no significant association between presenting BP, GRBS with mortality, NTproBNP, NIHSS or Barthel Index.

Stroke was classified based on Oxfordshire community stroke project (OCSP) classification. Partial anterior circulation infarct was the most common in our study compared to lacunar in Jenson et al and Posterior circulation infarct in Menon et al(124,149).

OCSP	PRESENT STUDY	JENSON et al(149)	MENON et al(124)
TACI	31%	37% (TACI+PACI)	35 %
PACI	41%		9 %
LS	11%	50%	12 %
POCI	17%	13%	44 %

TABLE 41: OCSP CLASSIFICATION COMPARISON

Mean NTproBNP was highest in TACI and lowest in Lacunar infarcts which is significant statistically (F value 10.71 , P value <0.001) this was similar to study by

Menon et al where they found BNP levels was more in TACI (F=4.609 , P value 0.005)(124) and lower levels of NTproBNP in lacunar strokes was also found by Gomez-choco et al(155) .

OSCP was correlated with death and significant association was found between total anterior circulation infarct and death (p value 0.001). There was significant correlation between NIHSS values on day of admission and OCSP. It was highest in total anterior circulation stroke 19.95±5 and lowest in Posterior circulation infarct 3.64±1.69 (F value 50.994, P value <0.001).

There was statistically significant association between OSCP and Barthel index at 3rd month

BI was highest in posterior circulation infarct 90.5±13 and lowest in total anterior circulation infarct 21.25±20.13 (F value 25.774, P value <0.001) suggesting that TACI had high stroke deficit and poor prognosis compared to Posterior and lacunar strokes.

Middle cerebral artery was the most common arterial territory involved in our study which is similar to study done by Ebrahim et ai in Iran(156). In our study Carotid Doppler showed normal study in 30.18% patients almost similar to 33% by Menon et al. Atheromatous changes were seen in rest of the patients in our study where as 45 % had atheromatous disease in study done by Menon et al(124).

We compared the biochemical parameters of our study with that done by Menon et al and found to be almost similar. We did not find any significant association between biochemical parameters and outcome following stroke.

	PRESENT STUDY	Menon et al(124)
HB (gm%)	13.42±1.956	12.90±2.11
PCV (%)	39.19±5.904	-
MCV (fl)	81.20±7.769	-
TOTAL COUNTS(Thousand/mm^3)	13.42±5.270	9.49±3.34
PLATELETS (Thousand/mm^3)	268.77±93.188	270±98
BLOOD UREA (mg/dl)	31.09±10.194	-
SERUM CREATININE (mg/dl)	0.83±0.380	1.22±0.30
SODIUM (meq/L)	134.70±5.436	136±5
POTASSIUM (meq/L)	4.11±0.911	3.90±0.51
RBS (mg/dl)	153.20±86.015	-
FBS (mg/dl)	155.23±102.447	105±43
PPBS (mg/dl)	196.64±101.526	139±63
HBA1C	8.28±2.898	-
SERUM CHOLESTEROL (mg/dl)	183.09±43.338	107±46
TRI GLYCERIDES(mg/dl)	138.08±53.799	145±64
HDL CHOLESTROL(mg/dl)	41.30±10.191	41±11
LDL CHOLESTEROL(mg/dl)	112.30±38.155	98±32

TABLE 42: BIOCHEMICAL PARAMETERS COMPARISON

There were 17 (26.5%) death in our study by the end of 3 months. 8 patients (12.5%) died within 7 days of admission compared to 24.3% seen in study by Naveen et al and 18.85% by Chen et al. Our study has low in hospital mortality compared to other

studies. Although age and BP at presentation predicted death in other studies we did not find any association similar to study by Naveen et al(146,149–151).

We compared demographic parameters, clinical and laboratory parameters among survivors and deceased patients and found no significant association between them.

The average NIHSS on day of admission was 12.81±7. 53.12% people were having score of 5-15 suggesting moderate stroke. The average NIHSS score at admission in males was 13.92±6.99 and in females 11.08±6.79. Gender and age with NIHSS was correlated and there was no significance. The average NIHSS on admission was 10±7 in study by Menon et al and 9.78±5.06 by a study by Chen et al. Our study had a higher NIHSS at admission compared to other studies(124,150). In our study NIHSS of patients who survived was 10.11±5.189 and those who died was 20.29±5.882 which was significant statistically p value <0.001. Chen et al found significant association between NIHSS of survivors and deceased but in a similar study in India there was no such association(150,151). In study by Naveen et al only in hospital short term mortality was considered and Chen et al included even cardioembolic strokes in their study.

	PRESENT STUDY	Naveen et al(151)	Chen et al(150)
NIHSS SURVIVORS	10.11±5.189	10.52±3.3	8.69±4.87
NIHSS DECEDENTS	20.29±5.882	15.8±3.3	14.48±2.54
P VALUE	<0.001	0.661	<0.001

TABLE 43: NIHSS SCORE COMPARISON

Median NTproBNP measured on the day of admission was 776.70±1023.6 pg/ml and at day 7 was 223.53±268.39 pg/ml. There was statistically significant decrease in NTproBNP values from admission to day 7(p value <0.001). Garcia-Berrocosso et al in their metanalysis of different studies have found studies using different methods and principles in calculating BNP/NTproBNP values. They concluded that NTproBNP was elevated and associated with mortality after stroke irrespective of NIHSS, age or gender(148).

In study conducted by Chen et al the median NTproBNP was 1,035.50 pg/mL , Jenson et al found the median NTproBNP at 6 months following stroke to be 147 pg/ml similar studies in India have found the NTproBNP levels to be 435±613 ng/ml by Menon et al(124,149,150).

