"ROLE OF HDL IN CEREBRO VASCULAR ACCIDENT,COMPARATIVE STUDY OF HDL IN ISCHEMIC STROKE AND HEMORRHAGIC STROKE"

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With reference to the above, we wish to inform you that your proposed research project titled **"ROLE OF HIGH-DENSITY LIPOPROTEIN CHOLESTROL IN CEREBROVASCULAR ACCIDENT AND COMPARION OF HIGH-DENSITY LIPOPROTEIN LEVEL IN ISCHEMIC AND HEMORRHAGIC STROKE",** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee.

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LIST OF ABBREVIATIONS

ABCA1: ATP-Binding Cassette Transporter A1

ACA: Anterior Cerebral Artery

AHA: American Heart Association

ANOVA: Analysis of Variance

BMI: Body Mass Index

CETP: Cholesteryl Ester Transfer Protein

CI: Confidence Interval

CT: Computed Tomography

CVA: Cerebrovascular Accident

CVD: Cardiovascular Disease

DM: Diabetes Mellitus

HDL: High-Density Lipoprotein

HTN: Hypertension

ICH: Intracerebral Hemorrhage

IHD: Ischemic Heart Disease

LCAT: Lecithin-Cholesterol Acyltransferase

LDL: Low-Density Lipoprotein

MCA: Middle Cerebral Artery

MRI: Magnetic Resonance Imaging

MRS: Modified Rankin Scale

NIHSS: National Institutes of Health Stroke Scale

OR: Odds Ratio

PCA: Posterior Cerebral Artery

RCT: Randomized Controlled Trial

SAH: Subarachnoid Hemorrhage

SD: Standard Deviation

TG: Triglycerides

TC: Total Cholesterol

TIA: Transient Ischemic Attack

VLDL: Very Low-Density Lipoprotein

WHO: World Health Organization

ABSTRACT

Introduction: Cerebrovascular accidents (CVAs) represent a significant global health burden, with dyslipidemia emerging as a crucial modifiable risk factor. While the relationship between low-density lipoprotein (LDL) and stroke risk is well-established, the role of high-density lipoprotein (HDL) remains less clearly defined, particularly regarding its differential association with stroke subtypes. This study aimed to investigate the role of HDL in cerebrovascular accidents and compare HDL levels between ischemic and hemorrhagic stroke subtypes.

Methods: This observational study included 98 stroke patients admitted to KLES Dr. Prabhakar Kore Hospital, Belagavi, over a one-year period. Demographic characteristics, risk factor profiles, lipid parameters, and stroke characteristics were documented. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS), and functional outcomes were evaluated using the Modified Rankin Scale (MRS). Statistical analysis included descriptive statistics and comparison between stroke subtypes using appropriate tests.

Results: The study population had a mean age of 55.8 years with slight female predominance (53.1%). Hypertension (65.3%), diabetes (41.8%), and overweight/obesity (76.6%) were prevalent risk factors. Ischemic strokes (83.7%) were more common than hemorrhagic strokes (16.3%). Low HDL cholesterol (<50 mg/dL) was observed in 90.8% of patients. Significantly higher HDL levels were found in hemorrhagic stroke patients (44.3±7.5 mg/dL) compared to ischemic stroke patients (35.3±7.7 mg/dL) ($p<0.001$). No significant differences were observed between stroke subtypes regarding other lipid parameters, comorbidities, stroke severity, or functional outcomes.

Conclusion: This study demonstrates a high prevalence of low HDL cholesterol among stroke patients and identifies a significant difference in HDL levels between ischemic and hemorrhagic stroke subtypes. These findings suggest that HDL cholesterol might play a differential role in the pathogenesis of stroke subtypes and could potentially serve as a biomarker for stroke classification. Future research should focus on elucidating the mechanistic links between HDL and stroke subtypes and developing targeted interventions to address dyslipidemia in stroke prevention.

Keywords: Cerebrovascular accident, stroke, high-density lipoprotein, ischemic stroke, hemorrhagic stroke, dyslipidemia, risk factors, stroke outcomes.

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INTRODUCTION

Cerebrovascular accidents (CVA), commonly known as strokes, represent a significant global health burden, ranking as the second leading cause of death worldwide and a major cause of disability.[1] The intricate relationship between lipid metabolism and stroke pathophysiology has emerged as a crucial area of research, with particular attention being drawn to the role of High-Density Lipoprotein (HDL).[2] While traditional perspectives have primarily focused on HDL's atheroprotective functions in cardiovascular disease, its potential significance in cerebrovascular events presents a compelling avenue for investigation.[3]

HDL, often referred to as "good cholesterol," exhibits multiple physiological functions beyond reverse cholesterol transport, including anti-inflammatory, antioxidant, and endothelial protective properties.[4] Recent evidence suggests that HDL's pleiotropic effects may play a crucial role in both the pathogenesis and outcomes of different stroke subtypes.[5] The relationship between HDL levels and stroke risk has been observed to follow a complex pattern, with some studies indicating that the association may differ between ischemic and hemorrhagic strokes.[6]

The differentiation between ischemic and hemorrhagic strokes is fundamental not only for therapeutic decision-making but also for understanding the underlying pathophysiological mechanisms.[7] Ischemic strokes, accounting for approximately 87% of all strokes, occur due to vessel occlusion, while hemorrhagic strokes result from vessel rupture. The role of HDL in these distinct pathological processes may vary significantly, potentially influencing both risk assessment and therapeutic approaches.[8]

In the Indian context, the burden of stroke is particularly concerning, with estimates suggesting a prevalence rate of 84-262/100,000 population in rural areas and 334-424/100,000 population in urban areas.[1] The unique genetic, dietary, and environmental factors in the Indian population may influence lipid profiles and their association with stroke outcomes, necessitating region-specific research.[9]

Despite growing evidence supporting HDL's involvement in cerebrovascular health, there remains a significant gap in our understanding of its differential roles in ischemic versus hemorrhagic strokes.[10] This observational study, conducted at KLES Dr. Prabhakar Kore Hospital, Belagavi, aims to elucidate these relationships by comparing HDL levels across stroke subtypes and examining their potential implications for risk stratification and patient outcomes.

Understanding these associations could have substantial clinical implications, potentially influencing preventive strategies and therapeutic approaches in stroke management.[7] This study's findings may contribute to the development of more targeted interventions and improved risk assessment tools for different stroke subtypes in the Indian population.

AIMS AND OBJECTIVES

Objectives:

1. To study serum HDL level in patient with cerebrovascular accident
2. To compare the levels of serum HDL between two categories of stroke.
3. Percentage of site involvement in ischemic and hemorrhagic stroke.

REVIEW OF LITERATURE

CEREBROVASCULAR DISEASES OF BRAIN[11]

Cerebrovascular disorders encompass some of the most prevalent and devastating conditions: ischemic stroke, hemorrhagic stroke, and cerebrovascular anomalies including intracranial aneurysms and arteriovenous malformations (AVMs).[11] These conditions cause approximately 200,000 deaths annually in the United States and represent a significant source of disability. The frequency of cerebrovascular disorders increases with age, and as the elderly population grows, stroke deaths in the United States are projected to double by 2030. Most cerebrovascular diseases manifest through the sudden onset of a focal neurologic deficit, as though the patient was unexpectedly struck.[11]

STROKE[11]

Definition: This abrupt beginning of a neurologic deficit caused by a localised vascular origin is what defines a stroke, also known as a cerebrovascular accident.[11]

Acute Ischemic Stroke

Although an acute stroke is sometimes called a cerebrovascular accident, it's crucial to understand that a stroke is not an accident. It is more accurately and meaningfully referred to as "brain attack," which has a similar meaning to "heart attack." Acute stroke occurs when underlying cerebrovascular disorders cause acute neurological impairments to arise suddenly in a vascular area that affects the brain, retina, or spinal cord.[12] Stroke has a substantial impact on morbidity and mortality and affects a variety of patient demographics. There are two types of strokes: ischaemic and hemorrhagic. Intracerebral and subarachnoid haemorrhages are two further subtypes

of hemorrhagic strokes. The Trial Org 10172 in Acute Stroke Treatment (TOAST) classification system distinguishes multiple categories among ischaemic strokes:[12]

- "Cardioembolism
- Small vessel occlusion
- Large artery atherosclerosis
- Stroke of undetermined etiology
- Stroke of other determined etiology (possible or probable depending on ancillary study results")[13]

The capacity of the doctor to classify a particular subtype diagnosis as probable or plausible based on the degree of certainty is a crucial component of classification.[13] A diagnosis is deemed "probable" whenever alternative possible explanations have been ruled out and clinical symptoms, neuroimaging data, and diagnostic study results match a specific subtype.[13] On the other hand, a diagnosis is marked as "possible" when neuroimaging evidence and clinical findings point to a particular subtype but further research has not been done. The probable and feasible categories enable doctors to choose the most accurate subgroup diagnosis because many patients only receive a few diagnostic tests.[13]

Epidemiology[14]

"Stroke was responsible for 1 in 6 cardiovascular disease-related deaths in 2021; in the United States, a stroke occurs every 40 seconds, meaning that a stroke-related death occurs roughly every 3 minutes and 14 seconds.[14] Over 795,000 Americans experience a stroke each year, with roughly 610,000 of those being first-time incidents.[14] About 185,000 of these strokes, or about one-fourth of all instances,

happen to people who have had strokes before.[15] About 87% of all strokes are ischaemic strokes, which stop blood flow to the brain. The Framingham Heart Study reports a decrease in the incidence of stroke. However, the majority of the cohort was made up of White people".[15]

"Between 2018 and 2019, the cost of stroke in the United States was close to $56.5 billion, which included lost productivity from missed workdays, medication, and medical bills. More than half of stroke survivors 65 and older have mobility issues, making stroke a major cause of severe long-term impairment."[16]

Racial and ethnic differences in stroke incidence and outcomes are evident; non-Hispanic Black adults are almost twice as likely as White adults to have their first stroke, and both non-Hispanic Black and Pacific Islander adults have the highest rates of stroke-related death. Additionally, the number of stroke-related deaths rose from 38.8 per 100,000 in 2020 to 41.1 per 100,000 in 2021.[17]

Etiology

"A thrombotic or embolic event that reduces blood supply to a part of the brain is the cause of an ischaemic stroke. A thrombus (clot) within the vascular itself, usually as a result of atherosclerotic disease, arterial dissection, fibromuscular dysplasia, or inflammatory diseases, obstructs blood flow to the brain in a thrombotic event.[18] Debris from other parts of the body obstructs blood flow via the damaged vessel during an embolic event. An artery-to-artery embolic stroke can occur distally from any proximal source, usually the heart, and can be caused by an embolism source that is proximal, such as an atherosclerotic plaque in the internal carotid artery.[18] On rare occasions, the source could come from the right side of the circulation and proceed to

the cerebral vascular system via a right-to-left shunt, like a patent foramen ovale. The cause of the stroke has an impact on the prognosis and results".[18]

Cardioembolism: Patients in this category have arterial obstructions that are most likely the result of a heart-related embolism. Based on their propensity for embolism, cardiac sources are divided into high-risk and medium-risk groups.[19] A possible or likely diagnosis of cardioembolic stroke requires the identification of at least one cardiac embolism source. The results of brain imaging and clinical examinations are similar to those reported for large-artery atherosclerosis.[19] A clinical diagnosis of cardiogenic stroke is supported by evidence of a prior transient ischaemic attack (TIA), stroke in numerous vascular areas, or systemic embolisms.[19] It is important to rule out any big artery atherosclerotic causes of embolism or thrombosis. A probable cardioembolic stroke occurs when a patient has a medium-risk cardiac embolism source and no other evident cause for the stroke.[19]

Large artery atherosclerosis: Atherosclerosis is most likely the cause of the clinical and brain imaging findings in these patients, which show either severe (> 50%) narrowing or total blockage of a major brain artery or branch cortical artery. Clinical manifestations can include brainstem or cerebellar dysfunction or signs of cerebral cortical damage (e.g., aphasia, neglect, or reduced motor function).[20] The clinical diagnosis can be supported by the presence of a carotid bruit, a history of intermittent claudication, TIAs in the same vascular region, or weak pulses. A possible major artery atherosclerotic origin is suggested by lesions in the brainstem, cortex, cerebellum, or subcortical hemisphere that are greater than 1.5 cm in diameter and show up on computed tomography (CT) or magnetic resonance imaging (MRI).[20] More proof that a significant intracranial or extracranial artery has more than 50% stenosis must be provided by duplex imaging or arteriography. Potential causes of

cardiogenic embolism should be ruled out during diagnostic testing.[20] It is impossible to diagnose a stroke caused by major artery atherosclerosis if duplex or arteriographic investigations seem normal or exhibit very slight alterations.[20]

Small vessel occlusion: Patients with strokes that are often categorised as lacunar infarcts in other systems fall under this group. Patients shouldn't show symptoms of cerebral cortical dysfunction; instead, they should present with one of the common clinical lacunar syndromes.[21] The clinical diagnosis is supported by a history of hypertension or diabetes mellitus. Patients should also show a significant brainstem or subcortical hemisphere lesion with a diameter of less than 1.5 cm, or have normal CT or MRI results.[21] It is anticipated that there will be no possible causes of cardiac embolism, and an examination of the main extracranial arteries shouldn't show stenosis greater than 50% in an artery on the same side.[21]

Stroke of undetermined etiology: Determining the cause of a stroke is often difficult. Even after a thorough evaluation, some patients have no probable cause. Others just get a quick assessment, leaving the cause unknown.[22] Patients with two or more possible stroke causes are also included in this category, which makes it challenging for doctors to make a conclusive diagnosis.[22] For example, a stroke of unknown aetiology would be diagnosed in a patient who presents with a medium-risk cardiac embolism source in addition to another possible cause of the stroke.[22] Likewise, a patient with 50% ipsilateral carotid stenosis and atrial fibrillation or 50% ipsilateral carotid stenosis and conventional lacunar syndrome would be included in this group.[22]

Stroke of other determined etiology: "Patients with rare stroke aetiology, such as nonatherosclerotic vasculopathies, hypercoagulable conditions, or haematologic illnesses, make up this group. Regardless of the size or location of the lesion, patients

should present with clinical symptoms and CT or MRI findings suggestive of acute ischaemic stroke.[23] One of these uncommon stroke causes should be identified by diagnostic procedures like arteriography or blood tests.[23]To rule out the causes of cardiac embolism and big artery atherosclerosis, more research should be done".[23]

Risk factors for stroke[24]

Nonmodifiable risk factors

- Age
- Gender
- Race
- Ethnicity
- Genes

Modifiable risk factors

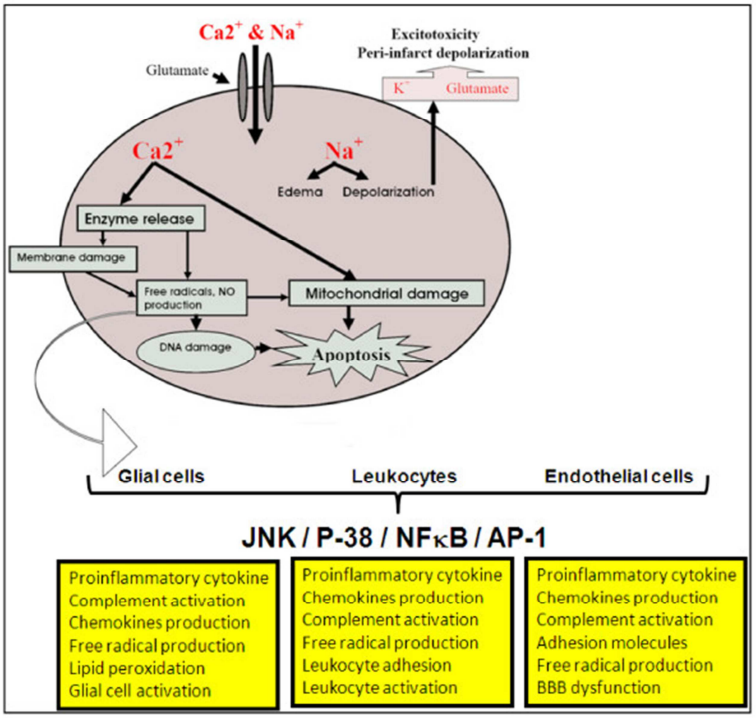
- Smoking
- Physical inactivity
- Dietary Habits
- Obesity
- High blood pressure (BP)
- Cardiac Diseases
- Atrial fibrillation
- Carotid Stenosis
- Diabetes

Ischemic Stroke Pathogenesis

Energy failure, loss of cell ion homeostasis, acidosis, elevated intracellular calcium levels, excitotoxicity, free radical-mediated toxicity, production of arachidonic acid products, cytokine-mediated cytotoxicity, complement activation, disruption of the blood-brain barrier (BBB), glial cell activation, and leukocyte infiltration are just a few of the many processes that contribute to the complex pathophysiology of stroke.[24] In the severely impacted ischemic-core regions, these coordinated and interconnected actions may result in ischaemic necrosis. The centre of the brain tissue that is subjected to the most severe reduction in blood flow experiences fatal damage and necrotic cell death within minutes of cerebral ischaemia.[24] There is a zone of less damaged tissue surrounding this necrotic core that is still metabolically active but functionally silent due to decreased blood supply. Initial cellular and organelle enlargement, followed by nuclear, organelle, and plasma membrane breakdown, nuclear structure and cytoplasmic organelle disintegration, and the release of cell contents into the extracellular environment are the morphological characteristics of necrosis. [25, 26] The area where salvaging through post-stroke therapy is feasible is the ischaemic penumbra, which borders the infarct core and makes up as much as 50% of the total lesion volume during the early phases of ischaemia. [27] The penumbra zone of a focused ischaemic infarct is an example of less severe ischaemia, which develops more slowly, is dependent on particular gene activity, and may eventually lead to apoptosis.[28] According to recent studies, many neurones in the peri-infarct zone, also known as the ischaemic penumbra, may not undergo apoptosis for several hours or days, which may allow them to recover for a while after the stroke begins.[28] Apoptosis, which eliminates redundant cells through energy-dependent programmed cell death, seems to be a more orderly process than necrosis. Apoptotic cells are

disassembled from the inside out in a systematic way to reduce harm and disturbance to nearby cells.[26] The intrinsic and extrinsic routes are the two main ways that apoptosis is triggered. Experiments conducted in the past ten years have yielded a wealth of fresh data describing the apoptotic pathways that follow an ischaemic stroke.[26]

Figure 1: Major Cellular Patho-Physiological Mechanisms of Ischemic Stroke.



