“ESTIMATION OF THE LIPOPROTEIN (a) IN ACUTE ISCHAEMIC STROKE”

REG NO. BG0114013

Dissertation

Submitted to the
KLE University, Belagavi, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D.
in
GENERAL MEDICINE

DEPARTMENT OF MEDICINE,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
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ENDORSEMENT

This is to certify that the dissertation entitled **"ESTIMATION OF THE LIPOPROTEIN (a) IN ACUTE ISCHAEMIC STROKE"** is a bonafide research work done by **CANDIDATE REG NO. BG0114013**.

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LIST OF ABBREVIATIONS USED

°C	-	Degree centigrade
2D	-	2 dimensional
AHA	-	American Heart Association
APLA	-	Antiphospholipid syndrome
Apo (a)	-	Apolipoprotein (a)
Apo-B	-	Apolipoprotein B
ARIC	-	Atherosclerosis risk in communities
CAT	-	Computerized axial tomography
CeVD	-	Cerebrovascular disease
CHD	-	Coronary heart diseases
CI	-	Confidence interval
CNS	-	Central nervous system
CT	-	Computed tomography
CVA	-	Cerebrovascualar accident
CVD	-	Cerebrovascular disease
DALYs	-	Disability adjusted life-years
DM	-	Diabetes mellitus
e.g.	-	For example
ED	-	Emergency department
ELISAs	-	Enzyme-linked immunosorbent assays
EMS	-	Emergency Medicine Section
ESR	-	Erythrocvte sedimentation rate
g/day	-	Grams per day
HDL	-	High density lipoprotein

HTN	-	Hypertension
IA	-	Intraarterial
ICH	-	Intracerebral haemorrhage
ICVD	-	Ischemic cerebrovascular disease
IDL	-	Intermediate-density lipoprotein
LDL	-	Low density lipoprotein
Lp(a)	-	Lipoprotein(a)
mg/dL	-	Milligrams per deciliter
MRI	-	Magnetic resonance imaging
n	-	Total number
NCEP	-	National Cholesterol Education Program
NIHSS	-	National Institutes of Health Stroke Scale
OC	-	Oral contraceptive
p value	-	Probability value
PAN	-	Polyarteritis nodosa
SAH	-	Subarachnoid haemorrhage
TC	-	Total Cholesterol
TG	-	Triglycerides
TGL	-	Triglycerides
TIA	-	Transient ischemic attack
UK	-	United Kingdom
US	-	United States
USA	-	United States of America
VLDL	-	Very low density lipoprotein
w/v	-	Weight / volume

WHO	-	World Health Organization
µg/ml	-	Micrograms per milliliter

ABSTRACT

Background and objectives

Lipoprotein(a) is considered as an independent risk factor for atherosclerosis. The present study was aimed to evaluate the role of lipoprotein(a) as a marker for ischaemic stroke.

Methodology

The present one year cross-sectional study was conducted from January 2015 to December 2015. A total of 100 patients presenting with Iscahemic stroke in the Department of Medicine and Department of Neuro-Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi were studied. All the patients were investigated for Lipoprotein(a) levels.

Results

Majority of the patients that is, 78% were males and male female ratio was 3.45:1. The most common age group was 61 to 70 years (28%) and the mean age was 56.04 ± 14.02 years. Weakness (79%), altered sensorium (53%), were the common presentations Hypertension (29%), was the most common risk factor followed by diabetes mellitus (20%). More than half of the study population (55%) had raised Lipoprotein A levels (≥30 mg/dL). The mean lipoprotein(a) levels were 32.95 ± 15.24 mg/dL and ranged between 12.2 to as high as 86.2 mg/dL. Majority of the patients (81%) had raised cholesterol levels and mean cholesterol levels were 175 ±40.88 mg/dL. Most of the patients had raised Low density lipoprotein levels (68%) and the mean LDL levels were 124 ±44.8 mg/dL. 68% of the patients had raised Triglyceride levels and mean triglyceride

levels were noted as 134.1 ±56.97 mg/dL. Raised lipoprotein(a) levels were associated with hypercholesteolaemia ($p<0.001$), LDL ($p=0.047$), raised triglycerides levels ($p=0.021$) and risk factors viz. diabetes mellitus, and both diabetes mellitus and hypertension ($p<0.001$). However raised lipoprotein(a) was independent of sex ($p=0.961$), age ($p=0.646$) and HDL levels ($p=0.373$).