ADMISSION	PRESENT STUDY	Naveen et al(151)	Chen et al(150)
NTproBNP(pg/ml) ALIVE	328.94±239.353	233.5 (145.25-379.5)	926.30
NTproBNP (pg/ml) DEAD	2014.65±1320.546	769(1171-1842)	3280
P VALUE	<0.001	<0.001	<0.001

TABLE 44: NTproBNP COMPARISON

The difference in NTproBNP values between studies may be because only in hospital short term mortality was considered in Naveen et al and Cardiac causes of stroke were

also included in the study by Chen et al and different methods were used to estimate NTproBNP levels between studies.

In the study by Naveen et al they found that NTproBNP levels after 7 days declined in survivors but was elevated in deceased patients(151) in our study we found that NTproBNP was decreased both in survivors and non survivors and was statistically significant.

DAY 7	PRESENT STUDY	Naveen et al(151)
NTproBNP(pg/ml) ALIVE	287.64±223.5	78(60-133.25)
NTproBNP (pg/ml) DEAD	794.58±852.62	1591(1171-1842)
P VALUE	<0.001	<0.001

TABLE 45: DAY 7 NTPproBNP COMPARISON

Chen et al found significant association between gender and NTproBNP levels and Menon et al found association between age and NTproBNP values. There was no correlation between age and NTproBNP levels in study done by Naveen et al similarly we did not find any association between age , gender and NTproBNP levels(124,150,151).

The average Barthel Index(BI) at end of 3 months was 59.68±28.86 which was almost similar to 57±30 found in Menon et al study and in study done by Jenson et al the median BI was 20 at 6 months after stroke(124,149) . 21.28% of patients had BI of less than 40 suggesting complete dependency and 51.06% had score between 40-85

suggesting mild independency and 27.66 patients had > 85 suggesting that they could perform routine tasks without or minimal help.

In our study we found that females and Non smokers had better BI score at end of 3 months when compared to Males and smokers. There was no relationship between age and BI.

We found that NIHSS had a significant negative correlation with Barthel index at 3 months (R^2=0.770, spearman correlation co-efficient = -0.86, p value = <0.001). No such association was found in study by Menon et al(124). NIHSS had a significant association with death, those who died had a significantly high NIHSS levels than in survivors which was similar to study by Chen et al but Naveen et al did not find any such association(150,151). The optimal cut off for NIHSS in predicting death as determined by ROC analysis was 14.5 with sensitivity of 94.1% and specificity of 86% compared to 12.5 (82.6% sensitivity and 77.8% specificity)in the study by Chen et al(150). NIHSS failed to predict functional outcome in our study similar to that by Menon et al(124)

NIHSS	PRESENT STUDY	CHEN ET AL (150)
CUT OFF VALUES	14.5	12.5
SENSITIVITY	94.1%	82.6%
SPECIFICITY	86%	77.8%
ROC AREA	0.926	0.852
95% CONFIDENCE INTEERVAL	0.841-1.000	0.781-0.923

TABLE 46: COMPARISON OF NIHSS IN PREDICTING MORTALITY

We compared NTproBNP levels with NIHSS on day of admission and Barthel Index at 3rd month and found significant positive correlation between NIHSS and NTproBNP (R^2=0.443; spearman correlation coefficient=0.843, p value <0.001) suggesting that high NTproBNP is associated with increased severity of stroke and negative correlation between NTproBNP and Barthel index (R^2=0.824; spearman correlation coefficient -0.923, p value <0.001) suggesting that high NTproBNP had a worse functional outcome.

Similar results were also found in study by Menon et al where they found positive relation between BNP and NIHSS (R^2=2.55 ,p value <0.01) and a negative correlation between BNP and BI (R^2=-0.064 ,p value <0.01)(124). Similar positive correlation between NIHSS and NTproBNP was found in studies done by Naveen et al (0.891) and Chen et al (r=0.259, p value 0.004)

In our study the optimal cut-off point in our study for NTproBNP in predicting death as determined by ROC analysis was 960pg/ml with sensitivity of 94.1 % and specificity of 97.9 % compared to 1583.50pg/ml (sensitivity 82.6%, specificity70.7%) in the study by Chen et al(150) it might be high in their study as they included even cardiac causes of stroke. We found that NTproBNP cut off of 431.5pg/ml had a sensitivity of 90.0 % and specificity of 81 % in predicting BI score of <40 and dependency after stroke.

NTPROBNP	PRESENT STUDY	CHEN ET AL (150)

CUT OFF VALUES	960 pg/ml	1583.50 pg/ml
SENSITIVITY	94.1%	82.6%
SPECIFICITY	97.9%	70.7%
ROC AREA	0.995	0.788
95% CONFIDENCE INTEERVAL	0.984-1.000	0.683-0.892

TABLE 47: COMPARISON OF NTproBNP IN PREDICTING MORTALITY

We compared NTproBNP and NIHSS in predicting mortality and found that NTproBNP is a better predictor of mortality when compared to NIHSS

	NTproBNP	**NIHSS**
CUT OFF VALUES	960 pg/ml	14.5
SENSITIVITY	94.1%	94.1%
SPECIFICITY	97.9%	86%
ROC AREA	0.995	0.926
95% CONFIDENCE INTEERVAL	0.984-1.000	0.841-1.000

TABLE 48: COMPARISON BETWEEN NIHSS AND NTproBNP IN PREDICTING MORTALITY

In our study we showed that a serum NTproBNP value of 960 pg/ml predicted mortality and 435.1 pg/ml predicted disability.