Glutamate excitotoxicity

Excessive accumulation of excitatory amino acids causes hazardous elevations in intracellular calcium, which in turn mediates a large amount of ischemia-induced neuronal damage. [29] Paradoxically, this rise in intracellular calcium triggers several signalling pathways that ultimately result in cell death, even though it is an inherent defensive response to prevent ischaemia by initiating a reaction to extreme cell stress.[29] Numerous ionic species enter the cell as a result of energy-dependent cellular

pumps failing shortly after cerebral blood flow is reduced or stopped because glucose-dependent ATP synthesis is reduced.[30]Through osmosis, this results in cellular depolarisation and swelling. Via ligand-gated and voltage-dependent ion channels, calcium ions (Ca+2) enter the cell and activate a variety of lipases, kinases, proteases, and endonucleases, which sets off the intrinsic apoptotic cascade and ultimately results in cell death.[30] After ischaemia, glutamate, the brain's primary excitatory neurotransmitter, builds up in the extracellular space and activates its receptors. [31] Changes in intracellular ion concentrations, especially those of Ca2+ and sodium ions (Na+), are brought about by glutamate receptor activation. Neuronal survival may be negatively impacted at earlier post-ischemia timepoints by elevated intracellular Na+. [32] The unique sensitivity of CNS neurones to abrupt oxygen and glucose deprivation exacerbates the inflammatory paradox of cellular self-injury; the catastrophic temporal and anatomical nature of stroke combines with these facts to create consequences that are hard to treat medically, posing a challenge beyond the current capabilities of modern medicine.[32]

Oxidative stress

There is mounting evidence that the pathogenesis of ischaemic stroke involves a strong relationship between oxidative stress and apoptosis.[33] Like other bodily cells, neurones are often subject to baseline oxidative stress from both endogenous and external causes.[33] Highly reactive compounds with one or more unpaired electrons are known as free radicals. Free radicals have the ability to react with proteins, lipids, and DNA, resulting in varied degrees of malfunction and damage.[33] Nitric oxide (NO), hydroxyl radicals, and superoxide anion radicals are among the free radicals that contribute to stroke-induced brain damage. Antioxidant enzymes and free radical scavengers typically prevent or lessen the harmful effects of free radicals.[34] The

mitochondria, which generate superoxide anion radicals during electron transport, are the main source of oxygen-derived free radicals (commonly referred to as "reactive oxygen species") during ischemic-stroke injury. Through the cyclooxygenase and lipooxygenase pathways, arachidonic acid metabolism is another potentially significant generator of superoxide in post-ischemic neurones.[35] After ischaemic tissue reperfusion, active microglia and peripheral leukocytes that have infiltrated can also produce oxygen free radicals through the NADPH oxidase system. 36 This oxidation is thought to be a significant apoptotic trigger following an ischaemic stroke and results in further tissue damage.[35]

One of the many NO synthase (NOS) isoforms converts L-arginine into NO. The brain's neurone subpopulations express the neuronal form (nNOS), which needs calcium/calmodulin to activate.[37] Inflammatory cells including monocytes and microglia exhibit inducible NOS (iNOS). In general, these two isoforms cause brain damage when ischaemia occurs.[37] Endothelial cells (eNOS) include a third isoform that has vasodilatory properties and probably helps by enhancing local blood flow. It has been demonstrated that NMDA receptor stimulation increases nNOS's production of nitric oxide (NO) and may contribute to excitotoxic-mediated damage in ischaemic stroke. NO can combine with superoxide at its production point to form peroxynitrite ($ONOO^-$), another extremely reactive oxygen species, and it diffuses readily across membranes.[37] After a stroke, reactive nitrogen species and oxygen-derived free radicals both trigger a number of cell death pathways, including inflammation and apoptosis. Additionally, decreased oxygen availability causes lactate to build up through anaerobic glycolysis, which causes acidosis.[38]

Lipid peroxidation[39,40]

Acidosis disrupts intracellular protein synthesis in addition to generating various oxygen radical species.[39] The pathophysiology of stroke seems to be significantly influenced by lipid peroxidation. Membrane lipid peroxidation causes neuronal death by producing 4-hydroxynonenal (4-HNE), an aldehyde that covalently alters and impairs the function of membrane transporters, including "Na+/K+ ATPase, glucose transporters, and glutamate transporters.[39] Ca2+ and free radicals can activate neuroprotective transcription factors, such as nuclear factor-κB (NF-κB), hypoxia-inducible factor 1, and interferon regulatory factor 1" although they can also be harmful by direct effects. Certain transcription factors trigger the production of proinflammatory genes (like interferon-inducible protein-10) and endothelial cell adhesion molecules (like selectins, ICAM-1, and VCAM-1), as well as inflammatory cytokines (like IL-1, IL-6, and TNF-α) and chemokines (like IL-8 and MCP-1)[40]

Inflammation[41,42]

Following an ischaemic insult, proinflammatory mediators can be secreted by a number of resident cell types within brain tissue. These consist of neurones, microglia, astrocytes, and endothelial cells. In post-stroke brain tissue, transcription factor activation leads to elevated cytokine protein levels and improved expression of endothelial cell adhesion molecules (CAMs).[41] Microglia, particularly in the area of penumbral injury, are thought to play a significant part in the inflammation that occurs in the brain after a stroke.[42] Numerous proinflammatory cytokines, as well as harmful metabolites and enzymes, are produced by activated microglia. In addition to microglial cells, astrocytes also contribute significantly to the inflammation of the brain following a stroke. These cells have the ability to produce neuroprotective substances including metallothionein-2, TGFβ1, and erythropoietin as well as proinflammatory cytokines.[42] The overall glial role may vary at different post-stroke

timepoints due to the mixed nature of microglial and astrocyte products (both protective and destructive factors), with regenerative or protective activities taking place days to weeks after the onset of ischaemia.[42] When figuring out their pathophysiological involvement in stroke and creating novel stroke treatments, these factors add layers of complexity.[42]

Blood Brain Barrier (BBB) dysfunction[43]

The blood brain barrier (BBB) is proof that the brain endothelium is very different from other organs. Like other organs following ischaemic injury, it reacts to stroke injury by becoming more permeable, losing its barrier function, and degrading the basal lamina of the vessel wall.[43] Similar to this, there is strong evidence that acute ischaemic stroke contributes to the damage process by improving the contacts of the brain endothelium with intravascular cells (platelets, leukocytes) and extravascular CNS cells (astrocytes, microglia, neurones).[43] As a result of all these stroke reactions, the cerebral vasculature develops the following characteristics:[43]

1) "reduced endothelial barrier function,

2) pro-adhesive for circulating cells,

3) pro-inflammatory,

4) pro-thrombogenic, and

5) inadequate capillary perfusion of brain tissue".

Each inflammatory reaction tilts in the same harmful direction, compounding these normal physiological function abnormalities, until the host CNS cells and tissues are harmed. In fact, this is the main issue preventing prompt and efficient stroke therapy.[43]

Leukocyte infiltration

There is strong evidence linking leukocytes to the pathophysiology of stroke damage. Three main lines of evidence support the idea that leukocytes mediate tissue damage and microvascular dysfunction brought on by reperfusion:[44]

1) Leukocytes build up in post-ischemic tissues before tissue damage occurs,

2) animals that are rendered neutropenic show a reduced injury response to ischaemic stroke, and

3) using monoclonal antibodies (mAbs) that target particular leukocyte or endothelial CAMs to prevent leukocyte-endothelial cell adhesion also offers significant protection against stroke injury.[40] Therefore, polymorphonuclear leukocytes—mostly neutrophils—are strongly linked to a poor stroke outcome. In the acute post-stroke phase, neutrophils penetrate the brain parenchyma and stick to endothelial ischaemic brain vasculature.[44] On the other hand, it is yet unclear what pathophysiological importance lymphocyte recruitment into the brain following ischaemic stroke has. T-lymphocytes, however, have been implicated in mediating reperfusion injury in post-ischemic brain tissue in recent investigations.[44] It is currently unclear how neutrophils and lymphocytes may interact in the pathogenesis of stroke..[44]

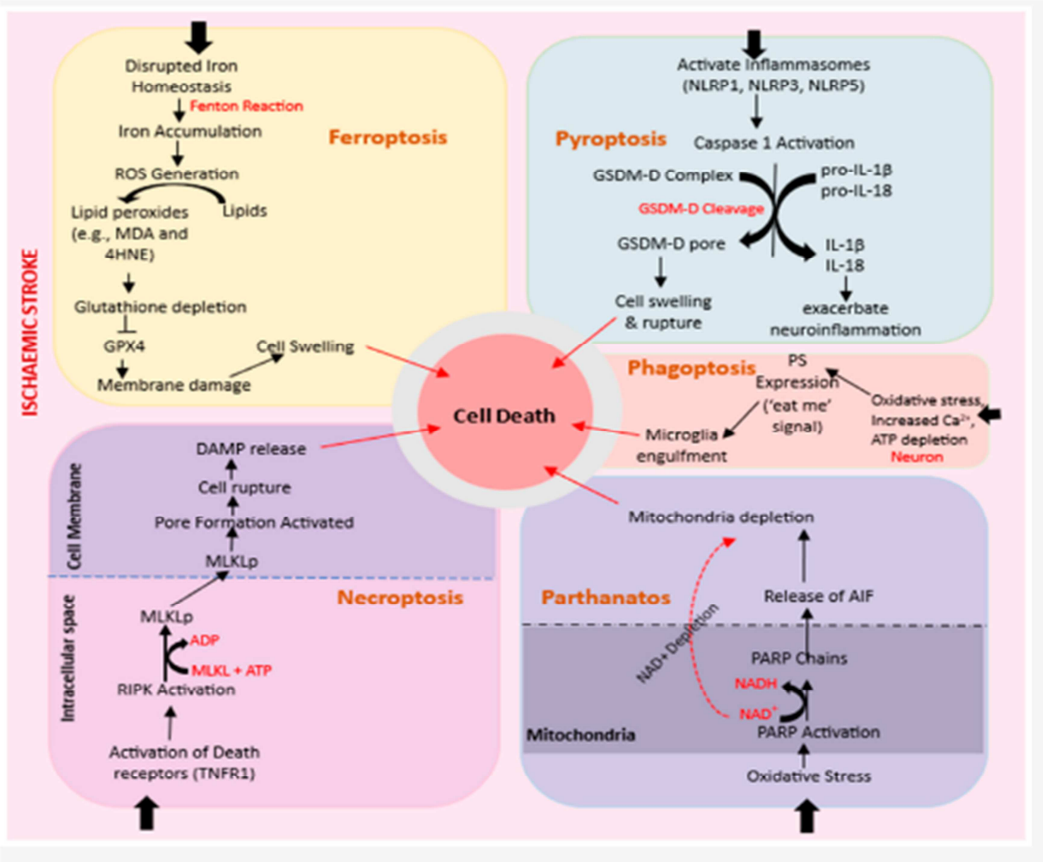
Apoptosis

In order to create apoptotic bodies, apoptosis entails a sequence of internal and/or external processes that cause neurones to shrink and cytoplasm to condense before the nuclear membrane is broken. In the intrinsic pathway, the usual glycolytic oxidative phosphorylation pathway that produces ATP is disrupted by a diminished availability of nutrients and oxygen to the cell.[45] As a result, the anaerobic route prevails and the

amount of ATP generated is not enough to sustain cellular functions.[45] An overabundance of excitatory amino acid neurotransmitters, particularly glutamate, are released into the extracellular space as a result of calcium ion buildup in the cell, which causes an ionic imbalance (Na+/Ca2+ influx and K+ efflux). Following this procedure, a series of cytotoxic events occur in the cytoplasm and nucleus, such as DNA breakage (caused by DNA damage), reactive oxygen species (ROS) produced by mitochondrial metabolism that damages cellular membranes, and calpain activation (caused by calpain).[45] The activity of inflammatory signalling factors generated by astrocytes, microglia, and oligodendrocytes as a result of cerebrovascular damage is part of the extrinsic pathway, which frequently happens either alone or in concert with the intrinsic pathway. Proinflammatory cytokines and receptors such as TNF-α/β, chemokines, interleukin 1β, TNF-related apoptosis-inducing ligand receptor (TRAIL-R), and Fas ligand (FasL) are examples of these inflammatory signalling factors.[45] By activating the downstream effector caspase-3 or BID, which mediates apoptosis through the mitochondrial-dependent route, these receptors at the neuronal cell membrane set off an apoptotic process.[45]

Five other pathways, in addition to apoptosis, can cause cell death after an ischaemic stroke: ferroptosis, phagoptosis, parthanatosis, pyroptosis, and necroptosis.[45] Developing focused therapeutic strategies requires an understanding of the complex interactions between these many cell death processes in the context of ischaemic stroke. Combining knowledge from these processes may result in better ways to reduce neuronal damage and enhance the prognosis of ischaemic stroke patients.[45]

Figure 2: Different Forms of Cell Death Associated with Ischemic Stroke.



Cerebral Autoregulation

Under physiological settings, cerebral blood vessel resistance—which is directly correlated with their diameter—is the primary regulator of cerebral blood flow. Vasoconstriction has the opposite effect from vasodilation, which increases cerebral blood flow and brain blood volume. Furthermore, variations in cerebral perfusion pressure affect cerebral blood flow.[46]

The capacity to sustain comparatively constant cerebral blood flow in the face of mild variations in perfusion pressure is known as cerebral autoregulation. Autoregulation's precise mechanisms are still not fully understood, but they most likely involve several pathways.[46] "Research indicates that the smooth muscle of the cerebral vessels responds directly to variations in perfusion pressure by contracting when the pressure

is raised and relaxing when the pressure is lowered. Furthermore, although the precise molecules involved are still unknown, declines in cerebral blood flow may cause blood vessel dilatation by releasing vasoactive chemicals. Additionally, endothelial cells' release of nitric oxide seems to support autoregulation".[46]

Although there are individual variances in the top and lower limits, cerebral blood flow management by autoregulation typically functions within the mean arterial pressure (MAP) range of 60 to 150 mm Hg. [46]Cerebral blood flow increases or decreases passively in response to pressure variations beyond this range because the brain's capacity to adjust for variations in perfusion pressure is reduced. At low pressures, this passive reaction can cause ischaemia, while at high pressures, it can cause oedema.[46]

Cerebral autoregulation is compromised in some pathological situations, including ischaemic stroke. Cerebral blood arteries widen to enhance cerebral blood flow as cerebral perfusion pressure drops.[23] Cerebral blood flow, however, decreases if the drop in perfusion pressure is greater than the brain's ability to compensate. To maintain brain oxygen supply, the oxygen extraction fraction first rises. Other mechanisms then come into play as cerebral blood flow continues to decline.[46]

Under 50 mL/100 g/min of cerebral blood flow, protein synthesis is reduced. At 35 mL/100 g/min, protein synthesis entirely stops, while glucose utilisation momentarily rises. Anaerobic glycolysis starts and glucose utilisation drastically decreases when cerebral blood flow falls to 25 mL/100 g/min, which causes lactic acid buildup and tissue acidosis.[46] At 16 to 18 mL/100 g/min cerebral blood flow, neural electrical failure takes place, and at 10 to 12 mL/100 g/min, membrane ion homeostasis failure follows. 23 Usually, this threshold signals the start of an infarction.[46]

Autoregulation adjusts to function at elevated arterial pressures in hypertensive

people. Restoring normal blood pressure in these people may exacerbate autoregulation dysfunction after a stroke, further decreasing cerebral blood flow.[46]

Concept of the Ischemic Penumbra

The infarct core is formed when brain tissue that depends solely on one artery for blood supply has an infarct during an acute ischaemic stroke.[47] The ischaemic penumbra, which surrounds this core, sustains a certain level of blood flow by collateral circulation. On the other hand, the penumbra shrinks and the infarct core enlarges as infarction swelling increases.[47] Cerebral perfusion is roughly 50 mL/100 g/min under normal circumstances. When perfusion falls below 30%, or less than 15 mL/100 g/min, brain cells start to die. Thus, the brain tissue is ischaemic but not infarcted when blood flow is decreased but still exceeds 30% of the normal rate, underscoring the crucial idea that "time is brain." Given the different intervention time windows based on these physiological insights, this theory emphasises the significance of prompt revascularisation therapy in acute ischaemic stroke.[48]

History and Physical[48]

Determining the onset of symptoms is crucial since ischaemic strokes happen abruptly. Clinicians utilise the time the patient was last seen in their normal state of health, free of new neurological symptoms, as a reference point if the precise minute the symptoms began is unknown. When assessing whether intravenous (IV) thrombolytics should be administered, this predetermined timeline is essential.[48] Examining possible underlying reasons is another crucial clinical assessment component that helps predict the mechanism of the stroke. Common vascular risk factors include diabetes, smoking, hypertension, and a history of stroke or TIA should be taken into account. The treating physician should also determine the history of

heart conditions, including cardiomyopathy, recent myocardial infarction, and atrial fibrillation.[48] The examination is also greatly influenced by variables such as symptoms of hypercoagulopathy, recent chiropractic adjustments, and history of neck injuries.

For any patient suspected of having a stroke, a neurological examination is essential. Listening for a neck bruit, which could be an indication of vascular irregularities, is crucial, as is keeping an eye on vital signs and heart rhythms.[48] With 11 categories and scores ranging from 0 to 42, the National Institutes of Health Stroke Scale (NIHSS) is the industry standard for determining the severity of strokes. These include gaze direction, vision, face symmetry, arm and leg motor skills, limb coordination, sensory perception, linguistic abilities, speech clarity, level of consciousness (LOC) instructions, LOC queries, LOC commands, and attention to both sides of the body.[48] Each score on the stroke scale is determined by the patient's assessment performance rather than their anticipated abilities, and it should be completed in a certain order.

Table 1: National Institutes of Health Stroke Scale

Category	Score Meaning	Score
1a -- LOC Instructions	0:Fully alert, 1:Not Fully Alert, but not drowsy, 2:Obtunded or requires minor stimulation to stay alert, 3:Unresponsive or requires repeated stimulation	
1b. LOC Questions	0: Answers both questions correctly, 1: Answers 1 question correctly, 2: Answers neither question correctly	
1c. LOC Commands	0: Performs both tasks correctly, 1: Performs 1 task correctly, 2: Performs neither task correctly	
2. Best Gaze	0: Normal; 1: Partial gaze palsy; 2: Forced deviation	
3. Visual Field Testing	0: No visual loss; 1: Partial hemianopia; 2: Complete hemianopia; 3: Bilateral hemianopia (blind including cortical blindness)	
4. Facial Palsy	0: Normal symmetrical movements; 1: Minor paralysis; 2: Partial paralysis; 3: Complete paralysis of 1 or both sides	
5. Motor Arm (score both left and right)	0: No drift; 1: Drifts down; 2: Some effort against gravity; 3: No effort against gravity; 4: No movement	
6. Motor Leg (score both left and right)	0: No drift; 1: Drifts down; 2: Some effort against gravity; 3: No effort against gravity; 4: No movement	
7. Limb Ataxia	0: Absent; 1: Present in 1 limb; 2: Present in 2 limbs	
8. Sensory	0: Normal; 1: Mild to moderate sensory loss; 2: Severe to total sensory loss	
9. Best Language	0: Normal; 1: Mild to moderate aphasia; 2: Severe aphasia; 3: Mute or global aphasia	
10. Dysarthria	0: Normal; 1: Mild to moderate dysarthria; 2: Severe dysarthria or anarthria	
11. Extinction and Inattention	0: No abnormality; 1: Visual, tactile, auditory, spatial, or personal inattention; 2: Profound hemi-inattention or neglect to more than 1 modality	
		Total

Evaluation

It is strongly advised to follow a structured stroke procedure in order to speed up examination. Patients who qualify for thrombolytics due to acute ischaemic stroke should have a door-to-needle time of 60 minutes.[49]

The following are the objectives of the first phase:[49]

• Maintaining medical stability, with an emphasis on breathing, circulation, and airway

Reversing any problems that are causing the patient's issue as soon as possible

Assessing if the patient qualifies for endovascular thrombectomy or IV thrombolytic treatment

• Attempting to identify the pathophysiologic cause of the patient's neurological symptoms

Vital signs, respiration, circulation, and airway are all assessed at the earliest stage of the patient's care. Patients run the risk of aspiration and asphyxiation and may have respiratory problems due to high intracranial pressure (ICP).[49] To guarantee proper breathing and oxygenation, endotracheal intubation can be required.[49]

Given that hypoglycemia is easily ruled out as a cause of neurological abnormalities, a fingerstick glucose check should be conducted.[49]

Within 20 minutes of presentation, a plain CT head is advised for patients in order to rule out haemorrhage. Vascular imaging should be taken into consideration for potential endovascular intervention in hospitals or stroke centres that offer emergency care.[49]Endovascular therapy shouldn't postpone the delivery of thrombolytics, nevertheless.[49]

A specialised MRI method called diffusion-weighted imaging (DWI) gauges the transport of water molecules within tissue. Because DWI can identify cytotoxic

oedema, a characteristic of early infarction, minutes after the stroke begins, it is especially sensitive for identifying acute ischaemic strokes.[49] Compared to other MRI sequences like Fluid-Attenuated Inversion Recovery (FLAIR), DWI can detect brain infarction significantly earlier. It may take up to 4.5 hours for a FLAIR sequence to reveal symptoms of a brain infarction, but a DWI scan can identify abnormalities within minutes of a stroke.[50] It indicates that the ischaemic stroke happened less than 4.5 hours ago if the DWI exhibits stroke symptoms but the FLAIR sequence does not. Because individuals who have had a stroke less than four and a half hours ago may be eligible for early IV thrombolysis, which could reverse neurological impairments, this period is critical.[50]

"An ECG, troponin levels, complete blood count (CBC), electrolytes, blood urea nitrogen (BUN), creatinine (Cr), and coagulation factors are further diagnostic tests. Given that coronary artery disease is frequently linked to stroke, the medical professional should assess an ECG and troponin". An infection or anaemia may be revealed by a CBC.[49] Electrolyte imbalances should be corrected by medical professionals since they can affect mental status and make diagnosing ischaemic stroke more difficult. Because contrast tests can deteriorate renal function, BUN and Cr should be followed.[49] Increased levels of coagulation factors, such as PT, PTT, and INR, may indicate a hemorrhagic stroke aetiology, hence they should also be obtained.[49]

"The US Food and Drug Administration (FDA) highly advises employing a teleradiology system for image interpretation for suspected stroke patients in institutions lacking professional imaging interpretation".[51] The choice to administer IV alteplase is aided by the interpretation of rapid imaging. It is very advised that radiologists and telestroke neurologists consult and reach a consensus.[51] For thrombolytic administration, a telephone consultation might be taken into

consideration in places lacking an internal stroke team or telestroke protocol. There is not much data to support this recommendation.[51]

Hemorrhagic Stroke

When blood vessels burst, blood flows into the brain, causing hemorrhagic stroke. Subarachnoid haemorrhage (SAH) and intracerebral haemorrhage (ICH) are two additional subtypes of hemorrhagic stroke.[52]

Epidemiology

Ten to twenty percent of strokes each year are hemorrhagic strokes. In the US, UK, and Australia, the haemorrhage rate for stroke is 8–15%, but in Japan and Korea, it is 18–24%. The annual incidence is between 12 and 15 cases per 100,000. Asians and those in low- and middle-income nations have a higher incidence.[53] It is more common in men and gets worse as people age.[53] The incidence is increasing globally, primarily in Asian and African nations. According to Japanese studies, controlling hypertension lowers the incidence of ICH. High-income countries have a case fatality rate of 25–30%, but low- to middle-income countries have a rate of 30–48%. The effectiveness of critical care determines the ICH fatality rate.[53]

