"SERUM BILIRUBIN AS A SEVERITY AND PROGNOSTIC INDICATOR IN ACUTE ISCHEMIC STROKE – A HOSPITAL BASED ONE YEAR OBSERVATIONAL STUDY IN KLE'S DR PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTRE, BELAGAVI"

BY

REG NO: BG0117013

Dissertation

Submitted to KAHER, Belagavi, Karnataka

In partial fulfilment of the requirements for the degree of

M.D.

IN

GENERAL MEDICINE

DEPARTMENT OF GENERAL MEDICINE

J. N. MEDICAL COLLEGE

BELAGAVI- 590010. KARNATAKA

APRIL - 2020

KLE ACADEMY OF HIGHER EDUCATION AND RESEARCH, BELAGAVI, KARNATAKA

Endorsement by the HOD/ Principal/ Head of the Institution

This is to certify that the dissertation **entitled "SERUM BILIRUBIN AS A SEVERITY AND PROGNOSTIC INDICATOR IN ACUTE ISCHEMIC STROKE – A HOSPITAL BASED ONE YEAR OBSERVATIONAL STUDY IN KLE'S DR PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTRE, BELAGAVI"** is a bonafide research work done by **REG NO: BG0117013.**

DR. ARATHI DARSHAN
MD (GENERAL MEDICINE)
Professor and Head,
Department of General Medicine,
J. N. Medical College,
Nehru Nagar, Belagavi – 10

Date :
Place : Belagavi

DR.(Mrs.) N.S. MAHANTSHETTI
M.D (PAEDIATRICS)
Principal,
J. N. Medical College,
Nehru Nagar, Belagavi – 10

Date :
Place : Belagavi

PLAGIARISM ACCEPTED LETTER

JAWAHARLAL NEHRU MEDICAL COLLEGE
(A constituent unit of KLE Academy of Higher Education & Research Deemed-to-be University)
Accredited 'A' Grade by NAAC (2nd Cycle) Placed in Category "A" by MHRD (GoI)
Nehru Nagar, Belagavi-590 010, Karnataka-India

Website : http/www.jnmc.edu
E-Mail : Principal@jnmc.edu
Office :+91-(0)831 2471350
FAX :+91 (0)831-2470759

Ref. No. : JNMC/PG/2255 Date : 20-9-2019

To,

REG NO: BG0117013

Sub: Acceptance Letter

Sir/Madam,

The softcopy of thesis entitled " SERUM BILIRUBIN AS A SEVERITY AND PROGNOSTIC INDICATOR IN ACUTE ISCHEMIC STROKE – A TERTIARY HOSPITAL BASED ONE YEAR OBSERVATIONAL STUDY IN BELAGAVI" has been submitted for Anti-Plagiarism check through Turnitin software. The scan has been carried out and the scanned output reveals a match percentage of 8% (Eight percentage) which is within the acceptable limits of 10% as per the guidelines given by UGC.

Thanking you,

Yours sincerely,

Coordinator
Department of General Medicine
J. N. M. C. Belagavi.

Dr. POOJA S. MOTIMATH
M.D. General Medicine
Consultant General Medicine
KMC Reg. No. 105678
KLES Dr. Prabhakar Kore Hospital &
MRC, Belagavi.

Chairman,
Antiplagiarism Committee

KAHER J.N. MEDICAL COLLEGE BELAGAVI

ABBREVIATIONS

ACA	-	Anterior Cerebral Artery
MDA	-	Malondialdehyde
AIS	-	Acute Ischemic Stroke
MI	-	Myocardial Infarction
ALT	-	Alanine Transaminase
MRA	-	Magnetic Resonance Angiography
AST	-	Aspartate Transaminase
MRI	-	Magnetic Resonance Imaging
BOX	-	Bilirubin Oxidative Metabolites
MRS	-	Modified Rankin Scale
MR Score	-	Modified Rankin scale score
B-UGT	-	Bilirubin-UDP Glucuronosyl Transferase
NIHSS	-	National Institute of Health Stroke Scale
CAD	-	Coronary Artery Disease
NMDAR	-	NMDA Glutamate Receptor
CADASIL	-	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy nNOS - Neuronal Nitric Oxide Synthase
CNS	-	Central Nervous System
NO	-	Nitric Oxide
CO	-	Carbon Monoxide
NOX	-	NADPH Oxidase
CSF	-	CerebroSpinal Fluid

O2	-	Super Oxide Anion
CT	-	Computed Tomography
OH	-	Hydroxyl Radical
CTA	-	Computed Tomography Angiography
ONOO	-	Peroxy Nitrite
DB	-	Direct Bilirubin
PCA	-	Posterior Cerebral Artery
DIC	-	Disseminated Intravascular Coagulation
PET	-	Postitron Emission Tomography
DM	-	Diabetes Mellitus
PTT	-	Partial Thromboplastin Time
EDH	-	Extradural Hemorrhage
ROS	-	Reactive Oxygen Species
ES	-	Embolic Stroke
rt-PA	-	Recombinant Tissue - Plasminogen Activator
ETC	-	Electron Transport Chain
SAH	-	Sub Arachnoid Hemorrhage
G6PD	-	Glucose 6 Phosphate Dehydrogenase
SDH	-	Subdural Hemorrhage
HDL	-	High Density Lipoprotein
SHT	-	Systemic Hypertension
HI	-	Hemorrhagic Infarction
SLE	-	Systemic Lupus Erythematosus
HO	-	Hemeoxygenase
SPECT	-	Single-photon emission computed tomography

IB	-	Indirect Bilirubin
TB	-	Total Bilirubin
ICH	-	Intra Cranial Hemorrhage
TC	-	Total Cholesterol
ICT	-	Intra Cranial Tension
TG	-	Triglyceride
INR	-	International Normalized Ratio
TIA	-	Transient Ischemic Attack
LDL	-	Low Density Lipoprotein
TTP	-	Thrombotic Thrombocytopenic Purpura
DIC	-	Disseminated Intravascular Coagulation
MCA	-	Middle Cerebral Artery
VCAM	-	Vascular Cell Adhesion Molecule

ABSTRACT

BACKGROUND & OBJECTIVES:

Stroke is a common cause of mortality and morbidity and has an increasing prevalence across the world.[1] Bilirubin is now being considered an antioxidant which increases in response to diseases associated with increased oxidative stress. Thus, various studies have been done to see the role of bilirubin in conditions like coronary artery disease which are associated with oxidative stress. Bilirubin being an antioxidant may limit the neurologic damage after a stroke. It may have a preventive or a therapeutic role.[2] There is insufficient data about the role of bilirubin and how bilirubin levels predict the severity of stroke and influence its prognosis. This study was conducted to improve our understanding of the same.

MATERIALS AND METHODS:

This study was conducted from January 2018 to December 2018 on 64 ischemic stroke patients admitted at KLE'S Dr.Prabhakar kore hospital at Belagavi, Karnataka. This was an observational study and purposive sampling was done. Informed consent was taken for all cases included in the study.

All adult patients > 18 years of age presenting with cerebro vascular accident and proved as ischemic stroke on CT scan or MRI scan. Patients with hemorrhagic stroke, hemolytic anaemias, hepatobiliary disease, patients on hepatotoxic drugs were excluded.

A detailed history was taken and clinical features were assessed. Basic laboratory tests were conducted such as complete blood counts, liver function tests, renal function tests. National Institute of Health Stroke Scale, serum total bilirubin and direct bilirubin levels were assessed at the time of admission. Modified Rankin scale was performed at the time of discharge.

The patients were empirically divided into Group 1 or low total bilirubin group with serum total bilirubin values less than 0.7mg/dL and Group 2 or high total bilirubin group with values greater than or equal to 0.7mg/dL. Likewise, they were divided into Group 1 or low direct bilirubin group with serum direct bilirubin values less than 0.2mg/dL and Group2 or High direct bilirubin values greater than or equal to 0.2mg/dL. They were then analysed with their NIHSS scores for assessing stroke severity. MR scores of 0-3 were considered good outcome and 4-6 as poor outcome and compared to the bilirubin groups and assessed for the correlation of level of functional disability at the time of discharge with bilirubin levels.

RESULTS

A total of 64 subjects/patients were included in the final analysis.

Mean age of patients in this study was 60.25 years (SD - 12.54Years) with the highest number of patients belonging to the age group 50-59 years. Out of 64 patients, 45 patients were male and 19 were females. Majority of the patients were males constituting 70.3%.

The most common presenting complaints were related to the motor system(87.5%) followed by cranial nerve symptoms, speech related symptoms and the least being sensory symptoms. Hypertension was the most common risk factor in the patients included in the study and was seen in 50% of study population. The other risk factors were diabetes mellitus (34%), alcoholism (30%) and smoking(23%). 44% patients had a blood pressure of more than 140/90 mmHg at the time of admission.

Middle cerebral artery territory was the most common site of involvement seen in 73.4% patients.

HDL levels were low in 37 patients (57.81%).45.31%% (29 patients) had high LDL levels. 20.3% had high levels of triglycerides. High levels of cholesterol were seen in 13(20.31%) .

The mean total bilirubin level in the patients was 0.68±0.34 mg/dl (mean±SD). 34.3% (22) of ischemic stroke patients in the study had serum total bilirubin levels 0.7 mg/dl or more. Direct bilirubin levels were 0.25+/-0.15 mg/dl (mean+/-SD) and 40 patients (62.5%) had direct bilirubin 0.2 mg/dl or more.

Mean NIHSS Score for Group 1(Low) total bilirubin group was 9.37 and for Group 2(High) bilirubin group was 10.9, which was statistically not significant (p value > 0.05). This indicates that there was no significant correlation between total bilirubin and severity of symptoms at the time of admission.

The mean NIHSS for Group 1(Low)direct bilirubin was 9.37 and 10.95 for Group 2(High) direct bilirubin. There was no statistically significant correlation between NIHSS and direct bilirubin levels.

Mean MR Score for the Group 1 total bilirubin group was 2.0 (1.58,SD) and for Group 2 total bilirubin group was 2.5 (1.46 ,SD), which is statistically not significant

Mean MR Score for the Group 1 direct bilirubin group was 2.21 (1.61, SD) and for Group 2 direct bilirubin group was 2.23 (1.54, SD), which is statistically not significant (p value -0.89).

CONCLUSIONS:

The current study has documented no association between the bilirubin levels and stroke severity, prognosis and residual functional impairment. There is a need to conduct large scale prospective studies to further assess the association between serum bilirubin and stroke severity and its impact on outcomes and mortality.

KEYWORDS: Acute ischemic stroke; Bilirubin; Oxidative stress

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Stroke is known to be one of the commonest causes of mortality across the world[1]. Stroke is becoming a very important cause of disability and premature death in developing countries like India. Over the last few decades, a rise in non communicable diseases including stroke has been considered to be related primarily to demographic changes and enhanced by the prevalence of the risk factors. Bilirubin is now considered as an antioxidant that can cause the progression of diseases caused by oxidative stress, stroke being one such disease.

Oxidative stress that leads to the production of free radicals is found to be an important mechanism of brain damage in Acute Ischemic Stroke (AIS). Bilirubin being an antioxidant, it is synthesised in response to oxidative stress and can indicate the severity of it.

In the study, we aimed to find the association of serum bilirubin with AIS. Various studies conducted during the acute phase of ischemic stroke found that lower levels of serum bilirubin are related to positive outcomes in stroke patients and hence, bilirubin can indicate the severity of oxidative stress.

Yun Luo et al (2012)[2] reported that both Direct Bilirubin (DB) and Total Bilirubin (TB) are indicative of the severity of ischemic stroke.

Sandra Pineda et al (2008)[3] reported an association between higher direct bilirubin on admission and greater stroke severity.

AIMS AND OBJECTIVES

- To determine the association of serum bilirubin with the severity and prognosis of acute ischemic stroke
- To determine the association between serum bilirubin and functional disability at the time of discharge by assessment with Modified Rankin scale.

REVIEW OF LITERATURE

BILIRUBIN

Formation

Hemoglobin is the major source of bilirubin of around 80%. [4]

The catabolism of heme is carried out by hemeoxygenase. Iron is oxidized to ferric form to constitute hemin which is further reduced by NADPH to form heme and an oxygen is added between two pyrrole rings. Similarly ferric iron is formed by the oxidation of ferrous iron. On consequent addition of oxygen, there will be production of ferric iron, CO and also biliverdin which results from the splitting of tetra pyrin ring.

In mammals bilirubin is formed by the reduction of Methylene Bridge present between pyrrole III and IV in biliverdin with the help of the enzyme biliverdin reductase.

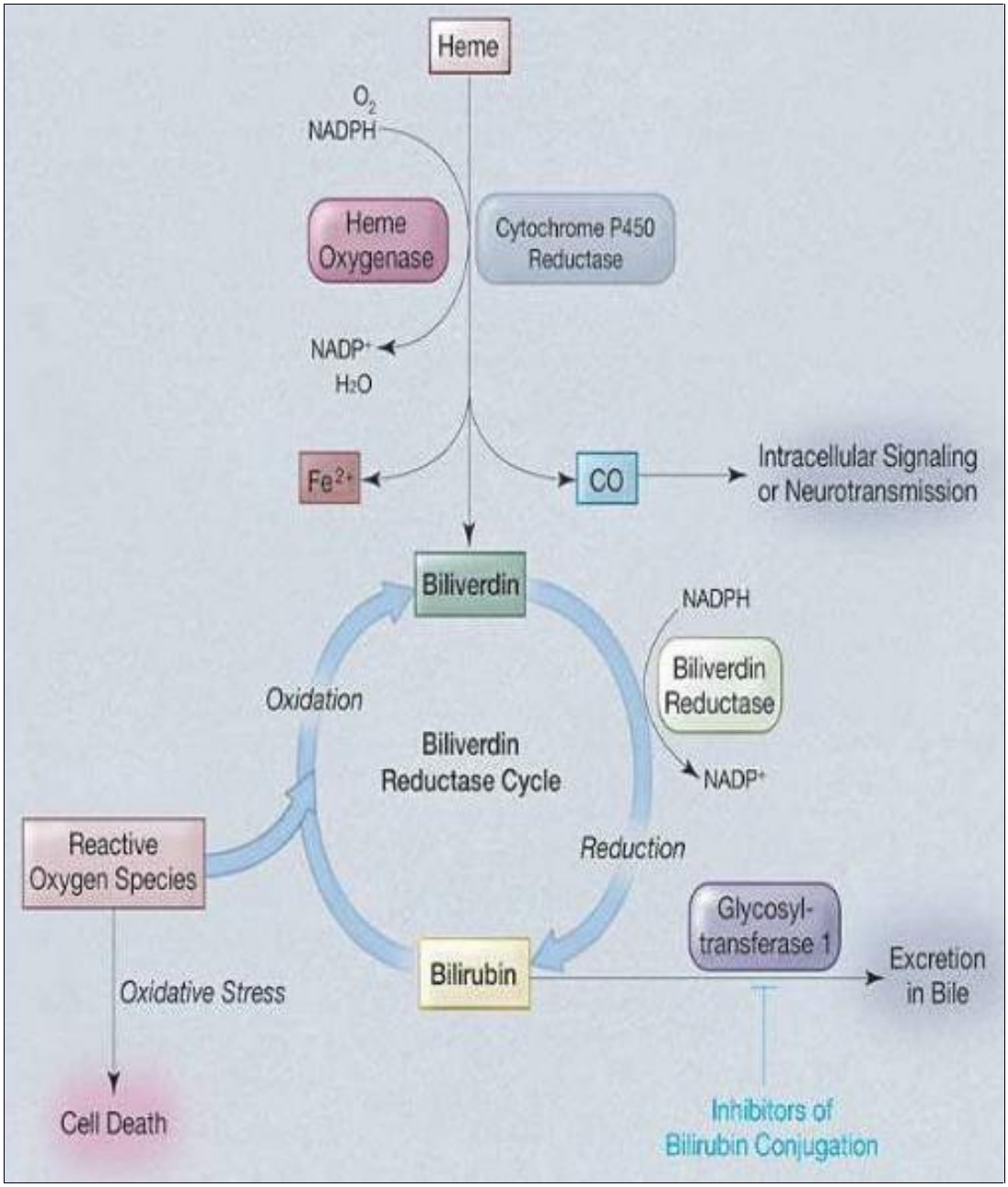


FIGURE 1: BILIRUBIN FORMATION

Conjugation

Bilirubin is non polar and is converted to polar form in hepatocytes by the addition of glucuronic acid by a process known as conjugation.

This process is catalyzed by specific glucuronosyl Transferase (B-UGT) present in endoplasmic reticulum which utilizes UDP-glucuronic acid as a donor of glucuronosyl group. Bilirubin monolglucuronide is an intermediate and gets converted to bilirubin diglucuronide which is the major form of bilirubin in bile, whereas in pathological conditions, bilirubin monoglucuronide is the predominant form in plasma. Bilirubin-UGT can be induced by number of drugs. The rate limiting step of bilirubin metabolism is the secretion into bile mediated by an active transport mechanism. This process is mediated by the MRP-2 (Multidrug resistance like protein-2). The transport of conjugated bilirubin is inducible by the same drugs that can induce the conjugation of bilirubin.

Intestinal bacteria cause conversion of conjugated bilirubin to urobilinogens . On reaching the terminal ileum and the large intestine, the glucuronide present in the conjugated bilirubin is taken out by the action of bacterial enzyme (Beta-Glucuronidases) and reduced by fecal flora to colorless urobilinogens which are tetrapyrrole compounds.

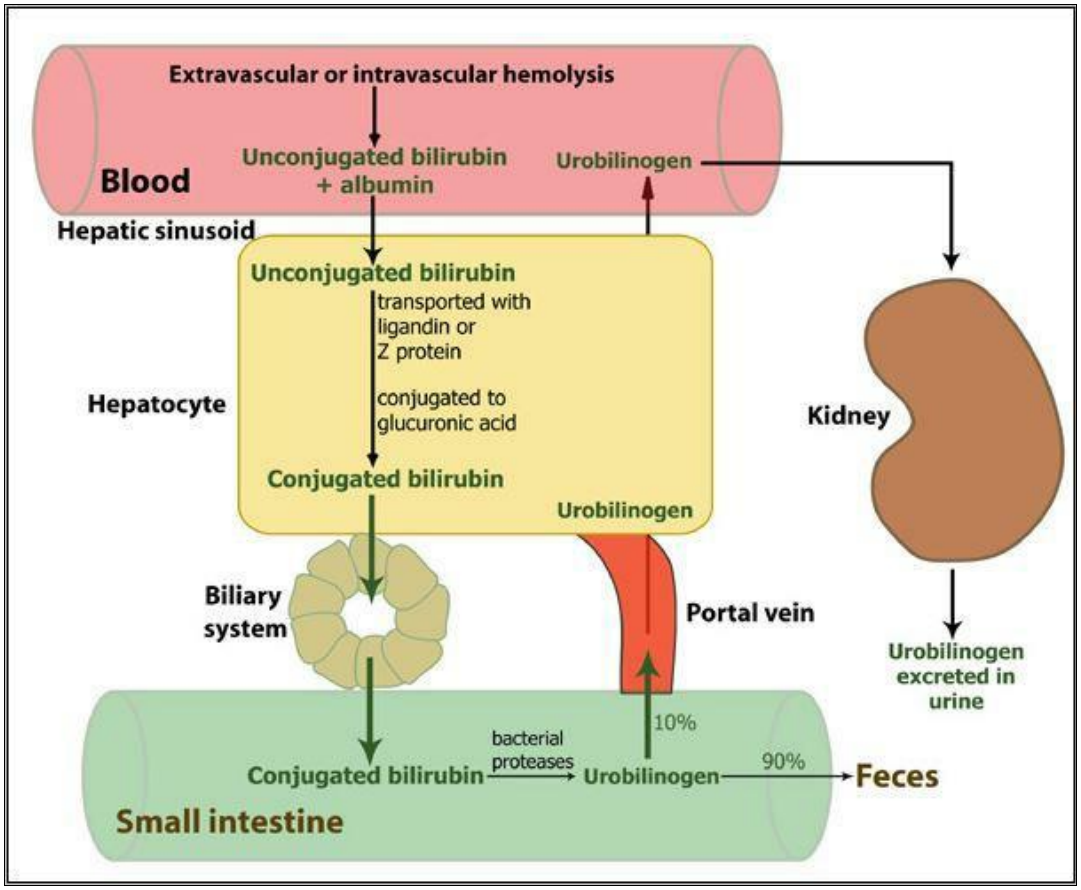


FIGURE 2: BILIRUBIN METABOLISM

A small fraction of urobilinogen is reabsorbed in the terminal ileum and the large intestine and re-excreted through the liver which is called as called enterohepatic urobilinogen cycle .Under pathological conditions, like liver disease or excess bilirubin production, urobilinogen can also be excreted in urine. In the colon, a majority of the urobilinogens are oxidized to urobilins and are excreted in the feces. Oxidation of residual uribilinogen to urobilins causes darkening of feces on standing in air.

STROKE EPIDEMIOLOGY

Stroke incidence and also mortality are increasing as a result of modernization and increased life expectancy. Worldwide, each year 15 million people suffer from stroke.[5] Of those one third die and one third are left permanently disabled.[6]

In developing countries there is a decreasing trend of infectious and malnutrition related diseases, whereas stroke incidence is increasing in recent decades as a result of dietary changes, decreased physical activity, and increased tobacco use.

By 2040, in low and middle income countries, around a billion adults over the age of 65 years are estimated to be at a risk of developing a stroke.[7] In addition to the age, hypertension and tobacco use are the major risk factors worldwide.

MAJOR TYPES OF STROKE

Stroke occurs as a result of disruption of blood flow to a part of brain either because of blood vessel occlusion as in acute ischemic stroke (AIS) or blood vessel rupture causing bleeding either into the brain (Intracerebral hemorrhage-ICH) or around the brain (subarachnoid hemorrhage -SAH).