NTproBNP	**MORTALITY**	**DISABILITY**

CUT OFF VALUES	960 pg/ml	435.1 pg/ml
SENSITIVITY	94.1%	90%
SPECIFICITY	97.9%	81%
ROC AREA	0.995	0.946
95% CONFIDENCE INTEERVAL	0.984-1.000	0.884-1.000

TABLE 49: NTproBNP IN PREDICTING MORTALITY AND DISABILITY

In our study we demonstrated that there is strong association between NTproBNP and mortality following stroke. It is a better predictor of death than NIHSS. We also found strong association between NTproBNP and functional outcome.

CONCLUSION

Serum NTproBNP is significantly elevated in patients after acute ischemic stroke and is strongly associated with stroke severity and functional outcome at 3 months.

Measuring NTproBNP on day of admission can predict all cause mortality and functional dependence at 3 months after acute ischemic stroke.

SUMMARY

64 cases of acute ischemic stroke were studied and followed up for 3 months.

Stroke incidence was more in individuals between the age group 61-80 years and more common in males when compared to females. Females had late presentation compared to males.

Motor weakness was the most common presenting complaint, Diabetics was the most common risk factor in our study.

GCS had significant association with NTproBNP, NIHSS and Barthel Index and low GCS on presentation had increased risk of mortality. GCS was significantly lower in individuals who died 8.12±4.13 compared to 13.57±2.465 in survivors.

We did not find any significant association between presentation GRBS, BP, biochemical parameters with mortality and morbidity.

Females and non smokers had better outcome at end of 3rd month. There was no association between Age, Gender and risk factors with mortality.

MCA was the most common arterial territory involved and 12 patients had > 70% ICA or carotid artery stenosis.

PACI was the most common type of stroke in our study. Total Anterior Circulation Infarct had significant association with NTproBNP level, NIHSS score and BI scores.

NTproBNP predicted large anterior circulation strokes and their functional dependency at 3 months.

Average NIHSS on day of admission was 12.81±7, among deceased it was 20.29±5.882. NIHSS on day of admission is significantly associated with mortality and Barthel Index. NIHSS could predict death but failed to predict functional dependence at 3 months.

The median NTproBNP on admission was 776.70±1023.6 pg/ml it was significantly elevated in deceased patients 2014.65±1320.546 pg/ml compared to 328.94±239.353 in alive. We demonstrated that NTproBNP is significantly elevated in patients after acute ischemic stroke and is strongly associated with stroke severity (NIHSS) and functional outcome (BI) at 3 months.

The average BI score at 3 months was 52.59±32.05 and is strongly associated with NTproBNP, NIHSS and GCS.

Combined NIHSS and NTproBNP assessment can be used to predict mortality.

Serum NTproBNP value of 960 pg/ml predicted mortality and 435.1 pg/ml predicted disability.

Measuring NTproBNP on day of admission can predict all cause mortality and functional dependence at 3 months after acute ischemic stroke.

LIMITATIONS OF THE STUDY

- Limited sample size.

- Occult cardiac conditions including paroxysmal Atrial Fibrillation or occult AF could not be totally ruled out.

- The size and volume of infarct, cause of mortality was not evaluated in the study.

RECOMMENDATIONS

- Further studies with larger sample size are required to assess the prognostic importance and to estimate a standard cut value of serum NTproBNP level to predict mortality and morbidity after acute ischemic stroke.

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ANNEXURE

PROFORMA

1. IP No: 2. Date: 3.Serial No:

4. Name: 5. Age: 6.Gender:

7. Occupation:

8. Date of admission: 9. Date of discharge:

10. Address with phone no:

11. Chief complaints:

12. Past history:

13. Drug/ Treatment therapy:

14. Personal history:

15. General physical examination (at admission):

PR: BP: Temp:

Respiratory rate: SpO_2: GRBS :

Pallor: Icterus: Cyanosis:

Clubbing: Lymphadenopathy: Oedema:

16. Systemic examination:

CVS:

RS:

PA:

CNS:

17. Diagnosis:

18. Duration of hospital stay:

19. INVESTIGATIONS:

- COMPLETE BLOOD COUNT :

- RENAL FUNCTION TEST

  BLOOD UREA : SERUM CREATININE :

- RBS:

  HBA1C: FBS : PPBS:

- SERUM ELECTROLYTES

  Na+ : K+:

- CT SCAN BRAIN:

- ECG :
- 2D ECHO :

- CHEST X RAY :
- CAROTID DOPPLER :

- LIPID PROFILE :
- OTHERS :

	ADMISSION	DAY 7	DISCHARGE	1 MONTH	3 MONTHS
NIHSS SCORE					
BARTHEL INDEX					
PLASMA NT PRO BNP					

SIGNATURE

PATIENT INFORMATION SHEET

STUDY TITLE: "N-TERMINAL PRO BRAIN NATRIURETIC PEPTIDE (NT-proBNP) AS A MARKER FOR RISK STRATIFICATION AND PREDICTION OF FUNCTIONAL OUTCOME IN ACUTE ISCHEMIC STROKE"

STUDY LOCATION: R L Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar.

DETAILS-

Stroke is the second most common cause of death and third most common cause of disability worldwide. Assessing stroke severity and predicting morbidity and mortality are essential while taking treatment decisions and family counseling.

There is a need of a biomarker to predict prognosis. A biochemical parameter which is fast and inexpensive will add additional valuable and time-sensitive prognostic information during the early evaluation of acute ischemic stroke, especially during the thrombolytic therapy. This study aims to assess the prognostic importance of NT-proBNP in acute ischemic stroke.