Etiology

Hypertension is the most common hemorrhagic stroke cause.[54]

- Long-term hypertension results in smooth muscle fragmentation, arterial media degeneration, and elastic lamina rupture. The arterioles also develop lipohyalinosis, fibrinoid necrosis of the subendothelium, microaneurysms, and localised dilatations. Charcot-Bouchard aneurysms are the name given to the microaneurysms.[54]

- The small penetrating arteries that emerge from the anterior, middle, or posterior cerebral arteries or the basilar arteries are frequently the locations of intracerebral haemorrhage caused by hypertension.[54]
- Non-lobar intracranial haemorrhage (ICH) is caused by hypertensive alteration, and small artery branches with a diameter of 50–700 μm frequently have many rupture sites linked to platelet and fibrin aggregation layers. Postpartum ICH, another name for ICH, can also be brought on by acute hypertension, as in eclampsia.[54]

"In older individuals, **cerebral amyloid angiopathy (CAA)** is a significant primary cause of lobar intracerebral haemorrhage.[55]

- This condition, which is frequently linked to changes in the gene producing apolipoprotein E, produces ICH in older adults and is characterised by amyloid-β peptide accumulation in capillaries, arterioles, and small and medium-sized arteries in the cerebral cortex, leptomeninges, and cerebellum.[55]
- Young individuals may develop a familial condition, which is usually linked to abnormalities in the gene that codes for the amyloid precursor protein.[55]
- The incidence of CAA rises with age; almost 50% of those over 70 have CAA. CAA may result in recurrent bleeding".[55]

Other Important Risk Factors

- "Chronic alcoholism, moderate to heavy alcohol use, and cigarette smoking are important risk factors.[56]
- Because chronic liver illness causes thrombocytopenia and coagulopathy, it also raises the risk of ICH.[56]

- Low triglycerides and decreased low-density lipoprotein cholesterol are additional risk factors".[56]
- Compared to monotherapy, dual antiplatelet medication has a greater risk of ICH.
- The risk of cerebral haemorrhage is increased by sympathomimetics such cocaine, heroin, amphetamine, ephedrine, and phenylpropanolamine.[56]
- The risk of ICH is increased by cerebral microbleeds (CMBs) linked to diabetes mellitus, hypertension, and cigarette smoking. [56]
- Male sex and advanced age. After age 55, the incidence of ICH rises. After 70 years, the relative risk is 7.[56]
- Glioblastoma, lymphoma, metastasis, meningioma, pituitary adenoma, and hemangioblastoma are among the tumours that are more likely to bleed.[56]

"A ruptured aneurysm, arteriovenous malformation, vasculitis, cerebral artery dissection, dural sinus thrombosis, and pituitary apoplexy are among the common causes of spontaneous subarachnoid haemorrhage (SAH). Pregnancy, substance addiction, oral contraceptive pills, and hypertension are risk factors".[56]

Because of the lack of cerebrovascular autoregulation, eclampsia is associated with intracranial haemorrhage of pregnancy (ICHOP), also known as intracerebral or subarachnoid haemorrhage. [56]

Pathophysiology

The thalamus (15%), cerebral lobes (10–20%), pons and brain stem (10–20%), cerebellum (10%), and basal ganglia (50%) are among the often bleeding areas.[52] Glia and neurones are disrupted by the haematoma. Oligemia, neurotransmitter release, mitochondrial malfunction, and cellular oedema are the outcomes of this. Thrombin induces oedema and inflammation by activating microglia.[56]

The hematoma's compression of brain tissue and elevated intracranial pressure (ICP) cause the main damage. [57]

Glutamate-induced excitotoxicity, oedema, inflammation, disruption of the blood-brain barrier (BBB), haemoglobin and iron release from the clot, and the overproduction of free radicals such reactive oxygen species (ROS) are the causes of secondary damage.[57]

The haematoma often becomes larger in three to twelve hours. In one-third of cases, haematoma expansion happens within three hours. Within 24 hours, perihematomal oedema rises, peaks in 5–6 days, and lasts for up to 14 days.[52] The haematoma is surrounded by a region of hypoperfusion. Haematoma growth, intraventricular haemorrhage, perihematomal oedema, and inflammation are some of the factors that contribute to the worsening of ICH. [52] Early on, a cerebellar haematoma compresses the fourth ventricle, resulting in hydrocephalus. [52]

Both perimesencephalic and non-perimesencephalic spontaneous subarachnoid haemorrhages can occur in non-aneurysmal SAH. The interpeduncular cistern is where bleeding mainly happens in perimesencephalic SAH. Perimesencephalic nonaneurysmal SAH (PM-SAH) is predisposed to by physical activity, such as the Valsalva manoeuvre, which raises intrathoracic and cerebral venous pressure. The blood distribution in non-perimesencephalic SAH (NPM-SAH) is diffuse.[58]

History and Physical

Facial palsy, hemiparesis, aphasia, and headache are common stroke manifestations. The appearance of hemorrhagic stroke is usually immediate and progressive. Symptoms of hemorrhagic stroke often include acute onset headache, nausea, stiff neck, elevated blood pressure, and fast progressing neurological symptoms. The location and extent of the haemorrhage are related to the symptoms.[59]

• Large haematomas are more likely to cause headaches.[59]

• Vomiting is a common symptom of cerebellar haematoma and implies elevated intracranial pressure.[59]

• Lobar haemorrhage manifests as seizures, aphasia, and hemianopia; coma is caused by involvement of the brainstem's reticular activating system. Numbness, tingling, and weakness can potentially be a prodrome of lobar haemorrhage.[59]

• Basal ganglia and thalamic haemorrhage are characterised by contralateral sensorimotor impairments.[59]

• The primary characteristic of thalamic haemorrhage is the loss of all sensory modality.[60]

• Cranial nerve dysfunction with contralateral weakness implies brainstem haematoma;

• Pontine haematoma usually results in coma and quadriparesis;[60]

• Thalamic haematoma extension into the midbrain can induce vertical gaze palsy, ptosis, and unreactive pupil.[60]

Elevated ICP symptoms, including bradycardia, vomiting, and lethargy, are caused by cerebellar haemorrhage. Haematoma enlargement or worsening oedema is indicated by progressive neurological decline.[60]

Clinical manifestations of subarachnoid haemorrhage include vomiting, syncope, photophobia, nuchal stiffness, convulsions, a strong "thunderclap" headache, and a lowered state of consciousness. Positive meningismus symptoms include the Brudzinski sign (involuntary hip flexion when extending the patient's neck) and the Kernig sign (pain when straightening the knee with the leg flexed 90 degrees).[60]

Evaluation[61,62]

The first test is usually computerised tomography (CT). Over the course of hours, haemorrhage attenuation rises from 30 to 60 Hounsfield units (HU) during the hyperacute phase to 80 to 100 HU. Anaemia and coagulopathy may cause attenuation to diminish.[61] For up to two weeks, the vasogenic oedema surrounding the haematoma may worsen. Because of its sensitivity, CT is regarded as the "gold standard" for detecting acute haemorrhages. For the identification of acute haemorrhage, gradient echo and T2* susceptibility-weighted magnetic resonance imaging (MRI) provide sensitivity comparable to CT. When it comes to detecting previous bleeding, these sequences are more sensitive than CT.[61,62]

The haematoma may seem isodense to brain tissue during the subacute period, necessitating magnetic resonance imaging (MRI). The formula AxBxC/2 can be used to determine the haematoma volume, where A and B stand for the greatest and perpendicular diameters, respectively.[62] The vertical height of the haematoma is denoted by C. High mortality is linked to intracerebral haemorrhages larger than 60 millilitres. Haematoma expansion, intraventricular haemorrhage, infratentorial location, and contrast extravasation on CT scan (spot sign) are additional unfavourable prognostic variables. Early MRI haemorrhage detection is made possible by the paramagnetic characteristics of deoxyhemoglobin.[62] When it comes to identifying acute bleeding, gradient echo (GRE) imaging is comparable to CT.[62] Primary haemorrhage and hemorrhagic infarct transformation can be distinguished by MRI. Vascular abnormalities, such as tumours, cerebral vein thrombosis, and cavernomas, are among the underlying causes of secondary haemorrhage that can be identified by MRI. [61,62]

Ongoing bleeding linked to death is indicated by contrast extravasation in CT angiograms (CTAs). Arteriovenous malformation (AVM), ruptured aneurysm, dural venous sinus (or cerebral vein) thrombosis (DVST/CVT), vasculitis, and Moya-Moya

syndrome are among the secondary hemorrhagic stroke causes that can be ruled out with multidetector CT angiography (MDCTA).

Some features of imaging aid in the differentiation of underlying diseases: [61,62]

- Multiple parieto-occipital lobe haemorrhages of varying ages are indicative of cerebral amyloid antipathy.[62]
- A hemorrhagic infarction is suggested by bleeding in an arterial region.

  Anticoagulation-induced haemorrhages exhibit many bleed stages inside a single haematoma with fluid level; vasculitis is indicated by small ischaemic and hemorrhagic lesion combinations.[62]
- Moyamoya disease is characterised by haemorrhage with arterial obstruction.

  For SAH, digital subtraction angiography (DSA) including four vessels is required. To confirm a negative DSA for aneurysm, further testing is required. At 1-week and 6-week intervals, repeat angiography is recommended.[62]

  These simple CT scan results should raise suspicions about vascular abnormalities:
- Haemorrhage under the spine[62]

  A cortical vein along the assumed venous drainage channel; enlarged arteries or calcifications along the ICH boundaries; hyperattenuation within a dural venous sinus; an unusual haematoma shape; oedema out of proportion to the assumed ICH time; an unusual haemorrhage location[62]
- Additional aberrant brain anatomy (such as a mass)

  In certain situations, further MRI is helpful in determining the secondary causes of ICH:
- The site of the lobar haemorrhage
- Under 55 years old, and

- No prior history of hypertension

  Conditions that suggest cerebral venous thrombosis warrant the use of magnetic resonance venography, often known as CT venography:

- Location of the haemorrhage;
- Volume of relative oedema;
- Abnormal signal in the cerebral sinuses

  Blood tests that identify bleeding or coagulation abnormalities and haematological illnesses that cause haemorrhage include bleeding time, clotting time, platelet count, peripheral smear, prothrombin time (PT), and activated partial thromboplastin time (aPTT).[61,61] To rule out hepatic or renal failure as reasons, liver and renal function tests are required. "Antinuclear antibodies (ANA), anti-double-stranded DNA (ds-DNA) antibodies, complement, anti-Ro [SS-A] and anti-La [SS-B] antibodies, cytoplasmic staining and perinuclear staining, antineutrophil cytoplasmic antibodies (c- and pANCA), thyroid antibodies, rheumatoid factor, anti-endothelial antibodies, and quantitative immunoglobulin evaluation are among the tests for vasculitis". [61,62]

HDL AND STROKE

HDL: Structure and Function

Proteins, phospholipids, and cholesterol combine to form lipoprotein complexes. HDL's high protein content makes it the densest and smallest lipoprotein. Apolipoprotein A-I (apoA-I) makes up 70% of the protein component, which makes up around 50% of its mass.[63]

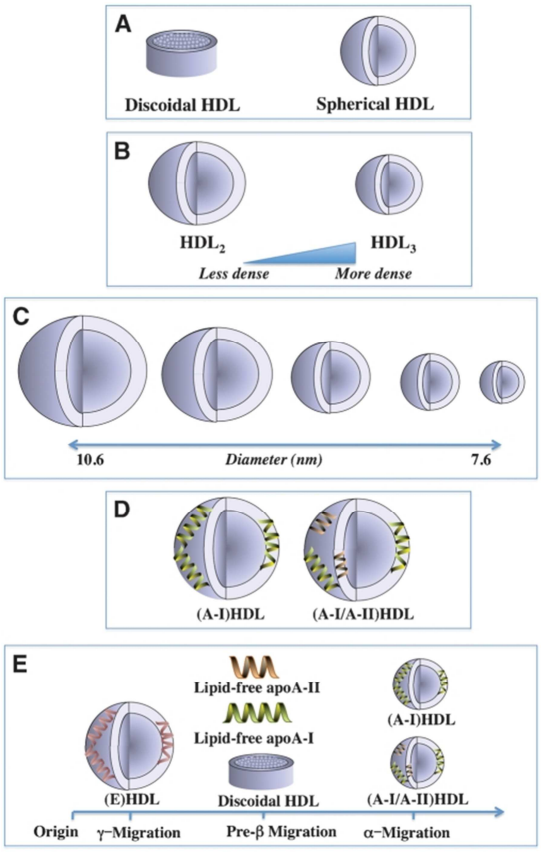
The 243-amino acid protein ApoA-I is produced in the gut (30%) and liver (70%) and released into the serum in a lipid-free form. Lipid-poor pre-β-HDL is created when

individual apoA-I molecules combine with cholesterol, membrane phospholipids, and other apoA-I molecules. With maturation and the addition of cholesterol, lipid-poor HDL takes on a double-belt-like shape that eventually becomes spherical.[63]

Lipid-poor β-HDL can use the ATP-binding cassette A-1 (ABCA-1) receptor to take up cholesterol from arterial wall macrophages. Lecithin-cholesterol acyltransferase subsequently esterifies cholesterol after it has moved into lipid-poor HDL. Mature spherical lipoproteins are formed when cholesterol packs into the HDL core after becoming esterified.[63]

"Mature spherical HDL can unload cholesterol by two main mechanisms. Cholesterol transfer back to the liver occurs through interaction with the scavenger receptor-B1 (SR-B1) receptor on hepatocytes, leading to bile formation and gut secretion".[63] "Alternatively, cholesterol can transfer from mature HDL to low-density lipoprotein (LDL) or very-low-density lipoprotein (VLDL), a process dependent on cholesteryl ester transfer protein (CETP). This creates cholesterol recycling, potentially back into the artery wall".[63]

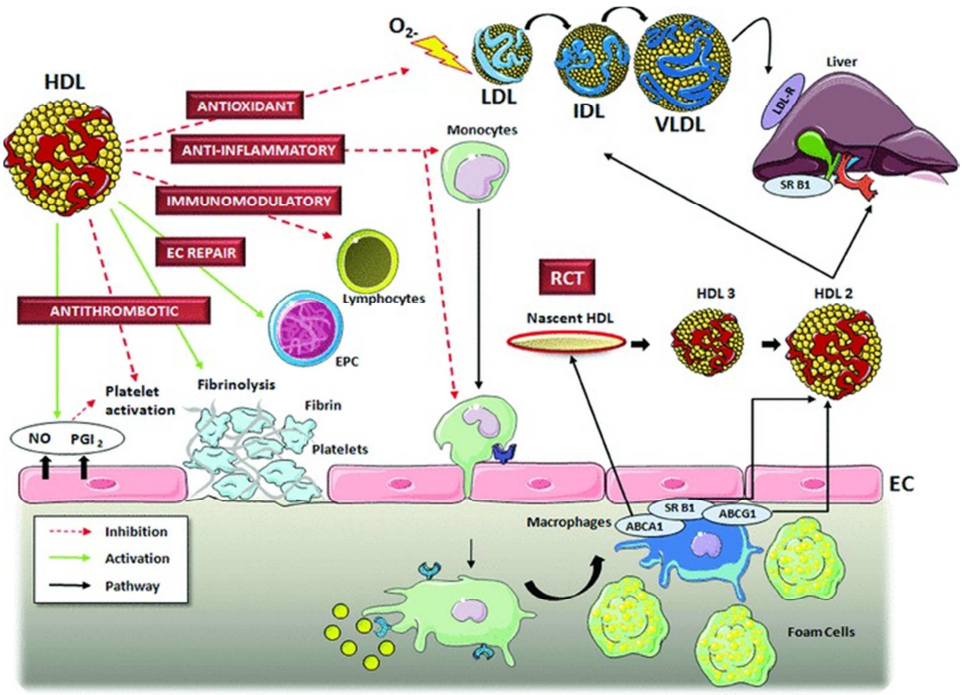
Figure 3: HDL heterogeneity. Human plasma HDL consist of several particle subpopulations that vary widely in shape (A), density (B), size (C), composition (D), and surface charge (E).



Mechanisms of Action[63]

Through a number of processes, including as reverse cholesterol transport, antioxidant, anti-inflammatory, antithrombotic, and endothelial function alteration, HDL prevents atherosclerosis.[63]

Figure 4: HDL's anti-atherosclerosis properties include inhibition of endothelial adhesion molecule expression and LDL oxidation, and promotion of reverse cholesterol transport.



HDL moves cholesterol from the arterial wall to the liver for elimination in a process known as reverse cholesterol transport. Through HDL interaction with ABCA-1, SR-B1, or passive diffusion, cholesterol is extracted from macrophages in the subintima of the vessel wall. HDL cholesterol is taken to the liver for excretion once it has been esterified.[63]

In both cell-free and artery-wall coculture investigations, HDL and apoA-1 can inhibit lipid oxidation, a major atherosclerosis mechanism, in contrast to Vitamin E, a far weaker antioxidant.[63] One important lipid hydroperoxide and paraoxonase carrier that helps prevent and reverse oxidative damage is HDL.

In addition to its antioxidant properties, HDL inhibits inflammation by reducing the expression of cytokines including interleukin-1 and tumour necrosis factor-α, which

mediate the overexpression of leukocyte endothelial adhesion molecules. This has been shown in cell cultures where normal functioning HDL can be added to prevent monocyte chemotactic activity.[63]

Lastly, HDL may enhance endothelial function by promoting prostacyclin release and lower thrombotic risk by preventing platelet activation and aggregation.[63]

Epidemiology[63]

"In the United States, low HDL (<40 mg/dL) affects 35% of men and 15% of women. Low HDL prevalence is expected to increase due to rising obesity, diabetes, and metabolic syndrome rates."[63]

Serum HDL Cholesterol and Stroke Risk

"More recent epidemiological research has reinforced the negative correlation between serum HDL-C and stroke risk. The British Cohort[65], the Honolulu Heart Program[66], the Atherosclerosis Risk in Communities (ARIC) study[67], the Oyabe study[68], the Dubbo study[69], the Copenhagen City Heart Study70, and the Israeli Ischaemic Heart Disease Study were among the large cohort studies that addressed this subject.[71] While several studies found nonsignificant trends towards an inverse link between serum HDL-C and ischaemic stroke risk, the majority of research showed a significant inverse association, albeit utilising varied HDL reference levels.[71] Middle-aged and older men and women from America, Australia, Europe, Hawaii, Israel, and Japan were among the populations under study. All of these results point to a reduction in the risk of ischaemic stroke in the future due to elevated baseline blood HDL-C levels. This inverse association has also been shown in case-control studies."[72]

Measuring HDL Function: Better Than HDL-C Levels?[63]

Research has indicated that HDL function varies from person to person. The apoA1Milano variation, for instance, provides protection against atherosclerosis due to its enhanced function and longer plasma residence time.[63] Variability in HDL function may help to explain why many heart attacks and strokes happen to people with normal HDL-C levels and why some people with advanced atherosclerosis have extremely high HDL-C.[63] Studies have revealed that HDL from certain people with cardiovascular disease is dysfunctional and actually pro-inflammatory, despite the fact that normal HDL is anti-inflammatory. Individuals with metabolic syndrome and those with low HDL-C and hypertriglyceridemia are at risk for malfunctioning HDL.[63]

Numerous tests are available to measure HDL function, some of which quantify its inflammatory and anti-inflammatory characteristics. It has been demonstrated that HDL's inflammatory/anti-inflammatory activity balance can more accurately differentiate CHD patients from control people than serum HDL-C levels.[63] Additionally, there is evidence that taking statins may positively enhance HDL function. It is yet unknown how HDL function affects ischaemic stroke, especially atherosclerotic stroke.[63]

Treatment Strategies

Current Guideline Recommendations

According to the American Diabetes Association (ADA) and Adult Treatment Panel (ATP) guidelines, dyslipidemic therapy should focus on reaching LDL-C objectives in individuals with low HDL-C levels, with serum HDL-C levels as a secondary goal.[73] For people with diabetes, metabolic syndrome, or HDL levels less than 40

mg/dL, the Expert Group on HDL, a working group that reported on low HDL-C levels, recommended further fibrate or niacin medication.[73] The significance of increasing HDL-C in lowering the risk of cardiovascular disease and stroke has also been emphasised by recent studies.[74]

Raising Serum HDL-C

For every 1 mg/dL increase in baseline HDL-C, serum HDL-C can reduce cardiovascular risk by 5.5%. Serum HDL-C can be raised by a variety of pharmacological and nonpharmacological methods. Those with the highest baseline HDL-C levels (≥60 mg/dL) seem to benefit the most from lifestyle-associated HDL-C changes.[63] Although several of these lifestyle changes have been demonstrated to lower the incidence of stroke generally, it is unknown how they will affect low-HDL people who are most at risk for cardiovascular disease.[63]