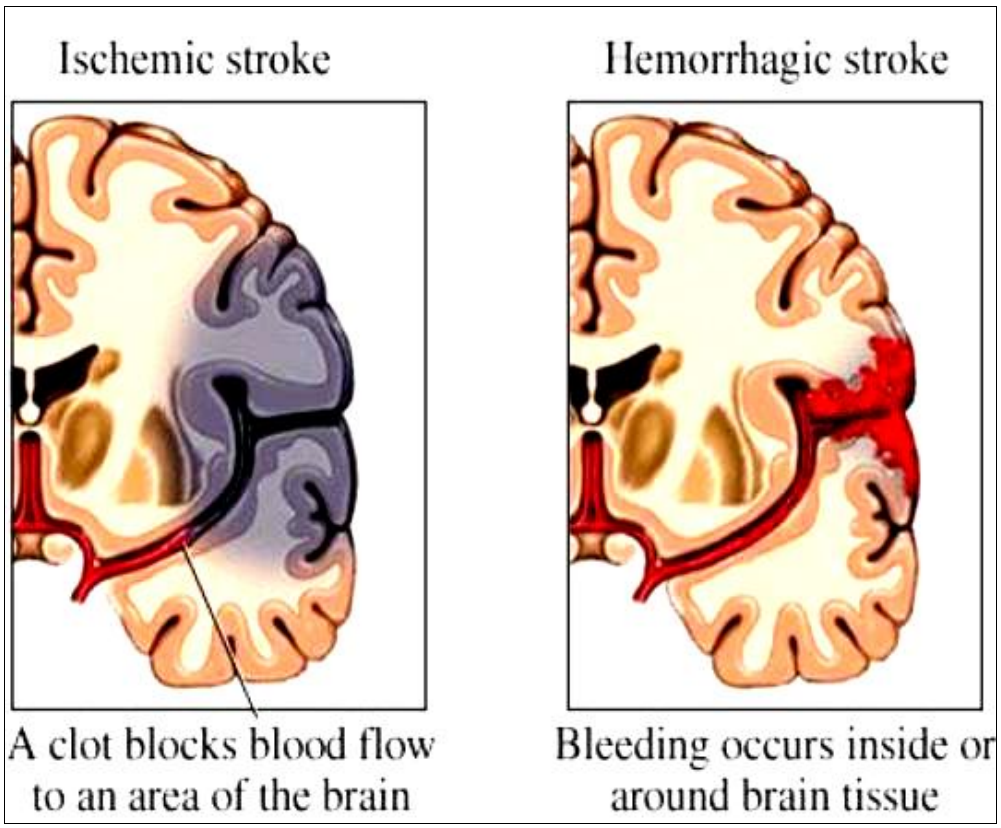


FIGURE 3: ISCHEMIC STROKE & HEMORRHAGIC STROKE

STROKE DEFINITIONS

Stroke is defined as the clinical syndrome of rapid onset of neurological deficit (usually focal) lasting more than 24 hours or leading to death, with no apparent cause other than a vascular one.

Completed stroke is defined as the deficit which becomes maximal within 6 hours.

Stroke-in-evolution is defined as the progression of clinical symptoms and signs over first 24 hours.

In minor stroke, patients usually recover without significant neurological deficits within a week.

Transient ischemic attacks (TIA) don't cause permanent brain damage and symptoms resolve spontaneously. In TIA, neurological symptoms last less than 24 hours, but the duration of most TIAs is between 5 and 30 minutes. TIA is a warning sign indicating that a stroke may occur at any time consequently.

RISK FACTORS OF STROKE

TABLE 1- NON MODIFIABLE AND MODIFIABLE RISK FACTORS OF STROKE[8]

Non modifiable	Modifiable-well documented
Gender	Cigarette smoke
Age	Physical inactivity
Genetics	Poor diet
Race/ethnicity	Diabetes
Low birth weight	Hypertension
	Dyslipidaemia
	Atrial fibrillation
	Carotid artery stenosis
	Post menopausal hormonal therapy
	Sickle cell disease

TABLE 2 - ISCHEMIC STROKE - ARTERIAL ETIOLOGY[9]

Thrombosis	Embolism	Luminal obstruction	Systemic hypoperfusion
Atherosclerotic plaque Lipohyalinosis of small vessel Tumor invasion TTP/DIC Antiphospholipid antibody syndrome Sickle cell disease	**Cardioaortic** Cardiac thrombus Cardiac vegetations Cholesterol Tumor **Artery-to-artery** Atheroma fragments **Decompression illness** **Paradoxical** Amniotic fluid embolism Vasculopathy Deep venous thrombus fragments Cholesterol embolism Air embolism	**Vasculitis** Vasospasm Subarachnoid hemorrhage Meningitis Drug-induced **Extrinsic artery compression** Masses Herniation **Non inflammatory vasculopath**y Sickle cell disease Migraine Buerger's disease Fibromuscular dysplasia CADASIL Moyamoya disease **Angiotrophic lymphoma** Lymphomatoid granulomatosis	Massive MI Shock Cardiac arrythmias Severe hypotension Hyperviscosity syndrome

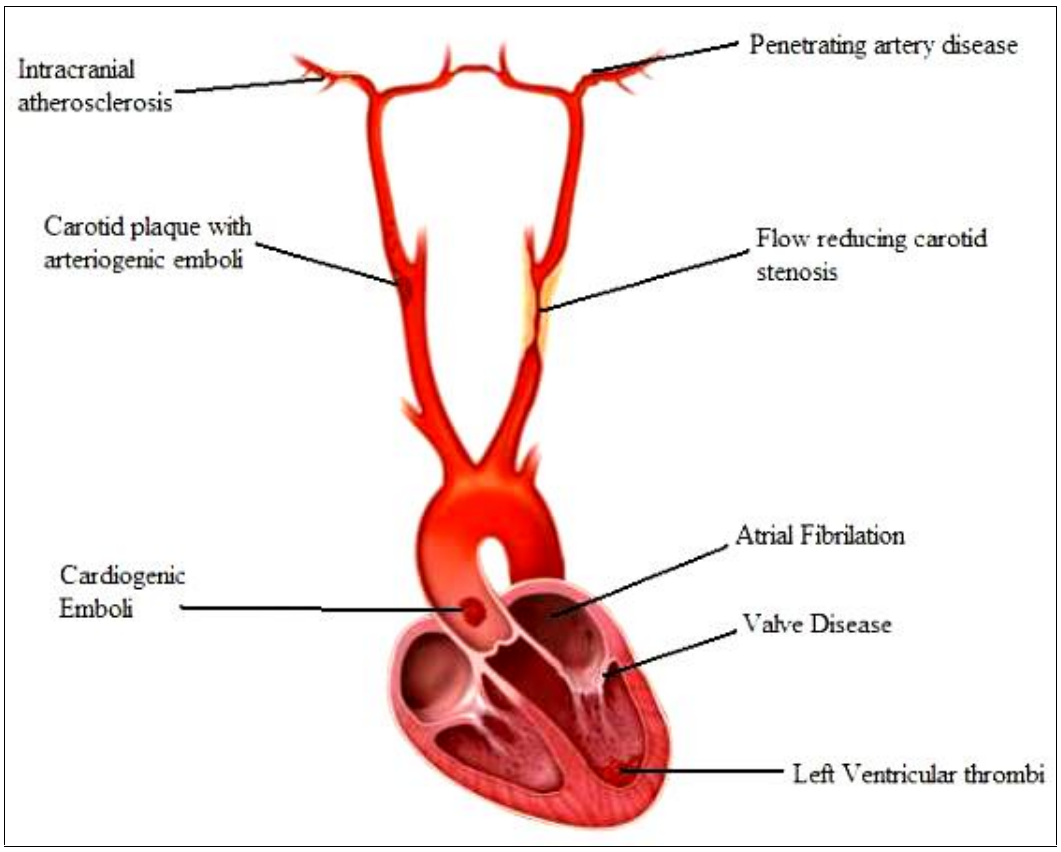


FIGURE :4 MECHANISM OF VESSEL OBSTRUCTIOIN IN ISCHEMIC STROKE[10]

ISCHEMIC STROKE - PATHOPHYSIOLOGY

Ischemic stroke occurs chiefly by 3 mechanisms which include:

Thrombosis

Embolism and

Hypotension (global ischemia).

There are also a number of other mechanisms causing ischemic stroke. However, the most infrequent causes of stroke are those caused by vasospasm which

can be seen in migraine, or after the occurrence of an SAH. Vasospasm is also seen in hypertensive encephalopathy and some forms of "arteritis".

THROMBOSIS

Atherosclerotic lesion is the most common pathological form of vascular obstruction causing thrombotic stroke. [11] Secondary changes that can occur in plaque include ulcerations, haemorrhage into the plaque, thrombosis and even calcifications. The plaque structure, consistency and composition usually determine the tendency of the plaque to get disrupted or ulcerated.

Adhesion followed by the aggregation of platelets to the wall of the vessel occurs resulting in the formation of small nidi of platelets and fibrin. Within one hour of the event, leucocytes at the site initiate an inflammatory response .[12,13]

Thrombotic occlusion of a vessel can occur in pathological conditions other than atherosclerosis such as fibromuscular dysplasia, vasculitis and dissection of the vessel wall.

Deep penetrating artery occlusion results in lacunar infarcts. The commonly affected sites are pons, basal ganglia and internal capsule.

Lacunar infarcts range from 3 mm to 20 mm in diameter. Chronic hypertension causes the small artery to become tortuous and then develop subintimal dissections and form micro-aneurysms which increase the susceptibility of arteriole to micro-thrombus occlusion.

Lipohyalinosis is an important cause and occurs due fibrin deposition.

EMBOLISM

Embolic stroke (ES) results from dislodging of embolus from a variety of sources in the central circulation.

Apart from atheromatous plaque, other sources of embolus in the central circulation are fat, air, metastasis, foreign bodies and bacterial clumps.

The most frequently affected sites of emboli are branches of cerebral and cerebellar arteries. Emboli lodge commonly in the middle cerebral artery distribution. [14]

The most important sources of emboli are the cardiac chambers (left side) and large arteries (e.g. thrombus from the internal carotid artery).

Embolus acts as a vascular irritant and causes vasospasm which determines the outcome of the stroke in addition to the vascular territory which gets affected. The vasospasm need not be limited to the site where the embolus seats, it can also affect the whole arterial tree.

Vasospasm is more common in young individuals on comparing with the elderly since they have more pliable, less atherosclerotic vessels.

Most of the embolic strokes turn in to haemorrhagic infarction (HI).

The pathogenesis of this haemorrhagic transformation of an infarct is a composite phenomenon which includes

1. During ischemia, both the brain parenchyma and the blood vessels are damaged. Upon automatic lysis of the embolus or breakage which can move

distally, blood to the ischemic microcirculation is restored resulting in a “red or haemorrhagic infarct, whereas “pale” or “anaemic infarcts” are the poorly perfused type.

2. Persistent occlusion can also result in bleeding and hence haemorrhagic transformation may not be associated with the distal movement of embolus every time.

In embolic stroke, both haemorrhage and ischemia occur together. Haemorrhagic transformation [15] of the infarct depends upon

Size of the infarct,

Adequacy of collateral circulation, and

Whether there was a usage of anticoagulants or an attempt at thrombolysis was made

Larger the infarct, higher are the chances of haemorrhagic transformation.

GLOBAL-ISCHEMIC OR HYPOTENSIVE STROKE

Hypotensive stroke is caused by the marked reduction in systemic blood pressure due to any cause. The susceptibility of neurons to ischemia is not uniform. The pyramidal cell layer of the hippocampus, the Purkinje cell layer of the cerebellar cortex and cerebral gray matter are most vulnerable. This is because of the abundance of glutamate in these neurons that makes them more susceptible to ischemia.

“Boundary zone” or “Watershed area” is the area that exists between the territories supplied by the major cerebral and cerebellar arteries and these are the commonest sites affected by the global ischemia.

The most commonly affected site is the parietal-temporal-occipital triangle which causes weakness as well as sensory loss of mainly the arm. Watershed infarcts constitute 10% of all ischemic strokes and around 40% of these occur in patients having carotid stenosis or occlusion[16]

ISCHEMIC STROKE - PATHOGENESIS AT CELLULAR LEVEL

Ischemia causes a sequence of events that ultimately leads to neuronal injury and death irrespective of the mechanism responsible for the vessel occlusion. [17] Blood flow reduction decreases the formation of adenosine triphosphate resulting in membrane depolarization. This is associated with the uncontrolled discharge of excitatory amino acids, which include glutamate, in to the extracellular fluid space which is called as excitotoxicity. This excitotoxic amino acid glutamate exerts its action on various receptors e.g. NMDA and AMPA, resulting in the calcium overloading of neuronal cells and thus, causing the activation of proteolytic enzymes.

The activated enzymes cause the degradation of both the intra as well as the extracellular structures and also result in the production of free radicals. Neuronal NO synthase is a calcium dependent enzyme and takes part in the formation of nitric oxide, which can react with superoxide generating the highly reactive radical peroxynitrite. [16] Ischemia results in expression of proinflammatory genes so that several inflammatory mediators are released mainly tumour necrosis factor and interleukin 1ß.

In addition, adhesion molecules are also expressed which results in the binding of neutrophils, monocytes and macrophages with endothelium causing microvascular occlusion and the blood cells cross the vessel wall and penetrate in to the brain

substance and exert their inflammatory action. The inflammatory cells can also form free radicals which can cause further damage.

Although excitotoxicity mainly leads to necrosis, there is also evidence of apoptosis after cerebral ischemia and it has been proposed that both necrosis and apoptosis are triggered in parallel during ischemia and that the predominance of one mechanism will be determined by specific conditions.

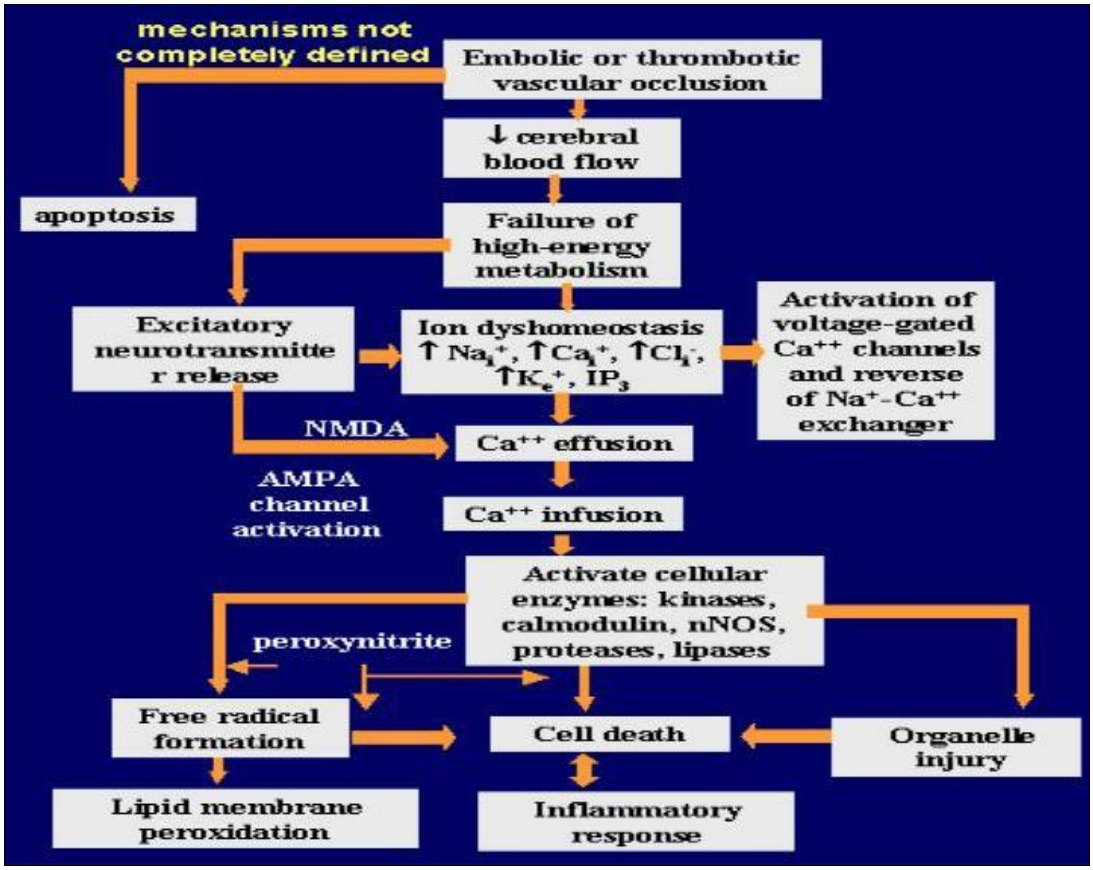


FIGURE 5: PATHOGENESIS OF ISCHEMIC STROKE

STROKE SYNDROMES

Anterior Cerebral Artery Syndromes

Medial portion of the frontal and parietal lobes are supplied by anterior cerebral artery. Infarction of these areas results in contralateral hemianesthesia and hemiparesis that affects the leg more than arm/face due to the topographic arrangement of the homunculus.

In addition damage to the medial part of frontal lobe results in impairment of behavioural and executive functions which can cause abulia[9] .

Anterior cerebral artery infarcts in dominant hemisphere may produce mutism, and whereas in nondominant hemisphere results in acute confusional state. In bilateral ACA infarcts, severe abulia can be present as akinetic mutism along with bladder incontinence.

Middle Cerebral Artery Syndromes

The remaining frontal and parietal lobes, are supplied by middle cerebral artery which also supplies the superior part of the temporal lobe.

Stroke affecting the main proximal part results in hemiparesis, hemianopia and hemianesthesia of the contralateral side. Ipsilateral gaze preference with attention related frontal lobe dysfunctions results.

In dominant MCA lesions, impairment of language functions occurs resulting in motor aphasia when the lesions are at Broca's area which is present in the posterior-inferior portion of frontal lobe. They can also present as sensory aphasia with lesions at Wernicke's area which is present in the temporal lobe in a postero-superior location.

Injury in the corresponding areas in the nondominant hemisphere results in subtle symptoms of language dysfunction in form of motor and sensory aprosodia.

Lesions of the distal part of the MCA or at the level of bifurcation can allow blood flow in the lenticulostriate arteries that spare the internal capsule as well as the basal ganglia. In this type of lesion, the pattern of motor and sensory deficits may be incomplete and irregular and, sparing the leg function especially because of the topographic arrangement of homunculus.[10]

Occlusion of superior division of MCA results in a syndrome of frontal lobe dysfunction, with prominent motor language deficits associated with a variable degree of sensory loss. Whereas lesions occurring in the inferior division of MCA cause a sensory language deficit and hemianopsia results. Gerstmann syndrome includes right-left confusion, acalculia, agraphia and finger agnosia which results from lesion in angular gyrus area.

Posterior Cerebral Artery Syndromes

The inferior temporal lobe and occipital lobe are supplied by posterior cerebral artery. The posterior cerebral artery lesions that don't involve the initial branches to deep structures result in contralateral homonymous hemianopia. Alexia without agraphia is seen in dominant hemisphere lesion. In this condition, reading is impaired by the combination of

1. Impaired connection between the receptive language area and contralateral visual field and
2. Unilateral visual field defect

This occurs due to infarction of the fiber tracts which pass through the corpus callosal splenium posteriorly.

Anton syndrome is characterized by confabulation, and cortical blindness due to damage to bilateral occipital lobes.

The combination of

1. Optic ataxia
2. Oculomotor apraxia and
3. Simultagnosia

Is caused by bilateral PCA infarcts that affect the posterior parietal lobes. This condition is known as Balint syndrome.

TABLE 3: LACUNAR SYNDROMES [18]

LACUNAR SYNDROMES		
Pure Motor	Posterior limb of internal capsule or thalamus	Contralateral hemiparesis
Pure sensory	Posterior limb of internal capsule or thalamus	Contralateral hemisensory loss
Sensory motor	Posterior limb of internal capsule or thalamus	Contralateral hemisensory loss, hemiparesis
Ataxic hemiparesis	Pons, basal ganglia, internal capsule, corona radiata	Contralateral hemiparesis with ataxia
Hemiballismus	Subthalamic nucleus lesion	Contralateral hemiballismus
Dysarthria- clumsy hand	Pons, basal ganglia, internal capsule, corona radiata	Contralateral upper limb ataxia and dysarthria
Dejerine - Roussy	Thalamus	Contralateral hemibody pain and hemisensory loss

DIAGNOSIS OF STROKE:

CT Scan

CT scan images are best used to detect haemorrhagic type of stroke and may not detect an infarction in the first 24 to 48 hours. The main disadvantage of CT scans are that small infarcts, infarcts in the posterior fossa may be easily missed. Small cortical infarcts may also be missed. [11]

Enhancing with contrast gives more details to help diagnose subacute infarcts. It also allows clear visualization of venous structures.

CT angiography (CTA), performed with iodinated contrast coupled with newer multidetector scanners can be used. This iodinated contrast allows better visualization of the intracranial arteries and those in the cervical region, and also intracranial veins. In this method, in one imaging session, aortic arch, and coronary arteries and intracranial veins can be visualized.

The ischemic penumbra can be detected by contrast study which delineates the area at risk of infarction surrounding the infarction. CT without contrast is the modality of choice in acute stroke patients because of its availability and speed, and CT perfusion imaging is also a useful adjunct.