Patients aged more than 18 years having acute ischemic stroke and admitted to R.L.Jalappa Hospital will be included in this study. Patients with Age > 80 years,Previous history of stroke,Head injury,Intracerebral bleed,Renal impairment,H/o seizure ,Patients with any evidence of CHF, myocardial infarction, cardiomyopathy, hypertensive heart diseases, valve diseases, and paroxysmal or chronic atrial fibrillation will be excluded from the study.

A history of stroke and risk factors such as hypertension, diabetes, coronary artery disease, smoking, and alcoholism will be enquired , serum NT-proBNP levels will be measured at admission and after 7 days in all patients, All patients will undergo CT SCAN brain ,All patients will also undergo ECG, screening 2D ECHO if necessary,All patient will undergo routine investigations CBC, RFT, SERUM ELECTROLYTES,

RBS,HBA1C,FBS,PPBS, LIPID PROFILE(if necessary).the cost for the above tests will be borne by the researcher. All patients will be followed up at the hospital for a period of one month.

Please read the following information and discuss with your family members. You can ask any question regarding the study. If you agree to participate in the study we will collect information (as per proforma) from you or from a person responsible for you or both. Relevant history will be taken. This information collected will be used only for dissertation and publication.

All information collected from you will be kept confidential and will not be disclosed to any outsider. Your identity will not be revealed. This study has been reviewed by the Institutional Ethics Committee and you are free to contact the member of the Institutional Ethics Committee.

There is no compulsion to agree to this study. The care you will get will not change if you don't wish to participate. You are required to sign/ provide thumb impression only if you voluntarily agree to participate in this study.

For further information contact

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SDUMC , KOLAR

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ರೋಗಿ ಮಾಹಿತಿ ಪತ್ರ

ಅಧ್ಯಯನದ ಶೀರ್ಷಿಕೆ: "**NT-pro** ಬ್ರೇನ್ ನ್ಯಾಟ್ರಿಯುರೆಟಿಕ್ ಪೆಪ್ಟೈಡ್ **(NT-proBNP) :**ತೀವ್ರ ರಕ್ತಕೊರತೆಯ **ಪಾರ್ಶ್ವವಾಯುವಿನ** ಅಪಾಯದ ಶ್ರೇಣೀಕರಣ ಮತ್ತು ಭವಿಷ್ಯದ ಕ್ರಿಯಾತ್ಮಕ ಫಲಿತಾಂಶದ ಮಾರ್ಕರ್"

ಸಂಸ್ಥೆಯ ಹೆಸರು: ಆರ್.ಎಲ್ ಜಲಪ್ಪ ಆಸ್ಪತ್ರೆ ಮತ್ತು ಸಂಶೋಧನಾ ಕೇಂದ್ರ – ಶ್ರೀ ದೇವರಾಜ್ ಅರಸ್ ಮೆಡಿಕಲ್ ಕಾಲೇಜ್ಗೆಜೋಡಿಸಲಾಗಿದೆ.

ವಿವರಗಳು- ಪಾರ್ಶ್ವವಾಯು ವಿಶ್ವಾದ್ಯಂತ ಸಾವಿನ ಎರಡನೇ ಅತ್ಯಂತ ಸಾಮಾನ್ಯ ಕಾರಣವಾಗಿದೆ ಮತ್ತು ಅಂಗವೈಕಲ್ಯದ ಮೂರನೇ ಸಾಮಾನ್ಯ ಕಾರಣವಾಗಿದೆ. ಚಿಕಿತ್ಸೆಯ ನಿರ್ಧಾರಗಳನ್ನು ಮತ್ತು ಕುಟುಂಬ ಸಮಾಲೋಚನೆ ತೆಗೆದುಕೊಳ್ಳುವಾಗ ಪಾರ್ಶ್ವವಾಯುವಿನ ತೀವ್ರತೆ, ಅಸ್ವಸ್ಥತೆ ಮತ್ತು ಮರಣವನ್ನು ಊಹಿಸುವುದು ಅತ್ಯಗತ್ಯ.

ರೋಗದ ಮುನ್ಸೂಚನೆಯನ್ನು ಊಹಿಸಲು ಒಂದು ಜೈವಿಕ ಮಾರ್ಕರಿನ ಅಗತ್ಯವಿರುತ್ತದೆ. ತೀವ್ರ ರಕ್ತಕೊರತೆಯ ಪಾರ್ಶ್ವವಾಯುವಿನ ಆರಂಭಿಕ ಮೌಲ್ಯಮಾಪನದಲ್ಲಿ, ವಿಶೇಷವಾಗಿ ಥ್ರಂಬೋಲಿಟಿಕ್ ಚಿಕಿತ್ಸೆಯ ಸಮಯದಲ್ಲಿ ವೇಗವಾದ ಮತ್ತು ಅಗ್ಗವಾದ ಜೀವರಾಸಾಯನಿಕ ನಿಯತಾಂಕ ಹೆಚ್ಚುವರಿ ಮೌಲ್ಯಯುತ ಮತ್ತು ಸಮಯ-ಸೂಕ್ಷ್ಮ ಪ್ರಜ್ಞಾವಿಸ್ತಾರಕ ಮಾಹಿತಿಯನ್ನು ನೀಡುತ್ತದೆ . ತೀವ್ರವಾದ ರಕ್ತಕೊರತೆಯ ಪಾರ್ಶ್ವವಾಯು ರೋಗದ ಮುನ್ನರಿವಿನಲ್ಲಿ BNPಯ ಪ್ರಾಮುಖ್ಯತೆಯನ್ನು ನಿರ್ಣಯಿಸುವುದು ಈ ಅಧ್ಯಯನದ ಗುರಿ.