Pharmacological Treatments

Fibrates

Fibrates efficiently reduce triglyceride levels and increase HDL-C levels. They are ligands for nuclear receptors called peroxisome proliferator-activated receptors (PPARs), which control inflammation, endothelial function gene expression, and the metabolism of fats and carbohydrates.[75] Even in the absence of LDL lowering, gemfibrozil has been demonstrated to decrease major cardiovascular events by increasing HDL and decreasing triglycerides. After six months, the stroke risk reduction from gemfibrozil treatment became apparent, with individuals with the lowest baseline HDL-C seeming to benefit the most.[75]

Niacin

Doses of 1-2 g of niacin per day can raise HDL-C by 20–30%. With fewer flushing episodes and minimal liver toxicity compared to other slow-release preparations, the extended-release (ER) niacin product niaspan is better tolerated.[76] Prostaglandin D2 is responsible for niacin flushing. Aspirin pretreatment for a few days can reduce this flushing by preventing the production of prostaglandin D2. Although stroke has not been assessed as an independent endpoint in niacin trials for cardiovascular disease, there have been notable decreases in cardiac endpoints.[76]

Statins

Numerous extensive studies have demonstrated that statins lower the risk of ischaemic stroke by roughly 20%. Stroke risk is predicted to decrease by 15.6% (95% CI, 6.7 to 23.6), for every 10% decrease in LDL-C. The effects of statin therapy on HDL-C differ depending on the drug and dosage; for instance, high-dose atorvastatin raised HDL-C by less than 3%, whereas high-dose rosuvastatin raised HDL-C by 14%.[63] There was no discernible HDL-C effect three months after statin introduction in a trial of stroke patients treated in hospitals.[63] Patients may experience different outcomes from statins; individuals with elevated triglycerides and low HDL-C are more likely to benefit from statin medication.[63]

Combination Therapy[63]

With statin and niacin combos showing 18–21% HDL-C increases, combined therapy may be the key to the most pronounced HDL-C gain.[63]

The HDL Atherosclerosis Treatment Study (HATS) demonstrated the advantages of taking niacin in addition to statin medication. The combination decreased significant clinical events and stopped the progression of angiographic atherosclerosis.[77] ER-

niacin was well tolerated when added to statin therapy, and adherence rates were higher than 90%. [78]

"In order to assess the benefits of concurrently lowering LDL and raising HDL cholesterol levels in patients randomised to ER-niacin plus simvastatin or simvastatin alone, the National Institutes of Health (NIH) is funding the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) trial. Fenofibrate plus a statin is being tested against a statin alone in individuals with type 2 diabetes as part of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial".[78]

Emerging Therapies

To increase HDL levels, a number of novel agent classes are being created. Currently under investigation are three of the most promising agent classes:[63]

- CETP inhibitors
- ApoA-I peptides
- PPAR agonists
- HDL Delipidation
- SR-BI receptor upregulators
- Endothelial lipase inhibitors
- CETP vaccines
- Liver X α/β agonists
- Gene therapy

REVIEW OF RELATED ARTICLES

Curb JD et al (2004)[66] "The authors looked at the connection between older men's HDL cholesterol levels and their risk of stroke. In 1991–1993, 2,444 men in the Honolulu Heart Program, ages 71–93, had their HDL cholesterol levels assessed. The subjects, who at baseline had no coronary heart disease, cancer, or common stroke, were monitored for thromboembolic and hemorrhagic stroke until late 1998. Although there was no correlation between HDL cholesterol and hemorrhagic events, the risk of thromboembolic stroke decreased steadily as HDL cholesterol levels rose ($p = 0.003$). Compared to males with high HDL cholesterol levels (≥1.6 mmol/liter (≥60 mg/dl)), men with low levels (<1.0 mmol/liter (<40 mg/dl)) had almost three times as many extra thromboembolic strokes (10.6/1,000 person-years vs. 3.6/1,000 person-years; $p = 0.001$). These results were not significantly impacted by controlling for other risk factors, however the relationships seemed to be strongest in older men with diabetes mellitus, hypertension, or "desirable" total cholesterol levels. These results imply that the risk of thromboembolic stroke in older men is inversely related to HDL cholesterol levels. More research is necessary to determine whether HDL cholesterol affects how other factors affect the risk of stroke in older men".[66]

Soyama Y et al (2003)[68] "This study looked at the link in a long-term cohort study of Japanese women and men, whose stroke rates are higher than those in Western nations. 132 patients experienced a stroke during follow-up, including 81 occurrences of ischaemic stroke. Subjects with low HDL-C (<30 mg/dL [0.78 mmol/L]) had age-adjusted incidence rates for all stroke of 103.4 in men and 49.3 in women per 10,000 person-years, which were significantly higher than those with high HDL-C (≥60 mg/dL [1.56 mmol/L]) (26.4 in men and 15.5 in women). For ischaemic stroke, a comparable correlation was observed. Participants with low vs high HDL-C had

multivariate-adjusted relative risks for both ischaemic stroke incidence and all stroke incidence of 2.89 (95% CI, 1.35 to 6.20) and 2.92 (95% CI, 1.17 to 7.32), respectively. Sex, age, body mass index, blood pressure, serum total cholesterol, alcohol use, and smoking did not affect the relationships. According to their findings, this 10-year follow-up study of Japanese men and women showed a substantial and independent relationship between lower HDL-C levels and an increased risk of both ischaemic stroke incidence and all stroke incidence".[68]

Wannamethee SG, et al (2000)[65] "The association between serum HDL cholesterol, total cholesterol, and stroke risk was investigated in this study. They came to the conclusion that the risk of nonfatal stroke was considerably reduced by greater HDL cholesterol levels. On the other hand, there was a slight positive correlation between nonfatal strokes and high total cholesterol. The significance of modifiable stroke risk factors that are known to affect HDL cholesterol concentrations is highlighted by the clear negative relationship between HDL cholesterol and stroke observed in hypertensives".[65]

Simons LA et al (1998)[69] "The cohort, which was initially studied in 1988, included 2805 men and women who were 60 years of age or older. Following linkage to hospital and death records, a Cox proportional hazards model was used to analyse the prediction of ischaemic stroke by putative risk variables. 95 participants had a fatal stroke, and 356 men and women had an ischaemic stroke episode (ICD-9-CM 433 to 437). Age, female sex (48% lower risk), marital status (30% lower risk), previous stroke history (227% higher risk), antihypertensive medication use (37% higher risk), being in the highest blood pressure reading category (67% higher risk), atrial fibrillation presence (58% higher risk), HDL cholesterol (36% lower risk for each 1-mmol/L increment), impaired peak expiratory flow (77% higher risk for tertile I than

tertile III), physical disability (59% higher risk), and depression score (41% higher risk for tertile III than tertile I) were all significant independent stroke predictors in the multivariate model".[69]

Tanne D et al (1997)[71] "Using data from the Israeli Ischaemic Heart Disease Study's long-term follow-up, this paper sought to evaluate the relationship between HDL-C levels and ischaemic stroke mortality. Over a 21-year follow-up period, this prospective study of middle-aged and older males from a healthy, working population showed an independent negative correlation between HDL-C and ischaemic stroke mortality".[71]

Sacco RL et al (2001)[72] "examined the relationship between ischaemic stroke and HDL-C in an older group with a wide range of racial and ethnic backgrounds. They came to the conclusion that, in older adults and across racial or ethnic groupings, elevated HDL-C levels are linked to a lower risk of ischaemic stroke. These findings confirm HDL-C as a significant modifiable stroke risk factor and add to the body of research linking lipids to stroke".[72]

Alkhaneen H et al (2022)[79] "The purpose of this study was to examine the serum lipid profiles of patients who had hemorrhagic and ischaemic strokes. In this retrospective, comparative analysis, 41% of patients were female and 59% of patients were male, with a mean stroke presentation age of 68±13. The average BMI was 30±8. Both stroke subtypes were dominated by obesity (BMI ≥30). The most common comorbidity among patients was hypertension. Seventy-one percent of people had diabetes. 114 individuals with ischaemic stroke and 87 with hemorrhagic stroke were included in the study. When ischaemic and hemorrhagic stroke patients' serum lipid profiles were compared across stroke categories, there was no statistically significant difference in total cholesterol, triglycerides, and LDL-C levels".[79]

Saproo N et al (2021)[80] "Lipid profiles from ischaemic and hemorrhagic stroke patients were compared in this observational study. Total cholesterol (TC) was 175.2 mg/dl for hemorrhagic stroke and 192.4±41.6 mg/dl for ischaemic stroke. Thirty-two percent of hemorrhagic stroke patients had altered LDL. Seventy-six percent of ischaemic stroke patients had abnormal LDL. For hemorrhagic and ischaemic stroke, the mean triglyceride (TG) levels were 122±34.6 mg/dl and 141±43.3 mg/dl, respectively. The risk of an ischaemic stroke rose as LDL and total cholesterol levels rose. Thus, lipid abnormalities were a significant risk factor for stroke. Although there were notable increases in total cholesterol levels in both groups, a strong correlation was seen between ischaemic stroke and high LDL and aberrant HDL. The study unequivocally stated that routine screening of serum lipid profiles is necessary for high-risk patients".[80]

Qie R et al (2021) [81] "Clarifying the dose-response relationship between HDL-C level and the risk of both total stroke and stroke subtypes was the goal of this systematic review and meta-analysis. The researchers derived estimates adjusted for the greatest number of confounding factors after conducting a comprehensive search of the PubMed, Embase, and Web of Science databases until July 30, 2020, for prospective cohort studies reporting the HDL-C-stroke link. They came to the conclusion that elevated HDL-C levels are linked to a higher risk of intracerebral haemorrhage but a lower risk of ischaemic and total stroke".[81]

Watanabe J et al (2020)[82] examined the connection between incidence stroke subtypes and HDL-C (high-density lipoprotein cholesterol) levels. 11,027 individuals without a history of stroke, ages 18 to 90, were recruited from 12 Japanese villages. After controlling for conventional risk factors, Cox regression models examined stroke subtypes based on HDL-C concentration categories: 1.04-1.55 mmol/L, ≥1.56

mmol/L, and <1.03 mmol/L (reference). A mean follow-up of 10.7 years revealed 412 stroke occurrences. There was no discernible correlation between HDL-C and the incidence of subarachnoid haemorrhage or cerebral infarction. In women (hazard ratio = 0.23; 95% CI = 0.06-0.89), but not in men (hazard ratio = 0.73; 95% CI = 0.27-1.97), a high HDL-C concentration is linked to a lower risk of intracerebral haemorrhage. Therefore, especially in women, a high HDL-C content may offer protection against intracerebral haemorrhage.[82]

Gu X et al (2019)[83] comprised six cohort studies with 267,500 participants conducted in China. Hazard ratios and 95% CIs were calculated using Cox proportional hazards regression models and limited cubic spline analysis, which also investigated both linear and nonlinear lipid-stroke correlations. The median follow-up period was six to nineteen years. In 2,295,881 person-years, 8,072 strokes occurred. For ischaemic stroke, the multivariable adjusted hazard ratios (95% CIs) were 1.08 (1.05-1.11), 1.08 (1.04-1.11), and 1.07 (1.05-1.09) for every 1 mmol/L rise in TC, LDL-C, and triglycerides, respectively. Participants with TC <120 mg/dL had hazard ratios (95% CIs) for hemorrhagic stroke of 1.43 (1.11-1.85) compared to those with TC 160-199.9 mg/dL. The hazard ratios (95% CIs) for ischaemic stroke and hemorrhagic stroke were 1.23 (1.12-1.35), 1.13 (1.04-1.22) for those with HDL-C <40 and 40-49.9 mg/dL, respectively, compared to those with HDL-C 50-59.9 mg/dL. With ischaemic stroke, restricted cubic spline models revealed nonlinear correlations for HDL-C and triglycerides and linear relationships for TC and LDL-C (all P<0.001). There was no correlation between hemorrhagic stroke and LDL-C or triglycerides (all P>0.05), although there were linear associations with TC and HDL-C (P=0.029 and <0.001, respectively). Conclusions: Triglycerides, LDL-C, and TC all had favourable correlations with ischaemic stroke. TC dropped below 120 mg/dL, increasing the risk

of hemorrhagic stroke. Triglycerides and LDL-C did not correlate with hemorrhagic stroke. When HDL-C drops below 50 mg/dL, the risk of an ischaemic or hemorrhagic stroke may increase.[83]

Liu X et al (2019)[84] 42,005 Chinese volunteers aged 20–80 who had not previously experienced a stroke were enrolled in this prospective cohort study and divided into three stroke subtype groups: ischaemic, hemorrhagic, and total. Ischaemic and hemorrhagic stroke were combined to produce the total stroke result. 781 patients experienced a stroke (623 ischaemic and 158 hemorrhagic) throughout the 3.6-year average follow-up period. Multivariable-adjusted hazard ratio [HR], 1.52, 95% CI, 1.14-2.03, and total stroke risk (HR, 1.45, 95% CI, 1.12-1.87) were significantly higher in men with the highest TC/HDL-C quartile. Additionally, TC/HDL-C had the highest area under the receiver operating characteristic curve (AUC) for predicting both ischaemic (AUC, 0.868) and total stroke (AUC, 0.874). With AUCs of 0.850 and 0.861, respectively, the highest TG quartile in women was substantially linked to an elevated risk of ischaemic stroke (HR, 1.99, 95% CI, 1.11-3.59) and total stroke (HR, 1.85, 95% CI, 1.07-3.20). In neither sex are there any lipid factors that are substantially linked to hemorrhagic stroke. In conclusion, TG shown more utility in predicting stroke risk in women, while the TC/HDL-C ratio may be a better indicator of stroke risk in males. Potential targets for stroke prevention include TC/HDL-C and TG, which may aid in identifying those at high risk for stroke.[84]

MATERIALS AND METHODS

Study design: Cross sectional study

Study area: Department of General Medicine, KLEs Dr.Prabhakar Kore Hospital, Belgavi, Karnataka.

Study period: Research study was conducted from January 2023 to July 2024. Below is the work plan.

Table 1: Work plan of the study with percentage of allocation of study time and duration in months

Work plan	% of allocation of study time	Duration in months
Understanding the problem, preparation of questionnaire.	5-10%	January 2023
Pilot study, Validation of questionnaire, data collection and manipulation	Upto 80%	February 2023 to January 2024
Analysis and interpretation	5-10%	February 2024 to April 2024
Dissertation write-up and submission	5-10%	May 2024 to July 2024

Sample size: The formula used for sample size calculation is,

$$n = \left(\frac{Z_{\alpha/2} * \sigma}{d}\right)^2$$

Where,

Σ is the expected standard deviation of the population,

d is acceptable margin of error and for 95% confidence level

$Z_{\alpha/2}$, value is 1.96.

HDL value of ischemic stroke and Hemorrhagic stroke patients were 1.02 ± 0.27 mmol/L and 1.01 + 0.24 mmol/L respectively. Hence, the HDL value in CVA patients was 1.0157 + 0.2576 mmol/L. Considering this at 95% confidence level and 5% of mean as maximum error, the sample size is given by,

$$n = \left(\frac{1.96 * 0.2576}{0.05 * 1.0157}\right)^2$$

n= 98.84 ~ 99

Hence, the minimum sample size required is 99 subjects. Larger the sample size, better the precision.

Sampling technique: All consecutive patients fulfilling inclusion criteria were included in study, statistical analysis was done by convenient sampling.

Inclusion criteria:

1. Both Male and Female
2. Patient admitted with CVA with neurological weakness

Exclusion criteria:

1. Patient refusal
2. Pre-existing cardiac diseases
3. Presumptive diagnosis of stroke with no evidence on CT
4. CVA with tumour
5. CVA with trauma
6. Liver disease

METHODOLOGY:

Study Design and Ethical Considerations

"This hospital-based cross-sectional study was conducted at the Tertiary Care Centre, Belagavi. The study received approval from the Institutional Ethics Committee, and written informed consent was obtained from all participants or their legal representatives before enrollment".

Data Collection and Clinical Assessment

A detailed clinical history was obtained from all enrolled patients or their attendants, including demographic information, risk factors, and comorbidities. All patients underwent thorough physical and neurological examinations. The location and extent of the stroke were documented based on neuroimaging findings. For analysis of site involvement, the brain was divided into anatomical regions (frontal, parietal, temporal, occipital lobes, basal ganglia, thalamus, brainstem, and cerebellum), and the percentage involvement of each site was calculated for both stroke types.

Laboratory Analysis

Blood samples for HDL measurement were collected within 24 hours of admission, following a minimum 8-hour fasting period. Serum HDL levels were measured using the enzymatic colorimetric method in the hospital's central laboratory. Quality control measures were implemented to ensure accuracy and reliability of the laboratory results. The laboratory technicians were blinded to the clinical details and stroke type of the patients.

Radiological Assessment

All patients underwent either non-contrast CT scan or MRI brain (or both when indicated) at admission. The choice of imaging modality was based on the clinical scenario and physician discretion. The images were interpreted by experienced radiologists who were blinded to the patients' HDL levels. The type of stroke, location, and extent of involvement were documented systematically.

Ethical Considerations

The study was conducted after obtaining approval from the Institutional Ethics Committee. Written informed consent was obtained from all patients or their legal representatives before enrollment in the study. Patient confidentiality was maintained throughout the study period, and data was stored securely with access limited to the research team.

Documentation and Data Management

All clinical data, laboratory results, and radiological findings were recorded in a standardized case report form. The data was then transferred to an electronic database with appropriate backup measures. Regular quality checks were performed to ensure data accuracy and completeness. Missing or inconsistent data were verified with source documents and corrected as needed.

Study Outcomes

The primary outcomes of interest were the comparison of HDL levels between ischemic and hemorrhagic stroke patients and the analysis of anatomical site involvement in both stroke types. Secondary outcomes included the correlation of HDL levels with stroke severity and the pattern of anatomical distribution in different stroke subtypes.

STATISTICAL ANALYSIS

Data was entered in excel sheet and analyzed using SPSS version 21. Results were presented in tabular and graphical forms Mean, median, standard deviation and ranges were calculated for quantitative data. Qualitative data were expressed in terms of frequency and percentages. Student t test (Two Tailed) was used to test the significance of mean and P value <0.05 was considered significant.

RESULTS

Table 1 shows the age distribution of the study participants. The majority of patients were in the 61-70 years age group (38.8%), followed by 41-50 years (26.5%), 51-60 years (19.4%), and 30-40 years (15.3%). This indicates that cerebrovascular accidents were more common in older age groups, with almost 40% of cases occurring in patients aged 61-70 years.

Table 1: Distribution of patients according to age

Age (in years)	Frequency	Percentage
30-40	15	15.3%
41-50	26	26.5%
51-60	19	19.4%
61-70	38	38.8%
Total	**98**	**100%**

Graph 1: Distribution of patients according to age

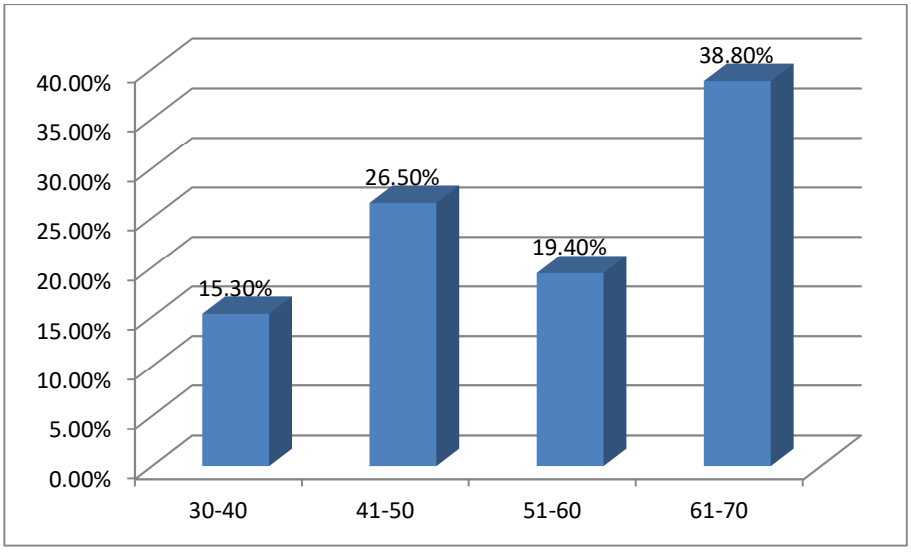


Table 2 and Graph 2 show the gender distribution among stroke patients. There was a slight female predominance with 53.1% female patients and 46.9% male patients, suggesting a marginally higher stroke risk in females in this study population.