TABLE 4: CT SCAN FINDINGS [1]

Time of infract	Findings
Hyperacute stage: within 12 hours of stroke	50-60% of patients show no abnormal findings in this stage. • Presence of dense MCA sign. • Lenticular nucleus obscuration. • Insular ribbon sign. • Grey-white interface enhancement loss
Acute stage: lasts 12 to 24 hrs	In this stage, basal ganglia will be hypodense. • Sulcal effacement.
Days: 1-7 days	• Mass effect • Wedge-shaped hypodense area in gray and white matter. • Haemorrhagic Transformation
Weeks : 1-8	• Resolution of mass effect • Persistence of contrast enhancement
Months to years	• Encephalomalacia • Volume loss

MRI Scan

MRI clearly shows the location and extent of infarction in all areas, including cortical and posterior fossa structure. Regarding intracranial bleed, it can identify but is not as sensitive as CT in the diagnosis of haemorrhagic stroke. More reliable and highly précised images can be obtained using higher field strength magnets.

Diffusion- weighted imaging modality is more sensitive than CT for early brain infarction or standard MRI [10] .

MR perfusion imaging can be done using gadolinium contrast. Areas with poor perfusion but appearing normal in diffusion sequence are considered as ischemic penumbra. The decision to undertake revascularization procedures can be based on the MRI findings. MRA is a good option to use for the detection of stenosis of extracranial and intracranial parts of internal carotid arteries. On comparing with conventional x-ray angiography, MRA overestimates the of stenosis severity. Extracranial or intracranial arterial dissection can be visualized by a sequence named as MRI with fat saturation. This technique detects even the clotted blood in the vessel wall.

The disadvantages of MRI are it is time consuming, cost ineffectiveness, less availability and more than these, insensitive in detecting blood products on comparing it with CT. Claustrophobia is also a considerable disadvantage.

Most of the stroke protocols suggest CT because of these issues. But for clear description of extent of tissue injury after the acute period and distinguishing new from old infarction, MRI is superior. In diagnosing TIA, it has considerable significance. It is highly sensitive in detecting new infarction, which is a strong predictor of stroke occurrence subsequently.

TABLE 5: MRI FINDINGS

Time of Infarct	Findings
Immediate	Hyperintense on DWI. Contrast enhancement. Alterations in perfusion.
<12 hrs	Gyral edema, Sulcal effacement. Loss of gray-white interfaces (T1).
12 to 24 hrs	Hyperintensity (T2) Enhancement of meninges adjacent to infarct. Mass effect.
1 to 3 days	Enhancement of meninges Begins decline, Hemorrhagic Transformation Signal abnormalities on T1WI, T2WI.

Cerebral angiography

Conventional x-ray cerebral angiography is considered as an imaging modality for diagnosing atherosclerotic stenoses and also other vascular pathologies such as vasculitis, vasospasm, aneurysms, fibromuscular dysplasia, arteriovenous fistula, intraluminal thrombi, and collateral channels.

Endovascular techniques may be used in performing balloon angioplasty, deploying stents, treating aneurysms by embolization, and also in opening occluded vessels with mechanical thrombectomy devices during acute stroke.

In Conventional angiography there are risks of arterial damage, embolic stroke, groin haemorrhage, and renal failure. So, it should be reserved where less invasive techniques are inadequate.

Ultrasound techniques

B-mode ultrasound image with a Doppler ultrasound can detect and quantify the stenosis present in the extracranial part of internal carotid artery, especially at its origin. Transcranial Doppler (TCD) can be used in assessing the flow in the main cerebral arteries and also in detecting stenosis.

In addition TCD can assist in thrombolysis and rtPA administration . MR angiography can be combined with transcranial and carotid ultrasound.

Perfusion technique

Cerebral blood flow can be quantified by PET and xenon techniques but these are not usually applied in clinical practice, being used only in research purposes.

MR perfusion techniques and Single-photon emission computed tomography (SPECT) are other perfusion techniques which detect relative cerebral blood flow.

COMPLICATIONS OF STROKE[8]

Urinary tract infection

Aspiration Pneumonia

Bed sores

Deep vein thrombosis

Hypoxemia

Hyperglycemia

Hyponatremia and seizures

Constipation

Dehydration

Frozen Shoulder and subluxation contractures

TREATMENT OF ISCHEMIC STROKE

Stroke is an emergency condition irrespective of the severity of neurological dysfunction. Stroke management includes general care, specific treatment and treatment of complications.

First step in the management of stroke is confirmation of diagnosis as there are various mimics that exist for stroke which include

- Seizure
- Migraine with aura
- Hypoglycemia
- Wernicke's encephalopathy
- Hypertensive encephalopathy
- CNS tumor, CNS abscess
- Drug toxicity and
- Psychogenic

GENERAL MANAGEMENT OF STROKE

- Fever and glycemic control
- Blood pressure management
- Fluid management
- Treatment of underlying etiology.

Blood Pressure Control [19]

If the systolic BP is between 185-220 mmHg or diastolic BP is between 105-120 mmHg, no need of introducing antihypertensive medications unless there are conditions that endanger life which coexist including

- Acute renal failure
- Acute myocardial infarction/Left ventricular failure.
- Aortic dissection

If there is a plan of starting rtPA therapy, BP >185/110 mmHg should be treated.

If the Systolic BP > 220 mmHg, diastolic BP 120-140 mmHg, an antihypertensive should be immediately administered which includes sodium nitroprusside, nicardipine, captopril, nitroglycerine and labetalol.

SPECIFIC TREATMENT

- Recanalization
- Anticoagulantion
- Aspirin
- Neuroprotective treatment
- Therapeutic hypothermia
- Craniectomy
- Rehabilitation

INTRAVENOUS THROMBOLYSIS

Treatment should be started within 3 hours of stroke onset. Treatment by this means can result in complete improvement at 24 hours and complete recovery or near normalcy at 3 months. The major risk is symptomatic bleeding in brain. But there is no mortality benefit by this treatment. Regimen for IV rt-PA treatment is infusion 0.9 mg/kg over 1 hour, 10 % as bolus dose over 1 minute. Anticoagulants and antiplatelet agents should not be initiated for the first 24 hours of fibrinolysis. This is recommended in the setting of early ischemic changes on CT, irrespective of its extent.

TABLE 6: IV rt-PA INDICATIONS/CONTRAINDICATIONS [10]

Indications	Contraindications
•Diagnosis of stroke clinically • Duration ≤3 hours • CT Scan - No hemorrhage or edema of >1/3 of the MCA territory • Age ≥18 years • Patient or surrogates • Consent	• Rapidly improving symptoms • Minor stroke • Sustained BP >185/110 mm Hg in spite of treatment • Glucose <50 or >400 mg/dL; Platelets <100,000; Hematocrit <25% • Heparin use within 48 h and prolonged PTT, or elevated INR • Prior stroke or head injury in preceding 3 months, prior ICH • Major surgery in the preceding 14 days • Gastrointestinal tract bleeding in the preceding 21 days • Recent myocardial infarction • Coma or stupor

ANTIPLATELET AGENTS

Aspirin (325 mg) should be initiated within 24-48 hours after stroke onset.

ANTICOAGULATION

All patients with atrial fibrillation of non-valvular origin and cardiac disease should be given anticoagulation. Anticoagulation is not recommended in preventing early recurrent stroke, or improving stroke outcome, and within 24 hours of treatment with IV rtPA. The contraindications are large infarction, uncontrolled BP and advanced microvascular changes.

SURGERY

Decompressive evacuation of space-occupying infarction in cerebellum is effective in preventing and also treating herniation which results in brain stem compression. Decompressive surgery is also effective for malignant edema of cerebral hemisphere.

MANAGEMENT OF COMPLICATIONS

The major complication includes raised ICT, seizures and hemorrhagic transformation. Raised ICT can be managed by non-pharmacologic measures including head end elevation of bed, avoiding hypotonic solutions and hypoxia, and hyperventilation. Raised ICT can be treated pharmacologically by IV mannitol, IV or oral glycerol. Furosemide and steroids are contraindicated. Decompressive surgery is also an option.

MEASUREMENT OF STROKE OUTCOMES

Stroke severity at presentation predicts stroke outcomes. National Institutes of Health Stroke Scale (NIHSS) a measure of stroke-related neurologic deficits, has been studied extensively in various clinical trials and found to be a useful predictor of stroke outcomes. The NIHSS is an excellent scale for clinicians to interpret the severity of a stroke. Physicians and also trained health care professionals caring for patients with strokes can use it for stroke assessment. NIHSS score may underestimate the severity of a posterior circulation stroke because most of the variables are related to symptoms of anterior circulation territory. Similarly, it also underestimate the right middle cerebral artery stroke severity because the language function is controlled by the left hemisphere. There are different outcome scales which measure different dimensions of recovery and disability.

Modified Rankin Scale (MRS) for assessment of functional independence.

Glasgow Outcome Scale (GOS) for assessment of general level of disability and recovery.

Barthel Index (BI) for assessment of ability of self-care and mobility.**NIH STROKE SCALE (NIHSS) SCORE** [20]

1. Level of consciousness - 5 points
2. Best gaze on eye movements -2 points
3. Field of vision - 3 points
4. Facial movements - 3 points
5. Hemiparesis and hemiplegia in extremities- 4 points
6. Each limb is graded individually (4 points for each limb)

7. Ataxia in each limb - 2 points
8. Sensation on both sides of the body - 2 points
9. Language (presence of aphasia) - 3 points
10. Dysarthria - 2 points
11. Extinction (formerly 'neglect') -2 points

Interpretation of NIHSS Score

0 – No stroke

1-4 – Minor/Mild stroke

5-15 – Moderate stroke

16-20 – Moderate to severe stroke

21-42 – Severe stroke

MODIFIED RANKIN SCALE [21]

It is a scoring system used for assessing the functional outcome after a stroke.

0- Patients don't have any symptoms

1. In spite of symptoms, patients don't have significant abnormality or disability; they areable to do usual daily activities.
2. Patients have mild disability; not able to carry out all activities which could be done previously, but able to take care of themselves without assistance
3. Patients have moderate disability; need some help, but can walk without assistance
4. Moderate to severe disability; can't walk without assistance and need help even for self-body care.
5. Severe disability; patient is bedridden and needs constant nursing care
6. Dead

Total score: 0 to 6

OXIDATIVE STRESS

Oxidative stress results from an imbalance between the generation of reactive oxygen species and the antioxidant defence. [22]

Increased ROS production through the entire course of AIS, especially in the initial phase can induce the functional and structural damage of neuronal cells. [23]

Low antioxidant activity in the plasma is related to higher level of neurological dysfunction in acute stroke.

Oxidative stress and Acute Ischemic Stroke

High metabolic activity which results in the formation of high levels of ROS, along with relatively reduced catalase make the neurons vulnerable to oxidative stress.

ROS reacts with lipids in the brain to produce peroxyl radicals causing damage to the neuronal membrane by oxidation of its lipids. The combination of all these results in the increased vulnerability of the CNS to damage.

A decrease in mitochondria redox potential resulting in ROS production from the ETC, mainly at cytochrome III becomes the chief source of free radical generation during ischemia.[24-26]

Excitotoxicity after ischemia results in excess cytosolic free Ca2+. This leads to overloading of the mitochondrial proton circuit, resulting in failure of oxidation along with increased ROS production.

Increased ROS formation in mitochondria leads to the improper functioning of the ETC, leading to low ATP production, altered calcium homeostasis, more free radical generation, and mitochondrial dysfunction.[27]

In an animal study, transient MCA occlusion was found to result in more ROS generation and mitochondrial dysfunction. Over-expression of mitochondrial Hsp70/Hsp75 or antioxidant treatment results in decreased ROS concentration attenuates mitochondrial dysfunction.

During the acute phase of stroke, nNOS gets activated as a result of high influx of Ca2+ through NMDA receptors resulting in the increased production of NO. Neuronal NO synthase (nNOS), enzyme is tethered to the NMDA receptor complex by a protein called postsynaptic density protein-95 (PSD95).

During stroke, there is dramatic increase in nitric oxide production in the brain because of the increased activity of NO synthases. Peroxynitrite (ONOO−) and OH- are formed as a result of combination of NO with H2O2 and O2- which strongly contributes to brain damage during ischemia.

After ischemia, NO-induced dysfunction and subsequent ONOO− causes increased generation of mitochondrial free radicals thus causing dysfunction of cellular membranes. This results in necrosis.[26-27]

In another study, after MCA occlusion, the nitric oxide concentration in the ischemic area increased to micromolar levels. Glutamate receptor antagonists could inhibit the sudden increase in NO levels. It is suggested by the study that higher levels of NO metabolite in CSF are directly proportional to brain injury and deterioration of neurological function. [28,29]

Oxidative/nitrosative stress can lead to the damage of membrane lipids, cell proteins and DNA and also initiates cascade reactions, resulting in mitochondrial dysfunction and caspases activation and also that of signal transduction pathways, finally leading to neuronal death.

Results from various studies concluded that oxidative stress plays an important role in the pathogenesis of ischemic stroke.

Mosher Muhammad Hussein Kossi et al concluded that oxidative stress is an important event in thrombotic stroke and may have an unfavourable effect on stroke outcome. [30]

Ayaka Ozkul et al 2007 showed the harmful effects of oxidative stress in the outcome of acute ischemic stroke. [31]

Jaspreet Kaur et al 2011 concluded that oxidative stress contributes to the pathogenesis of acute ischemic stroke and TIA and also the imbalance between the oxidant and antioxidant activity may contribute to the severity of stroke. [32]

Nai-Wen Tsai et al 2014 concluded that large-vessel disease has higher oxidative stress but less antioxidant defense than small-vessel disease. [33]

BILIRUBIN AS A MARKER OF OXIDATIVE STRESS

Kazuhiro Utani 2001 et al proposed that bilirubin metabolites in urine may act as a marker of oxidative stress in septic patients. [34]

Mehmet Davutoglu et al 2008 concluded that bilirubin has significant positive correlation with MDA and NO and negative correlation with anti-oxidant enzyme activities. [35]

Kenji Dohi 2003 proposed that bilirubin levels serve as a useful marker of oxidative stress in patients with hemorrhagic stroke. [36]

Nesrine salah el din abdul hamim et al (Cairo university 2001) concluded that bilirubin level increases as a response to oxidative stress and contributes to plasma antioxidant property.[37]

ANTIOXIDANT ROLE OF BILIRUBIN

Various studies found that bilirubin is a powerful antioxidant: Unconjugated, conjugated, free and albumin- bound bilirubin were all found to be effective scavengers of peroxyl radicals. They are able to prevent peroxidation of LDL. [38]

Under physiological conditions, bilirubin can decrease the formation of atheromatous plaque by the prevention of formation of oxidized LDL.

Various animal and human studies have shown that bilirubin is a physiological antioxidant.

Yamaguchi and co-workers identified biotripyrrins (oxidative metabolites of bilirubin) in the urine of healthy humans and ascorbic acid depleted rats treated with endotoxin. [38]

In the same study, on feeding a documented physiological antioxidant ascorbic acid, secretion of bilirubin metabolites was reduced and also, there was suppression of the endotoxin-stimulated concentration of HO mRNA in liver.

In another animal study, ischemia and reperfusion of rat liver resulted in induction of HO-1and production of biotripyrrins. And there was attenuation of both HO induction and biotripyrrin production on feeding with ascorbic acid in this model.

These results denote that bilirubin protects against oxidative stress.

In an experimental study performed on pig hearts, cardiac ischemia followed by reperfusion was associated with accentuated expression of HO-1 mRNA and increased reactive vascular HO-1.

Dennery et al experiments using Gunn rats proposed the antioxidant role of bilirubin. [39]

Another study of vascular balloon injury resulting in oxidative stress and intimal cell proliferation in rat carotid arteries showed the protective role of bilirubin as an antioxidant.

And this study suggested that increased HO activity and high bilirubin serve a protective role against injury-mediated proliferation of intimal cell.

Various human studies have shown similar findings and bilirubin is believed to be an antioxidant in humans as well.

For example, oxidative stress results in depletion of antioxidants like bilirubin and increased hydroperoxides.

Infants with disorders of oxygen radical mediated injury, such as Retinopathy Of Prematurity, Intraventricular Hemorrhage, bronchopulmonary dysplasia, and necrotizing enterocolitis, show lower circulating bilirubin on comparing with healthy controls.

Similarly, antioxidant status and serum bilirubin concentrations were found to be correlating in premature neonates.

BILIRUBIN AND INFLAMMATION

Role of bilirubin in inflammatory processes and immune reactions has also been documented. Nakagami et al. found that both bilirubin and biliverdin inhibit complement-mediated reactions and the administration of biliverdin inhibits Forssman anaphylaxis reaction in guinea pigs. These findings suggest the protective role of bile pigments by their anticomplement activity.

The correlation between inflammatory processes and bilirubin is supported by evidence that augmented activity of heme oxygenase [41] results in faster recovery of inflammation whereas attenuated activity of this enzyme results in inflammatory response augmentation.

Bilirubin exerts its anti-inflammatory actions by the following mechanisms:

- Decreasing vascular endothelial proliferation by inhibition of NFkB
- Inhibits oxidant-mediated activation of leukocytes
- Anticomplement activity
- Inhibition of leukocyte migration via suppression of VCAM [41]

BILIRUBIN AND ATHEROSCLEROSIS

Bilirubin offers protection against oxidation of lipoproteins and lipids and thereby reducing the formation of atheroma plaque [42,43]. So, patients with low bilirubin concentrations may have augmented atherogenic plaque formation as a result of increase in lipids and lipoproteins oxidation. [44]

Bilirubin – Heme oxygenase activity

Increased HO activity may account for the antiatherogenic property of bilirubin. This is documented by increased heme oxygenase activity resulting in increased formation of CO, iron, and biliverdin and the pathophysiology of atherosclerosis could be affected by changes in any one of these three metabolites.

For example, HO-1 reduces the heme concentration thereby preventing heme mediated cell injury.

In addition, haemoglobin can act as a scavenger of nitric oxide that affects NO mediated vasodilatation.

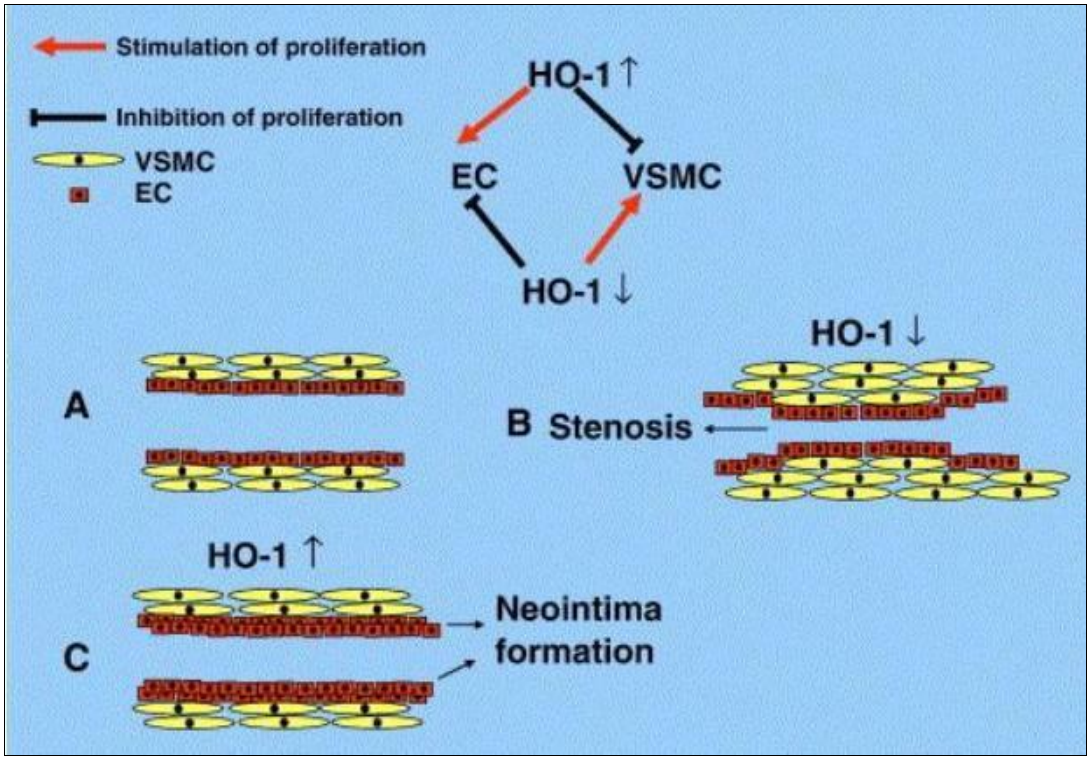


FIGURE 6: ILLUSTRATING ROLE OF HEME OXYGENASE IN STENOSIS AND NEOINTIMA FORMATION

A. Normal

B. Vascular smooth muscle proliferation by low concentration of HO-1 which eventually results in stenosis.

C. Increased HO-1, by inhibiting vascular smooth muscle proliferation inhibits neointmal formation.

SMOKING AND SERUM BILIRUBIN

Smoking induces oxidation of lipids due to exposure to LDL. It also increases the uptake of modified LDL by macrophages. It has already been established that smoking lowers serum bilirubin concentration in males.

HYPERTENSION AND SERUM BILIRUBIN

Ho Jun Chin et al 2009 concluded, that increase in bilirubin level but within the physiological range had a negative correlation with the incidence of hypertension[45] . This effect of bilirubin was more evident in non-smokers and females.

PERIPHERAL VASCULAR DISEASE AND SERUM BILIRUBIN

The NHANES study concluded that higher the serum total bilirubin level lower the incidence of peripheral arterial disease. Whereas patients with low serum bilirubin levels had increased carotid intima- media thickness and also abnormal flow-mediated dilation which are useful in predicting cardiovascular disease in normal individuals. All these findings show that increased bilirubin levels decrease the risk of acquiring cardiovascular disease in normal subjects.