ಆರ್.ಎಲ್.ಜಲಪ್ಪ ಆಸ್ಪತ್ರೆಯಲ್ಲಿ ದಾಖಲಾಗಿರುವ ತೀವ್ರ ರಕ್ತಕೊರತೆಯ ಪಾರ್ಶ್ವವಾಯು ಹೊಂದಿರುವ 18 ವರ್ಷಗಳಿಗಿಂತ ಹೆಚ್ಚಿನ ವಯಸ್ಸಿನ ರೋಗಿಗಳನ್ನು ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಸೇರಿಸಲ್ಪಡಲಾಗುವುದು.> 80 ವರ್ಷಗಳ ವಯಸ್ಸಿನ ರೋಗಿಗಳು, ಪಾರ್ಶ್ವವಾಯುವಿನ ಹಿಂದಿನ ಇತಿಹಾಸ, ತಲೆ ಗಾಯ, ಇಂಟ್ರಾಸೆರೆಬ್ರಲ್ ರಕ್ತಸ್ರಾವ, ಮೂತ್ರಪಿಂಡದ ದುರ್ಬಲತೆ, ಮುಷ್ಟಿ ರೋಗ , CHF, ಹೃದಯಾಘಾತ, ಕಾರ್ಡಿಯೋಮಿಯೊಪತಿ, ಹೈಪರ್ಟೆನ್ಸಿವ್ ಹೃದಯ ರೋಗಗಳು, ಮತ್ತು ಪ್ಯಾರೋಕ್ಸಿಸಮಲ್ ಅಥವಾ ದೀರ್ಘಕಾಲದ AF ರೋಗಿಗಳನ್ನು ಅಧ್ಯಯನದಿಂದ ಹೊರಗಿಡಲಾಗುತ್ತದೆ.

ರಕ್ತದೊತ್ತಡ, ಮಧುಮೇಹ, ಪರಿಧಮನಿಯ ಕಾಯಿಲೆ, ಧೂಮಪಾನ ಮತ್ತು ಆಲ್ಕೊಹಾಲ್ ಸೇವನೆ ಮತ್ತು ಪಾರ್ಶ್ವವಾಯುವಿನ ಅಪಾಯದ ಅಂಶಗಳ ಇತಿಹಾಸವನ್ನು ವಿಚಾರಿಸಲಾಗುತ್ತಿದೆ. ಎಲ್ಲಾ ರೋಗಿಗಳಲ್ಲಿ NTproBNP ಮಟ್ಟವನ್ನು ದಾಖಲಾತಿಯಲ್ಲಿ ಅಳೆಯಲಾಗುತ್ತದೆ, ಎಲ್ಲಾ ರೋಗಿಗಳು CT SCAN ಮಿದುಳು ಪರೀಕ್ಷೆ ಗೆ ಒಳಗಾಗುತ್ತಾರೆ, ಎಲ್ಲಾ ರೋಗಿಗಳ ECG, ಅಗತ್ಯವಿದ್ದರೆ 2D ECHO ಅನ್ನು ಪರೀಕ್ಷಿಸಲಾಗುವುದು. ಎಲ್ಲಾ ರೋಗಿಗಳಿಗೆ CBC, RFT, SERUM ELECTROLITES, RBS,HBA1C LIPID PROFILE ರಕ್ತ ಪರೀಕ್ಷೆ ನಡೆಯಲಿದೆ. ಎಲ್ಲಾ ರೋಗಿಗಳನ್ನು ಆಸ್ಪತ್ರೆಯಲ್ಲಿ ಅನುಸರಿಸಲಾಗುವುದು.

ಕೆಳಗಿನ ಮಾಹಿತಿಯನ್ನು ಓದಿ ಮತ್ತು ನಿಮ್ಮ ಕುಟುಂಬ ಸದಸ್ಯರೊಂದಿಗೆ ಚರ್ಚಿಸಿ. ಅಧ್ಯಯನದ ಬಗ್ಗೆ ನೀವು ಯಾವುದೇ ಪ್ರಶ್ನೆಯನ್ನು ಕೇಳಬಹುದು. ನೀವು ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ಒಪ್ಪಿಕೊಂಡರೆ ನಾವು ನಿಮ್ಮಿಂದ (ಮಾಹಿತಿ ಪ್ರಕಾರ) ಅಥವಾ ನಿಮಗೆ ಜವಾಬ್ದಾರರಾಗಿರುವ ವ್ಯಕ್ತಿಗಳಿಂದ ಮಾಹಿತಿಯನ್ನು ಸಂಗ್ರಹಿಸುತ್ತೇವೆ.