Table 2: Distribution of patients according to gender

Gender	Frequency	Percentage
Female	52	53.1%
Male	46	46.9%
Total	**98**	**100%**

Graph 2: Distribution of patients according to gender

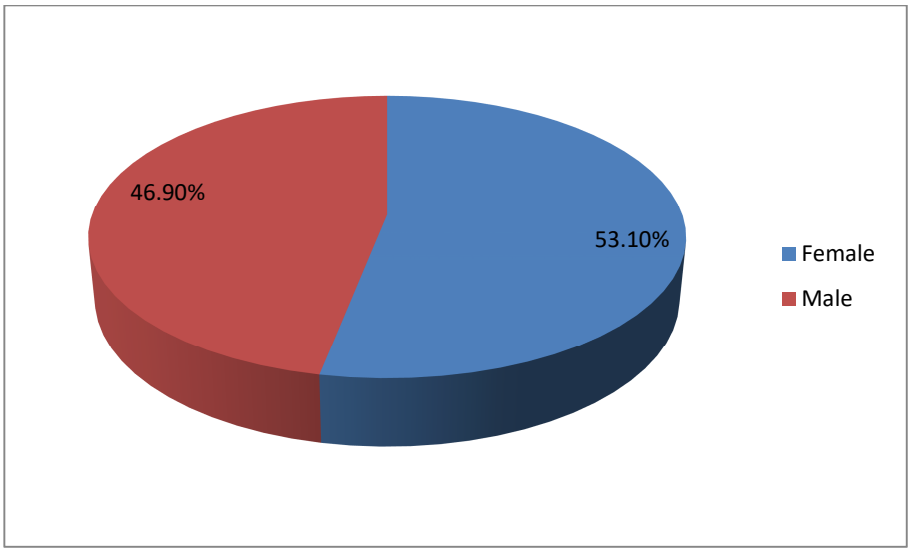


Table 3 and Graph 6 show the prevalence of co-morbidities among stroke patients. Hypertension was the most common co-morbidity (65.3%), followed by diabetes (41.8%). This highlights the significant role of cardiovascular risk factors in stroke pathogenesis, particularly hypertension.

Table 3: Distribution of patients according to Co-morbidities

Co-morbidities	Frequency	Percentage
Diabetes	41	41.8%
Hypertension	64	65.3%

Graph 3: Distribution of patients according to Co-morbidities

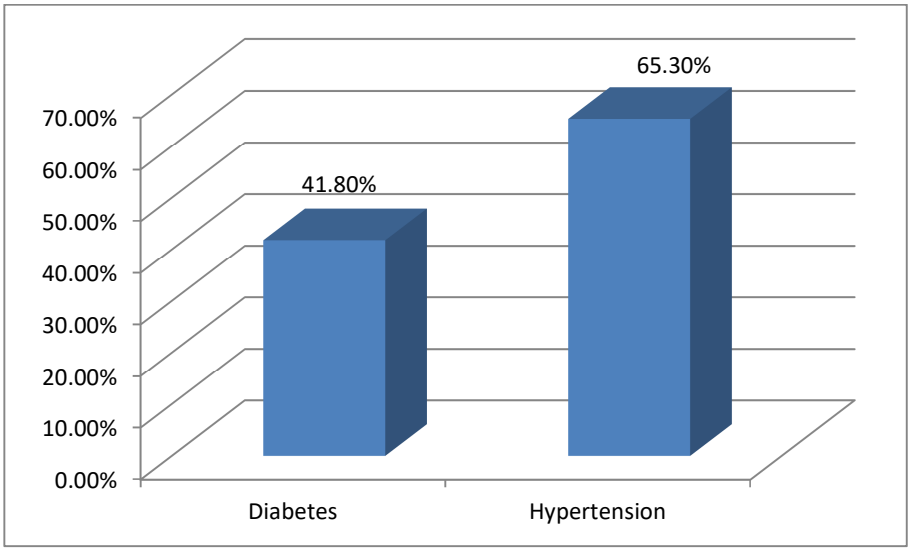


Table 4 shows that 31.6% of stroke patients were smokers, while 68.4% were non-smokers. This is included in Graph 6 with other risk factors, showing that smoking, while a known risk factor, was less prevalent than hypertension and diabetes in this study population.

Table 4: Distribution of patients according to smoking

Smoking	Frequency	Percentage
Yes	31	31.6%
No	67	68.4%
Total	**98**	**100%**

Graph 4: Distribution of patients according to smoking

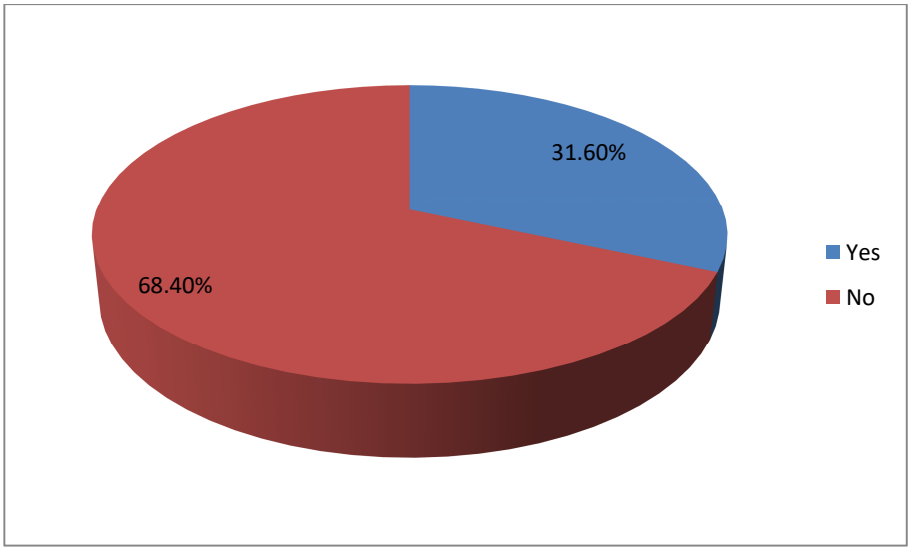


Table 5 and Graph 7 show the BMI distribution among stroke patients. The majority (53.1%) were overweight (BMI 25-29.9), while normal weight and obesity each accounted for 23.5% of patients. No patients were underweight, suggesting that excess body weight is a significant risk factor for stroke.

Table 5: Distribution of patients according to BMI

BMI	Frequency	Percentage
<18.5	-	-
18.5-24.9	23	23.5%
25-29.9	52	53.1%
>30	23	23.5%
Total	**98**	**100%**

Graph 5: Distribution of patients according to BMI

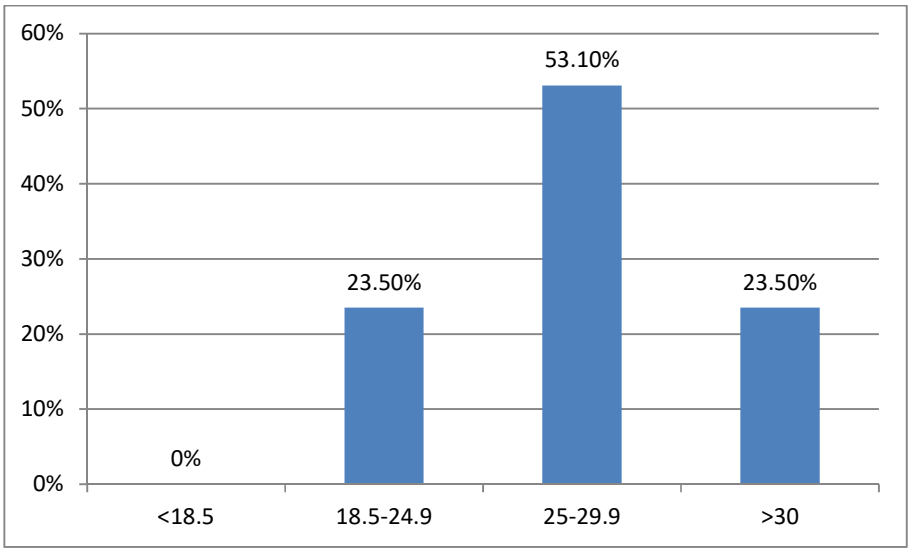


Table 6 and Graph 3 show the distribution of stroke types. The vast majority (83.7%) suffered from ischemic stroke, while only 16.3% had hemorrhagic stroke, consistent with the general epidemiological pattern where ischemic strokes are significantly more common.

Table 6: Distribution of patients according to type of stroke

Type of stroke	Frequency	Percentage
Haemorrhagic	16	16.3%
Ischemic	82	83.7%
Total	**98**	**100%**

Graph 6: Distribution of patients according to type of stroke

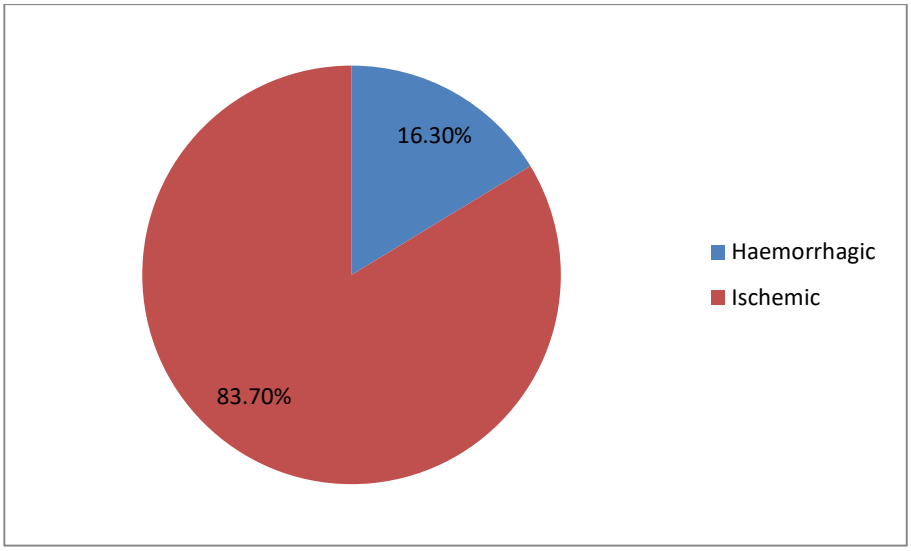


Table 7 shows that 60.2% of patients had elevated total cholesterol levels (>200 mg/dl). This is depicted in Graph 4 among other lipid abnormalities, suggesting a potential association between hypercholesterolemia and stroke risk.

Table 7: Distribution of patients according to Total cholesterol

Total cholesterol	Frequency	Percentage
<200	39	39.8%
>200	59	60.2%
Total	**98**	**100%**

Graph 7: Distribution of patients according to Total cholesterol

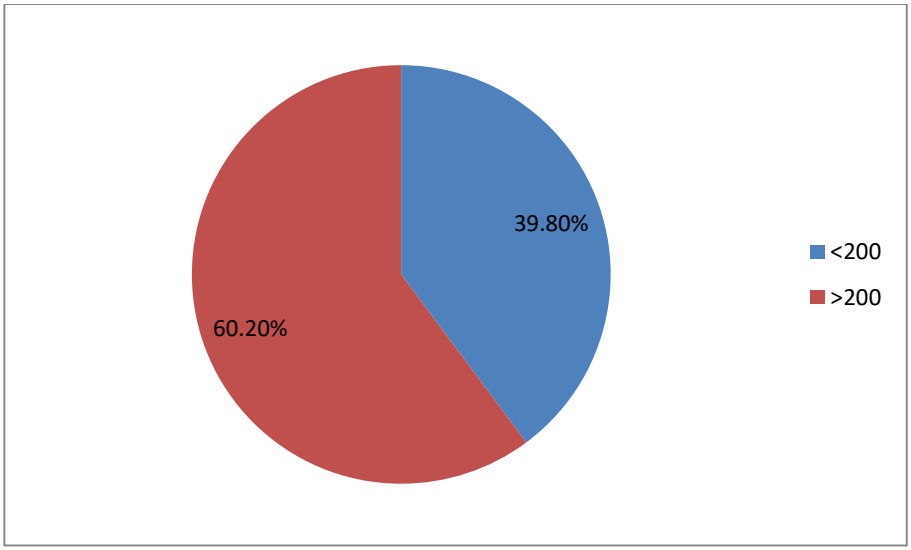


Table 8 shows that 64.3% of patients had elevated triglyceride levels (>150 mg/dl), also visualized in Graph 4, indicating a high prevalence of hypertriglyceridemia in the stroke population.

Table 8: Distribution of patients according to triglycerides

Triglycerides	Frequency	Percentage
<150	35	35.7%
>150	63	64.3%
Total	**98**	**100%**

Graph 8: Distribution of patients according to triglycerides

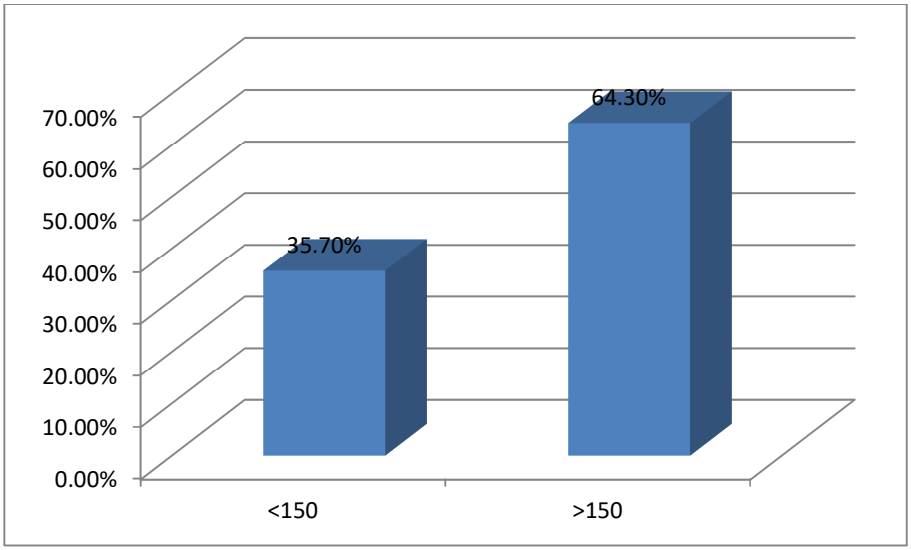


Table 9 shows that 81.5% of patients had elevated LDL levels (>100 mg/dl), included in Graph 4, suggesting a strong association between elevated LDL cholesterol and stroke occurrence.

Table 9: Distribution of patients according to LDL

LDL	Frequency	Percentage
<100	18	18.4%
>100	80	81.5%
Total	**98**	**100%**

Graph 9: Distribution of patients according to LDL

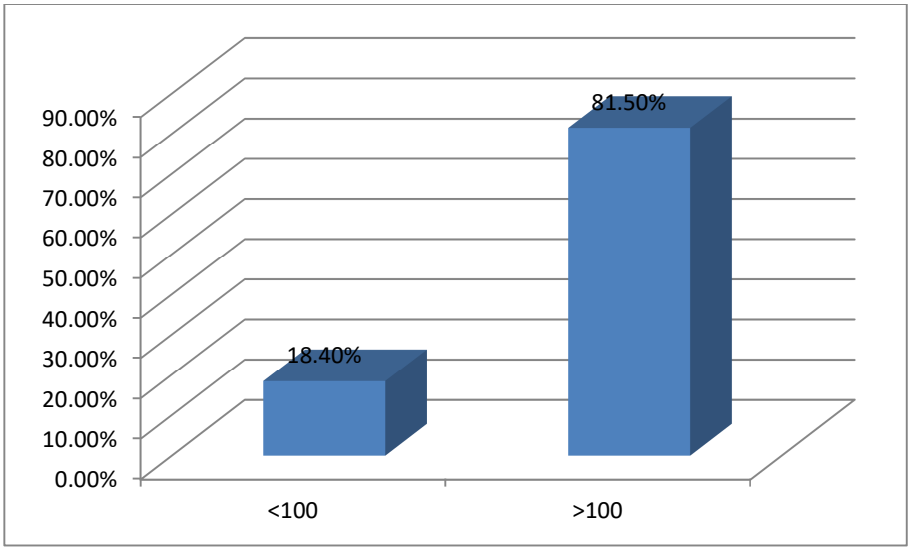


Table 10 and Graph 4 show that 90.8% of patients had low HDL levels (<50 mg/dl), which was the most prevalent lipid abnormality. This remarkable finding highlights the potential significant role of low HDL in stroke pathogenesis, aligning with the main focus of this study.

Table 10: Distribution of patients according to HDL

HDL	Frequency	Percentage
>50	9	9.2%
<50	89	90.8%
Total	**98**	**100%**

Graph 10: Distribution of patients according to HDL

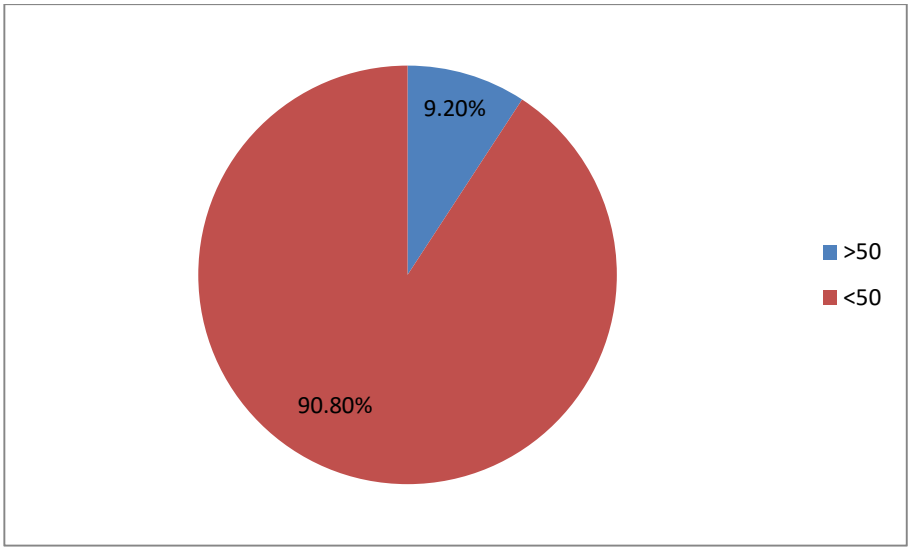


Table 11 shows the anatomical distribution of stroke lesions. The most common sites were the brainstem (19.4%), middle cerebral artery territory (15.3%), and internal capsule (14.3%), reflecting the vascular anatomy of the brain and common patterns of cerebrovascular pathology.

Table 11: Distribution of patients according to site of lesion

Site of lesion	Frequency	Percentage
Anterior cerebral artery	9	9.2%
Basal ganglia	8	8.2%
Brainstem	19	19.4%
Cerebellum	10	10.2%
Internal capsule	14	14.3%
Intraventricular	3	3.1%
Lobar	6	6.1%
Middle cerebral artery	15	15.3%
Posterior cerebral artery	6	6.1%
Thalamus	8	8.2%
Total	**98**	**100%**

Graph 11: Distribution of patients according to site of lesion

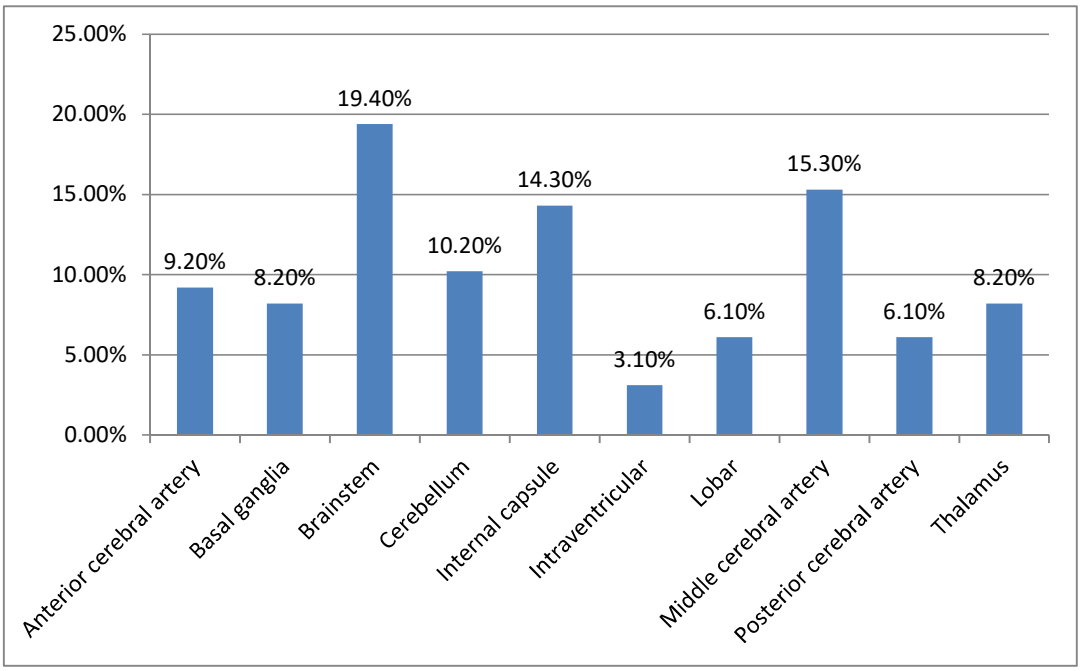


Table 12 (repeated) and Graph 8 show stroke severity based on the NIH Stroke Scale. The majority of patients (61.2%) had moderate stroke severity (NIHSS 5-15), followed by mild strokes (19.4%), moderately severe strokes (17.3%), and severe strokes (2%), indicating that most patients presented with moderate stroke severity.