CORONARY ARTERY DISEASE AND SERUM BILIRUBIN

Multiple studies showed inverse relationship between bilirubin concentration and incidence of coronary artery disease[42,43,46,47] . In The Framingham offspring study, it had been found that higher bilirubin levels were associated with decreased risk of acquiring cardiovascular disease in men.

Laura J.Horsfall et al concluded that lower bilirubin is a risk factor for developing CAD and mortality.

RHEUMATOLOGICAL DISEASES AND SERUM BILIRUBIN

In various studies, inverse relationship was found between serum bilirubin levels and some rheumatological disorders such as

- Wegener granulomatosis
- Systemic lupus erythematosus
- Rheumatoid arthritis

There is an inverse association between SLE and serum bilirubin levels. The prognosis of SLE patients is related to the efficiency of antioxidant defense systems. But the low serum bilirubin levels may be caused by the consumption of bilirubin during oxidative stress in SLE. This concept might apply for Wegener granulomatosis and Rheumatoid arthritis where the same results have been found.

DEPRESSION AND SERUM BILIRUBIN

Wai Kwong Tang suggested that the bilirubin is a novel, important biological marker for the risk of developing depression in ischemic stroke patients [48].

On univariate analysis, it was found that more severe stroke was associated with higher bilirubin, reflecting the intensity of oxidative stress in the early phase. Thus, more severe the stroke, greater the risk of post stroke depression.

In the study, the association found between the bilirubin level and post stroke depression was independent of the severity of stroke. So there must be some other possible mechanism for the association between these two. Among the stroke patients, high levels of psychological stress were noted. There is evidence that urine bilirubin metabolites correlate positively with psychological stress. Thus, like high cortisol, high bilirubin level may denote a higher level of perceived stress, resulting in increased risk of depression.

BILIRUBIN IN NEONATE

Transient increase in unconjugated bilirubin commonly occurs in new borns which is called as as “physiologic jaundice,”. It usually resolves without any consequences. Physiologic jaundice offers protection against oxidative stress causing damage to neonatal tissue.

But the unconjugated bilirubin levels may increase above the physiologic range from additional sources of hemolysis. Trauma during birth, G6PD deficiency and ABO or Rh blood incompatibilities are the additional sources of hemolysis.

This pathologic increase in bilirubin can be neurotoxic resulting in neonatal bilirubin encephalopathy (kernicterus). Basal ganglia and other brain stem nuclei are affected by acute bilirubin encephalopathy. Thus, bilirubin has been found to confer both neuroprotective antioxidant characteristics as well as neurotoxic properties. A complete knowledge of the interactions between bilirubin and central nervous system is needed since it may have profound clinical implications in the treatment modalities used in the critical care setting.

BILIRUBIN AND NEUROPROTECTION

Unconjugated bilirubin can't cross the intact blood brain barrier. This prevents its accumulation in the CNS since most of the unconjugated bilirubin found in plasma is bound to albumin. When bilirubin acts as an antioxidant, biliverdin is formed by the oxidation of bilirubin, but again bilirubin is formed by the action of biliverdin reductase.

This explains how even in low concentrations in neuronal cell cultures, bilirubin exerts its powerful antioxidant property. HO-2 constitutes the major form of heme oxygenase in the central nervous system, whereas HO-1 is found in specific cell types in the brain such as microglia and macrophages.

Recently, in an animal study done in rats, after the occlusion of middle cerebral artery, post-treatment with propofol, there was evidence of attenuation of ischemic damage partly by up regulation of HO-1.

Similarly, an experimental study done in mouse following cerebral ischemia showed greater damage of neurons in HO-2 knockout mice compared to normal counterparts, supporting the concept of neuroprotective role of bilirubin.

BILIRUBIN AND NEUROTOXICITY

Bilirubin not only serves a protective role in neurological diseases, there is evidence showing the role of bilirubin in the progression of neurological dysfunction in various pathological conditions.

In most of these pathological states, there is an increase in bilirubin levels above physiologic range so that the toxic effects of bilirubin exceed the protective role. This effect will result in damage to the central nervous system.

The neurotoxic effects of bilirubin start above a certain micromolar concentrations, and when that level is reached, it will aggregate and adhere to cellular membranes, resulting in the disruption normal function.

Drugs can compete with bilirubin for albumin-binding sites, resulting in increase of plasma bilirubin levels.

For example, bilirubin can be displaced from albumin by fatty acid components which leads to amplification of bilirubin related neurotoxicity in susceptible patients.

NEUROTOXICITY OF INDIRECT BILIRUBIN

Maria Alexandra Brito et al observed the role of unconjugated bilirubin in promoting lipid peroxidation, ROS formation and protein oxidation in synaptosomal membrane systems. [49]

Similarly, in another study it has been proposed that the pathogenesis of encephalopathy by hyperbilirubinemia is due to the action of unconjugated bilirubin by induction of oxidative stress. [50]

Cristina Bellarosa in 2011 proposed that an increase in unconjugated bilirubin (UCB) can result in bilirubin encephalopathy. Oxidative and Endoplamic Reticulum stress are suggested to be involved bilirubin induced neurotoxicity. [51]

NEUROTOXICITY OF BILIRUBIN AND HEMORRHAGIC STROKE

When a weakened blood vessel ruptures, hemorrhagic stroke occurs which results in bleeding into the brain substance and neuronal injury subsequently. There are additional complications in hemorrhagic stroke patients resulting in secondary damage which occur days after the initial event such as cerebral ischemia and vasospasm.

HO-1 in the brain is induced by the blood present locally, resulting in increased production of unconjugated bilirubin.

There is clinical evidence which supports the concept that the environment immediately around the hematoma is highly contributive to oxidative reactions, augmenting the conversion of bilirubin into bilirubin oxidation products. Bilirubin oxidation products in CSF have temporal relationship with the time of onset of cerebral vasospasm, and proved to be vasoactive. They can either cause or contribute to vasospasm and also the resulting delayed neurologic dysfunction following hemorrhagic stroke. [52]

ISCHEMIC STROKE AND SERUM BILIRUBIN

In 1971, Herishanu et al found that hyperbilirubinemia was prevalent in patients with acute ischemic stroke during the first 48 hours after the onset of stroke symptoms, whereas liver enzymes and other values were normal in the same patients. They couldn’t substantiate this discrepancy.

There are studies supporting the evidence of protective role of bilirubin in the incidence of cardiovascular and cerebrovascular diseases. [53,54,55]

But it has been proposed by various studies that during the acute phase of ischemic stroke, bilirubin levels get elevated and patients with higher level of bilirubin have severe disease and worse outcomes.

Bilirubin causes brain damage by

- Mitochondrial enzyme inhibition,
- Disruption of DNA synthesis, and
- Attenuation of protein production.

Nicholas V Mendezl [56] et al 2013 explained about the role of bilirubin in ischemic stroke . In Ischemic stroke, when blood flow to a part of brain is obstructed either by thrombus or embolus, there will be a hypoxic ischemic state which produces downstream hypoxic-ischemic conditions resulting in increased oxidative stress.

In these conditions, HO-1 induction takes place resulting in amplification of bilirubin formation. It has been proposed that the serum bilirubin level is a biomarker of the degree of ischemic damage following stroke.

These findings suggest the bilirubin may be used as an early prognostic marker of stroke severity and outcome during the management of patients having ischemic stroke.

MATERIALS AND METHODS

Source of data

- Patients admitted in the wards and ICU of Departments of General Medicine, Neurology at KLES Dr.Prabhakar Kore Hospital, Belagavi fulfilling the inclusion criteria.

Method of collection of the data

- **INCLUSION CRITERIA**

- All adult patients > 18 years of age presenting with cerebro vascular accident and proved as ischemic stroke on CT scan or MRI scan within 24 hours of stroke

- **EXCLUSION CRITERIA**

- Hemorrhagic stroke
- Hemolytic anemias
- Hepatobiliary disease
- Patients on hepatotoxic drugs

METHODOLOGY

- Patients admitted at KLES hospital with acute ischemic stroke were confirmed by CT/MRI Brain were included in the study after obtaining Informed consent and Institutional ethical clearance.
- A detailed history was taken and clinical features were assessed.

- Basic laboratory tests were conducted such as complete blood counts, liver function tests, renal function tests.
- National Institute of Health Stroke Scale, serum total bilirubin and direct bilirubin levels were assessed at the time of admission. Patients were arbitrarily divided into the groups of
    1. Group 1(High) total bilirubin with levels less than to 0.7mg/dL and Group 2(Low) total bilirubin with values greater than and equal to 0.7mg/dL.
    2. Group 1(Low) direct bilirubin with levels less than 0.2mg/dL and Group 2(High) direct bilirubin with levels greater than and equal to 0.2mg/dL.
    3. Groups according to the severity of stroke were made based on the NIHSS scores as minor/mild stroke(0-4), moderate stroke(5-15), moderate to severe stroke(16-20) and severe stroke(21-42).
- Modified Rankin scale was performed at the time of discharge. The subjects were divided into good outcome with scores of 0-3 and poor outcome with scores of 4-6.
- For analysis,
    1. BP greater than and equal to 140/90mmHg was considered high and less than 140/90 mmHg was considered normal.
    2. HDL levels greater than and equal to 40mg/dL were considered high and less than 40mg/dL were considered low.

3. LDL levels greater than and equal to 100mg/dL were considered high and less than 100mg/dL were considered low.

4. Triglyceride levels greater than and equal to 150mg/dL were considered as high and less than 150mg/dL were considered low.

5. Total cholesterol levels greater than and equal to 200mg/dL were considered as high and less than 200mg/dL were considered as low.

1. All the patients fulfilling the inclusion criteria and willing to participate, were included in the study.

STUDY DESIGN:

A ONE YEAR HOSPITAL BASED OBSERVATIONAL STUDY

Period of study – 1ST January 2018 to 31ST December 2018

- Study design: Observational study
- Study period: The study was conducted from January 2018 to December 2018
- Sample size: calculated using the formula

  $N= z_a^2 P(1-P) / d^2$

  For a 5% level of significance, z_a is 1.96

  P is the prevalence of the disease which is 20%

  d is the percentage likely difference in the prevalence which is 10%.

  On application N = 61.46 and a sample size of 64 was taken
- Sample Method: Purposive sampling.

All consecutive patients fulfilling the inclusion criteria were included in the study.

INVESTIGATIONS

- Complete blood count
- Renal function tests
- Liver function tests
- Serum Total Bilirubin and Direct Bilirubin levels
- Lipid Profile
- RBS
- ECG
- CT/MRI Brain

Statistical Methods Used:

- R i386 3.5.1 and advanced excel has been used for the analysis. Continuous variables are represented by mean ± sd form and categorical variables by frequency table. Chi-square/Fisher Exact test has been used to check the association between categorical variables. Comparison has been done using t-test/Mann Whitney U-test. p-value less than 0.05 have been considered as significant.

RESULTS

Sample data contains 64 subjects of age 60.25 ± 12.54 years consisting of 45 (70.3%) male subjects and remaining 19 (29.6%) female subjects. Summary statistics are given in following tables.

Table 7: Distribution of subjects by Age group

Factor	Sub-category	Total Number	Percentage (%)
Age	**30-39**	2	3.1%
	40-49	12	18.7%
	50-59	14	21.8%
	60-69	20	31.2%
	70-79	13	20.3%
	Above 80	3	4.6%
Age (in years)		60.25 ± 12.54	

From table 7, we observe that majority (31.2%) of the subjects are of the Age group “60-69”, followed by “50-59” (21.8%), “70-79”(20.3%). There are only 3 and 2 subjects are with age Above 80 and between 30-39 respectively.

Figure 7: Distribution of subjects by Age group

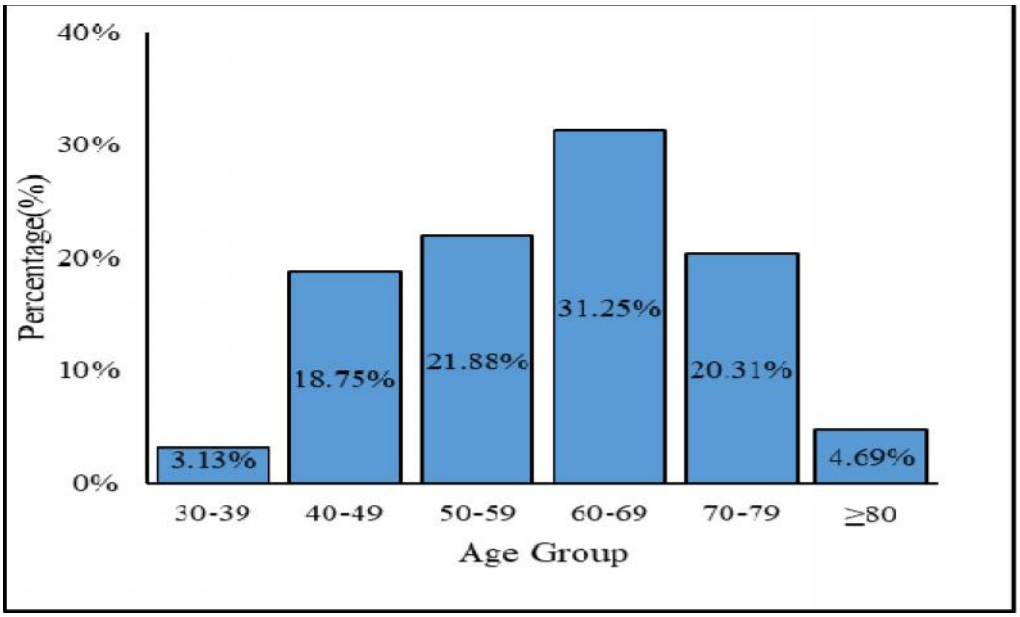


Table 8: Distribution of subjects by Gender

Factor	Sub-category	Total Number	Percentage (%)
Gender	**Male**	45	70.3%
	Female	19	29.6%

From table 8, we observe that there are 45(70.3%) male and 19(29.6%) female subjects in the sample.

Figure 8: Distribution of subjects by Gender

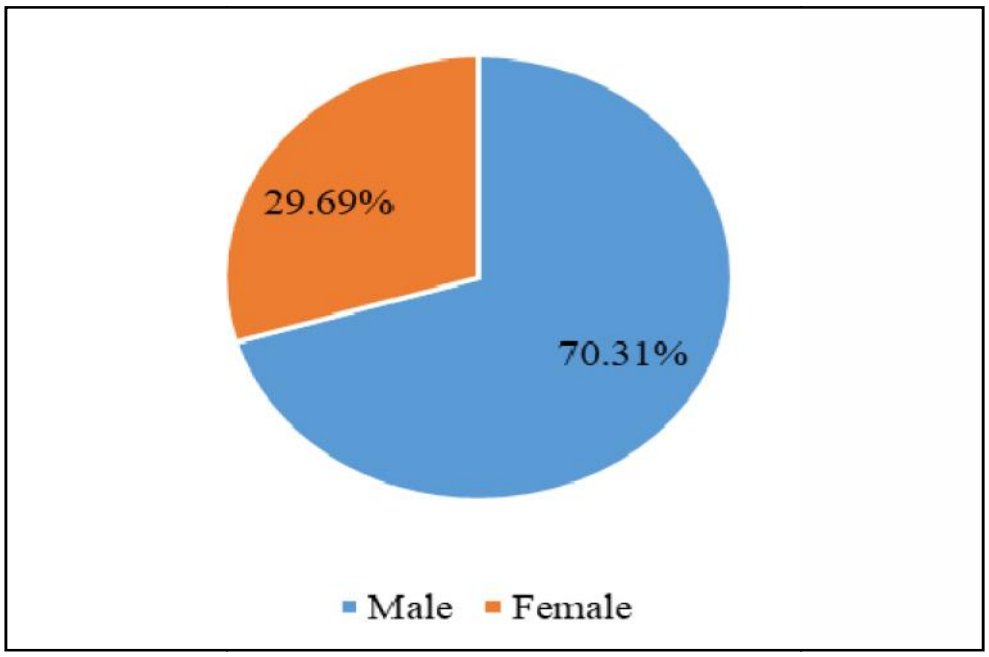


Table 9: Distribution of subjects by Chief Complaints

Factor	Sub-category	Total Number	Percentage (%)
Chief Complaints	**Motor**	56	87.5%
	Cranial Nerve	43	67.1%
	Speech	39	60.9%
	Sensory	11	17.1%

From table 9, we observe that amongst the total subjects, 56(87.5%) subjects had motor chief complaints whereas 43(67.1%) had complaints related to Cranial Nerve abnormalities, followed by 39(60.9%) with speech related complaints and 11(17.1%) with sensory complaints.

Figure 9: Distribution of subjects by Chief Complaints

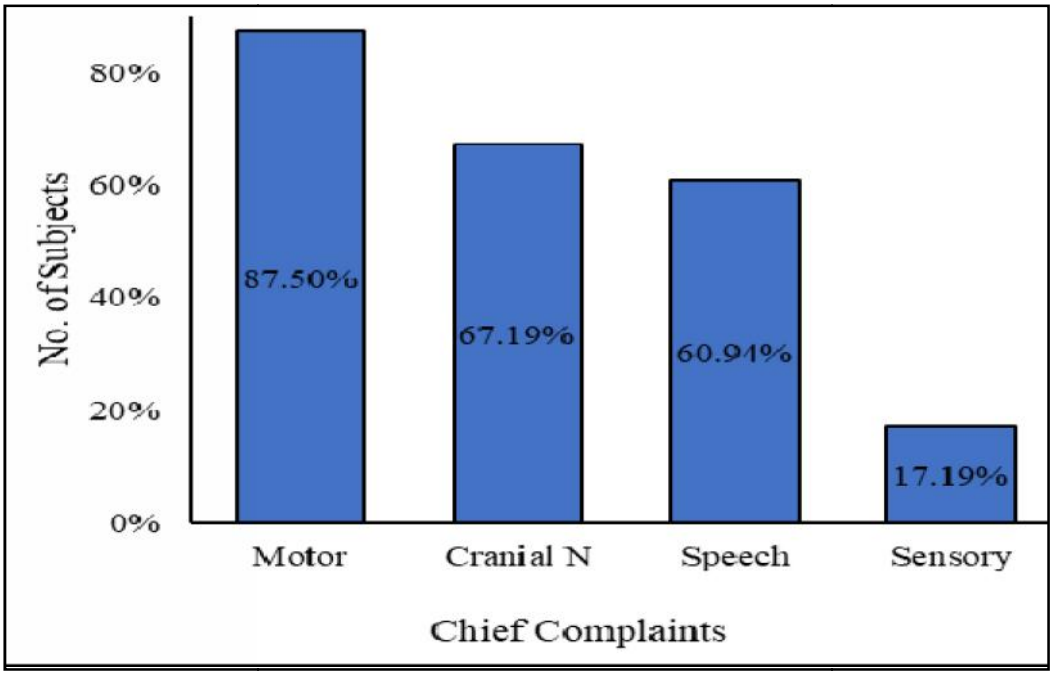


Table 10: Distribution of subjects by Risk factors

Factor	Sub-category	Total Number	Percentage (%)
Risk Factor	**DM**	22	34%
	HTN	32	50%
	Smoker	15	23%
	Alcoholic	19	30%

Abbreviation: DM: Diabetes Mellitus; HTN: Hypertension

From table 10, we observe that Hypertension is present in 50% of the total subjects, 34% subjects have Diabetes Mellitus whereas 30% of the total subjects are Alcoholic and 23% subjects are smokers.

Figure 10: Distribution of subjects by Risk factors

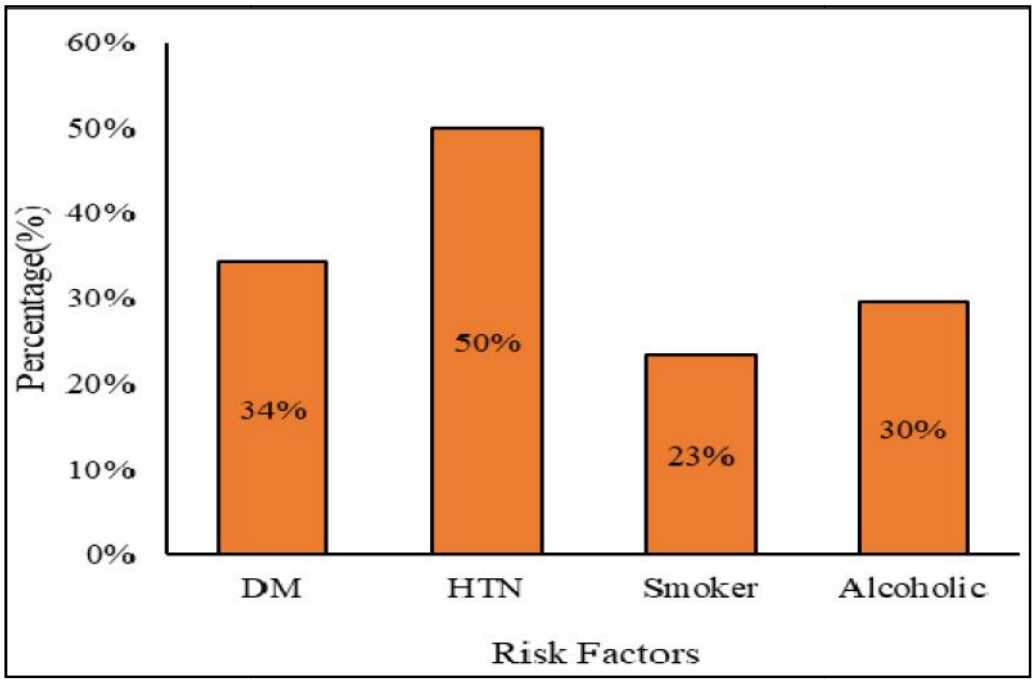


Table 11: Distribution subjects by Blood pressure

Factor	Sub-category	Total Number	Percentage (%)
Blood Pressure	**High (> or equal to 140/90 mmHg)**	28	44%
	Normal (<140/90mmHg)	36	56%

From table 11, we observe that 28% of the total subjects have High blood pressure and 56% subjects have Normal blood pressure.