Conclusion and interpretation

Lipoprotein(a) is raised in patients with ischaemic stroke. Furthermore, the rise in lipoprotein a levels is associated with hypercholesterolaemia, raised LDL levels, hypertriglyceridemia and diabetes mellitus. However, the rise in lipoprotein(a) levels are not influenced by sex, age and HDL.

Keywords

Ischaemic stroke; Lipoprotein(a); Lipid profile;

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INTRODUCTION

Stroke is a syndrome of rapidly developing clinical signs of focal (or global) disturbance of cerebral function with symptoms lasting for more than 24 hr or longer or resulting in death with no apparent cause other than vascular origin.[1-3] Incidence of cerebrovascular disease (CVD) (stroke) increases considerably with age, affecting many people in their "Golden year of life."[2] Even though frequency of stroke varies from place to place, cerebral thrombosis is the most frequent form encountered in clinical studies followed by intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH).[3,4] Even though the incidence of stroke is increasing, mortality rate is decreasing in the recent years.[5,6]

Cerebrovascular disease (CVD) and Coronary heart diseases (CHD) are responsible for around 40%–50% of all deaths in developed countries and out of this 10%–12% are due to stroke.[6,7] Recently, there is a decline in the mortality from stroke which may be due to socioeconomic changes, early diagnosis and treatment of stroke, hypertension and other risk factors.[4]

Majority of stroke are ischaemic (80%); while others result from primary haemorrhage either intracerebral or into the subarachnoid space. Acute ischemic stroke is result of stroke caused by thrombosis or embolism and is more common than hemorrhagic stroke. Ischemic strokes constitute 85–87% of all cases.[8] Hemorrhagic stroke constitute spontaneous intracerebral hemorrhage and subarachnoid hemorrhage, and account for the remaining of cases.

According to the World Health Organization, stroke is the second leading cause of death world-wide.[9] Thus, cerebrovascular disease is a huge public health problem imposing both as a large disease burden and a large economic burden on our country.[10] The mortality rate of stroke in the acute phase is as high as 20% and it remains higher for several years after the acute event in stroke patients than in the general population.[11] Stroke is an illness of escalating socioeconomic importance, especially among the ageing population.[9]

In some geographical areas or within or some racial and ethnic groups, stroke incidence may be unusually high. Incidence of stroke varies considerably from country to country. Based on the review of available information in India, the prevalence of stroke was estimated as 203 per 100,000 population above 20 years, amounting to a total of about 1 million cases.[7] Upto 85% of all strokes are of ischaemic origin.[8]

Atherosclerosis occurring in arteries supplying the brain, both large and small is the most common cause of ischemic stroke. Atherosclerosis occurring in proximal aorta is also a source of atherogenic brain emboli. Large artery atherosclerotic infarction occurs when there is an impediment to normal perfusion, usually caused by a severe arterial stenosis or occlusion due to atherosclerosis and coexisting thrombosis or artery to artery embolism. Microatheroma, lipohyalinosis, and other occlusive diseases of the small penetrating brain arteries are the most frequent causes of small, sub-cortical "lacunar" infarcts. About 20% of ischaemic strokes are due to cardiogenic embolism, most commonly from atrial fibrillation. A variety of other occlusive disorders may be the primary cause or variably contribute to stroke pathogenesis.[14] Accordingly, stroke is also an important cause of morbidity

and long term disability, up to 40% of survivors are not expected to recover their independence and self-care.[11]

Numerous risk factors are involved in the development of stroke, such as hypertension, cigarette smoking, hyperlipidemia and diabetes mellitus.[14] Diabetes mellitus and ischaemic stroke often arise together. People with diabetes have more than double the risk of ischaemic stroke after correction for other risk factors, relative to individuals without diabetes. Hyperglycaemia occurs in 30-40% of patients with acute ischaemic stroke in diabetic as well as non diabetic patients.[15]