Table 12: Distribution of patients according to NIH Stroke Scale

NIHSS	Frequency	Percentage
<5	19	19.4%
5-15	60	61.2%
16-20	17	17.3%
21-42	2	2%
Total	**98**	**100%**

Graph 12: Distribution of patients according to NIH Stroke Scale

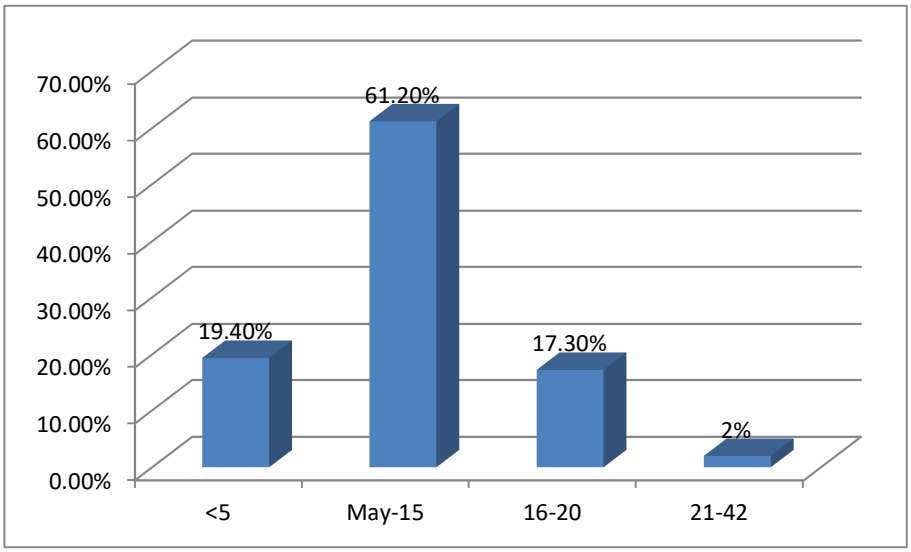


Table 13 shows that 74.5% of patients had good functional outcomes (Modified Rankin Scale 0-2), while 25.5% had poor outcomes (MRS 3-6), suggesting that despite various risk factors, most patients achieved relatively favorable functional outcomes.

Table 13: Distribution of patients according to Modified Rankin Scale

MRS	Frequency	Percentage
Good outcome (0-2)	73	74.5%
Poor outcome (3-6)	25	25.5%
Total	**98**	**100%**

Graph 13: Distribution of patients according to Modified Rankin Scale

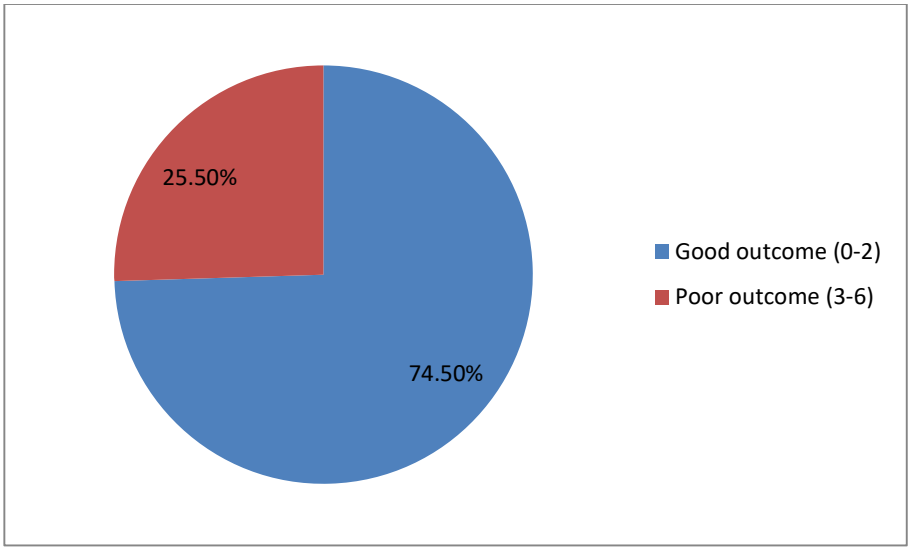


Table 14 shows the average hospital stay was 6.89 days (SD 2.45), suggesting efficient management protocols and possibly favorable early recovery patterns.

Table 14: Distribution of patients according to hospital stay

Hospital stay (days)	
Mean	6.89
SD	2.45

Graph 14: Distribution of patients according to hospital stay

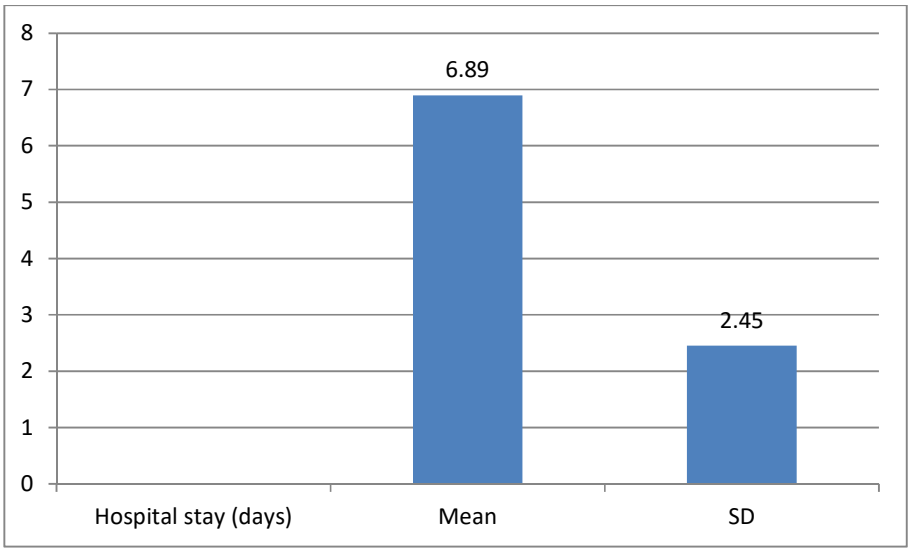


Table 15 shows the relationship between stroke type and age. Hemorrhagic strokes were more common in younger age groups (37.5% in 41-50 years), while ischemic strokes were more prevalent in older patients (41.5% in 61-70 years). However, this trend did not reach statistical significance (p=0.08).

Table 15: Association of type of stroke with age

Age (in years)	Type of stroke		p-value
	Haemorrhagic	Ischemic	
30-40	5 (31.2%)	10 (12.2%)	0.08
41-50	6 (37.5%)	20 (24.4%)	
51-60	1 (6.2%)	18 (22%)	
61-70	4 (25%)	34 (41.5%)	
Total	**16 (100%)**	**82 (100%)**	

Graph 15: Association of type of stroke with age

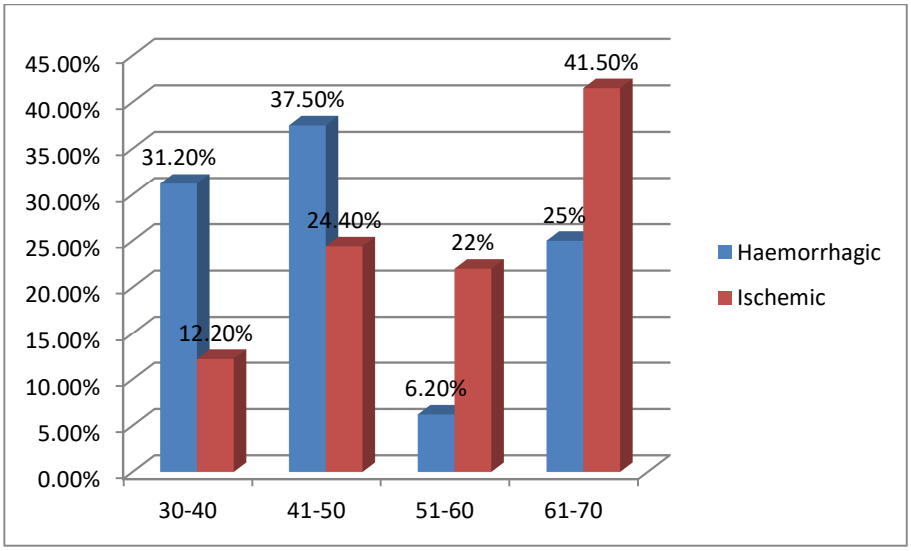


Table 16 shows no significant difference in the prevalence of diabetes and hypertension between hemorrhagic and ischemic stroke patients (p=0.46 and p=0.75 respectively).

Table 16: Association of type of stroke with Co-morbidities

Co-morbidities	Type of stroke		p-value
	Haemorrhagic	Ischemic	
Diabetes	8 (50%)	33 (40.2%)	0.46
Hypertension	11 (68.8%)	53 (64.6%)	0.75

Graph 16: Association of type of stroke with Co-morbidities

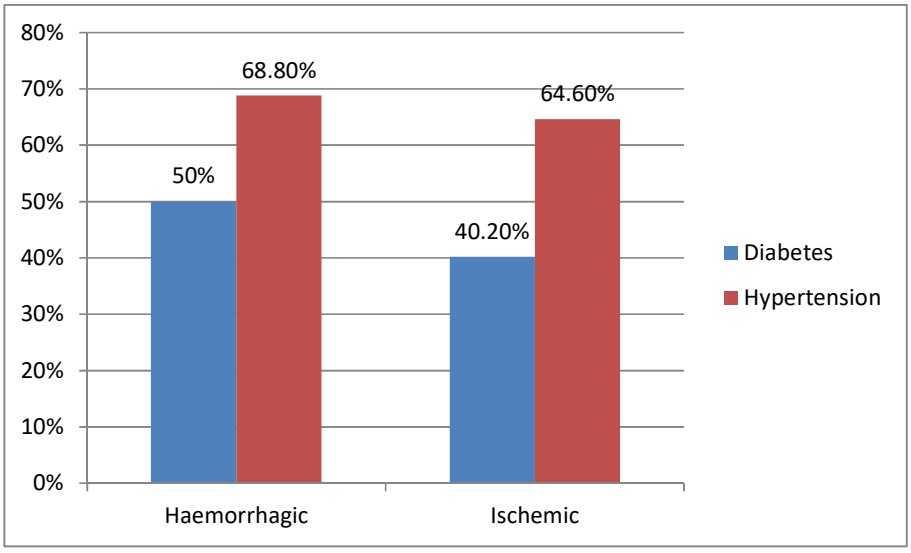


Table 17 and Graph 5 show a key finding of the study: HDL levels were significantly higher in hemorrhagic stroke patients (44.3±7.5 mg/dl) compared to ischemic stroke patients (35.3±7.7 mg/dl), with a highly significant p-value of <0.001. Other lipid parameters showed no significant differences between stroke types.

Table 17: Association of type of stroke with lipid profile

Lipid profile (mg/dl)	Type of stroke		p-value
	Haemorrhagic	**Ischemic**	
HDL	44.3±7.5	35.3±7.7	**<0.001**
Total cholesterol	214.4±22.7	206.5±35.1	0.39
LDL	133.5±25.2	136.9±39.1	0.73
Triglycerides	183.06±54.3	171.2±64.1	0.49

Graph 17: Association of type of stroke with lipid profile

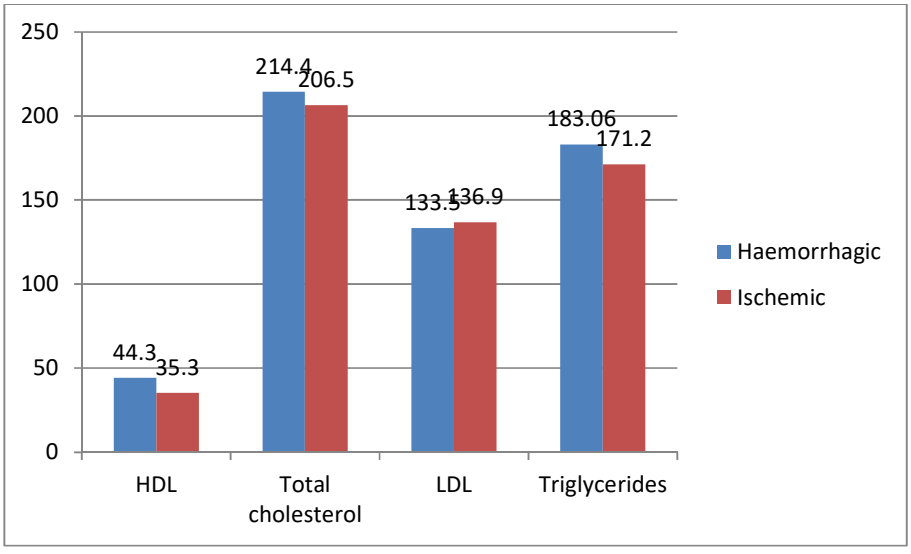


Table 18 shows no significant difference in stroke severity between hemorrhagic and ischemic strokes (p=0.23), though hemorrhagic strokes tended to have more cases in the moderate severity range.

Table 18: Association of type of stroke with NIH Stroke Scale

NIHSS	Type of stroke		p-value
	Haemorrhagic	Ischemic	
<5	1 (6.2%)	18 (22%)	0.23
5-15	12 (75%)	48 (58.5%)	
16-20	2 (12.5%)	15 (18.3%)	
21-42	1 (6.2%)	1 (1.2%)	
Total	**16 (100%)**	**82 (100%)**	

Graph 18: Association of type of stroke with NIH Stroke Scale

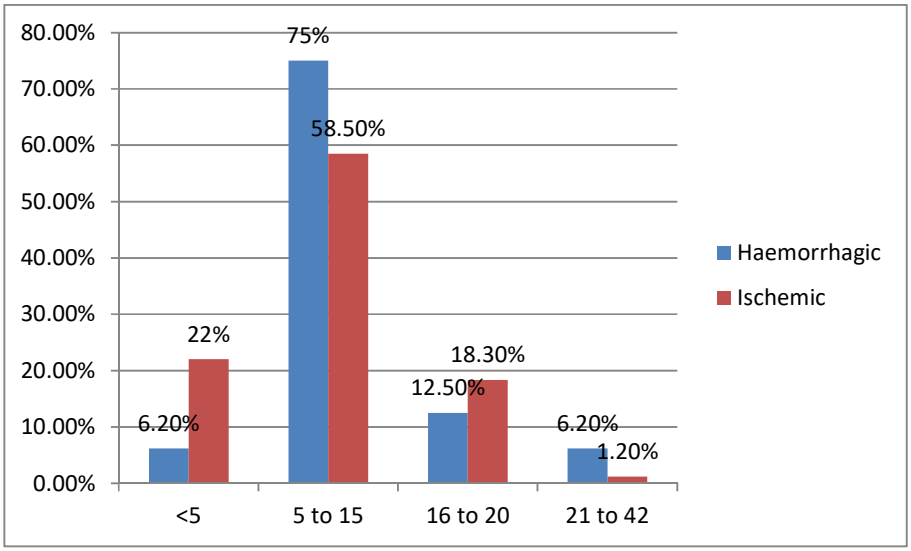
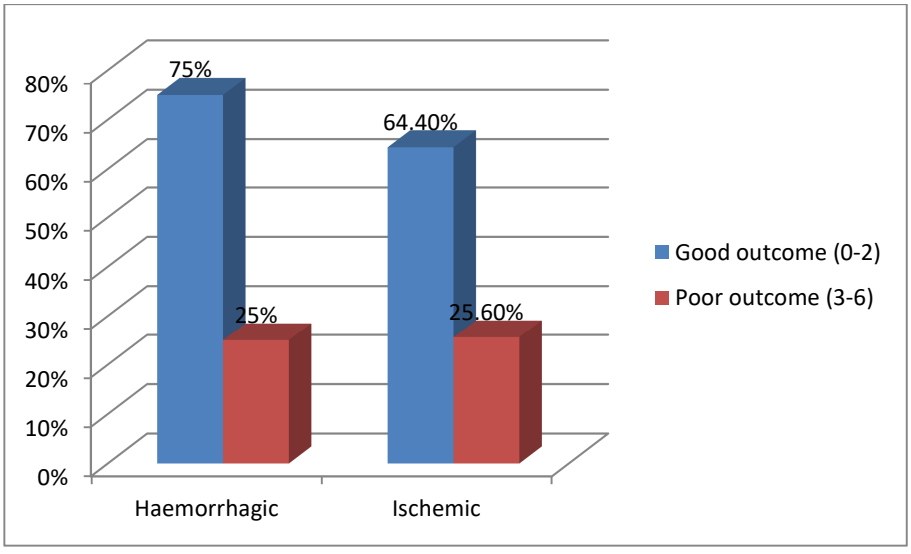


Table 19 shows similar proportions of good functional outcomes between hemorrhagic (75%) and ischemic strokes (64.4%), with no significant difference (p=0.95), suggesting that stroke type alone did not significantly predict functional outcomes.

Table 19: Association of type of stroke with Modified Rankin Scale

MRS	Type of stroke		p-value
	Haemorrhagic	**Ischemic**	
Good outcome (0-2)	12 (75%)	61 (64.4%)	0.95
Poor outcome (3-6)	4 (25%)	21 (25.6%)	
Total	**16 (100%)**	**82 (100%)**	

Graph 19: Association of type of stroke with Modified Rankin Scale



DISCUSSION

Cerebrovascular accidents (CVAs) remain one of the leading causes of morbidity and mortality worldwide, representing a significant public health concern with substantial socioeconomic implications. The etiopathogenesis of stroke is multifactorial, with various modifiable and non-modifiable risk factors contributing to its occurrence. Among these, dyslipidemia has emerged as a crucial modifiable risk factor, with particular attention being directed toward the role of high-density lipoprotein (HDL) cholesterol. HDL, often referred to as "good cholesterol," plays a vital role in reverse cholesterol transport and possesses anti-inflammatory, antioxidant, and antithrombotic properties. This study aimed to investigate the role of HDL in cerebrovascular accidents and compare HDL levels between ischemic and hemorrhagic stroke subtypes. The present discussion contextualizes our findings within the broader scientific literature, examining the implications for clinical practice, stroke prevention strategies, and potential therapeutic interventions targeting HDL metabolism.

Demographic Characteristics

Age Distribution

In our study, the majority of stroke patients (38.8%) were in the 61-70 years age group, followed by 26.5% in the 41-50 years age group. The mean age of presentation aligns with the established understanding that stroke risk increases with advancing age. These findings are consistent with those reported by Mahmood et al., who found that the incidence of stroke doubled with each decade after the age of 55 years in their population-based study.[87] Similarly, Putaala et al. observed that while stroke can occur at any age, the risk progressively increases with aging, with a notable acceleration after 60 years.[88]

However, our study also revealed a concerning trend: 41.8% of patients were below 50 years of age, suggesting a significant burden of premature stroke in our population. This finding mirrors the observations made by Kaul et al. in their study of stroke epidemiology in India, where they noted a decade-earlier occurrence of stroke compared to developed nations.[89]This earlier onset might be attributed to various factors, including genetic predisposition, lifestyle changes, increased prevalence of risk factors like diabetes and hypertension at younger ages, and possibly unique environmental exposures in the Indian subcontinent.

The age distribution pattern observed in hemorrhagic stroke deserves special attention. In our cohort, hemorrhagic strokes were more common in younger age groups (31.2% in 30-40 years and 37.5% in 41-50 years) compared to ischemic strokes, although this difference did not reach statistical significance (p=0.08). This trend is consistent with findings from the INTERSTROKE study, which demonstrated that hemorrhagic strokes tend to occur at younger ages in low and middle-income countries.[90] Feigin et al., in their global burden of disease study, also reported similar age-related patterns in stroke subtypes, with hemorrhagic strokes having a relatively earlier onset.[91]

Gender Distribution

Our study revealed a slight female predominance (53.1%) among stroke patients. This finding differs somewhat from the traditional understanding that stroke is more common in males. However, several recent studies have challenged this notion. Reeves et al. demonstrated that while men have a higher incidence of stroke in younger age groups, this gender gap narrows with advancing age, and women eventually surpass men in stroke prevalence after the seventh decade of life.[92] The higher proportion of females in our study might be partially explained by the age distribution of our cohort, with a significant percentage (38.8%) falling in the 61-70 years category, where female

stroke prevalence tends to be higher.

Moreover, the female predominance observed in our study aligns with the findings of Appelros et al., who conducted a systematic review of epidemiological studies and found that while men had a 33% higher incidence of stroke overall, women had higher stroke severity, poorer functional outcomes, and higher mortality rates.[93] The complex interplay between hormonal factors, longer life expectancy in females, and potentially different risk factor profiles might contribute to these gender-based differences in stroke epidemiology.