Figure 11: Distribution of subjects by blood pressure

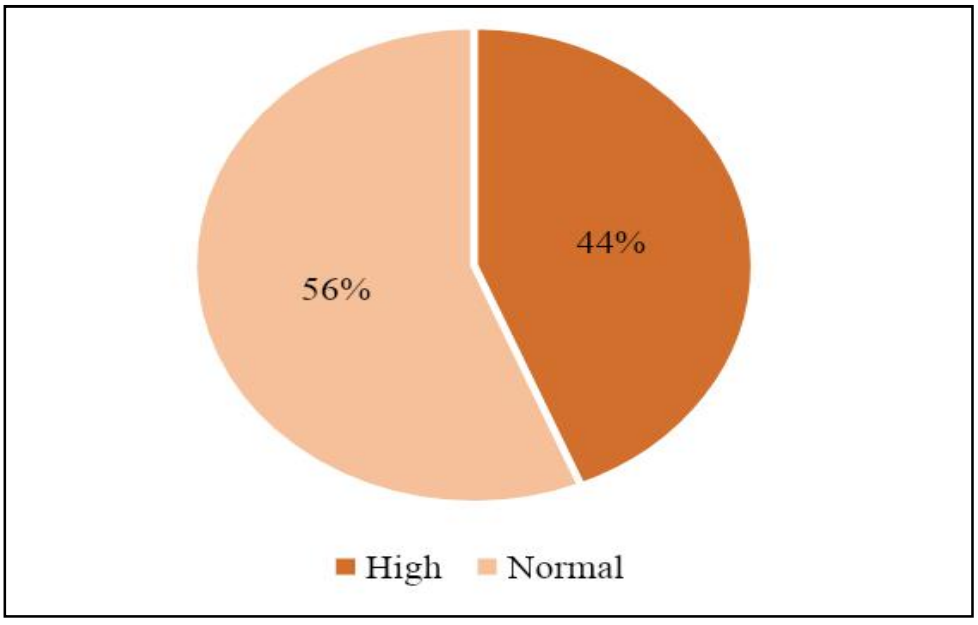


Table 12: Distribution of subjects by stroke territory

Factor	Sub-category	Total Number	Percentage (%)
Stroke Territory	**ACA**	1	1.5%
	MCA	47	73.4%
	PCA	2	3.1%
	ACA-MCA	5	7.8%
	MCA-PCA	7	10.9%
	Cerebellar	6	9.3%

From table 12, we observe that majority- 73.4% of the subjects had a stroke of the MCA territory followed by “MCA-PCA” territory with 10.9% .

Figure 12: Distribution of subjects by stroke territory

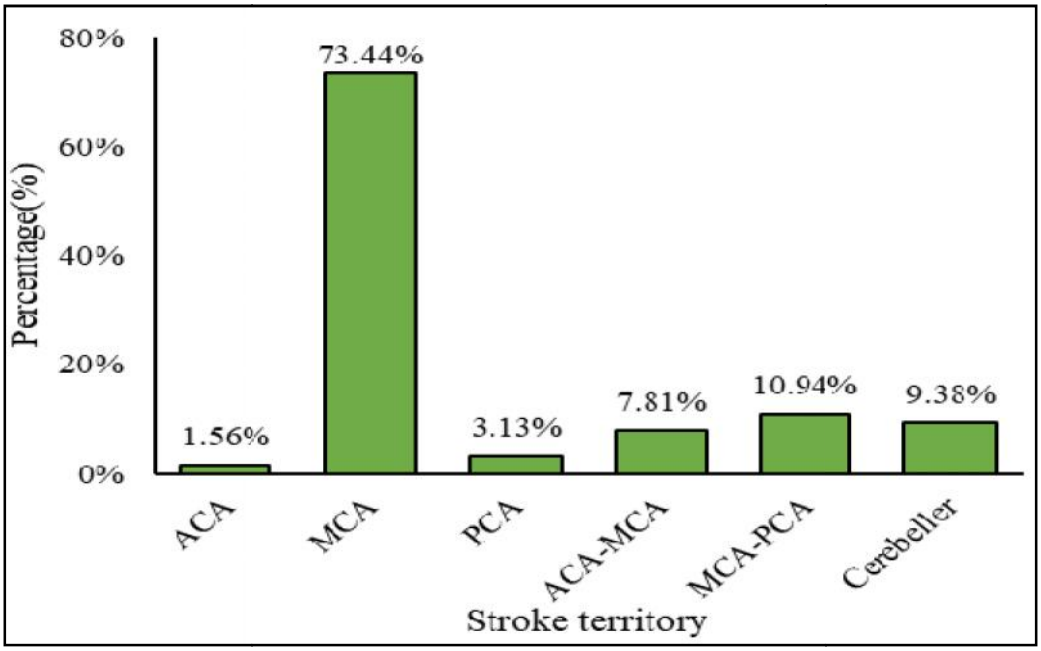


Table 13: Distribution of subjects by clinical features

Factor	Sub-category	Total Number	Percentage (%)
Clinical Features	**Motor**	55	85.93%
	Cranial Nerve	43	67.19%
	Speech	10	15.63%
	Sensory	12	18.75%

From table 13, we observe that amongst the total subjects, 55(85.93%) subjects had clinical features of the motor system whereas 43(67.19%) had features of cranial nerve dysfunction.

Figure 13: Distribution of subjects by clinical features

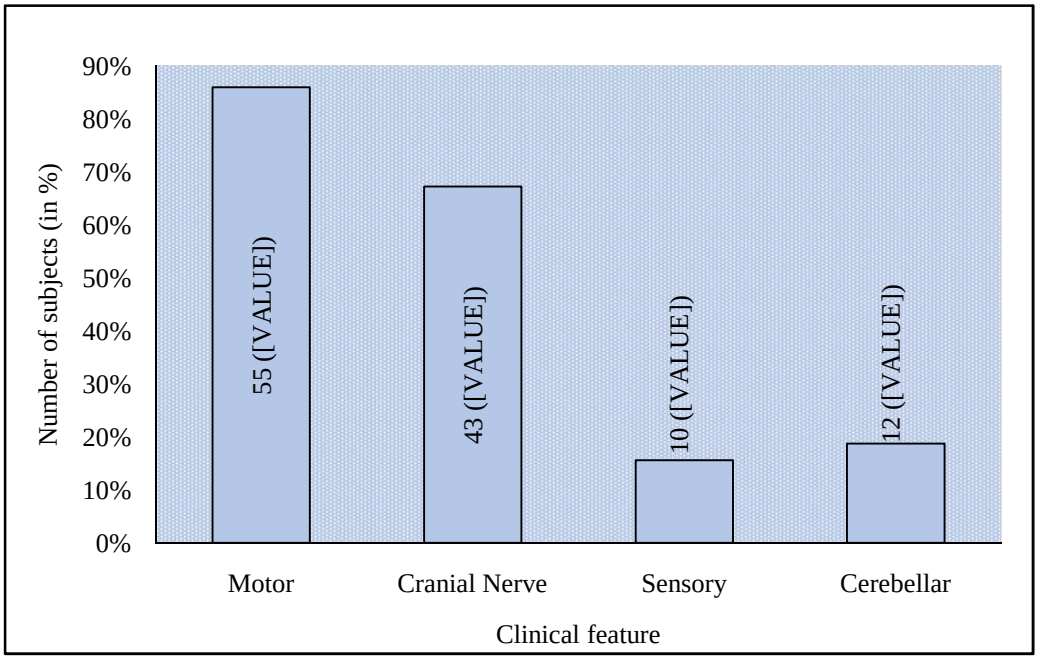


Table 14: Distribution of subjects by High density lipoprotein category

Factor	Sub-category	Total numbers	Percentage (%)
High density lipoprotein category	**High (> or equal to 40mg/dL)**	27	42.18%
	Low(<40mg/dL)	37	57.81%
High density lipoprotein		38.20±9.75mg/Dl	

From table 14, we observe that the mean HDL value is 38.20±9.75mg/dL. 37(57.81%) subjects are in the low HDL category whereas 27(42.18%) are in the high HDL category.

Figure 14: Distribution of subjects by HDL category

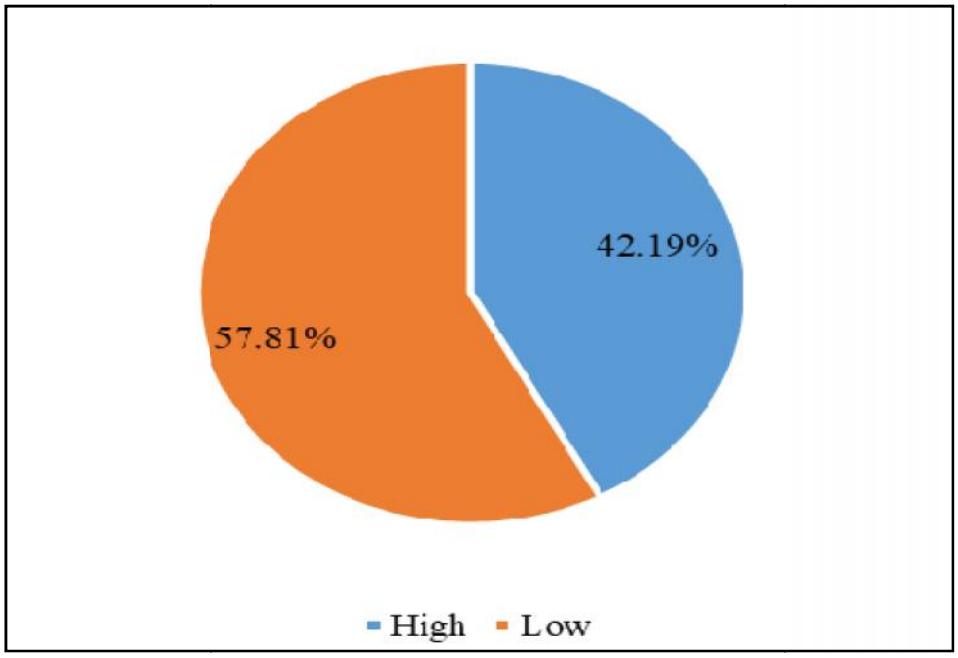


Table 15: Distribution of subjects by Low density lipoprotein category

Factor	Sub-category	Total numbers	Percentage (%)
Low-density lipoprotein category (LDL)	**High (> or equal to 100mg/dL)**	29	45.31%
	Low(<100mg/dL)	35	54.68%
Low density lipoprotein		97.53±40.94mg/dL	

From table 15, we observe that mean Low density lipoprotein value in the sample is 97.53±40.94 mg/dL. Also, 45.31% have high low density lipoprotein values.

Figure 15: Distribution of subjects by LDL category

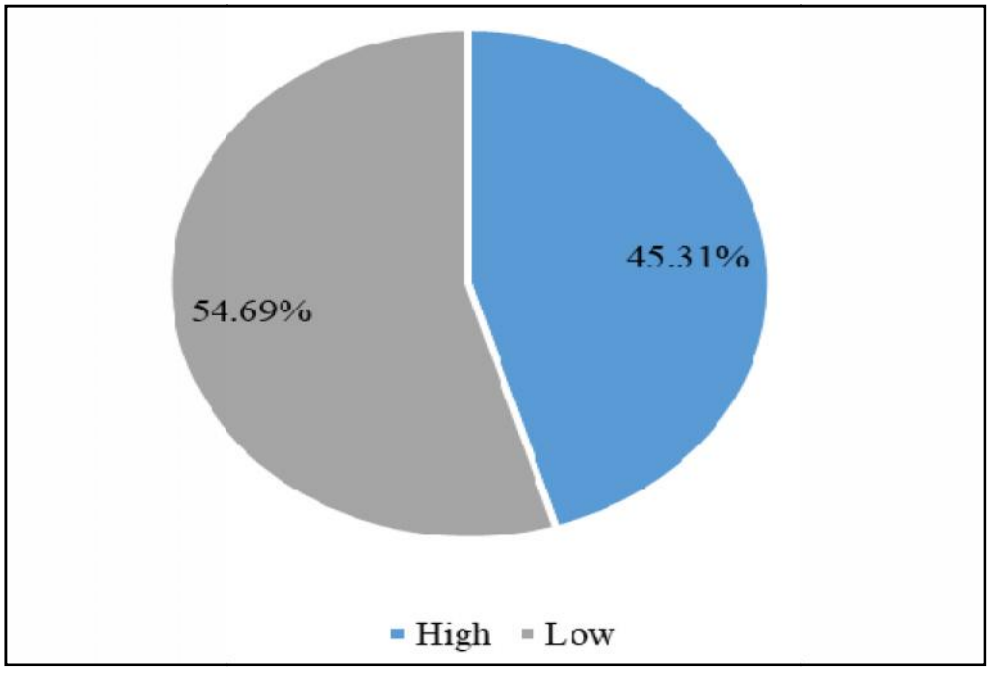


Table 16: Distribution of subjects by Triglycerides levels

Factor	Sub-category	Total numbers	Percentage (%)
Triglycerides category	**High(> or equal to 150mg/dL)**	18	28.12%
	Low(<150mg/dL)	46	71.87%
Triglycerides		135.09±81.59mg/dL	

From table 16, we observe that amongst the total subjects,28.12% have high triglyceride levels.

Figure 16: Distribution of subjects by Triglycerides

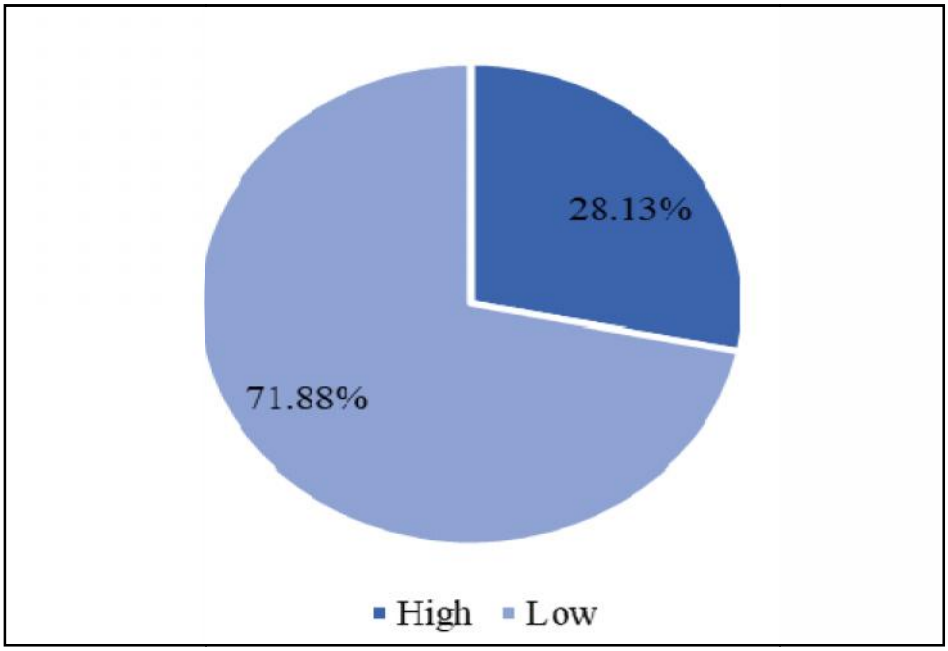


Table 17: Distribution of subjects by Total cholesterol category

Factor	Sub-category	Total numbers	Percentage (%)
Total Cholesterol category	**High (> or equal to 200mg/dL)**	13	20.31%
	Low(<200mg/dL)	51	79.68%
Total Cholesterol		160.19±45.00mg/dL	

From table 17, we observe that 20.31% of total subjects have high total cholesterol levels. Also, mean total cholesterol level in the sample is 160.19±45.00mg/dL.

Figure 17: Distribution of subjects by Total cholesterol

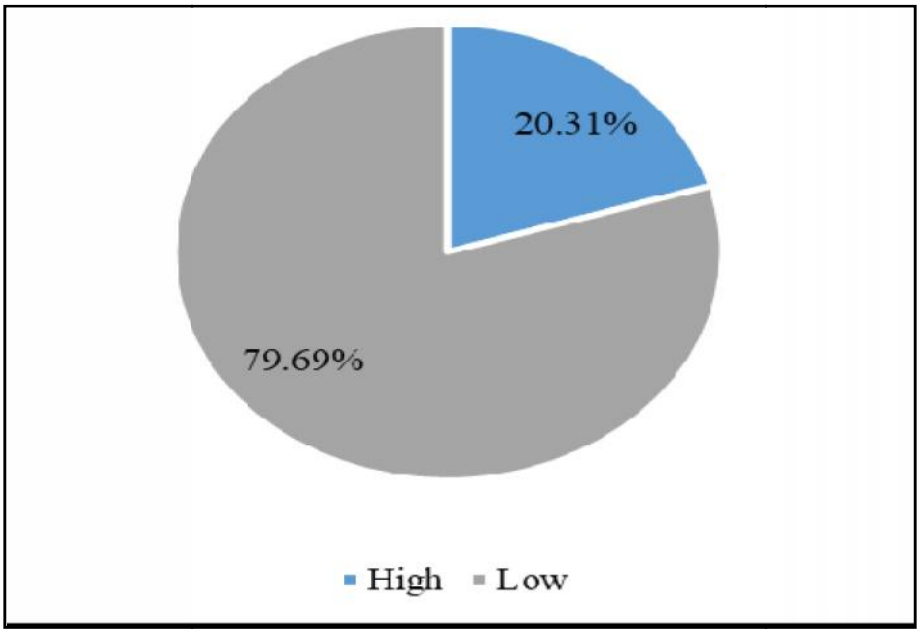


Table 18: Distribution of subjects by Total bilirubin level

Factor	Sub-category	Total numbers	Percentage (%)
Total bilirubin category	**Group 1 (<0.7mg/dL)**	42	65.62%
	Group 2(> or equal to 0.7mg/dL)	22	34.37%
Total bilirubin		0.68±0.34mg/dL	

From table 18, we observe that, 42(65.62%) subjects in the sample fall into group 1 with lower bilirubin levels and 22(34.37%) had higher total bilirubin and fell into group 2.

Figure 18: Distribution of subjects by Total bilirubin

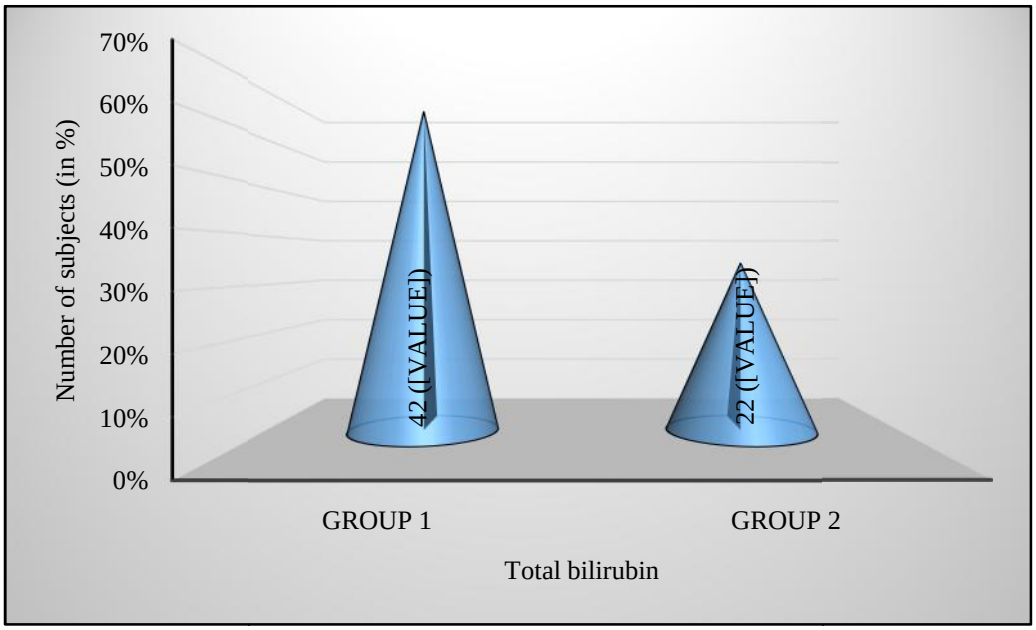


Table 19 : Distribution of subjects by Direct bilirubin level

Factor	Sub-category	Total numbers	Percentage (%)
Direct bilirubin category	**Group 1(<0.2mg/dL)**	24	37.50%
	Group 2	40	62o.50%
Direct bilirubin		0.25±0.15mg/dL	

From table 19, we observe that majority of the subjects i.e. 40 in the sample had high level direct bilirubin and fell into group 2 while 24 had lower direct bilirubin and fell into group 1.