Lipoprotein (a) is a LDL like particle, discovered as a sinking prebeta lipoprotein. This variant lipoprotein fraction contains one molecule of an apolipoprotein B100 and another large protein called apolipoprotein (a) [Apo (a)]. Following its discovery Lp(a) was shown in case control studies to be associated with CHD.[16-18] It has been demonstrated that there is a structural homology between Apo (a) and plasminogen.[19] Ninety percent of Lp(a) concentration is under genetic regulation. Despite this genetic regulation, some metabolic abnormalities may have effect on Lp(a) levels in plasma. Notable among them are (1) acute phase response, (2) diabetes, and (3) liver and renal failure.[16] Studies on general population have shown that Lp(a) levels are skewed, i.e., it ranges from 1 to 200 mg/dl with geometric mean of about 10 mg/dl.[20] Certain pharmacological agents and disease conditions also influence the circulating Lp(a) levels.[20,21]

Accumulation of Lp(a) has been demonstrated in the arterial walls of human coronary and cerebral vessels.[22] Lp(a) particles are susceptible to oxidative modification and this modified Lp(a) is taken up by scavenger receptor macrophages

leading to intracellular cholesterol accumulation and foam cell formation, which contributes to atherogenesis.[20,23-27] Atherogenic lipoproteins include in addition to LDL, almost all classes of lipoproteins that contains Apo-B (VLDL, beta VLDL, IDL, Lp(a), and oxidized LDL). A common feature of these atherogenic lipoproteins is that they contain various amounts of cholesteryl esters and either Apo-B 100 or Apo-B 48. In addition Lp(a) contain Apo (a), a protein that is a disulfide linked to Apo –B and is homologous to plasminogen, Apo (a) may contribute to atherogenesis by mechanisms related to thrombosis.[28]

Lp(a) values can be increased as part of the acute phase response, and in diabetes mellitus, chronic renal failure, nephrotic syndrome, cancer, menopause, and hypothyroidism.[29]

Lp(a) values are decreased in liver failure and hyperthyroidism. Furthermore, nicotinic acid, tamoxifen, oestrogens, progesterone, and anabolic steroids might decrease Lp(a) concentrations. Fibrates have been shown, in some studies, to reduce Lp(a) concentrations, whereas statins might increase Lp(a) concentrations.[29]

Studies in subjects with average lipid profiles indicate that raised Lp(a) concentrations are associated with myocardial infarction, coronary artery disease, peripheral atherosclerosis and cerebral ischemia. Lipoprotein(a) is considered as an independent risk factor for atherosclerosis. Due to unique structural homology with plasminogen, it interferes with the function of plasminogen thus increasing thrombotic risk.[29]

Lipoprotein (a) has been observed to be increased in CHD, but very few studies comment on estimation of this parameter in the case of thrombotic stroke,

even though the etiopathogenesis is almost similar in both these conditions.[29] Compared with CHD, studies conducted in stroke patients are inconclusive, and not clearly proved, whether stroke is due to increased lipid profile, hypertension or due to the life style of an individual. Moreover, due to alteration in lipid profile which lipid parameter or the lipoprotein gets altered in the thrombotic stroke is not clear.[6]

Several studies have evaluated the association between Lp(a)and ischemic stroke. Several cross sectional studies and a few prospective studies provide contradictory findings regarding Lp(a) as a predictor of ischemic stroke.[20] The meager reports[6,29] available in Indian patients who have different social, living and dietary habits compared to western population, prompted us to undertake this study.

Keeping this in mind, the present study was sought to evaluate the role of Lp (a) as a marker for ischaemic stroke.

OBJECTIVES

The objective of this study was to evaluate the role of lipoprotein (a) as a marker for ischaemic stroke.

REVIEW OF LITERATURE

STROKE

Historical perspectives

The term “Stroke” or “Cerebrovascular accidents” has come to signify the abrupt impairment of brain function caused by a variety of pathological changes involving one (focal) or several (multifocal) intracranial or extracranial blood vessels.[30]

The concept of stroke was first noted from 460 to 370 before the Common Era by Hippocrates. At this time, the symptoms of convulsions and paralysis were referred to as apoplexy. Over the next several hundred years, scholars focused on physical symptoms and potential causes.