Risk Factor Profile

Comorbidities

Hypertension emerged as the most prevalent comorbidity in our study population, affecting 65.3% of stroke patients. This finding reinforces the well-established role of hypertension as a leading risk factor for both ischemic and hemorrhagic strokes. The INTERSTROKE study identified hypertension as the most important modifiable risk factor for stroke, with a population attributable risk of 51.8%.[90] Similarly, Katsanos et al. reported that hypertension increases the risk of stroke by approximately two to four times, with the risk being directly proportional to the severity of hypertension.[94]

Interestingly, our data showed a similar prevalence of hypertension in both hemorrhagic (68.8%) and ischemic (64.6%) stroke subtypes, with no significant statistical difference ($p=0.75$). This observation supports the concept that hypertension represents a shared risk factor for both major stroke subtypes, albeit through potentially different pathophysiological mechanisms. In ischemic stroke, hypertension contributes to accelerated atherosclerosis and arterial stiffness, while in hemorrhagic stroke, it primarily leads to small vessel damage and subsequent rupture.

Diabetes mellitus was present in 41.8% of our stroke patients, a prevalence higher than that reported in many Western studies. The substantial burden of diabetes in our cohort reflects the emerging diabetes epidemic in India and its significant contribution to cerebrovascular disease. Banerjee et al. reported that diabetes increases the risk of stroke by 1.5 to 3 times and is associated with poorer outcomes and higher recurrence rates.[95] The mechanisms linking diabetes to stroke are multifaceted, including accelerated atherosclerosis, endothelial dysfunction, increased platelet aggregability, and impaired fibrinolysis.

The association between diabetes and stroke subtypes in our study yielded an interesting observation: diabetes was more prevalent in hemorrhagic stroke patients (50%) compared to ischemic stroke patients (40.2%), although this difference did not reach statistical significance (p=0.46). This finding contrasts with some previous studies that suggested diabetes predominantly increases the risk of ischemic stroke. For instance, Shah et al. found that diabetes was associated with a 2.5-fold increased risk of ischemic stroke but had a less clear association with hemorrhagic stroke.[96] The higher prevalence of diabetes in our hemorrhagic stroke subgroup warrants further investigation and might reflect unique population characteristics or the complex interplay between diabetes and other risk factors.

Body Mass Index (BMI)

Our study revealed that the majority of stroke patients (53.1%) were overweight (BMI 25-29.9 kg/m²), while 23.5% were obese (BMI >30 kg/m²). This high prevalence of elevated BMI underscores the significant contribution of excess weight to stroke risk. These findings align with those of Strazzullo et al., who conducted a meta-analysis of prospective studies and found that overweight and obesity were associated with progressively increasing risk of ischemic stroke.[97]

The relationship between BMI and stroke is multifaceted and likely mediated through various mechanisms, including the promotion of hypertension, diabetes, dyslipidemia, and a proinflammatory state. Furthermore, adipose tissue, particularly visceral fat, is metabolically active and secretes various cytokines and adipokines that can influence vascular health.

Interestingly, while no patient in our cohort was underweight (BMI <18.5 kg/m²), 23.5% had normal BMI (18.5-24.9 kg/m²) yet still developed stroke. This observation highlights that while obesity is a significant risk factor, stroke can occur across the entire BMI spectrum, and other risk factors play crucial roles in stroke pathogenesis.

Smoking Status

In our study, 31.6% of stroke patients were smokers. This prevalence aligns with the established understanding that smoking significantly increases stroke risk. The pathophysiological mechanisms linking smoking to stroke include promotion of atherosclerosis, increased platelet aggregability, reduced fibrinolytic activity, decreased HDL levels, and direct endothelial damage from oxidative stress.

Peters et al. conducted a meta-analysis of 81 prospective studies and found that smoking increased the risk of stroke by approximately 50%, with a clear dose-response relationship.[98]

Moreover, they observed that stroke risk decreased significantly after smoking cessation, highlighting the importance of tobacco control measures in stroke prevention.

The relatively lower prevalence of smoking in our cohort (31.6%) compared to some other studies might partly reflect the gender distribution (53.1% females), as smoking rates tend to be lower among women in the Indian context. Additionally, the prevalence

might be underestimated due to potential underreporting, especially among female patients, owing to sociocultural factors.

Lipid Profile Analysis

Total Cholesterol and LDL Cholesterol

Our study revealed that 60.2% of stroke patients had elevated total cholesterol levels (>200 mg/dL), and a striking 81.5% had elevated LDL cholesterol levels (>100 mg/dL). These findings underscore the significant contribution of dyslipidemia to stroke risk in our population. The association between elevated total cholesterol and LDL cholesterol with ischemic stroke is well-established, primarily through their role in atherogenesis.

Amarenco et al., in their systematic review and meta-analysis, found that statin therapy significantly reduced the risk of stroke, with a 21% risk reduction for each 1 mmol/L decrease in LDL cholesterol.[99] This benefit was observed across various patient subgroups, including those with no prior history of stroke or coronary heart disease, highlighting the causal relationship between LDL cholesterol and stroke.

When comparing stroke subtypes, our data showed slightly higher mean total cholesterol levels in hemorrhagic stroke patients (214.4±22.7 mg/dL) compared to ischemic stroke patients (206.5±35.1 mg/dL), although this difference was not statistically significant (p=0.39). Similarly, LDL cholesterol levels were comparable between hemorrhagic (133.5±25.2 mg/dL) and ischemic (136.9±39.1 mg/dL) stroke patients (p=0.73).

The relationship between lipid parameters and hemorrhagic stroke is complex and somewhat controversial. While some studies have suggested an inverse association between total cholesterol levels and hemorrhagic stroke risk, others have found no

significant relationship. Wang et al. conducted a meta-analysis of prospective studies and found that while elevated total cholesterol increased the risk of ischemic stroke, the relationship with hemorrhagic stroke was less clear.[100] Our findings suggest that in our population, dyslipidemia, particularly elevated total cholesterol and LDL cholesterol, might contribute to both stroke subtypes, albeit through different pathophysiological mechanisms.

Triglycerides

Elevated triglyceride levels (>150 mg/dL) were observed in 64.3% of our stroke patients, highlighting the significant prevalence of hypertriglyceridemia in this population. The role of triglycerides in stroke pathogenesis has been somewhat controversial, with some studies suggesting an independent association and others proposing that the relationship is mediated through other risk factors.

In our cohort, mean triglyceride levels were higher in hemorrhagic stroke patients (183.06±54.3 mg/dL) compared to ischemic stroke patients (171.2±64.1 mg/dL), although this difference did not reach statistical significance (p=0.49). This observation contrasts with some previous studies, such as the one by Pikija et al., who found a stronger association between elevated triglycerides and ischemic stroke, particularly large-vessel occlusive subtype.[101]

The complex relationship between triglycerides and stroke might be partly explained by the heterogeneity of triglyceride-rich lipoproteins and their various atherogenic properties. Furthermore, hypertriglyceridemia often coexists with other metabolic abnormalities, such as low HDL cholesterol, insulin resistance, and hypertension, forming a cluster of interrelated risk factors.

High-Density Lipoprotein (HDL) Cholesterol

The most striking finding of our study was the high prevalence of low HDL cholesterol levels (<50 mg/dL) among stroke patients, affecting 90.8% of the cohort. This observation underscores the potential significant role of low HDL cholesterol in stroke pathogenesis in our population. Numerous epidemiological studies have demonstrated an inverse relationship between HDL cholesterol levels and stroke risk. For instance, the Northern Manhattan Study found that each 5 mg/dL increase in HDL cholesterol was associated with a 24% reduced risk of ischemic stroke after adjusting for other risk factors.[102]

When comparing stroke subtypes, our data revealed a statistically significant difference in HDL cholesterol levels between hemorrhagic (44.3±7.5 mg/dL) and ischemic (35.3±7.7 mg/dL) stroke patients ($p<0.001$). This finding suggests that while low HDL cholesterol is prevalent in both stroke subtypes, it might have a more pronounced role in ischemic stroke pathogenesis.

The protective effects of HDL cholesterol against atherosclerosis and thrombosis are attributed to various mechanisms, including reverse cholesterol transport, antioxidant properties, anti-inflammatory effects, and enhancement of endothelial function. These mechanisms primarily influence the pathogenesis of ischemic stroke, particularly the atherothrombotic subtype.

However, the relationship between HDL cholesterol and hemorrhagic stroke is less well understood. Some studies have suggested that extremely low HDL cholesterol levels might increase the risk of hemorrhagic stroke, potentially through mechanisms such as endothelial dysfunction and impaired vessel wall integrity. Conversely, others have proposed that very high HDL cholesterol levels might be associated with increased

hemorrhagic stroke risk in certain populations. The higher HDL cholesterol levels observed in our hemorrhagic stroke patients compared to ischemic stroke patients align with this complex, potentially U-shaped relationship.

Several factors might contribute to the high prevalence of low HDL cholesterol in our study population. Genetic variations in genes involved in HDL metabolism, such as CETP, ABCA1, and LCAT, are known to influence HDL cholesterol levels and are prevalent in certain ethnic groups. Dietary patterns, particularly those high in refined carbohydrates and low in omega-3 fatty acids, can also lower HDL cholesterol levels. Furthermore, lifestyle factors such as physical inactivity and smoking, along with comorbidities like diabetes and metabolic syndrome, are associated with reduced HDL cholesterol.

The significant difference in HDL cholesterol levels between ischemic and hemorrhagic stroke patients in our study suggests that HDL cholesterol might have differential effects on stroke subtypes and could potentially serve as a biomarker for stroke classification. This finding has important implications for risk stratification, preventive strategies, and therapeutic interventions.

Stroke Characteristics

Stroke Subtypes and Anatomical Distribution

In our cohort, ischemic strokes (83.7%) were markedly more prevalent than hemorrhagic strokes (16.3%), which aligns with the established global pattern where ischemic strokes constitute approximately 80-85% of all strokes. This distribution is consistent with findings from Feigin et al., who reported a similar proportion in their global burden of disease study.[91]

The anatomical distribution of stroke lesions in our study provides valuable insights into the vascular territories most commonly affected in our population. The brainstem (19.4%) and middle cerebral artery territory (15.3%) were the most frequent sites, followed by the internal capsule (14.3%). This distribution partially reflects the vascular anatomy and blood flow patterns in the cerebral circulation. The middle cerebral artery, being the largest branch of the internal carotid artery and supplying a substantial portion of the cerebral hemisphere, is a common site for ischemic events.

The relatively high prevalence of brainstem lesions in our cohort is noteworthy and might have implications for clinical presentation, management strategies, and outcomes. Brainstem strokes, although often smaller in size, can lead to significant neurological deficits due to the concentration of critical neural pathways in this region.

Stroke Severity and Outcomes

The National Institutes of Health Stroke Scale (NIHSS) is a widely used tool for assessing stroke severity, with higher scores indicating more severe deficits. In our study, the majority of patients (61.2%) had moderate stroke severity (NIHSS 5-15), while 19.4% had mild strokes (NIHSS <5), and 19.3% had severe or very severe strokes (NIHSS >15).

When comparing stroke subtypes, we observed a trend toward higher stroke severity in hemorrhagic strokes, with 18.7% of hemorrhagic stroke patients having an NIHSS >15, compared to 19.5% of ischemic stroke patients. However, this difference did not reach statistical significance ($p=0.23$). This observation aligns with the general understanding that hemorrhagic strokes, on average, tend to be more severe and are associated with higher mortality rates, although the outcome depends on various factors, including hematoma size, location, and presence of intraventricular extension. The

Modified Rankin Scale (MRS) is a commonly used measure of functional outcome after stroke, with scores ranging from 0 (no symptoms) to 6 (death). In our cohort, 74.5% of patients had a good functional outcome (MRS 0-2), while a quarter (25.5%) had a poor outcome (MRS 3-6). This relatively favorable outcome profile might reflect the stroke severity distribution in our cohort, with a majority having mild to moderate strokes. Additionally, effective acute management and rehabilitation strategies might have contributed to better functional recovery.

Interestingly, when comparing functional outcomes between stroke subtypes, we found no significant difference between hemorrhagic and ischemic strokes, with 75% of hemorrhagic stroke patients and 64.4% of ischemic stroke patients achieving good functional outcomes (p=0.95). This observation is somewhat unexpected, given the generally accepted notion that hemorrhagic strokes tend to have poorer outcomes. Several factors might explain this finding, including the anatomical distribution of lesions, patient demographics, comorbid conditions, and the quality of acute care and rehabilitation services.

The mean hospital stay in our study was 6.89 days (SD 2.45), which is comparable to or slightly longer than the average length of stay reported in many high-income countries. The hospital stay duration is influenced by various factors, including stroke severity, complications, comorbidities, and the availability of rehabilitation services and home care support.

Implications for Clinical Practice and Future Research

Risk Factor Modification

The high prevalence of modifiable risk factors in our stroke population, including hypertension (65.3%), diabetes (41.8%), elevated BMI (76.6% overweight or obese),

smoking (31.6%), and dyslipidemia (90.8% with low HDL, 81.5% with high LDL), underscores the critical importance of aggressive risk factor modification in stroke prevention. These findings suggest that a significant proportion of stroke burden in our population could potentially be prevented through effective risk factor management.

Comprehensive stroke prevention strategies should focus on a multifaceted approach, including lifestyle modifications (such as smoking cessation, regular physical activity, and healthy dietary patterns), optimal management of comorbidities (particularly hypertension and diabetes), and appropriate lipid-lowering therapies. The INTERSTROKE study estimated that addressing ten modifiable risk factors could potentially prevent approximately 90% of strokes worldwide, highlighting the enormous potential of preventive interventions.[90]

HDL as a Therapeutic Target

The striking finding of low HDL cholesterol prevalence (90.8%) among our stroke patients, coupled with the significant difference in HDL levels between ischemic and hemorrhagic stroke subtypes, suggests that HDL might represent a promising therapeutic target for stroke prevention, particularly ischemic stroke.

However, translating this epidemiological association into effective therapeutic strategies has proven challenging. Several clinical trials targeting HDL cholesterol levels, particularly those using CETP inhibitors, have failed to demonstrate significant cardiovascular benefits despite substantial increases in HDL cholesterol levels. These disappointing results have led to a paradigm shift in our understanding of HDL, with increasing recognition that HDL functionality might be more important than HDL cholesterol levels per se.

Future research should focus on developing therapies that enhance specific aspects of HDL functionality, such as cholesterol efflux capacity, anti-inflammatory properties, or antioxidant activities, rather than merely increasing HDL cholesterol levels. Additionally, personalized approaches based on genetic profiles, HDL subclass distribution, or HDL proteome might yield more successful outcomes.

Ethnic and Regional Variations

Our study provides valuable insights into the stroke characteristics and risk factor profile in a specific region of India. The observed patterns, particularly the relatively young age of stroke onset, high prevalence of diabetes and low HDL cholesterol, and slightly different distribution of stroke subtypes and anatomical sites compared to Western populations, highlight the importance of regional and ethnic considerations in stroke epidemiology and management.

These variations might reflect a combination of genetic, environmental, socioeconomic, and healthcare system factors. Understanding these regional differences is crucial for developing tailored preventive strategies, diagnostic approaches, and treatment protocols that address the specific needs and challenges of diverse populations.

Biomarkers for Stroke Classification and Prognosis

The significant difference in HDL cholesterol levels between ischemic and hemorrhagic stroke patients observed in our study suggests that HDL cholesterol might serve as a potential biomarker for stroke classification. In clinical scenarios where neuroimaging is not immediately available or conclusive, such as in resource-limited settings or in cases with very early presentation, lipid parameters, including HDL cholesterol, might provide valuable additional information to guide initial management decisions.

Furthermore, the association between lipid parameters and stroke outcomes warrants further investigation. Identifying reliable prognostic markers could help in risk stratification, guiding treatment intensity, and informing discussions with patients and families about expected recovery trajectories.

Limitations and Future Directions

Study Limitations

Our study, while providing valuable insights, has several limitations that should be acknowledged. The single-center design and relatively small sample size limit the generalizability of our findings to broader populations. The cross-sectional nature of the study prevents establishing causal relationships between lipid parameters and stroke occurrence or outcomes. Additionally, while we collected data on various risk factors, residual confounding from unmeasured variables cannot be excluded.

Regarding lipid measurements, we relied on a single blood sample obtained after stroke onset, which might not accurately reflect the patient's pre-stroke lipid profile due to the acute phase response. Furthermore, we did not assess advanced lipid parameters, such as HDL subfractions, apolipoprotein levels, or functional assays of HDL capacity, which might provide more nuanced insights into the relationship between lipids and stroke.

Future Research Directions

Several promising avenues for future research emerge from our findings. Longitudinal studies with larger, diverse cohorts are needed to establish causal relationships and explore the temporal dynamics between lipid parameters and stroke risk. More detailed characterization of lipid profiles, including advanced lipoprotein analyses, genetic

markers, and functional assays, could provide deeper insights into the pathophysiological mechanisms linking lipids to stroke.

The differential association of HDL cholesterol with stroke subtypes observed in our study warrants further investigation. Studies specifically designed to explore the relationship between HDL-related parameters and hemorrhagic stroke, which has received relatively less attention compared to ischemic stroke, could yield valuable insights.

Finally, intervention studies targeting HDL metabolism, particularly those focusing on enhancing specific aspects of HDL functionality rather than merely increasing HDL cholesterol levels, represent an important frontier in stroke prevention research.

Conclusion

In conclusion, our study demonstrates a high prevalence of low HDL cholesterol among stroke patients, with a significant difference in HDL levels between ischemic and hemorrhagic stroke subtypes. These findings, along with the observed patterns of other risk factors and stroke characteristics, contribute to our understanding of stroke epidemiology in the specific population studied and highlight the potential role of HDL as a biomarker and therapeutic target in cerebrovascular disease. Future research should focus on elucidating the mechanistic links between HDL and stroke subtypes, developing more effective interventions targeting HDL metabolism, and exploring the utility of lipid parameters in stroke classification and prognosis.

CONCLUSION

This study provides valuable insights into the role of high-density lipoprotein (HDL) in cerebrovascular accidents and its differential association with ischemic and hemorrhagic stroke subtypes. The findings demonstrate a significantly high prevalence of low HDL cholesterol levels among stroke patients, affecting 90.8% of the study population. More importantly, a statistically significant difference in HDL levels was observed between hemorrhagic (44.3±7.5 mg/dL) and ischemic (35.3±7.7 mg/dL) stroke patients ($p<0.001$), suggesting that while low HDL is common in both stroke subtypes, it may play a more pronounced role in ischemic stroke pathogenesis.

The study also highlights the substantial burden of modifiable risk factors in the study population, including hypertension (65.3%), diabetes (41.8%), overweight/obesity (76.6%), elevated LDL cholesterol (81.5%), and hypertriglyceridemia (64.3%). These findings underscore the critical importance of comprehensive risk factor management in stroke prevention strategies. The relatively young age of onset observed, with 41.8% of patients below 50 years, raises concerns about the increasing burden of premature stroke in the region and emphasizes the need for early preventive interventions.

The lack of significant differences in functional outcomes between ischemic and hemorrhagic stroke subtypes, despite the general understanding that hemorrhagic strokes tend to have poorer prognosis, warrants further investigation into factors influencing recovery and rehabilitation in different stroke subtypes. This finding may have implications for clinical management and prognostication.

In conclusion, this study contributes to the growing body of evidence supporting the importance of HDL cholesterol in cerebrovascular health and suggests that HDL levels might serve as a potential biomarker for stroke classification. Future research

should focus on elucidating the mechanistic links between HDL and stroke subtypes, developing more effective interventions targeting HDL metabolism, and exploring the utility of lipid parameters in stroke classification and prognosis. The findings emphasize the need for aggressive risk factor modification, including strategies to improve HDL levels and functionality, as part of comprehensive stroke prevention efforts.

SUMMARY

INTRODUCTION

Cerebrovascular accidents (CVAs) represent a significant global health burden, with dyslipidemia emerging as a crucial modifiable risk factor. While the relationship between low-density lipoprotein (LDL) and stroke risk is well-established, the role of high-density lipoprotein (HDL) remains less clearly defined, particularly regarding its differential association with stroke subtypes. This study aimed to investigate the role of HDL in cerebrovascular accidents and compare HDL levels between ischemic and hemorrhagic stroke subtypes

AIMS AND OBJECTIVES

Objectives:

4. To study serum HDL level in patient with cerebrovascular accident
5. To compare the levels of serum HDL between two categories of stroke.
6. Percentage of site involvement in ischemic and hemorrhagic stroke.

MATERIAL AND METHODS

This observational study included 98 stroke patients admitted to KLES Dr. Prabhakar Kore Hospital, Belagavi, over a one-year period. Demographic characteristics, risk factor profiles, lipid parameters, and stroke characteristics were documented. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS), and functional outcomes were evaluated using the Modified Rankin Scale (MRS). Statistical analysis included descriptive statistics and comparison between stroke subtypes using appropriate tests.