ಸಂಬಂಧಿತ ಇತಿಹಾಸವನ್ನು ತೆಗೆದುಕೊಳ್ಳಲಾಗುವುದು. ಸಂಗ್ರಹಿಸಿದ ಈ ಮಾಹಿತಿಯನ್ನು ಪ್ರೌಢಪ್ರಬಂಧ ಮತ್ತು ಪ್ರಕಟಣೆಗಾಗಿ ಮಾತ್ರ ಬಳಸಲಾಗುತ್ತದೆ. ನಿಮ್ಮಿಂದ ಸಂಗ್ರಹಿಸಿದ ಎಲ್ಲಾ ಮಾಹಿತಿಯನ್ನು ಗೌಪ್ಯವಾಗಿರಿಸಲಾಗುವುದು ಮತ್ತು ಯಾವುದೇ ಹೊರಗಿನವರಿಗೆ ಬಹಿರಂಗಪಡಿಸಲಾಗುವುದಿಲ್ಲ. ನಿಮ್ಮ ಗುರುತನ್ನು ಬಹಿರಂಗಪಡಿಸಲಾಗುವುದಿಲ್ಲ. ಈ ಅಧ್ಯಯನವು ಸಾಂಸ್ಥಿಕ ನೀತಿಶಾಸ್ತ್ರ ಸಮಿತಿಯಿಂದ ಪರಿಶೀಲಿಸಲ್ಪಟ್ಟಿದೆ ಮತ್ತು ನೀವು ಸಂಸ್ಥೆಯ ಎಥಿಕ್ಸ್ ಸಮಿತಿಯ ಸದಸ್ಯರನ್ನು ಸಂಪರ್ಕಿಸಲು ಮುಕ್ತವಾಗಿರುತ್ತೀರಿ. ಈ ಅಧ್ಯಯನಕ್ಕೆ ಒಪ್ಪಿಗೆ ನೀಡಲು ಯಾವುದೇ ಕಡ್ಡಾಯವಿಲ್ಲ. ನೀವು ಭಾಗವಹಿಸಲು ಬಯಸದಿದ್ದರೆ ನೀವು ಪಡೆಯುವ ಕಾಳಜಿ ಬದಲಾಗುವುದಿಲ್ಲ. ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ನೀವು ಸ್ವಯಂಪ್ರೇರಣೆಯಿಂದ ಒಪ್ಪಿಕೊಳ್ಳುವುದಾದರೆ ಮಾತ್ರ ಹೆಬ್ಬೆರಳ ಗುರುತು/ಸಹಿ ನೀಡಬೇಕಾಗುತ್ತದೆ . ಹೆಚ್ಚಿನ ಮಾಹಿತಿಗಾಗಿ ಸಂಪರ್ಕಿಸಿ

ಡಾ. ಮನೋಜ್ ಎ ಜಿ (ಸ್ನಾತಕೋತ್ತರ ಪದವಿ ವಿದ್ಯಾರ್ಥಿ)

ಜನರಲ್ ಮೆಡಿಸಿನ್ ಇಲಾಖೆ

SDUMC, ಕೋಲಾರ್

ಸಂಪರ್ಕ ಸಂಪರ್ಕ ಸಂಖ್ಯೆ: 7676742616

INFORMED CONSENT FORM

Name of the investigator: DR. MANOJ A G

Name of the organisation: R L JALAPPA HOSPITAL AND RESEARCH CENTRE ATTACHED TO SRI DEVARAJ URS MEDICAL COLLEGE

Name of the participant: SI no:

I Mr./Mrs. have been explained in my own understandable language, that I will be included in a study which is "N-TERMINAL PRO BRAIN NATRIURETIC PEPTIDE (NT-proBNP) AS A MARKER FOR RISK STRATIFICATION AND PREDICTION OF FUNCTIONAL OUTCOME IN ACUTE ISCHEMIC STROKE" being conducted in RL JALAPPA HOSPITAL.

I have been invited to take part in this research study. The information in this document is meant to help me decide whether or not to take part. I have clarified my doubts regarding this study with the principal investigator.

I have been asked to participate in this study because I satisfy the eligibility criteria.

I request and authorise Dr. Manoj A G to perform the designated tests for my blood sample. My signature below constitutes my acknowledgement that the benefits, risks and limitations of this testing have been explained to my satisfaction by a qualified health professional.

Participants will undergo CT Brain, serum NT-proBNP,ECG,2D echo , CBC, RFT, SERUM ELECTROLYTES, RBS, LIPID PROFILE,HBA1C,FBS,PPBS.Participation is totally voluntary and there would be no payment for testing, the cost for all the tests will be borne by the investigator. All test results are treated with medical confidentiality and will not be disclosed to any outsider except if it is required by the law.

I give my consent to allow my sample to be used for medical research, test validation or education as long as my privacy is maintained.

I understand that I remain free to withdraw from this study at any time and this will not change my future care.

I have read and received a copy of patient information sheet. I understand the information provided in this document and I have had the opportunity to ask questions I might have about the testing, the procedure, the associated risk and alternatives.

Subject name and signature/ thumb impression

Date:

Parent’s/ guardian’s name/ thumb impression

Date:

Signature of the person taking consent

Date:

ರೋಗಿಯ ತಿಳುವಳಿಕೆ ಸಮ್ಮತಿ ನಮೂನೆ

ಸಂಶೋಧಕರ ಹೆಸರು: **ಡಾ. ಮನೋಜ್ ಎ ಜಿ**

ಸಂಸ್ಥೆಯ ಹೆಸರು: ಆರ್.ಎಲ್ ಜಲಪ್ಪ ಆಸ್ಪತ್ರೆಮತ್ತು ಸಂಶೋಧನಾಕೇಂದ್ರ – ಶ್ರೀ ದೇವರಾಜ್ ಅರಸ್ ಮೆಡಿಕಲ್ ಕಾಲೇಜ್ಗೆಜೋಡಿಸಲಾಗಿದೆ

ಪಾಲ್ಗೊಳ್ಳುವವರ ಹೆಸರು: ಕ್ರಮ ಸಂಖ್ಯೆ :

ನಾನು ಶ್ರೀ /ಶ್ರೀಮತಿ ನನಗೆ ಆರ್. ಎಲ್. ಜಲಪ್ಪ ಆಸ್ಪತ್ರೆಯಲ್ಲಿ ನಡೆಸಲಾಗುತ್ತಿರುವ ಅಧ್ಯಯನ

"NT-ಪ್ರೋ ಬ್ರೇನ್ಯಾಟ್ರಿಯುರೆಟಿಕ್ಪೆಪ್ಟೈಡ್ (NT-proBNP) :ತೀವ್ರ ರಕ್ತ ಕೊರತೆಯ ಪಾರ್ಶ್ವವಾಯುವಿನ ಅಪಾಯದ ಶ್ರೇಣೀಕರಣ ಮತ್ತು ಭವಿಷ್ಯದ ಕ್ರಿಯಾತ್ಮಕ ಫಲಿತಾಂಶದ ಮಾರ್ಕರ್" ದಲ್ಲಿ ನನ್ನನ್ನು ಸೇರಿಸಲ್ಪಡಲಾಗುವುದು ಎಂದು ನನಗೆ ಅರ್ಥವಾಗುವ ಭಾಷೆಯಲ್ಲಿ ವಿವರಿಸಲಾಗಿದೆ.