The first known description of stroke was given by Hippocrates who took the word “Apoplexy” common nonmedical use where it meant **“**Astonished**,** Suddenly benefit of one’s senses**”** and applied it descriptively to stroke.

- Jacob Werter, a Swiss physician was the first person to suggest that apoplexy was caused by disease of blood vessel in the brain.
- Thomas Willis described the circle of wills in 1664.
- Seddicot described spontaneous intracerebral haemorrhage in 1813.
- In 1828 Abberonbie, described the obliterative arterial disease of cerebral arteries.

- Johan Friedrich crell, emphasized the pultaceous or atheromatous elements in some arterial lesions although he did not use the term atheroma.
- Von Haller made similar observations and applying the term “atheroma” to the arterial lesions.
- In 1860, Rudolf Virchow described imbibition theory that states there was deposition of blood constituents on the laminal surface of the arterial wall during the formation and growth of atheromatous plaques. He considered that the early lesions of atherosclerosis were based on a “loosening” of the connective tissue ground substance of the intima as a result of “imbibition” of constituents of the passing blood.
- Von Rokitansky and the thrombogenic theory described the atheromatous deposition is by far the most frequent disease of the arteries and embodies the foundation of aneurysm formation and of many spontaneous arterial obliterations.
- Virchow’s concept of atherogenesis was that, all the structural changes were initiated by an invading stream of plasma. This is the origin of the so called “infiltrative” theory of atherosclerosis which certainly, in so far as lipid accumulation is concerned, appears even now to have much truth in it.
- Vogel in 1847 and Chalatow in 1913 observed that atherosclerotic plaques contained relatively large amounts of cholesterol.
- In 1825, Bonillord described localisation of lesion and aphasia.
- In 1860, Von Graafe used Helmoltz ophthalmoscope.
- In 1895, Hamrich Quinn introduced the technique of lumbar puncture which is so vital in the diagnosis of neurological illness.

- 1877 Osler reported a case of Subarachnoid and intracerebral haemorrhage due to ruptured aneurysm.
- In 1914, Ramasy hunt was the first to describe comprehensive description of spontaneous carotid occlusion without crest disease of the intracranial vessel producing cerebral infarction.
- Dandy performed the first air ventriculogram.
- Denny brown introduced the concept of vascular insufficiency.
- Platelet antiaggregating drugs like aspirin was used in 1971 for TIA's by Karim in 1978.
- Dr. GodFrey Honnsfield, a British physicist in 1972 introduced computerized axial tomography (CAT) technique into neuro radiology which resulted in award of noble prize in 1979. This lead to more precise categorization of ischaemic and hemorrhagic Cerebrovascular accident (CVA).

Within the last decade, the magnitude of research has grown exponentially. The term apoplexy has faded, and the term stroke has become common place in the medical setting.[31]

Definition

World Health Organization (WHO) defines stroke as rapid development of clinical signs of focal (or global) brain function disorders, with symptoms which last 24 hours or longer or lead to death, without other clear cause, except signs of blood vessel damage.[32]

Prevalence

Worldwide

It is estimated that approximately 4 million people suffer from stroke annually. Out of that number, approximately 570,000 cases occur in Europe and approximately 500,000 in United States of America. International epidemiological trials show that rates grow exponentially with age, from 0.3% in the third and fourth decade of life, all the way to 30% in the eighth and ninth decade of life, which makes an average of 1–2%. Recent data shows that the incidence of stroke in France is 114 cases per 100,000 persons per year, in Germany 350, in Italy 223, in Spain 141–220, and in UK 161.[32,33]

Although rates of stroke mortality and burden vary greatly among countries, low-income countries are the most severely affected. There has been a 42% decrease in stroke incidence in high-income countries and >100% increase in low- to middle-income countries.[34,35]

Morbidity and Mortality [36]

- 400-800 strokes per 100,000.
- 5.7 million Deaths.
- 16 million new acute strokes every year.
- 28,500,000 DALYs (disability adjusted life-year).
- 28-30 day case fatality ranges from 17%-35%.