Figure 19: Distribution of subjects by Direct bilirubin level

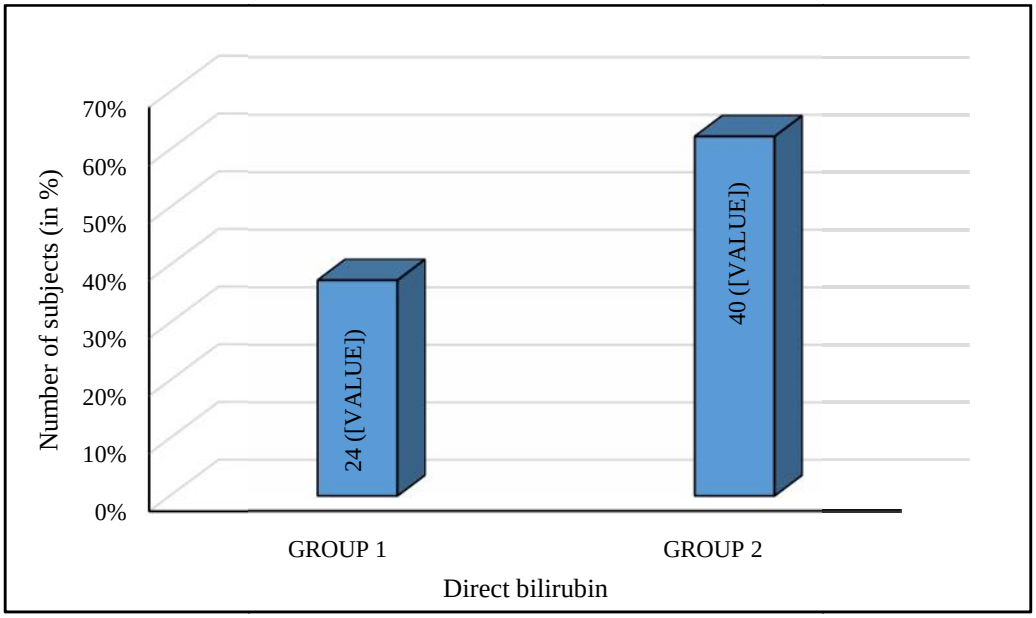


Table 20: Distribution of subjects by NIHSS category

Factor	Sub-category	Total numbers	Percentage (%)
NIHSS Category	**Minor**	13	20.31
	Moderate	38	59.38
	Moderate to severe	9	14.06
	Severe	4	6.25
NIHSS		10.5[0,31] [aa]	

Abbreviation: NIHSS: National Institutes of Health Stroke Scale; [aa] indicates median range

From table 20, we observe that there are 38 subjects with moderate NIHSS score followed by 13 subjects with minor NIHSS score, 9 with moderate-severe NIHSS score and 4 subjects are with severe NIHSS score in the sample.

Figure 20: Distribution of subjects by NIHSS category

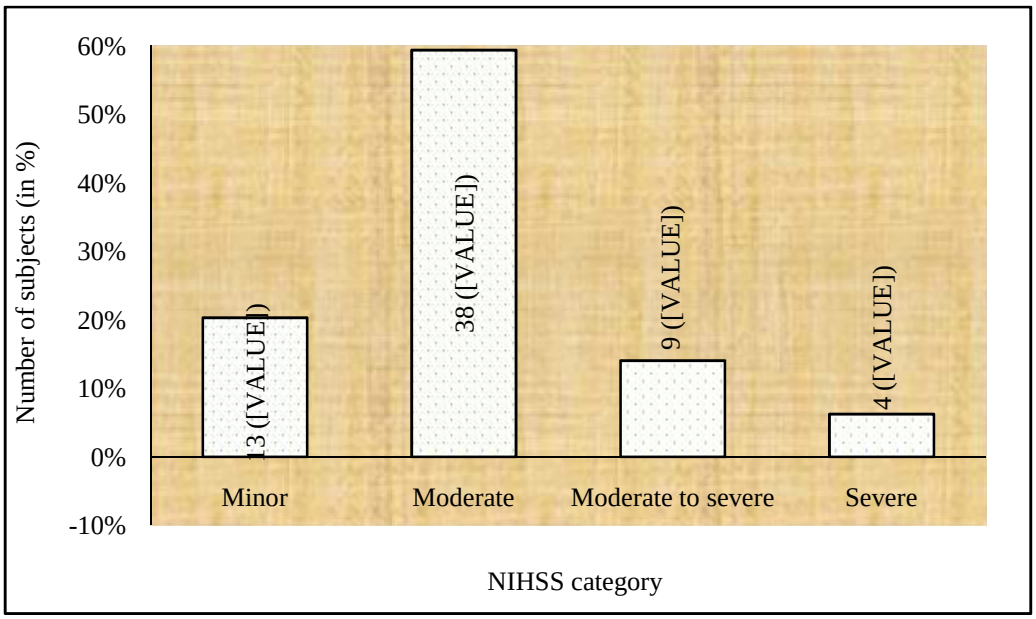


Table 21: Distribution of subjects by MRS category

Factor	Sub-category	Total numbers	Percentage (%)
MRS	**Poor**	13	20.31%
	Good	51	79.68%
MRS		2[0,6]	

Abbreviation: MRS: Modified Rankin Scale

From table 21, we observe that, there are 51 subjects with Good outcome MRS value and 13 subjects with Poor outcome MRS value. Figure 21 visualizes the results.

Figure 21: Distribution of subjects by MRS category

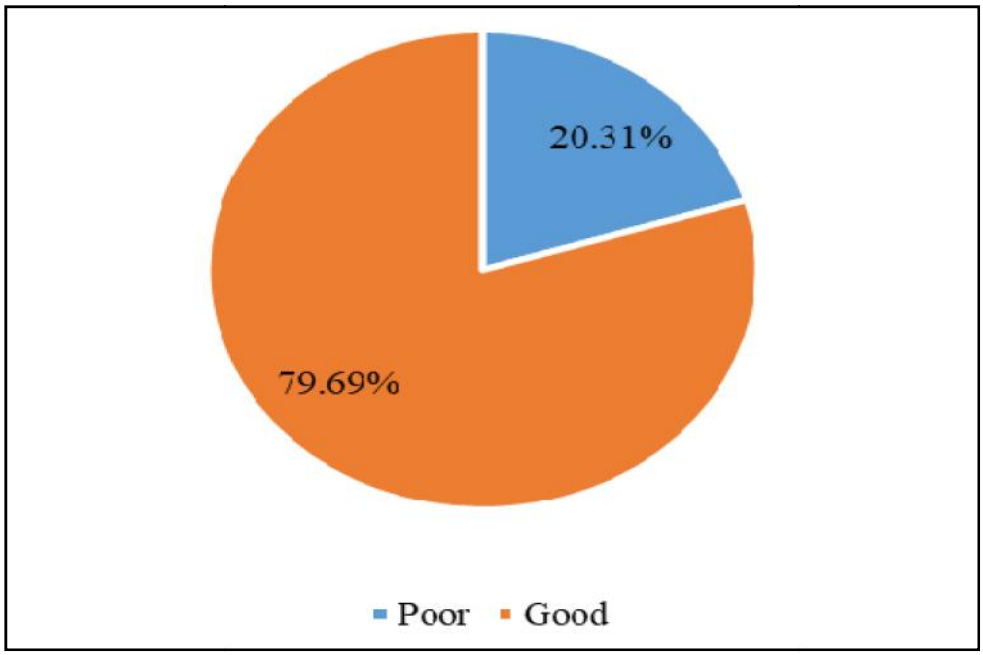


Table 22: Comparison of NIHSS, MRS with TB

Factor	Total Bilirubin Category		p-value
	Group 1	**Group 2**	
NIHSS	9.6904 ± 6.590	11.6363 ± 5.678	0.2448
MRS	2.0 ± 1.5848	2.5 ± 1.4690	0.1786[#]

[#]*indicates Mann-Whitney U test*

From table 22, using t-test, we conclude that the mean NIHSS is not significantly different over TB groups. Also, using Mann-Whitney U-test, we conclude that the median of MRS score is not significantly different over TB groups.

Using spearman correlation, we conclude that there is no significant correlation between NIHSS and Total bilirubin (rho=0.1881, p=0.1366). Also, there is no significant correlation of MRS with Total Bilirubin (rho=0.1486, p=0.2413).

Table 23: Association of TB with NIHSS category, MRS category

Factor	Sub-category	TB Category		p-value
		Group 1	Group 2	
NIHSS	Mild	10	3	0.6627 [F]
	Moderate	25	13	
	Moderate to severe	5	4	
	Severe	2	2	
MRS	Good	33	18	1[F]
	Poor	9	4	

[F] *indicates Fisher exact test*

From table 23, using fisher test, we conclude that Total Bilirubin and NIHSS are not significantly associated. Using fisher exact test, we conclude that MRS is not significantly associated with Total bilirubin.

Table 24: Comparison of NIHSS, MRS with DB

Factor	Direct Bilirubin Category		p-value
	Group 1	**Group 2**	
NIHSS	9.375 ± 5.87	10.950 ± 6.57	0.3381
MRS	2.21± 1.61	2.23 ± 1.54	0.8933[#]

[#] *indicates Mann-Whitney U test*

From table 24, using t-test, we conclude that mean NIHSS score is not significantly different between the groups of direct bilirubin. Also, using Mann Whitney U-test, we conclude that median of MRS score is not significantly different between the direct bilirubin groups. Using spearman rank correlation, we conclude that there NIHSS is not significantly correlated with Direct bilirubin (rho=0.1292, p=0.3091) and MRS is not significantly correlated with Direct bilirubin (rho=-0.0095, p=0.9409).

Table 25: Association of Direct Bilirubin with NIHSS category, MRS category

Factor	Sub-category	Direct Bilirubin		p-value
		Group 1	Group 2	
NIHSS	Mild	6	7	0.3352 [F]
	Moderate	15	23	
	Moderate to severe	1	8	
	Severe	2	2	
MRS	Good	19	32	1 [F]
	Poor	5	8	

[F] indicates Fisher exact test

From table 25, using fisher exact test, we conclude that Direct Bilirubin is not significantly associated with NIHSS categories of stroke severity. Also, we conclude that Direct bilirubin is not significantly associated with MRS level.

Inferences:

- Out of the total 64 subjects, 56 had complaints related to motor system whereas 67% had cranial nerves symptoms and the least (17.1%) had sensory complaints.
- Hypertension and diabetes mellitus are the common risk factors.
- 4 subjects had severe stroke by NIHSS category.
- Majority of the subjects had good outcome MRS score.
- There is no significant correlation of NIHSS with Total bilirubin as well as with Direct bilirubin.
- Total bilirubin is not significantly associated with NIHSS and MRS score.
- Direct bilirubin is not significantly associated with NIHSS and MRS score.

DISCUSSION

Bilirubin in recent days has gained importance because of its antioxidant properties. Various studies proposed the role of bilirubin in oxidative stress mediated diseases including diseases like coronary artery disease, stroke. There are studies which concluded that greater admission serum bilirubin levels were associated with greater stroke severity and poor short-term outcome.

Several studies have proved that the synthesis of bilirubin is induced in response to oxidative stress. So, the high bilirubin level at the admission found in ischemic stroke patients may be simply due to oxidative stress pathway induction and bilirubin may play no role in protection against neurological damage.

After obtaining institutional ethical committee clearance, this study was conducted on 64 ischemic stroke patients who fulfilled inclusion and exclusion criteria admitted at KLE's Dr.Prabhakar Kore hospital for a period of one year from January 2018 to December 2018. This was an observational study and purposive sampling was done. Informed consent was taken for all cases included in the study.

A detailed history was taken and clinical features were assessed. Basic laboratory tests were conducted such as complete blood counts, liver function tests, renal function tests. National Institute of Health Stroke Scale, serum total bilirubin and direct bilirubin levels were assessed at the time of admission. Modified Rankin scale was performed at the time of discharge.

Mean age of patients in this study was 60.25 years (SD - 12.54 years). 53% of ischemic stroke patients belonged to age group of 50 to 69 years of age suggesting

that advancing age is a risk for development of ischemic stroke. This is comparable to the population-based studies done by Dalal et al., [57] in Mumbai in which 66 years was the mean age of stroke, Sridharan et al.,[58] in Trivendum in which mean age for stroke was 67 years and Nagaraj et al.,[59] from which mean age was 54 years. This implies that elderly age is a risk factor for stroke.

Out of 64 patients included in the study, 45 patients were male and 19 were females. Majority of the patients were males, constituting 70.3%. This is comparable to a study done by Nagaraj et al., [59] in Bangalore where males constituted 67%. Dalal et al.,[57] from Mumbai reported that males had higher stroke incidence. This implies that males are at a higher risk of ischemic stroke compared to females.

Majority of the patients presented with motor weakness (87.5%), followed by cranial nerve abnormalities (67.1%), speech abnormalities (60.9%) and sensory abnormalities (17.1%) being the least common. This is comparable to the study done by Nagaraj et al.,[59] where motor weakness or paresis (92%) was the commonest presentation.

Hypertension was the most common risk factor in the patients included in the study and was seen in 50% of the study population. The other risk factors were diabetes mellitus in 34%, alcoholism seen in 30% and 23% of patients studied were smokers. 44% patients had blood pressure of more than 140/90 mmHg at the time of admission. This is comparable to studies done by Trivandrum registry[58] in which nearly 85% had hypertension, half had diabetes mellitus, and 26.8% of men smoked tobacco. In Mumbai registry[57], hypertension was the major risk factor.

Middle cerebral artery territory was the most common site of involvement; in 73.4% patients, followed by cerebellar artery in 9.3%, posterior cerebral artery involvement in 3.1% and anterior cerebral artery in 1.5%. Middle cerebral-posterior cerebral artery involvement was found in 10.9%, whereas middle cerebral artery-anterior cerebral artery involvement was found in 7.8%. This indicates that Middle cerebral artery is the most common territory involved in ischemic stroke and this is comparable to study done by Paciaroni M et al.,[62] in Perugia in which middle cerebral artery was the most common vascular territory involved.

The mean HDL levels were 38.20 mg/dl with standard deviation of 9.75 mg/dl. HDL levels in blood less than 40mg/dl were considered as low HDL. HDL levels were low in 37 patients (57.81%). LDL levels in blood ≧ 100 mg/dl were taken as high LDL. LDL levels were 97.53±40.94 mg/dl (mean±SD) and 45.31%% (29 patients) had high LDL levels. We considered 150mg/dl or more levels of triglycerides (TG) in blood as high TG. Triglycerides levels (TG) were 135±81.59 mg/dl (mean±SD) and 20.3% had high levels of triglycerides. Cholesterol levels were 160.19±45.00 (mean±SD) and high levels of cholesterol was seen in 13 (20.31%) ischemic stroke patients included in the study. Total cholesterol levels of 200mg/dl or more were considered as high cholesterol. This in comparable to studies done by Mary Grace et al., [60] in which 63.3% cases had high LDL cholesterol, 38.3% had high total cholesterol, 33.3% had low HDL and 21.7% had high triglycerides level. Siddeswari et al., [61] had reported low HDL in 77%, high LDL in 21%, high triglycerides in 17% and high cholesterol in 21% of ischemic stroke cases.

The mean total bilirubin levels in the patients was 0.68±0.34 mg/dl (mean±SD). The range of total bilirubin was 1.61mg/dl to 0.24mg/dl. Serum total bilirubin 0.7mg/dl or more was considered as Group 2(high). 34.3% (22) of ischemic stroke patients in the study had serum total bilirubin levels 0.7 mg/dl or more. Direct bilirubin levels were also measured and were 0.25+/-0.15 mg/dl (mean+/-SD) with a range of 0.1 – 1.1 mg/dl. 40 patients (62.5%) had high direct bilirubin values (Group 2).

National Institute of Health Stroke Scale (NIHSS) was used to assess the severity of stroke at the time of admission. NIHSS score of 1-4 indicated minor/mild severity, 5-15 as moderate, 16-20 as moderate to severe and >20 as severe. NIHSS score of mild severity was seen in 20.3% cases, 59.3% had moderate, 14% had moderate-severe and 6.2% had severe severity.

Modified Rankin (MR) Score was done to assess the outcome at the time of discharge. MR score of 0-3 was taken as good outcome and MR score of 4-6 as poor outcome. ln this study, MR Score of good outcome was seen in 58% of cases while 42% had MR Score of poor outcome.

In Group 1(Low) total bilirubin group (<0.7mg/dL), 4.7% had severe symptoms at the time of admission (NIHSS score of severe severity). Moderately severe symptoms were found in 11.9% of cases, whereas 59.5% had moderate symptoms and 23.8% had symptoms of mild severity. In Group 2(High) total bilirubin group (> or equal to 0.7mg/dL), 9% had severe symptoms at the time of admission. Moderately severe symptoms were found in 18% of cases, whereas 59% had moderate symptoms and 13.6% had symptoms of mild severity. Mean NIHSS Score for Group 1 total bilirubin group was 9.37 and for Group 2, bilirubin was 10.9 which

was statistically not significant (p value > 0.05). This indicates that there was no significant correlation between total bilirubin and severity of symptoms at the time of admission.

The mean NIHSS for Group 1 direct bilirubin group (<0.2mg/dL) was 9.37 and 10.95 for Group 2 direct bilirubin (> or equal to 0.2mg/dL). In Group 1(Low) direct bilirubin group, 8.3% had severe symptoms at the time of admission (NIHSS score of severe severity). Moderately severe symptoms were found in 4.16% of cases, whereas 62.5% had moderate symptoms and 25% had symptoms of mild severity. In Group 2(High) direct bilirubin group, 5% had severe symptoms at the time of admission. Moderately severe symptoms were found in 20% of cases, whereas 57.5% had moderate symptoms and 17.5% had symptoms of mild severity. There was no statistically significant correlation between NIHSS and direct bilirubin levels.

In this study, we found no correlation between severity of stroke and serum bilirubin (total and direct) at the time admission. This was in contrast to the study done by Ademiluyi et al.,[63] where they found significant correlation between severity of stroke and serum total bilirubin at the time admission. They took 120 ischemic stroke patients and divided them into two bilirubin groups; high and low, and compared the NIHSS score among the two groups. The group with higher total bilirubin had a greater stroke severity. Yun Luo et al.,[2] compared 531 Ischemic stroke patients and assessed serum bilirubin (total and direct) levels with NIHSS score between the two groups. The level of serum total bilirubin and direct bilirubin were significantly higher in acute ischemic stroke. Arsalan et al [64] in their study divided ischemic stroke cases into three groups of serum total bilirubin and compared them

with NIHSS score at the time of admission. Patients with higher total bilirubin were associated with higher stroke severity.

Mean MR Score for the Group 1 total bilirubin group was 2.0 (1.58, SD) and for high total bilirubin group was 2.5 (1.46 ,SD), which is statistically not significant. In Group 1 total bilirubin group, 78.5% had MR Score of good outcome and 21.4% had score of poor outcome. In Group 2 total bilirubin group, 81.8% had MR Score of good outcome while 18.2% had score of poor outcome.

Mean MR Score for the Group 1 direct bilirubin group was 2.21 (1.61, SD) and for Group 2 direct bilirubin group was 2.23 (1.54, SD) which is statistically not significant (p value -0.89). In Group 1 direct bilirubin group, 79.1% had MR Score of good outcomes and 20.8% had score of poor outcomes. In Group 2 direct bilirubin group, 80% had MR Score of good outcomes while 20% had score of poor outcomes.

In this study, both the (total and direct) groups were having near equal outcomes (MR Score) at the time of discharge and also there was no significant correlation between higher (Group 2) bilirubin group (direct and total) with greater stroke severity (NIHSS) at the time of presentation.

In a study by Arselan et al.,[64]bilirubin was tested in two MR score groups; poor outcome and good outcome. They found a mean serum total bilirubin of 0.76 for the good outcome MR score group and a mean serum total bilirubin of 1.05 for the poor outcome MR score group and p value (<0.005) was statistically significant. They found that patients with high serum total bilirubin had a poorer prognosis. But in our study, we did not find any significant correlation between the two (p>0.005).

Sandra Pineda et al.,[3] conducted a prospective study for five years on ischemic stroke patients. They measured serum bilirubin (total and direct) on admission, NIHSS on admission and MRS at discharge. A total of 743 ischemic stroke patients were studied with mean age being 67.3 years and 52.5% were males. It was found that there was no significant association between total bilirubin and severity of stroke (NIHSS) on admission. The direct bilirubin levels were significantly higher in patients with severe stroke on admission (NIHSS). They did not find any significant relationship between admission (total and direct) bilirubin and discharge outcome similar to our study. Perlstein et a1.,[65] reported that a 0.1 mg/dl increment in bilirubin level was associated with a 10% reduced odds of an adverse stroke outcome.

In this study, levels of direct and total bilirubin were not significantly associated with NIHSS and MRS. Hypertension and diabetes were found to be common risk factors for ischemic stroke. Further studies are warranted for the association of serum bilirubin and stroke outcome.

CONCLUSION

In this study we found no significant correlation between severity of stroke at the time of admission (NIHSS) with serum bilirubin levels.

At the time of discharge, both the bilirubin groups (total and direct) were not statistically different in terms of prognosis as evaluated by MR score.

LIMITATIONS OF STUDY

Further studies with higher sample size are needed.

Patients need long term follow-up to assess the prognostic significance of serum bilirubin in ischemic stroke.

SUMMARY

This study was conducted from January 2018 to December 2018 on 64 ischemic stroke patients admitted at KLE'S Dr.Prabhakar kore hospital at Belagavi, Karnataka. This was an observational study and purposive sampling was done. Informed consent was taken for all cases included in the study.

A detailed history was taken and clinical features were assessed. Basic laboratory tests were conducted such as complete blood counts, liver function tests, renal function tests. National Institute of Health Stroke Scale, serum total bilirubin and direct bilirubin levels were assessed at the time of admission. Modified Rankin scale was performed at the time of discharge.

Mean age of patients in this study was 60.25 years (SD - 12.54Years). 53% of ischemic stroke patients belonged to age group of 50 to 69 years of age suggesting that advancing age is a risk for development for ischemic stroke. Out of 64 patients, 45 patients were male and 19 were females. Majority of the patients were males constituting 70.3%.