ಈ ಸಂಶೋಧನಾ ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ನನ್ನನ್ನು ಆಹ್ವಾನಿಸಲಾಗಿದೆ. ಈ ದಾಖಲೆಯಲ್ಲಿರುವ ಮಾಹಿತಿಯು ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಬೇಕೇ ಅಥವಾ ಬೇಡವೇ ಎಂಬುದನ್ನು ನಿರ್ಧರಿಸಲು ನನಗೆ ನೆರವಾಗುವುದು. ಪ್ರಧಾನ ಸಂಶೋಧಕನೊಂದಿಗೆ ನಾನು ಈ ಅಧ್ಯಯನಕ್ಕೆ ಸಂಬಂಧಿಸಿದಂತೆ ನನ್ನ ಅನುಮಾನಗಳನ್ನು ಸ್ಪಷ್ಟಪಡಿಸಿಕೂಂಡಿದ್ದೆನೆ.

ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳುವಂತೆ ನನಗೆ ಸೂಚಿಸಲಾಗಿದೆ ಏಕೆಂದರೆ ನಾನು ಅರ್ಹತಾ ಮಾನದಂಡಗಳನ್ನು ಪೂರೈಸುತ್ತೇನೆ.

ನನ್ನ ರಕ್ತದ ಮಾದರಿಯನ್ನು ಗೊತ್ತು ಪಡಿಸಿದ ಪರೀಕ್ಷೆಗಳಿಗೆ ನಿರ್ವಹಿಸಲು ನಾನು ಡಾ.ಮನೋಜ್ ಎ ಜಿ ಅವರನ್ನು ವಿನಂತಿಸುತ್ತೇನೆ ಮತ್ತು ಅಧಿಕಾರವನ್ನು ನೀಡುತ್ತೇನೆ.

ಕೆಳಗಿನ ನನ್ನ ಸಹಿಯು, ಅರ್ಹ ಆರೋಗ್ಯ ವೃತ್ತಿಪರರಿಂದ ಪರೀಕ್ಷೆಯ ಅನುಕೂಲಗಳು, ಅಪಾಯಗಳು ಮತ್ತು ಮಿತಿಗಳನ್ನು ನನ್ನ ತೃಪ್ತಿಗೆ ವಿವರಿಸಲಾಗಿದೆ ಎಂದು ನನ್ನ ಅಂಗೀಕಾರವನ್ನು ರೂಪಿಸುತ್ತದೆ.

ಭಾಗವಹಿಸುವವರು CT ಬ್ರೈನ್, NT-proBNP, ECG, 2D ECHO, CBC, RFT, SERUM ಎಲೆಕ್ಟ್ರಾಲೈಟ್ಗಳು, RBS, LIPID PROFILE, HBA1C, FBS, PPBS ಒಳಗಾಗುತ್ತಾರೆ.

ಭಾಗವಹಿಸುವಿಕೆ ಸಂಪೂರ್ಣವಾಗಿ ಸ್ವಯಂ ಪ್ರೇರಿತವಾಗಿರುತ್ತದೆ ಮತ್ತು ಮಾದರಿ ಸಂಗ್ರಹಣೆಗೆ ಯಾವುದೇ ಹಣಕಾಸಿನ ಪಾವತಿಯಿಲ್ಲ.

ಎಲ್ಲಾ ಪರೀಕ್ಷೆಗಳಿಗೆ ಸಂಬಂಧಿಸಿದ ವೆಚ್ಚವನ್ನು ತನಿಖೆದಾರರು ಭರಿಸುತ್ತಾರೆ.

ಎಲ್ಲಾ ಪರೀಕ್ಷಾ ಫಲಿತಾಂಶಗಳನ್ನು ವೈದ್ಯಕೀಯ ಗೌಪ್ಯತೆಯೊಂದಿಗೆ ಪರಿಗಣಿಸಲಾಗುತ್ತದೆ ಮತ್ತು ಕಾನೂನಿನ ಅಗತ್ಯವಿದ್ದರೆ ಹೊರತುಪಡಿಸಿ ಯಾವುದೇ ಹೊರಗಿನವರಿಗೆ ಬಹಿರಂಗಪಡಿಸುವುದಿಲ್ಲ.

ನನ್ನ ಗೌಪ್ಯತೆ ನಿರ್ವಹಿಸಲ್ಪಡುವವರೆಗೆ ವೈದ್ಯಕೀಯ ಪರೀಕ್ಷೆ, ಪರೀಕ್ಷೆಯ ಮೌಲ್ಯಮಾಪನ ಅಥವಾ ಶಿಕ್ಷಣಕ್ಕಾಗಿ ನನ್ನ ಮಾದರಿಯನ್ನು ಬಳಸಲುನನ್ನ ಒಪ್ಪಿಗೆಯನ್ನು ನೀಡುತ್ತೇನೆ.

ನಾನು ಈ ಅಧ್ಯಯನದಿಂದ ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ಹಿಂತೆಗೆದುಕೊಳ್ಳಲು ಮುಕ್ತವಾಗಿರುತ್ತೇನೆ ಮತ್ತು ಇದು ನನ್ನ ಮುಂದಿನ ಕಾಳಜಿಯನ್ನು ಬದಲಿಸುವುದಿಲ್ಲ ಎಂದು ಅರ್ಥಮಾಡಿಕೊಂಡಿದ್ದೇನೆ.