Stroke in India

Estimates of the prevalence of stroke in India range from 44 to 843 per 100,000 population.[37,38] Based on the estimates by Dalal et al.[39] in 2008, age adjusted annual incidence per 100,000 population is 152.[39]

Morbidity and Mortality [36]

- Prevalence 90-222 per 100,000.
- 102,620 million deaths.
- 1.44-1.64 million cases of new acute strokes every year.
- 6,398,000 DALYs.
- 12% of strokes occur in the population aged <40 years
- 28-30 day case fatality ranges from 18-41%.

Classification of stroke[40]

Broadly, strokes are classified as either hemorrhagic or ischemic. Acute ischemic stroke refers to stroke caused by thrombosis or embolism and is more common than hemorrhagic stroke.[41]

There are many classifications according to etiology vascular territory and by time course etc.

1. Classification by time course:

    a. Transient ischaemic attack.

    b. Reversible ischaemic neurological deficit.

c. Stroke in evolution.

d. Completed stroke.

2. By arterial territory:

a. Internal carotid artery territory.

b. Vertebrobasilar territory.

c. Lenticulo-striate.

3. By underlying pathology:

a. Atheromatous occlusion of vessels.

b. Atheroembolism.

c. Lipohylinoid necrosis.

d. Charcot Bouchard aneurysm rupture.

4. According to cause:[40]

a. Atherosclerosis.

b. Embolism of cardiac origin.

C. Vasculitis: Primary central nervous system (CNS), PAN, Collagen Vascular Disease, temporal arteritis, infectious vasculitis.

d. Hematological Disorders: Hemoglobinopathies, hyperviscosity syndrome, hypercoagulability states, protein C and S deficiency, Antiphospholipid syndrome (APLA) syndrome.

e. Drugs: Cocaine, alcohol, amphetamines, OC pills.

f. Others: MoyaMoya, migraine, fibromuscular dysplasia.

g. Cerebral Venous Thrombosis.

h. Intracerebral haemorrhage

ISCHEMIC STROKE

Thrombotic cerebral infarction results from the atherosclerotic obstruction of large cervical and cerebral arteries, with ischemia in all or part of the territory of the occluded artery. This can be due to occlusion at the site of the main atherosclerotic lesion or to embolism from this site to more distal cerebral arteries.

Embolic cerebral infarction is due to embolism of a clot in the cerebral arteries coming from other parts of the arterial system, for example, from cardiac lesions, either at the site of the valves or of the heart cardiac cavities, or due to rhythm disturbances with stasis of the blood, which allows clotting within the heart as seen in atrial fribrillation.

Lacunar cerebral infarctions are small deep infarcts in the territory of small penetrating arteries, due to a local disease of these vessels, mainly related to chronic hypertension. Several other causes of cerebral infarction exist and are of great practical importance for patient management. As they are relatively rare they can be ignored for most epidemiological purposes.

In India, frequency of ischaemic stroke is between 60 to 80%.[38,42-44] Further, lacunar, large vessel and cardioembolic types occur at 18%, 41%, 10% respectively[45] while other determined and undetermined types occur in 10% and 20 respectively.[44]

Etiology[46]

Ischemic strokes result from events that limit or stop blood flow, such as extracranial or intracranial thrombo-embolism, thrombosis in situ, or relative hypoperfusion. As blood flow decreases, neurons cease functioning, and irreversible neuronal ischemia and injury begin at blood flow rates of less than 18 mL/100 g of tissue/min.

Pathophysiology

When an ischemic stroke occurs, the blood supply to the brain is interrupted, and brain cells are deprived of the glucose and oxygen they need to function. Ischemic stroke is a complex entity with multiple etiologies and variable clinical manifestations. Approximately 45% of ischemic strokes are caused by small or large artery thrombus, 20% are embolic in origin, and others have an unknown cause.[47]

Thrombosis can form in the extracranial and intracranial arteries when the intima is roughened and plaque forms along the injured vessel. The endothelial injury (roughing) permits platelets to adhere and aggregate, then coagulation is activated and thrombus develops at site of plaque. Blood flow through the extracranial and intracranial systems decreases, and the collateral circulation maintains function. When the compensatory mechanism of collateral circulation fails, perfusion is compromised, leading to decreased perfusion and cell death.[47]