Majority of patients presented with motor weakness (87.5%), followed by cranial nerve abnormalities (67.1%), speech abnormalities (60.9%) and sensory abnormalities (17.1%) being the least common. Hypertension was the most common risk factor in the patients included in the study and was seen in 50% of study population. The other risk factors were diabetes mellitus in 34%, alcoholism seen in 30% and 23% of patients were smokers. 44% patients had a blood pressure of more than 140/90 mmHg at the time of admission.

Middle cerebral artery territory was the most common site of involvement seen in 73.4% patients, followed by cerebellar artery in 9.3%, posterior cerebral artery involvement in 3.1% and anterior cerebral artery in 1.5%. Middle cerebral-posterior cerebral artery involvement was found in 10.9%, whereas middle cerebral artery- anterior cerebral artery involvement was found in 7.8%.

The mean HDL levels were 38.20 mg/dl with standard deviation of 9.75 mg/dl. HDL levels were low in 37 patients (57.81%). LDL levels were 97.53±40.94 mg/dl (mean±SD) and 45.31%% (29 patients) had high LDL levels. Triglycerides levels (TG) were 135±81.59 mg/dl (mean±SD) and 20.3% had high levels of triglycerides. Cholesterol levels were 160.19±45.00 mg/dL (mean±SD) and high levels of cholesterol were seen in 13(20.31%) .

The mean total bilirubin level in the patients was 0.68±0.34 mg/dl (mean±SD). The range of total bilirubin was 1.61mg/dl to 0.24mg/dl. 34.3% (22) of ischemic stroke patients in the study had serum total bilirubin levels 0.7 mg/dl or more. Direct bilirubin levels were also measured in this study and was 0.25+/-0.15 mg/dl (mean+/-SD) with a range of 0.1 – 1.1 mg/dl. 40 patients (62.5%) had direct bilirubin 0.2 mg/dl or more.

National Institute of Health Stroke Scale (NIHSS) was used to assess the severity of stroke at the time of admission. NIHSS score of mild severity was seen in 20.3% cases, 59.3% had moderate, 14% had moderate-severe and 6.2% had severe severity.

Modified Rankin (MR) Score was done to assess the outcome at the time of discharge. ln this study, MR Score of good outcome was seen in 58% of cases while 42% had MR Score of poor outcome.

In Group 1(Low) total bilirubin group, 4.7% had severe symptoms at the time of admission (NIHSS score of severe severity). Moderately severe symptoms were found in 11.9% of cases, whereas 59.5% had moderate symptoms and 23.8% had symptoms of mild severity. In Group 2 (High)total bilirubin group, 9% had severe symptoms at the time of admission. Moderately severe symptoms were found in 18% of cases, whereas 59% had moderate symptoms and 13.6% had symptoms of mild severity. Mean NIHSS Score for Group 1 total bilirubin group was 9.37 and for Group 2 bilirubin group was 10.9, which was statistically not significant (p value > 0.05). This indicates that there was no significant correlation between total bilirubin and severity of symptoms at the time of admission.

The mean NIHSS for Group 1(Low)direct bilirubin was 9.37 and 10.95 for Group 2(High) direct bilirubin. In Group 1 direct bilirubin group, 8.3% had severe symptoms at the time of admission (NIHSS score of severe severity). Moderately severe symptoms were found in 4.16% of cases, whereas 62.5% had moderate symptoms and 25% had symptoms of mild severity. In Group 2 direct bilirubin group, 5% had severe symptoms at the time of admission. Moderately severe symptoms were found in 20% of cases, whereas 57.5% had moderate symptoms and 17.5% had symptoms of mild severity. There was no statistically significant correlation between NIHSS and direct bilirubin levels.

Mean MR Score for the Group 1 total bilirubin group was 2.0 (1.58,SD) and for Group 2 total bilirubin group was 2.5 (1.46 ,SD), which is statistically not significant . In Group 1 total bilirubin group, 78.5% had MR Score of good outcome and 21.4% had score of poor outcome. In Group 2 total bilirubin group, 81.8% had MR Score of good outcome while 18.2% had score of poor outcome.

Mean MR Score for the Group 1 direct bilirubin group was 2.21 (1.61, SD) and for Group 2 direct bilirubin group was 2.23 (1.54, SD), which is statistically not significant (p value -0.89). In Group 1 direct bilirubin group, 79.1% had MR Score of good outcome and 20.8% had score of poor outcome. In Group 2 direct bilirubin group, 80% had MR Score of good outcome while 20% had score of poor outcome.

In this study, both the bilirubin (total and direct) groups had near equal outcomes(MR Score) at the time of discharge and also no significant correlation between bilirubin group (direct and total) with greater stroke severity(NIHSS) at the time of presentation.

In this study, stroke severity at the time of admission (NIHSS), functional disability at discharge by MR scale and serum bilirubin were noted. Here we found no correlation between serum bilirubin (total and direct) and severity of stroke (NIHSS) at the time of admission. Serum bilirubin (total and direct) and MR scale did not show any statistically significant correlation. And hence serum direct and total bilirubin as a prognostic indicator of ischemic stroke needs further study.

BIBLIOGRAPHY

1. Global Health Estimates. Geneva: World Health Organization; 2012. Available from: http://www.who.int/healthinfo/global_ burden_disease/en/ [cited 2016 June 1].
2. Luo, Yun & Li, Jing-Wei & Lu, Zheng-Juan & Wang, Chong & Guan, De-Ning & Xu, Yun. (2012). Serum Bilirubin after Acute Ischemic Stroke is Associated with Stroke Severity. Current neurovascular research. 9. 128-32. 10.2174/156720212800410876.
3. Pineda, Sandra & Bang, Oh Young & Saver, Jeffrey & Starkman, Sidney & W Yun, Susan & Liebeskind, David & Kim, Doojin & Sharma, Latisha & H Shah, Samir & Ovbiagele, Bruce. (2008). Association of Serum Bilirubin with Ischemic Stroke Outcomes. Journal of stroke and cerebrovascular diseases:the official journal of National Stroke Association. 17. 147-52. 10.1016/j.jstrokecerebrovasdis.2008.01.009.
4. Lipincott – Medical Physiology – 2nd Edition
5. UN Chronicle Health Watch. Atlas of Heart Disease and Stroke. 2005; 0105: 46.
6. Warlow C, Sudlow C, Dennis M, Wardlaw J, Sandercock, P. Stroke. Lancet 2003; 362: 1211–24.
7. Reddy K, Yusuf S. Emerging epidemic of cardiovascular disease in developing countries. Circulation 1998; 97:596–601.
8. Davidson’s principles and practices of Medicine, 20th edition.

9. Ischemic Stroke: Pathophysiology and Principles of Localization Editor: Alireza A tri, MD, PhD www.turner –white .com. Hospital Physician Board Review Manual
10. Harrisons Principles of Internal Medicine Volume 2, Page: 3275
11. Challa V. Atherosclerosis of the Cervicocranial arteries. In Toole JF (ed) cerebrovascular disorders. 5th edition. Lippincott Williams and Wilkins, Philadelphia, 1999.
12. Glaglov S, Zarins CB. What are the determinants of plaque instability and its consequences? J Vasc Surg 198; 9: 389-390. 1.
13. Falk E. Why do plaques rupture? Circulation 1992; 86:30-42.
14. Garcia JH, Ho Khang-Loon, Pantoni L. Pathology in Barnett, Henry JM, Mohr JP, Stein BM, Yatsu FM (eds), Stroke Pathophysiology, Diagnosis and Management. Third edition, Philadelphia, PA: Churchill Livingston; 1998
15. Lyden PD, Zivin JA. Hemorrhagic transformation after cerebral ischemia:Mechanisms and incidence. Cerebrovasc Brain Metab Rev.1993; 5:1-16.
16. Garcia JH, Anderson ML: Circulatory disorders and their effects on the brain.pp 715-822. In Davis RL, Robertson DM (eds): Textbook of Neuropathology, 3 rd edition. Williams & Wilkins, Baltimore 1997
17. Fisher M., Schaebitz W. An overview of acute stroke therapy. Past, present, and future. Arch Intern Med 2000;160:3196-3206
18. Labovitz DL, Boden-Albala B, Hauser WA, Sacco RL. Lacunar infarct or deep intracerebral hemorrhage: who gets which? The Northern Manhattan Study. Neurology 2007;68:606–8.

19. Bansal recent concept of stroke , Medicine update 135 -137 Guidelines for the Early Management of Patients With Acute Ischemic Stroke AHA/ASA Stroke guidelines http://stroke.ahajournals.org/lookup/doi/10.1161/STR
20. NIHSS, National Stroke Association Vol. XVI Issue 1, Jan,Feb 2006
21. MRS, The Lancet Neurology, Volume 5, Issue 7, Pages 603 - 612, July 2006. doi:10.1016/S1474-4422(06)70495-1
22. Sies H. Oxidative stress: introductory remarks. In: Oxidative Stress. New York: Academic Press, pp. 1–8 (1985).
23. Halliwell B. Antioxidant defence mechanisms: from the beginning to the end (of the beginning). Free Radical Res 31: 261-272 (1999).
24. Niizuma K, Endo H, Chan PH. Oxidative stress and mitochondrial dysfunction as determinants of ischemic neuronal death and survival. J Neurosci 109 (Suppl. 1): 133-138 (2009)
25. Piantadosi CA, Zhang J. Mitochondrial generation of reactive oxygen species after brain ischemia in the rat. Stroke 27: 327-331 (1996).
26. Niizuma K, Endo H, Chan PH. Oxidative stress and mitochondrial dysfunction as determinants of ischemic neuronal death and survival. J Neurosci 109 (Suppl. 1):133-138 (2009)
27. Piantadosi CA, Zhang J. Mitochondrial generation of reactive oxygen species after brain ischemia in the rat. Stroke 27: 327-331 (1996).
28. Andreyev AY, Kushnareva YE, Starkov AA. Mitochondrial metabolism of reactive oxygen species. Biochemistry 70: 200-214 (2005).
29. Cooper AJL, Kristal BS.: Multiple roles of glutathione in the central nervous system. Biol Chem 378:793-802 (1997).

30. Oxidative Stress in the Context of Acute Cerebrovascular Stroke Mohsen Muhammad Hussein El Kossi and Madeha Mahrous Zakhary Stroke. 2000;31:1889-1892, doi:10.1161/01.STR.31.8.1889
31. Journal of Clinical Neuroscience Volume 14, Issue 11, November 2007, Pages 1062–1066. Oxidative stress in acute ischemic stroke. Ayca Ozkul, Ali Akyol, Cigdem Yenisey, Esra Arpaci, Nefati Kiylioglu, Cengiz Tataroglu
32. Role of Oxidative Stress in Pathophysiology of Transient Ischemic Attack and Stroke. Jaspreet Kaur , Sarika Arora, Bhawna Singh ,LC Thakur , J Gambhir , KM Prabhu Int J Biol Med Res. 2011; 2(3): 611-615.
33. Association between Oxidative Stress and Outcome in Different Subtypes of Acute Ischemic Stroke . Nai-Wen Tsai, Ya-Ting Chang, BioMed Research International Volume 2014 (2014), Article ID 256879, 7 pages
34. Increased urinary excretion of bilirubin oxidative metabolites in septic patients: a new marker for oxidative stress in vivo. Otani K1, Shimizu S, Chijiiwa K, Yamaguchi K, Kuroki S, Tanaka M
35. Journal of Clinical Neuroscience Volume 14, Issue 11, November 2007, Pages 1062–1066. Oxidative stress in acute ischemic stroke. Ayca Ozkul, Ali Akyol, Cigdem Yenisey, Esra Arpaci, Nefati Kiylioglu, Cengiz Tataroglu
36. Dohi K et al. Transient elevation of serum bilirubin level in hemorrhagic stroke - bilirubin is marker of oxidative stress. Acta Neurochir Suppl. 2003;86:247-9
37. Oxidative stress markers and antioxidant level in neonatal hyperbilirubinemia , Nesrine Salah El-Din Abdel Hamid , Nahed Fahmy Helal
38. Wu TW. Is serum bilirubin a risk factor for coronary artery disease?. Clin Chem 1994;40:9-10

39. Yamaguchi T, Horio F, Hashizume T, Tanaka M, Ikeda S, Kakinuma A, Nakajima H. Bilirubin is oxidized in rats treated with endotoxin and acts as a physiological antioxidant synergistically with ascorbic acid in vivo. Biochem Biophys Res Commun 1995;214:11-19
40. Antioxidant and cytotoxic effects of bilirubin on neonatal erythrocytes. Mireles LC1, Lum MA, Dennery PA. Pediatr Res. 1999 Mar;45(3):355-62.
41. Platt JL, Nath KA. Heme oxygenase: protective gene or Trojan horse. Nat Med 1998;4:1364-1365
42. Molla, M., M. Gironella, R. Miquel, V. Tovar, P. Engel, A. Biete, J. M. Pique, J. Panes. 2003. Relative roles of ICAM-1 and VCAM-1 in the pathogenesis of experimental radiation-induced intestinal inflammation. Int. J. Radiat. Oncol. Biol. Phys
43. Schwertner HA, Jackson WG, Tolan G. Association of low serum concentration of bilirubin with increased risk of coronary artery disease. Clin Chem 1994;40:18-23.
44. Wu TW. Is serum bilirubin a risk factor for coronary artery disease?. Clin Chem 1994;40:9-10.
45. Platt JL, Nath KA. Heme oxygenase: protective gene or Trojan horse. Nat Med 1998;4:1364-1365.
46. The Bilirubin Level is Negatively Correlated with the Incidence of Hypertension in Normotensive Korean Population. Ho Jun Chin, Young Rim Song, and Suhnggwon Kim. J Korean Med Sci. Jan 2009; 24(Suppl 1): S50–S56. Can J Neurol Sci. 2013 Jan;40(1):80-4.

47. Hopkins PN, Wu LL, Hunt SC, James BC, Vincent GM, Williams RR. Higher serum bilirubin is associated with decreased risk for early familial coronary artery disease. Arterioscler Thromb Vasc Biol 1996;16:250-255.

48. Breimer LH, Wannamethee G, Ebrahim S, Shaper AG. Serum bilirubin and risk of ischemic heart disease in middle-aged British men. Clin Chem 1995;41:1504-1508.

49. Psychiatry Clin Neurosci. 2013 May;67(4):259-64. doi: 10.1111/pcn.12051. Association between high serum total bilirubin and post-stroke depression. Tang WK, Liang H, Chu WC, Mok V, Ungvari GS, Wong KS.

50. Maria Alexandra Britoa, Dora Britesa, D. Allan Butterfieldb. Centro de Patoge'nese Molecular-UBMBE, Faculdade de Farma'cia, University of Lisbon, Av. Das Forc.as Armadas, 1600-083 Lisbon, Portugal Department of Chemistry, Center of Membrane Sciences and Sanders- Brown Center of Aging, University of Kentucky, Lexington, KY 40506, USA. Accepted 31 July 2004, Available online 13 September 2004512- 520

51. Brain Res. 2004 hyperbilirubinemia, Nov 5;1026(1):33-43. Oxidative stress and A Injury link to between neocortical synaptosomes. Brito MA, Brites D, Butterfield DA.

52. Cristina Bellarosa, Unconjugated bilirubin mediated oxidative stress, ER stress and activation of Nrf2 pathwayQaisiya M.; Coda Zabetta C., Bellarosa C., Tiribelli C. "Bilirubin mediated oxidative stress involves antioxidant response activation via Nrf2 pathway" Cellular Signalling , Volume 26, Issue 3, March 2014, Pages.

53. Dohi K et al. Transient elevation of serum bilirubin level in hemorrhagic stroke - bilirubin is marker of oxidative stress. Acta Neurochir Suppl. 2003;86:247-9

54. Low Serum Bilirubin Level as an Independent Predictor of Stroke Incidence. A Prospective Study in Korean Men and Women Heejin Kimm, MD, PhD; Ji Eun Yun, PhD; Jaeseong Jo, BS; Sun Ha Jee, PhD

55. Perlstein TS, Pande RL, Beckman JA, Creager MA. Serum total bilirubin level and prevalent lower-extremity peripheral arterial disease: National Health and Nutrition Examination

56. The Bilirubin Level is Negatively Correlated with the Incidence of Hypertension in Normotensive Korean Population. Ho Jun Chin, Young Rim Song, and Suhnggwon Kim. J Korean Med Sci. Jan 2009; 24(Suppl 1): S50–S56. Can J Neurol Sci. 2013 Jan;40(1):80-4.

57. Clinical Implications of Bilirubin-Associated Neuroprotection and Neurotoxicity. Nicholas V Mendez, Jeffrey A Wharton, Jenna L Leclerc, Spiros L Blackburn, Martha V Douglas-Escobar, Michael D Weiss, Christoph N Seubert and Sylvain DorÃ

58. Population-Based Stroke Survey in Mumbai, India: Incidence and 28-Day Case Fatality - Abstract - Neuroepidemiology 2008, Vol. 31, No. 4 - Karger Publishers [Internet]. Available from: http ://www.karger.com/Arti cle/Abstract/ 165364

59. Sridharan SE, Unnikrishnan JP, Sukumaran S, Sylaja P N, Nayak SD, Sarma PS, et al. Incidence, Types, Risk Factors, and Outcome of Stroke in a Developing Country. Stroke. 2009 Apr 1 1212—8.

60. Nagaraja D, Gururaj G, Girish N, Panda S, Roy AK, Sarma GRK, et al. Feasibility study of stroke surveillance:Data from Bangalore, India. http://icmr.nic.in/ijmr/2009/October/1007.pdf [Internet]. 2009.
61. Grace M , Jacob KJ, Arya Vijay Kumar, Shameer V. K, et al. Role of dyslipidemia in stroke and comparison of lipid profile in ischemic and hemorrhagic stroke -a case control study. Int J Adv Med. 2016 Aug;3(3):694-698.
62. Siddeswari R, Manohar S, Sudarsi B, Suryanarayana B, Shravan kumar P, AbhiIashT. Pattern of dyslipidemia in ischemic stroke. J Med Allied Sci 2015;
63. Paciaroni M, Silvestrelli G, Caso V, Corea F, Venti M, Milia P, Tambasco N, Parnetti L, Gallai V, et al. Neurovascular territory involved in different etiological subtypes of ischemic stroke in the perugia Stroke Registry. European Journal of Neurology 2003, 10: 361—365.
64. Ademiluyi B, Sanya E , Wahab K et al. Relationship Between Admission Serum Bilirubin and Severity of Acute Ischemic Stroke in a Nigerian Tertiary Hospital. Neurology. April 5, 2016; vol. 86 no. 16 Supplement P5.239.
65. Arsalan H, Ismail M, Khattak MB, Anwar MJ, Murtaza Z, Khan F. Prognostic Significance Of Serum Bilirubin In Stroke. J . Ayub Med Coll Abbottabad, 2011 ;23(2)
66. Perlstein TS, Pandora RL, Creager MA, Weuve J, Beckman JA. Serum total bilirubin level , prevalent stroke, and stroke outcomes: NHANES 1999-2004 Am J Med 2008 ; 121 :781-8e1

ANNEXURE-I

INFORMED CONSENT

Title Of Research Study: "SERUM BILIRUBIN AS A SEVERITY AND PROGNOSTIC INDICATOR IN ACUTE ISCHEMIC STROKE – A HOSPITAL BASED ONE YEAR OBSERVATIONAL STUDY IN KLE'S DR PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTRE, BELAGAVI"

Principal Investigator:-

Dr. Soumya Parne

Post Graduate Student,

Department Of General Medicine,

JNMC, Belagavi.

Guide:-

Introduction and Purpose:-

He/She is a well-recognized case of Acute Ischemic Stroke and identification of a factor associated with this condition can help in planning out the treatment for a patient.

Procedure:

If you agree to be part of the research study, you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood and urine samples for the necessary investigations.

Risk and Benefits:

The only risk and possible discomfort you might get is while taking blood from your arm for the investigations. It may cause swelling, pain, redness (rarely happens) at the site from where the blood is drawn.

You may not be benefitted by these investigations but you will be part of this study which is going to be useful to others in the future.

Alternatives:

Taking part in this study is voluntary. You may choose not to take part in this study.

If you decide to take part you can later change your mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or sponsor may stop your participation in this study at any time. If you choose not to take part in the study, you will receive the standard treatment for patients with your condition.

Privacy and Confidentiality:

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

Institution / Sponsor's policy:

Does not apply to this research

Financial incentives for participation:

You will not be paid / offered any gifts /incentives for participating in the study.

Authorization to publish the results:

The results of the study would be forwarded to the KLE University, Belagavi as part of requirement towards the completion of MD degree, review and publishing.

In case of the queries during study or in future you may contact following persons,

1. Dr. Roopa M Bellad

   Chairman,

   JNMC Ethical

   Committee for Human Research

   J.N Medical College, Belagavi

   Phone No: 9480275601

CONSENT FORM

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read this consent form, or it has been read to me and has been explained to me in my vernacular language and all my questions have been answered. I will be given a copy of this consent form.

Signature / Left Thumb print of the Participant or legally authorized representative

Participant's name :……...

Signature / Left thumb impression :……...

of the participant

Name of the legally authorized :……...

representative / guardian

Signature / Left thumb impression :……...

Witness' name :……...

Signature / Left thumb impression :……...

Investigator's name and signature :……...