ರೋಗಿಯ ಮಾಹಿತಿಪತ್ರವನ್ನು ನಾನು ಓದಿದ್ದೇನೆ ಮತ್ತು ಪ್ರತಿಯನ್ನು ಸ್ವೀಕರಿಸಿದ್ದೇನೆ. ಈ ದಾಖಲೆಯಲ್ಲಿ ಒದಗಿಸಿದ ಮಾಹಿತಿಯನ್ನು ನಾನು ಅರ್ಥಮಾಡಿಕೊಂಡಿದ್ದೇನೆ ಮತ್ತು ಪರೀಕ್ಷೆ,

ಪ್ರಕ್ರಿಯೆ, ಸಂಬಂಧಿಸಿದ ಅಪಾಯ ಮತ್ತು ಪರ್ಯಾಯಗಳ ಬಗ್ಗೆ ನಾನು ಹೊಂದಿರುವ ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳಲು ನನಗೆ ಅವಕಾಶಕಲ್ಪಿಸಲಾಗಿದೆ.

ಹೆಸರು ಮತ್ತು ಸಹಿ / ಹೆಬ್ಬೆರಳುಗುರುತು ದಿನಾಂಕ:

ಪೋಷಕರ / ಪಾಲಕರ ಹೆಸರು /ಹೆಬ್ಬೆರಳು ಗುರುತು ದಿನಾಂಕ:

ಒಪ್ಪಿಗೆ ತೆಗೆದುಕೊಳ್ಳುವ ವ್ಯಕ್ತಿಯ ಸಹಿ ದಿನಾಂಕ:

KEY TO MASTER CHART

SL NO	➢	SERIAL NUMBER
UHID NO	➢	UNIQUE HOSPITAL IDENTITY NUMBER
M	➢	MALE
F	➢	FEMALE
RT	➢	RIGHT
LT	➢	LEFT
UL	➢	UPPER LIMB
LL	➢	LOWER LIMB
DOA	➢	DATE OF ADMISSION
DURATION	➢	DURATION OF HOSPITAL STAY
HTN	➢	HYPERTENSION
DM	➢	DIABETES MELLITUS
1	➢	PRESENT
0	➢	ABSENT
SBP	➢	SYSTOLIC BLOOD PRESSURE mmHg
DBP	➢	DIASTOLIC BLOOD PRESSURE mmHg
TEMP	➢	TEMPERATURE ^{0}F
RR	➢	RESPIRATORY RATE / MINUTE
SP02	➢	OXYGEN SATURATION
PICCKLE	➢	PALLOR, ICTERUS, CYANOSIS, CLUBBING, KOILYNYCHIA, SLNE, EDEMA
P	➢	PRESENT
A	➢	ABSENT

CVS	➢	CARDIOVASCULAR SYSTEM
RS	➢	RESPIRATORY SYSTEM
PA	➢	PER ABDOMEN
CNS	➢	CENTRAL NERVOUS SYSTEM
NVBS	➢	NORMAL VESICULAR BREATH SOUNDS
S1 S2	➢	FIRST AND SECOND HEART SOUNDS
HMF	➢	HIGHER MENTAL FUNCTION
GCS	➢	GLASGOW COMA SCALE
BERL	➢	BILATERAL EQUALLY REACTIVE TO LIGHT
UMN	➢	UPPER MOTOR NEURON
DTR	➢	DEEP TENDON REFLEX
B	➢	BICEPS JERK
T	➢	TRICEPS JERK
S	➢	SUPINATOR JERK
K	➢	KNEE JERK
A	➢	ANKLE JERK
CBC	➢	COMPLETE BLOOD COUNT
HB	➢	HEMOGLOBIN
PCV	➢	PACKED CELL VOLUME
MCV	➢	MEAN CORPUSCULAR VOLUME
TC	➢	TOTAL COUNT
RFT	➢	RENAL FUNCTION TESTS
RBS	➢	RANDOM BLOOD SUGAR
FBS	➢	FASTING BLOOD GLUCOSE
PPBS	➢	POST PRANDIAL BLOOD SUGAR

HBA1C	➢	GLYCATED HEMOGLOBIN
SC	➢	SERUM CHOLESTEROL
TG	➢	TRIGLYCERIDES
LDL	➢	LOW DENSITY LIPOPROTIEN
HDL	➢	HIGH DENSITY LIPOROTEIN
CT	➢	COMPUTED TOMOGRAPHY
MRI	➢	MAGNETIC RESONANCE IMAGING
ACA	➢	ANTERIOR CEREBRAL ARTERY
MCA	➢	MIDDLE CEREBRAL ARTERY
PCA	➢	POSTERIOR CEREBRAL ARTERY
PICA	➢	POSTERIOR INFERIOR CEREBELLAR ARTERY
TACI	➢	TOTAL ANTERIOR CIRCULATION INFARCTS
PACI	➢	PARTIAL ANTERIOR CIRCULATION INFARCTS
POCI	➢	POSTERIOR CIRCULATON INFARCTS
LS	➢	LACUNAR SYNDROMES
ECG	➢	ELECTROCARDIOGRAPH
NIHSS	➢	NATIONAL INSTITUTE HEALTH STROKE SCALE
NTproBNP	➢	N TERMINAL PRO BRAIN NATRIURETIC PEPTIDE
D0	➢	ON DAY OF ADMISSION
D7	➢	7^{th} DAY OF ADMISSION