During an embolic stroke, a clot travels from a distant source and lodges in cerebral vessels. Microemboli can break away from a sclerosed plaque in the carotid artery or from cardiac sources such as atrial fibrillation, patent foramen ovale, or a hypokinetic left ventricle. Emboli in the form of blood, fat, or air can occur during

surgical procedures, most commonly during cardiac surgery, but also after long bone surgeries.[47]

Less common causes of ischemic stroke include carotid dissection and the presence of coagulopathies, such as those resulting from antiphospholipid antibodies. Other causes include arteritis, infection, and drug abuse, such as the use of cocaine. While still not completely understood, the presence of periodontal disease and tooth loss is also an associated risk for ischemic stroke.[47]

As a thrombosis or emboli cause a decrease in blood supply to the brain tissue, events occur at the cellular level, referred to as the ischemic cascade. Neurons and support cells require a careful balance of variables such as temperature, pH, nutrition, and waste removal in their environment to function optimally. Intensive basic scientific research during the last two decades has given healthcare professionals an increased understanding of the ischemic cascade in the format of the precise environmental alterations involved in the pathophysiology of ischemic injury at the cellular level. Understanding the ischemic cascade has led to the concept of a therapeutic time window for treatment possibilities. Often, there is a core region of dead cells surrounded by an area of hypoperfused tissue. The hypoperfused area may be rescued; this area is referred to as the penumbra region.[47]

Neuroprotection is a broad term that refers to pharmacological and nonpharmacological treatments used to halt the cellular events in the ischemic cascade, forming the theoretical basis for many of the acute stroke therapies under study[41] as well as the rationale for intervening within a therapeutic time window following ischemic stroke.

History and clinical presentation

Assessment of the patient with a stroke begins with recognition of the event as a stroke in the prehospital phase of care and continues throughout care. Emergency medical technicians and ambulance staff members need training in the recognition of signs and symptoms of stroke. Tools such as the Face Arm Speech Test[48] and the shortened National Institutes of Health Stroke Scale[49] have been tested and found to be effective in increasing the diagnostic accuracy of ambulance staff. The has published standards for acute stroke prehospital care[50] which the AHA did not seek to duplicate but continued to emphasize the need for immediate diagnosis and evaluation.[51]

In the emergency department (ED), as the patient arrives, preferably by ambulance, a suspected stroke is treated as an acute event until diagnostic evidence suggests otherwise. Neurological assessment is based on both subjective and objective data, and a careful medical history is crucial to establish the exact time of onset of stroke signs and symptoms. Essential data to include are a quick history of timing of the event, pertinent past medical history, and risk factors. The full NIHSS can be used to guide the neurologic assessment.

Symptoms of Ischemic Stroke According to Cerebral Circulation[47]

<u>Brainstem</u>

- Hemiparesis or quadriparesis
- Motor or sensory loss in all four limbs
- Eye movement abnormalities, such as diploplia and dysconjugate gaze
- Oropharyngeal weakness

- Vertigo, tinnitus
- Nausea, vomiting
- Dysmetria

Cerebellurn

- Ipsilateral limb ataxia
- Gait ataxia

Vetebrobasilar circulation

- Symptoms correlate with brainstem and cerebellar functions as above
- Cranial nerve deficits in cranial nerves III – XII

Anterior Circulation Symptoms (Carotid artery)

- Contralateral motor and sensory loss
- Amaurosis fugax or transmonocular blindness (caused by emboli to retinal artery)

Anterior Cerebral Artery

- Confusion
- Personality change
- Incontinence
- Contralateral motor or sensory loss in leg greater than arm

Middle Cerebral Artery

- Contralateral motor or sensory loss (arm greater than leg)
- Contralateral motor loss in lower face
- Contralateral visual field loss
- Language deficit (dominant hemisphere)
- Spatial-perceptual deficit (nondominant hemisphere)

Posterior Cerebral Artery

- Contralateral sensory loss
- Ipsilateral visual field deficit
- Cortical blindness