Date:

Place:

NATIONAL INSTITUTE OF HEALTH STROKE SCALE (NIHSS)

IA. Level of consciousness	
Alert	0
Drowsy	1
Obtunded	2
Coma/unresponsive	3
1B. Orientation to questions	
Answers both correctly	0
Answers one correctly	1
Answers none correctly	2
IC. Response to commands	
Performs both correctly	0
Performs one correctly	1
Performs none correctly	2
2 Gaze	
Normal	0
Partial gaze palsy	1
Complete gaze palsy	2
3 Visual field	
No field defect	0
Partial hemianopia	1
Complete hemianopia	2
Bilateral hemianopia	3

4	Facial movement	
	Normal symmetric	0
	Minor unilateral weakness	1
	Partial unilateral weakness	2
5	Best motor arm	
	No drift	0
	Drift before 5 sec	1
	Falls before 10 sec	2
	No antigravity effort	3
6	Motor function leg	
	No drift Drift before 5 sec	0
	Falls before 10 sec	1
	No antigravity effort	2
7	Limb ataxia	
	No ataxia	0
	Ataxia in one limb	1
	Ataxia in two limbs	2
8	Sensory	
	No sensory loss	0
	Mild sensory loss	1
	Severe sensory loss	2
9	Best language	
	Normal	0
	Mild aphasia	1
	Severe aphasia	2
	Mute or global aphasia	3

10 Articulation

Normal	0
Mild dysarthria	1
Severe dysarthria	2

11 Extinction /lnattention

Absent	0
Mild loss (loss of one modality)	1
Severe loss (loss of two modalities)	2

MODIFIED RANKIN SCALE (MRS)

0— No symptoms.

1 = No significant disability. Able to carry out all usual activities, despite some symptoms.

2 = Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.

3= Moderate disability. Requires some help, but able to walk unassisted.

4= Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.

5= Severe disability. Requires constant nursing care and attention, bedridden, incontinent.

6= Dead

ANNEXURE-II

PROFORMA

CASE NO:

NAME: DATE:

AGE/SEX:

IP NO.:

ADDRESS:

DOA: DOD:

COMPLAINTS AT PRESENTATION:

H/O MOTOR WEAKNESS :

H/O SENSORY SYMPTOMS:

H/O CRANIAL NERVE INVOLVEMENT:

H/O SPEECH DISTURBANCES:

H/O BOWEL AND BLADDER DISTURBANCES:

H/O SEIZURES:

H/O LOSS OF CONSCIOUSNESS:

H/O HEAD INJURY:

PAST HISTORY:

H/O Diabetes Mellitus: Yes/No

H/O Hypertension: Yes/No

H/O Ischemic Heart Disease: Yes/No

H/O Tuberculosis: Yes/No

H/O Epilepsy: Yes/No

H/O Hepatobiliary disease: Yes/No

H/O Hemolytic Anemias : Yes/ No

PERSONAL HISTORY:

HABITS:

Alcohol: Yes/No

Smoking: Yes/No

GENERAL PHYSICAL EXAMINATION

Pulse Rate:

Blood Pressure:

Icterus: Yes/No

SYSTEMIC EXAMINATION:

Central Nervous System:

Higher Mental Functions:

Cranial Nerves:

Motor System:

Sensory System:

Reflexes:

Cerebellar signs:

Signs of meningeal irritation:

Skull and Spine:

Cardiovascular System:

Respiratory System:

Per Abdomen:

NIHSS SCORE

1 LEVEL OF CONSCIOUSNESS

2 HORIZONTAL EYE MOVEMENT

3 VISUAL FIELD TEST

4 FACIAL PALSY

5 MOTOR ARM

6 MOTOR LEG

7 LIMB ATAXIA

8 SENSORY

9 LANGUAGE

10 SPEECH

11 EXTINCTION AND INATTENTION

MODIFIED RANKIN SCORE AT DISCHARGE

INVESTIGATIONS:

Complete Blood Picture:

Renal Function Tests:

Liver Function Tests:-

Serum Total Bilirubin levels

Serum Direct Bilirubin Levels

RBS:

Lipid Profile:

ECG:

CT/MRI Brain:

ANNEXURE-III- ETHICAL CLEARANCE LETTER

K.L.E.UNIVERSITY'S
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
(Accredited 'A' Grade by NAAC)

Website: http//www.jnmc.edu
E-Mail : dome@jnmc.edu

Phone: (+ 91-(0)831 Office : 2471350
Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref: MDC/DOME/ 39

Date: 22/11/2017

REG NO: BG0117013

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"SERUM BILIRUBIN AS A SEVERITY AND PROGNOSTIC INDICATOR IN ACUTE ISCHEMIC STROKE –A HOSPITAL BASED ONE YEAR OBSERVATIONAL STUDY IN KLE'S DR. RABHAKAR KORE HOSPITAL AND MEDICAL RESEACH CENTRE BELAGAVI"**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Arathi Darshan)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

34

ANNEXURE -III MASTER CHART

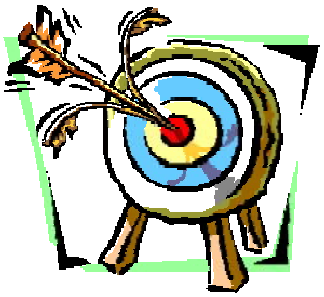
S.No.	Name	I.P No.	Age	Sex	Chief Complaints				DM	HTN	Smoker	Alcoholic	BP	HR	CNS					CT/MRI	ECG	RBS	Hb	HDL	LDL	TG	TC	TB	DB	NIHSS	MRS
					Motor	Cranial N	Speech	Sensory							HMF	Cranial N	Motor	Sensory	Cerebellar												
1	Ambaji Bhosale	851221	65	M	Y	N	Y	N	Y	Y	Y	Y	150/80	46	Aphasia	N	R Hemiparesis	N	N	L MCA	Sinus Brady	138	17.1	41	63	88	122	0.86	0.25	5	2
2	Bahubali Hosmani	848519	46	M	Y	N	Y	Y	N	N	N	N	130/70	80	Drowsy +Dysarthria	L Facial	L Hemiparesis	L Hemihypoanesthesia	N	R- MCA	N	98	11.9	59	177	180	272	0.59	0.26	16	4
3	Gopal Bhogan	850502	74	M	N	N	N	N	N	N	N	N	120/80	98	Unconscious	N	N	N	N	R PCA-MCA	LVH	135	7.4	44	37	34	88	0.47	0.28	31	5
4	Ishwar Dhanwade	852125	80	M	Y	Y	N	Y	Y	N	N	N	160/90	80	Dysarthria	R Facial Palsy	R Hemiparesis	R hemihypoanesthesia	N	L MCA	N	99	10.7	31	44	75	90	0.3	0.1	13	3
5	Kashavva Hanchinmani	851265	60	F	Y	Y	Y	N	Y	Y	N	N	230/130	90	Drowsy + Dysarthria	R Facial Palsy	R Hemiparesis	N	N	L ACA	LVH	406	13.2	34	180	109	236	0.25	0.1	10	3
6	Mahadev Khetriba	849936	77	M	Y	Y	Y	N	N	Y	N	N	170/100	88	Dysarthria	R Facial + R Hemianopsia	R Hemiparesis	N	R Ataxia	L MCA	N	144	15.7	38	108	90	164	1.49	0.37	11	3
7	Kalpana Bariker	885087	57	F	Y	N	N	N	N	N	N	N	200/100	78	N	N	L UL Monoparesis	N	N	R MCA-PCA	N	261	12.5	36	131	144	196	0.38	0.15	4	2
8	Mallikarjun Tilangji	845855	70	M	Y	Y	N	N	N	Y	Y	Y	120/80	86	Dysarthria	L Facial + L Hemianopsia	L Hemiplegia	N	N	R MCA	N	125	12.6	46	38	116	178	0.6	0.1	13	4
9	Shantayya Kukadimath	853408	67	M	N	N	Y	N	Y	Y	N	N	130/90	108	Drowsy + Aphasia	N	N	N	N	R MCA	N	245	15.3	37	94	140	159	0.67	0.22	9	0
10	Shivappa Byali	849649	74	M	Y	N	Y	Y	Y	Y	N	N	150/90	88	N	N	R Hemiparesis	R hemihypoanesthesia	N	L MCA	Sinus Brady	186	12.2	51	17	79	84	0.31	0.13	6	1
11	Kallavva Kamble	871954	80	F	Y	Y	Y	N	N	N	N	N	130/80	70	Dysarthria	R Facial	R Hemiparesis	N	N	L MCA	N	94	12.7	44	73	81	133	1.09	0.33	8	2
12	Mallikarjun Mugudur	861371	45	M	Y	Y	Y	N	N	N	Y	N	110/90	70	Aphasia	L Facial + L Hemianopsia	L Hemiparesis	L Hemihypoanesthesia	N	R ACA-MCA	N	140	14.6	31	143	136	201	0.43	0.17	23	4
13	Manisha Thakur	874656	54	F	Y	N	N	N	N	N	N	N	170/100	76	N	N	R Hemiparesis	N	N	L MCA	N	59	10.6	15	75	468	93	0.24	0.13	6	1
14	Girimalla Athanai	867215	46	M	Y	N	N	N	Y	N	N	N	110/90	70	N	N	N	N	N	R MCA	N	204	9.1	30	72	94	121	0.62	0.27	0	0
15	Yallappa Bhajantri	878450	52	M	Y	N	N	N	Y	Y	Y	Y	180/110	120	N	N	L UL Monoparesis	N	N	R MCA + Cerebellar	Old anterior infarct + Sinus Tachy	374	16.1	47	152	261	212	0.67	0.22	2	2
16	Amrappa Hunsi	857400	58	M	N	N	Y	N	Y	N	Y	N	110/100	60	Dysarthria	N	N	N	N	L MCA	N	151	17.5	32	139	203	212	0.64	0.31	3	0
17	Ayub Kadar Nadaf	854998	50	M	Y	Y	Y	N	Y	Y	N	Y	140/80	82	Drowsy + Dysarthria	N	L Hemiparesis	N	N	R MCA	N	120	13.8	29	146	197	214	0.67	0.38	14	1
18	Babasaheb Desai	857826	68	M	Y	Y	Y	Y	N	N	Y	Y	150/90	70	Dysarthria	L Facial + L Hemianopsia	L Hemiparesis	N	L Ataxia	R MCA	Afib	102	14.4	46	57	160	122	0.81	0.4	10	2
19	Beerappa Churamani	852602	78	M	Y	Y	Y	N	Y	Y	N	Y	110/70	70	Aphasia	R Facial + R Hemianopsia	R hemiplegia	N	N	L MCA	N	372	16.1	44	59	56	114	0.5	0.22	19	5
20	Kasturi Samadi	857718	49	F	N	Y	Y	N	Y	Y	N	N	200/110	70	Dysarthria	L Facial Palsy	N	N	N	R MCA	N	153	12.1	59	123	89	199	0.3	0.14	3	1
21	Kempanna Narsannavar	855697	30	M	Y	Y	N	Y	N	N	N	N	130/80	70	N	L Hemianopsia	L hemiparesis	L Hemianesthesia	N	R MCA	N	105	16.1	51	200	112	273	0.4	0.13	11	4
22	Maruti Montur	859322	67	M	Y	N	Y	N	Y	Y	Y	Y	110/80	74	Drowsy + Aphasia	N	R UL Monoparesis	N	N	L ACA-MCA	LVH	246	16	32	53	32	131	0.75	0.2	8	3
23	Paris Kamble	855558	46	M	Y	Y	Y	Y	N	N	N	N	120/80	86	Aphasia	R Facial Palsy	R Hemiplegia	R hemianesthesia	N	L ACA-MCA	N	177	16.8	47	124	91	189	0.88	0.46	22	4
24	Ramesh Patil	852149	61	M	Y	N	N	N	Y	Y	N	Y	130/80	82	Aphasia	N	L hemiplegia	N	N	R MCA	N	232	15.1	41	42	148	113	0.48	0.21	16	4
25	Ratnappa Kulagade	855791	91	M	Y	Y	Y	N	N	N	N	N	140/80	75	Aphasia	R Hemianopsia	R hemiplegia	N	N	L PCA	N	95	14.9	66	93	57	170	0.56	0.25	11	4
26	Rukmini Jayanache	856302	60	F	Y	Y	N	N	Y	N	N	N	140/90	80	N	R Facial Palsy	R Hemiparesis	N	N	L MCA	N	273	14.1	35	134	208	201	0.79	0.51	4	1
27	Savitri Panchal	855708	78	F	Y	N	Y	N	N	Y	N	N	140/90	120	Aphasia	N	R Hemiparesis	N	N	L MCA	Afib	196	15.4	60	130	63	149	0.94	0.4	12	3
28	Shreeya Shukla	854945	73	F	Y	N	N	N	N	Y	Y	Y	160/90	92	N	N	R UL Monoparesis	N	N	L ACA-MCA	N	92	12.9	32	139	106	192	0.41	0.17	2	0

35	Sundarraj Jeevapur	869031	47	M	N	N	N	N	N	N	N	N	100/80	70	N	N	N	N	L ataxia	R Cerebellar	N	166	16.6	40	150	65	203	0.54	0.12	2	1
36	Basayya Julagudd	861102	60	M	Y	Y	Y	N	N	N	N	N	140/100	76	Dysarthria	L oculomotor	Quadriplegia	N	N	B/L PCA+Cerbellar	N	73	16.2	28	125	163	186	0.74	0.16	19	5
37	Bhagirathi Goudar	861297	60	F	Y	Y	Y	N	N	N	N	N	150/100	98	Dysarthria	L facial palsy	L Hemiparesis	N	N	R MCA-PCA	Afib	156	8.6	41	58	86	124	0.34	0.16	9	1
38	Hanamant Dasand	860177	60	M	N	Y	N	N	N	N	Y	Y	150/90	80	Dysarthria	L Hemianopsia	N	N	L Ataxia	R MCA + R PCA	N	98	14.2	32	69	157	132	0.67	0.22	5	1
39	Kallappa Kademani	862751	55	M	Y	Y	N	N	N	N	N	Y	180/90	88	N	L Facial Palsy	L hemiparesis	N	L Ataxia	R MCA	N	94	13.8	34	53	130	113	0.42	0.22	5	0
40	Kamalawwa Belakud	853231	54	F	Y	Y	Y	N	N	Y	N	N	140/90	90	Aphasia	R Facial + R hemianopsia	R Hemiparesis	N	R Ataxia	L MCA	Afib	171	12.6	57	128	87	202	0.6	0.1	11	2
41	Fatima Basapuri	869482	54	F	Y	Y	Y	N	Y	N	N	N	140/90	102	Drowsy	R Facial	R Hemiparesis	N	N	L MCA	N	155	14.1	36	82	102	124	0.84	0.29	11	1
42	Pundalik Helicottal	861721	60	M	Y	N	N	Y	N	N	N	N	160/100	70	N	N	R Hemiparesis	R hemihypoanesthesia	N	L MCA	LVH	95	14.1	40	117	83	174	0.43	0.23	3	0
43	Rudrappa Mongal	861725	74	M	Y	Y	N	N	N	N	N	N	130/90	98	Drowsy + Dysarthria	L Facial Palsy	L Hemiplegia	N	N	R MCA	N	112	15.7	23	73	59	108	1.43	1.1	16	3
44	Shankar Mokashi	864111	55	M	Y	N	N	Y	N	N	Y	Y	160/100	70	N	N	L Hemiparesis	L Hemianesthesia	N	R MCA	LVH	199	11.7	34	150	134	211	0.35	0.13	5	0
45	Somanagouda Patil	863807	55	M	Y	Y	N	N	Y	Y	N	N	150/90	80	N	L Facial + L Hemianopsia	L Hemiparesis	N	L Ataxia	R MCA + R PCA	N	274	14.2	39	88	255	178	0.51	0.21	8	2
46	Basavaraj Parvati	865126	55	M	Y	Y	Y	N	Y	Y	N	N	210/70	100	Dysarthria	R Facial Palsy	R Hemiparesis	N	R Ataxia	B/L MCA	LVH	237	20.1	48	80	200	168	1.31	0.34	9	1
47	Adivayya Kalimath	866441	65	M	Y	N	N	N	N	Y	N	N	110/80	80	N	N	L UL Monoparesis	N	N	R MCA	N	95	11.1	26	132	155	189	0.57	0.22	7	0
48	Avinash Kochrekar	868325	63	M	Y	Y	Y	N	Y	N	N	N	130/80	70	Aphasia	L Hemianopsia	L hemiparesis	N	N	R ACA + R MCA	N	106	15	42	147	124	216	0.42	0.15	13	3
49	Basheer Ahmed Pathan	880084	30	M	Y	Y	Y	N	N	N	N	Y	150/90	88	Dysarthria	L Facial + L Hemianopsia	L Hemiplegia	N	N	R MCA	N	93	13	34	43	117	100	0.53	0.28	20	3
50	Bhimangouda Patil	866525	60	M	Y	Y	Y	N	N	Y	Y	Y	120/80	66	Aphasia	R Facial + R hemianopsia	R Hemiplegia	N	N	L MCA+L MCA-PCA	N	182	18.2	35	69	369	179	0.93	0.1	21	6
51	Chidanand Bushi	869077	75	M	Y	Y	Y	N	Y	Y	N	N	160/90	74	Dysarthria	L Facial Palsy	L Hemiparesis	N	L Ataxia	R MCA	N	197	14.2	40	125	126	190	1.32	0.41	11	3
52	Virabhadraiyya Hiremath	868773	60	M	N	Y	N	Y	Y	Y	N	N	130/80	88	N	L Facial Palsy	N	L Hemihypoanesthesia	N	R MCA	old anterior infarct	230	11.9	24	94	81	134	0.35	0.16	4	1
53	Shanta Khalile	869425	55	F	Y	Y	Y	N	N	N	N	N	130/80	90	Aphasia	R Facial Palsy	R Hemiparesis	N	N	L MCA	Afib	124	14.9	33	88	76	136	1.6	0.45	13	2
54	Gangavva Naikwadi	869244	67	F	Y	Y	Y	N	N	Y	N	N	110/80	72	Drowsy + Dysarthria	R Hemianopsia + R Facial	R Hemiparesis	N	N	L MCA	L BBB	132	13.8	35	76	250	161	0.76	0.2	13	3
55	Janakoji Gavade	868740	43	M	Y	Y	N	N	N	Y	N	N	130/70	88	N	L Hemianopsia	L Hemiparesis	N	N	R MCA	N	145	15.2	30	122	138	150	0.79	0.19	4	0
56	Krishnaji Palavi	869433	65	M	Y	Y	N	N	N	Y	Y	Y	140/80	72	N	R Facial Palsy	R Hemiparesis	N	R Ataxia	L Cerbellar	LVH	75	9.7	34	79	93	132	0.46	0.18	5	1
57	Neeta Patil	869041	52	F	Y	Y	Y	N	N	Y	N	N	130/80	90	Aphasia	R Hemianopsia	R Hemiparesis	N	N	L MCA	N	126	11.3	43	105	63	161	0.59	0.21	11	3
58	Annasaheb Chougala	868213	49	M	Y	Y	N	N	Y	Y	N	N	150/90	90	N	R Facial Palsy	R Hemiparesis	N	R Ataxia	L Cerbellar	LVH	131	12.8	27	67	76	109	0.4	0.14	8	2
59	Appasaheb Soudatti	875659	55	M	Y	N	Y	N	N	N	N	N	140/80	76	Aphasia	N	R UL Monoparesis	N	N	L MCA	N	147	12.5	37	86	106	144	1.61	0.47	3	1
60	Ashok Moogi	874137	60		Y	Y	N	N	N	Y	N	N	110/70	76	N	R Facial Palsy	R Hemiparesis	N	N	L MCA	Sinus Tachy	468	14.2	29	82	383	188	0.63	0.29	8	2
61	Bhaurao Chodankar	872145	68	M	Y	Y	Y	N	N	N	N	N	160/90	86	Dysarthria	L Facial + L Hemianopsia	L hemiplegia	N	N	R MCA	LVH	112	13.6	22	107	128	155	0.55	0.18	14	3
62	Shantaram Patil	859556	42	M	Y	Y	Y	N	N	N	Y	Y	140/90	82	Dysarthria + Aphasia	R Facial + R Hemianopsia	R Hemiplegia	N	N	L MCA	N	105	14.7	31	107	162	170	1.24	0.22	18	2
63	Budtor Fernandes	875465	76	M	Y	Y	Y	N	N	Y	Y	Y	160/90	58	Dysarthria	L Facial Palsy	L Hemiparesis	N	N	R MCA	LVH	112	14.4	27	181	147	237	0.79	0.16	7	3
64	Girija Chougala	874121	45	F	Y	Y	Y	N	N	Y	N	N	160/90	56	Aphasia	R Facial Palsy	R hemiparesis	N	N	L MCA	Sinus Brady	96	12.6	45	61	56	117	0.3	0.12	12	2

ANNEXURE-V

KEY TO MASTER CHART

Introduction



Objectives

Review of Literature

Methodology

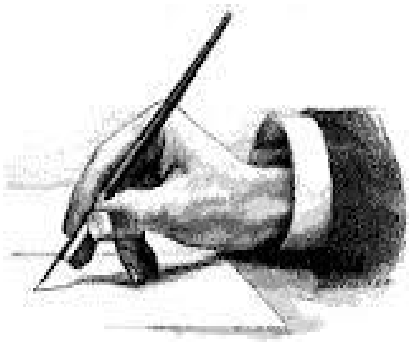
Results

Discussion

Conclusion

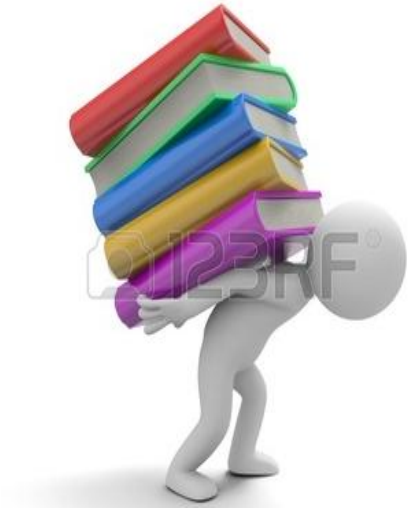
Summary

Bibliography



Annexure-I

Annexure-II



Annexure-III

Annexure-IV

Annexure-V