RESULTS

- A total of 98 stroke patients were included in the study, with the following key findings:

- Demographic characteristics revealed that the majority of patients (38.8%) belonged to the 61-70 years age group, followed by 41-50 years (26.5%). There was a slight female predominance (53.1%) in the study population. The prevalence of risk factors was notably high, with hypertension affecting 65.3% of patients, diabetes mellitus 41.8%, smoking 31.6%, and overweight/obesity 76.6%.

- Analysis of the lipid profile demonstrated significant abnormalities, with 60.2% of patients having elevated total cholesterol levels (>200 mg/dL), 81.5% with elevated LDL cholesterol (>100 mg/dL), 64.3% with elevated triglycerides (>150 mg/dL), and a striking 90.8% with low HDL cholesterol levels (<50 mg/dL). When comparing stroke subtypes, ischemic strokes (83.7%) were substantially more prevalent than hemorrhagic strokes (16.3%).

- The most significant finding was the statistically significant difference in HDL cholesterol levels between hemorrhagic (44.3±7.5 mg/dL) and ischemic (35.3±7.7 mg/dL) stroke patients ($p<0.001$), suggesting a differential association of HDL with stroke subtypes. No significant differences were observed between stroke subtypes regarding other lipid parameters, comorbidities, or stroke severity.

- Regarding stroke characteristics, the brainstem (19.4%) and middle cerebral artery territory (15.3%) were the most frequent sites of lesion. Most patients (61.2%) had moderate stroke severity (NIHSS 5-15), and 74.5% achieved

good functional outcomes (MRS 0-2). The mean hospital stay was 6.89 days (SD 2.45).

- These findings highlight the significant role of dyslipidemia, particularly low HDL cholesterol, in stroke pathogenesis and suggest potential utility of HDL as a biomarker for stroke classification. The high prevalence of modifiable risk factors emphasizes the importance of aggressive risk factor management in stroke prevention strategies.

CONCLUSION:

This study demonstrates a high prevalence of low HDL cholesterol among stroke patients and identifies a significant difference in HDL levels between ischemic and hemorrhagic stroke subtypes. These findings suggest that HDL cholesterol might play a differential role in the pathogenesis of stroke subtypes and could potentially serve as a biomarker for stroke classification. Future research should focus on elucidating the mechanistic links between HDL and stroke subtypes and developing targeted interventions to address dyslipidemia in stroke prevention.

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ANNEXURE – I - INFORMED CONSENT FORM

Consent form format

KAHERs JNMC
BELAGAVI
INFORMED CONSENT FORM

ROLE OF HIGH-DENSITY LIPOPROTEIN IN CEREBROVASCULAR ACCIDENT AND COMPARATIVE STUDY OF HIGH-DENSITY LIPOPROTEIN IN ISCHEMIC STROKE AND HEMORRHAGIC STROKE.

Name of Student/Principal Investigator:
Name of Guide/Co Investigators: MD GENERAL MEDICINE ,DEPARTMENT OF GENERAL MEDICINE,MEDICINE G UNIT,JAWAHARLAL NEHRU MEDICAL COLLEGE,BELAGAVI.

18.1 Introduction: : Stroke is the most common cause of death in the developed world after cancer and ischemic heart Disease and it is the most common cause of physical disability .Stroke represents the third most common death in the developed countries. Stroke is a common medical emergency. The incidence is rising steeply in many Developing countries because of adoption of less healthy life styles. It is difficult to treat and treatment is still not effective. Prevention is best option but ability to forecast the stroke is challenging making the detailed study of risk factor is essential .Stroke or cerebral vascular accident, is the sudden death of brain cells due to inadequate blood flow. The WHO clinically defines stroke as "the rapid development of clinical signs and symptoms of focal neurological disturbance lasting more than 24 hours or leading to death with no apparent cause other than vascular origin.

Stroke is the second commonest cause of death worldwide after coronary heart disease (CHD). Global burden of disease study estimated a population-based annual stroke incidence of India to be 89/100,000 in 2005 which is projected to increase to 91/100,000 in 2015 and 98/100,000 in 2030 . It is a major health problem in India. Developing countries like India are facing a double burden of communicable and non-communicable diseases. The estimated adjusted prevalence rate of stroke range 84 to 262/100,000 in rural and 334 to 424/100,000 in urban areas. The incidence rate is 119 to 145/100,000 based on the recent population studies. It has been found that stroke accounts for 0.9-4.5% of total medical admission and 9.2-30% of admissions to neurological wards. Studies have shown an increased prevalence of stroke in the young (<40 yrs old) in India ranging from 10 to 15% of allstrokes.

WHO estimates suggests that by 2054, 80% stroke case in the world would occur in low and middle income countries mainly India and China. Stroke is the sudden death of brain cells due to inadequate blood flow. It is a leading cause of serious long term disability. The effects of a stroke are determined by the extent and site of brain injury, but the clinical symptoms of stroke do not accurately predict its underlying cause or causes. Classic stroke

symptoms include the acute onset of unilateral paralysis, loss of vision, speech impairment, memory loss, impaired reasoning ability, coma or death.8 The risk factors include Diabetes, Hypertension, Dyslipidemia, Atherosclerosis, age, smoking and other rare causes. There is good evidence that modification of risk factors will reduce the risk of stroke.Recent studies shows that low level of HDL is an important risk factors for development of Atherosclerosis which is the precursor for cerebrovascular accident. My study is to see whether any difference in HDL level between two categories of stroke.

Explanation of procedure: ESTIMATION OF HDL CHOLESTEROL: METHOD: Phosphotungstic acid method, endpoint

PRINCIPLE: Chylomicrons(CM), LDL and VLDL are precipitated from serum or plasma with phosphotungstate in the presence of divalent cations such as Magnesium. The HDL cholesterol remains unaffected in the supernatant and is estimated using a cholesterol reagent.

Serum/plasma HDL + (LDL+VLDL+CM) (supernatant) (precipitate) Phosphotungstic acid, Mg2+

REAGENT COMPOSITION: Reagent1: precipitating reagent Phosphotungstic acid 2.4mmol/l Magnesium chloride 40mmol/l

HDL cholesterol standard – 25mg/dl

SAMPLE: Unhemolysed serum used

PRECIPITATION: Precipitation of LDL,VLDL and Chylomicrons done as follows:

Mixed well and the reaction mixture was allowed to stand for 10 min at room temperature, centrifuged at 4000 rpm for 10min and obtain a clear supernatant.The supernatant was used to determine the concentration of HDL cholesterol in the sample.

ASSAY PROCEDURE: Mixed well and incubated for 10 min at room temperature. The absorbance of the standard and the test samples were read at 505 nm against reagent blank.

CALCULATION HDL cholesterol (mg/dl)= Absorbance of test x conc.of standard x dilutionfactor Absorbance of standard = Absorbance of the test x 25x3 Absorbance of the standard = Absorbance of the test x 75 Absorbance of the standard Linearity-upto 125mg/d

ESTIMATION OF TOTAL CHOLESTEROL: METHOD: Cholesterol oxidase-Peroxidase Enzymatic, endpoint method. PRINCIPLE: The free cholesterol, liberated from the cholesterol esters by cholesterol esterase, is oxidised by cholesterol oxidase to cholestenone with the simultaneous production of hydrogen peroxide. The hydrogen peroxide reacts with 4 amino antipyrine and a phenolic compound in the presence of peroxidase to yield a red coloured complex. 1. Cholesterol ester +water CHE cholesterol + fatty acid 2. Cholesterol + oxygen CHO cholest-4-en-3one +H 2O 2 3. 2 H2O2 +

ANNEXURE – II

MASTER CHART

sl.no	age (yrs)	gender	stroke type	HDL (mg/dl)	Total cholesterol (mg/dl)	LDL (mg/dl)	Triglycerides (mg/dl)	hypertension	diabetes	smoking	site of lesion	NIHSS score	MRS score	BMI	hospital stay (days)
1	64	Male	Ischemic	35.3	222.6	142.9	221.8	Yes	Yes	No	Cerebellum	8	1	22.6	7
2	68	Female	Ischemic	33.8	178.1	102.6	208.7	No	No	Yes	Posterior Cerebral Artery	8	1	25.8	7
3	45	Female	Ischemic	53.6	191.4	101	183.9	Yes	No	Yes	Posterior Cerebral Artery	16	3	25.6	8
4	58	Male	Ischemic	36	179	103.2	199.1	Yes	Yes	No	Basal Ganglia	15	3	29.8	8
5	62	Female	Ischemic	34.5	199.7	137.7	137.3	Yes	No	No	Anterior Cerebral Artery	18	3	35.5	10
6	70	Male	Ischemic	35.4	245.6	173.7	182.5	Yes	No	Yes	Internal Capsule	17	3	23.8	11
7	38	Female	Ischemic	43.2	181.7	105.7	163.8	No	No	No	Cerebellum	6	1	19.5	4
8	36	Male	Hemorrhagic	48.9	218.9	124.8	225.9	Yes	No	Yes	Intraventricular	14	2	33	9
9	59	Male	Ischemic	35.5	122.6	62.7	121.9	Yes	Yes	No	Thalamus	15	3	29.2	7
10	53	Male	Ischemic	40	197.1	130.3	134	Yes	Yes	Yes	Brainstem	2	0	27.7	4
11	42	Female	Hemorrhagic	42	226.2	147.5	183.5	Yes	Yes	No	Lobar	11	2	29.3	7
12	57	Female	Ischemic	42.1	283.2	209	160.7	No	Yes	No	Brainstem	18	3	31.8	11
13	53	Male	Ischemic	42.4	257.5	194.7	101.8	Yes	Yes	No	Anterior Cerebral Artery	15	3	31.4	8
14	66	Male	Ischemic	32.2	196	137.7	130.4	No	No	No	Middle Cerebral Artery	-1	0	33.5	2
15	35	Female	Hemorrhagic	36.6	227.7	158.6	162.5	Yes	Yes	No	Lobar	9	2	27.4	4
16	47	Male	Ischemic	32.6	288.8	229.7	132.4	Yes	No	Yes	Brainstem	9	2	28.6	5
17	49	Male	Ischemic	34.3	175.7	126.6	74.2	No	No	No	Thalamus	1	0	27.3	4
18	50	Male	Ischemic	31.9	202	132.2	189.4	Yes	Yes	No	Basal Ganglia	11	2	28.1	6
19	61	Male	Ischemic	27.7	179.4	112.8	194.6	Yes	No	No	Basal Ganglia	4	1	23.5	4
20	65	Female	Ischemic	31.3	178.6	117.8	147.7	Yes	No	No	Middle Cerebral Artery	5	1	29.6	3
21	67	Female	Ischemic	29.6	206.6	146.4	153.1	Yes	Yes	Yes	Middle Cerebral Artery	17	3	31.2	10
22	65	Male	Ischemic	31.3	233.6	151.6	253.6	No	No	Yes	Thalamus	13	2	29.8	7
23	44	Female	Ischemic	29.2	227.9	149.3	247.1	Yes	Yes	Yes	Middle Cerebral Artery	3	1	21.5	3
24	69	Male	Ischemic	28.2	138.4	72.1	190.3	No	Yes	No	Anterior Cerebral Artery	7	1	28.1	5
25	57	Male	Ischemic	39.1	230.9	149.7	210.4	Yes	Yes	No	Brainstem	6	1	27.9	4
26	42	Female	Hemorrhagic	32.9	213.7	136.1	223.5	No	No	No	Basal Ganglia	16	3	29.7	10
27	41	Male	Ischemic	46.4	220.7	147	136.6	Yes	Yes	No	Brainstem	12	2	32.5	8
28	40	Female	Ischemic	41.1	251.3	163.6	233.2	Yes	Yes	No	Middle Cerebral Artery	10	2	19.4	6
29	42	Female	Hemorrhagic	57.3	235.8	121.2	286.3	Yes	Yes	No	Cerebellum	13	2	29.6	9
30	47	Female	Ischemic	36.3	211.1	130.4	221.9	Yes	Yes	No	Cerebellum	8	1	26.8	5
31	49	Male	Ischemic	16.3	263.6	223.3	120.1	Yes	No	No	Anterior Cerebral Artery	3	1	28.7	3
32	53	Female	Ischemic	32.2	182.7	128	112.7	No	Yes	Yes	Middle Cerebral Artery	7	1	23.1	4
33	41	Female	Hemorrhagic	35	240.2	166.3	194.3	No	Yes	No	Brainstem	12	2	30.1	9
34	45	Female	Ischemic	31.5	167.8	104.6	158.4	Yes	Yes	No	Middle Cerebral Artery	14	2	29.7	8
35	60	Female	Ischemic	37.1	224.2	139.8	236.5	Yes	No	No	Middle Cerebral Artery	7	1	28.5	5
36	35	Female	Hemorrhagic	50.2	200.7	127.4	115.6	No	No	No	Cerebellum	15	3	35.1	7
37	54	Female	Ischemic	31.4	206.4	146.7	141.7	No	No	No	Middle Cerebral Artery	4	1	30.6	6
38	35	Female	Hemorrhagic	43.5	165.3	89.3	162.5	Yes	Yes	No	Thalamus	20	3	28.8	10
39	41	Male	Ischemic	26.7	214.6	160.2	138.3	Yes	No	No	Thalamus	26	4	32.8	13
40	58	Male	Ischemic	44.3	237.8	172.2	106.3	Yes	Yes	Yes	Brainstem	5	1	34.2	6
41	64	Male	Ischemic	38	243.3	169.1	181	Yes	No	Yes	Basal Ganglia	10	2	30.5	5
42	37	Female	Ischemic	45.6	250.4	163	208.8	No	No	No	Thalamus	17	3	27.3	7
43	70	Female	Ischemic	25.5	214	157.9	152.9	Yes	No	Yes	Anterior Cerebral Artery	9	2	31.5	7
44	67	Female	Hemorrhagic	49.6	172.4	88.5	171.7	No	Yes	No	Lobar	0	0	24.6	1
45	43	Female	Ischemic	32.1	244.1	193.8	91	Yes	No	No	Internal Capsule	14	2	24	8
46	39	Female	Ischemic	39.7	235.3	143.4	260.8	No	No	No	Internal Capsule	12	2	30.4	9
47	47	Male	Ischemic	28.3	154.7	110.1	81.6	No	Yes	No	Cerebellum	8	1	26.9	6
48	41	Male	Ischemic	44.6	176.4	97.9	169.7	Yes	Yes	Yes	Brainstem	9	2	32	5
49	62	Female	Ischemic	23	251.3	205.5	114	Yes	No	No	Internal Capsule	14	2	25	10
50	37	Female	Ischemic	25.5	172.6	134.9	61.1	Yes	No	No	Brainstem	19	3	24.8	10
51	64	Male	Ischemic	36.3	156.2	66.4	267.5	Yes	No	No	Internal Capsule	8	1	29.8	8

52	54	Female	Ischemic	35	180.9	94.5	256.8	No	Yes	No	Internal Capsule	12	2	27.4	9
53	49	Male	Ischemic	38.2	217.9	163	83.4	Yes	Yes	Yes	Brainstem	18	3	29.8	11
54	36	Female	Ischemic	33.6	162.2	71.4	286.2	Yes	Yes	No	Middle Cerebral Artery	15	3	19.1	10
55	61	Female	Ischemic	36.1	185.3	119.6	148.1	Yes	No	No	Cerebellum	20	3	28.8	9
56	69	Male	Ischemic	32.3	208.7	115.8	302.9	No	Yes	Yes	Brainstem	10	2	20.4	8
57	63	Male	Ischemic	52.9	165.7	98.4	72.2	No	Yes	No	Internal Capsule	14	2	25.1	8
58	63	Female	Ischemic	37	169.9	86.5	232.1	Yes	Yes	Yes	Brainstem	8	1	29.7	6
59	35	Female	Ischemic	28.9	220.9	166.8	126.2	No	No	No	Basal Ganglia	18	3	20	10
60	43	Female	Ischemic	38.5	177.6	92.8	231.7	No	Yes	No	Anterior Cerebral Artery	16	3	27.1	9
61	59	Male	Ischemic	47.8	252.4	167.2	187.2	Yes	Yes	Yes	Cerebellum	5	1	24.9	7
62	44	Male	Hemorrhagic	43.4	247.8	163.8	203	Yes	No	No	Basal Ganglia	12	2	28.6	7
63	52	Male	Ischemic	50.1	194.4	107.2	185.3	No	No	No	Cerebellum	11	2	23.9	9
64	63	Female	Ischemic	39.5	144.5	48.9	280.6	No	No	No	Brainstem	12	2	27.9	9
65	68	Male	Ischemic	30.6	251.3	177.7	215.2	Yes	Yes	Yes	Thalamus	14	2	25.9	9
66	51	Female	Ischemic	25	183.6	126.7	159.4	No	No	No	Internal Capsule	5	1	25.5	5
67	68	Male	Ischemic	29	228.9	144.8	275.3	Yes	No	No	Basal Ganglia	10	2	27.2	4
68	48	Female	Ischemic	28.9	235.1	164.3	209.6	No	No	No	Internal Capsule	9	2	18.8	8
69	69	Female	Ischemic	34.9	200.5	141.1	122.3	No	No	No	Brainstem	7	1	27	6
70	40	Female	Ischemic	40.9	229.3	136.1	261.4	No	Yes	No	Brainstem	16	3	27.9	8
71	42	Male	Hemorrhagic	53.6	215.1	147.1	71.8	Yes	Yes	Yes	Lobar	21	4	25.3	10
72	66	Male	Hemorrhagic	40.9	197.1	117.9	191.7	No	Yes	Yes	Intraventricular	14	2	31.9	10
73	58	Male	Ischemic	32.5	156.6	90.2	169.3	No	No	Yes	Thalamus	10	2	30.6	7
74	53	Female	Hemorrhagic	54.9	213.9	114.4	223	Yes	No	Yes	Intraventricular	8	1	27.2	6
75	40	Male	Ischemic	37.6	216.9	130.5	243.9	Yes	No	Yes	Anterior Cerebral Artery	5	1	23.7	7
76	70	Male	Hemorrhagic	36	201.5	115.4	250.5	Yes	No	No	Lobar	14	2	29.1	8
77	69	Female	Ischemic	23.5	233.2	173.8	179.7	Yes	No	Yes	Middle Cerebral Artery	19	3	33	11
78	63	Male	Hemorrhagic	38.2	227.1	164.5	122	Yes	No	No	Lobar	11	2	31.3	6
79	52	Female	Ischemic	38.9	175.2	96	201.3	No	Yes	No	Brainstem	12	2	28.9	5
80	67	Male	Ischemic	41.3	212.4	132.9	191.2	Yes	No	No	Internal Capsule	10	2	24.8	5
81	70	Male	Ischemic	37.5	155.1	59.5	290.7	No	Yes	Yes	Brainstem	9	2	29.6	7
82	67	Male	Ischemic	44.2	190.4	145.1	5.6	Yes	No	Yes	Anterior Cerebral Artery	-4	-1	25.8	3
83	51	Female	Ischemic	16.7	196.9	174.5	28.5	No	No	Yes	Anterior Cerebral Artery	11	2	32.4	5
84	47	Male	Ischemic	28.7	232.9	185.2	95.1	Yes	No	Yes	Posterior Cerebral Artery	19	3	29.2	8
85	48	Female	Ischemic	30.5	209.5	131.9	235.7	Yes	Yes	No	Posterior Cerebral Artery	3	1	22.7	4
86	38	Male	Hemorrhagic	46.7	228.2	153.3	141.2	Yes	No	No	Cerebellum	11	2	28.4	9
87	46	Female	Ischemic	40.8	219	147.8	152.2	No	No	No	Middle Cerebral Artery	3	1	29.2	4
88	62	Male	Ischemic	29	258.2	199.2	150.1	Yes	No	No	Posterior Cerebral Artery	12	2	21.5	6
89	50	Female	Ischemic	28.1	219.3	165.1	130.4	Yes	No	Yes	Middle Cerebral Artery	5	1	27.4	6
90	61	Male	Ischemic	31.4	208.9	145.4	160.3	No	No	No	Internal Capsule	4	1	27	2
91	69	Male	Ischemic	32.1	175.4	106.1	185.8	Yes	Yes	No	Internal Capsule	20	3	32.2	11
92	52	Male	Ischemic	22.8	247.1	203.1	105.8	Yes	No	No	Posterior Cerebral Artery	2	0	27.5	5
93	63	Female	Ischemic	54.1	184.3	91.3	194.6	Yes	No	No	Brainstem	10	2	24	8
94	62	Female	Ischemic	39.2	208	152.9	79.3	Yes	No	No	Internal Capsule	7	1	27.7	6
95	67	Female	Ischemic	42.3	192.4	94.7	277	Yes	No	Yes	Middle Cerebral Artery	11	2	21.6	6
96	38	Female	Ischemic	41.9	263.4	187	172.3	Yes	No	No	Brainstem	6	1	25.9	4
97	70	Female	Ischemic	32.3	143.5	90.5	103.3	Yes	No	No	Middle Cerebral Artery	6	1	23.4	3
98	66	Female	Ischemic	51.5	237	160.9	123	Yes	No	No	Internal Capsule	15	3	30.5	8