In addition to these symptoms, determining dominance is important as the dominant hemisphere is primarily responsible for language function. Handedness determines dominance for most people. Right-handed people are left-hemisphere dominant; left-handed people are also left-hemisphere dominant about 60% of time. The clinical features that are more common with a dominant left cerebral hemisphere lesion include aphasia, agraphia, acalculia, apraxias, a left gaze preference, a right visual field deficit along with right-sided hemiparesis, and a right-sided hemisensory loss. Common features of a nondominant right cerebral hemisphere include neglect (left-sided hemiinattention), right gaze preference, left visual field deficit, dysarthria, flat affect, left-sided hemiparesis, and left-sided hemisensory loss.[47]

The presence of a transient ischemic attack or other conditions need to be ruled out to ensure that patients receive the appropriate treatment for their condition. A wide range of abnormalities can mimic a stroke, including hypoglycemia, migraine, seizure, and trauma.[47]

Conditions that Mimic Ischemic Stroke[47]

- Unrecognised seizures
- Confusional states
- Syncope

- Toxic or metabolic disorders including, but not limited to the following
    - Hypoglycaemia
    - Drug overdose
    - Hyponatraemia
    - Migrane
    - Concussion with head injury
    - Encephalopathies or encephalitis
    - Eclampsia
    - Brain tumors
    - Subdural hematoma

Diagnosis

Diagnostic studies help to confirm stroke, detect early potentially life-threatening complications, and direct specific care given; those recommended in the AHA guidelines are shown in Figure. These diagnostic tests are available in most EDs 24 hours a day. Blood glucose can be checked in the ambulance with a finger stick or upon ED arrival and is helpful in ruling out hypoglycemia as a cause for the event or hyperglycemia as a compounding factor.[47] A computed tomography (CT) scan without contrast is recommended to rule out the presence of a hemorrhagic stroke that would preclude the use of thrombolysis.[52] Adjunct studies may include a CT angiogram, magnetic resonance imaging (MRI), and cerebral angiography. A CT angiogram can be used to identify large vessel stenoses or occlusion. MRI allows for

better visualization of possible infarcted areas, and angiography is used when intraarterial (IA) thrombolysis is indicated or when surgical interventions are being considered.[47]

Recommended Tests in Evaluation of Acute Ischemic Stroke[47]

All Patients

- CT of the brain without contrast
- MRI can be considered at qualified centers
- Electrocardiogram
- Complete blood count with platelet count
- Serum electrolytes
- Blood glucose
- Prothrombin time, activated partial thromboplastin time, and international normalized ratio
- Renal function tests
- Oxygen saturation

Selected Patients

- Chest X ray
- Hepatic function tests
- Arterial blood gas levels (if hypoxia suspected)
- Markers of cardiac ischemia
- Lumbar puncture (if subarachnoid hemorihage is suspected and CT is negative)

- Erythrocvte sedimentation rate (ESR), syphilis serology
- Lipid profile
- Toxicology screen
- Blood alcohol level
- 2D echocardiography
- Pregnancy test
- Electroencephalogram (when seizures suspected)

Risk factors of stroke[46]

A risk factor is a characteristic of an individual or population associated with increased risk of disease compared to those without it. Multiple risk factors are associated with cerebral infraction and have been studied in great detail. Risk factor profile for ischaemic stroke differs and is variable in young and elderly patients. Various proatherothrombotic processes leading to macrovascular complications are well known. Diabetes mellitus, hypertension, smoking, alcoholism and dyslipidemia are some of the prominent modifiable risk factors for atherothrombotic ischaemic stroke. Other risk factors of stroke are raised homocystein, obesity, inadequate physical activity, migraine, oral contraceptives and hormonal supplements, fibrinogen and clotting factors, vasculitis, collagen vascular diseases and cardiac disorders to name a few. Age, gender, ethnic and geographical background, genetic inheritance and familial predisposition are some of the non-modifiable risk factors of ischaemic stroke. In spite of the adequate control of these conventional risk factors, the incidence of cerebral infarction is not curbed, emphasizing a need to look into novel and unrecognized risk factors. Risk factors for ischemic stroke include modifiable and nonmodifiable etiologies. Identification of risk factors in each patient can uncover clues to the cause of the

stroke and the most appropriate treatment and secondary prevention plan. Nonmodifiable risk factors include the following:

- Age
- Race
- Sex
- Ethnicity
- History of migraine headaches
- Sickle cell disease
- Fibromuscular dysplasia
- Heredity

Modifiable risk factors include the following:

- Hypertension
- Diabetes mellitus
- Cardiac disease - Atrial fibrillation, valvular disease, mitral stenosis, and structural anomalies allowing right to left shunting, such as a patent foramen ovale and atrial and ventricular enlargement
- Hypercholesterolemia
- Transient ischemic attacks (TIAs)
- Carotid artery stenosis
- Hyperhomocystinemia
- Lifestyle issues - Excessive alcohol intake, tobacco use, illicit drug use, obesity, physical inactivity
- Oral contraceptive use

Among the types of cardiac disease that increase stroke risk are atrial fibrillation, valvular disease, mitral stenosis, and structural anomalies allowing right-to-left shunting, such as a patent foramen ovale and atrial and ventricular enlargement.[46]

Lipoprotein(a)

Lipoprotein(a) [Lp(a)] has been considered a cardiovascular risk factor for many years. Owing to incomplete scientific evidence, screening for and treatment of high Lp(a) levels have to date been performed principally by lipid specialists. However, during the last few years, major advances have been achieved in understanding the causal role of elevated Lp(a) in premature cardiovascular disease (CVD).[53]

Lipoprotein(a) is a plasma lipoprotein consisting of a cholesterol-rich LDL particle with one molecule of apolipoprotein B100 and an additional protein, apolipoprotein(a), attached via a disulfide bond (Figure 1).1 Elevated Lp(a) levels can potentially increase the risk of CVD (i) via prothrombotic/anti-fibrinolytic effects as apolipoprotein(a) possesses structural homology with plasminogen and plasmin but has no fibrinolytic activity and (ii) via accelerated atherogenesis as a result of intimal deposition of Lp(a) cholesterol, or both.

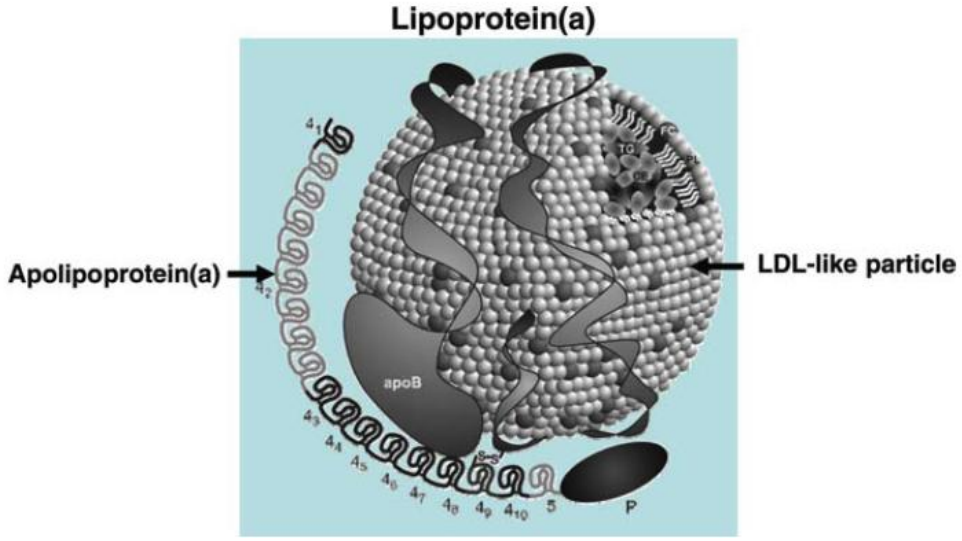


Figure 1. Lipoprotein(a) consists of an LDL-like particle to which apolipoprotein(a) is covalently linked. The LDL-like moiety is composed of a central core of cholesteryl esters (CE) and triglycerides (TG) surrounded by phospholipids (PL), free cholesterol (FC), and a single molecule of apolipoprotein B (apoB). Apolipoprotein(a) contains 10 different types of plasminogen kringle 4-like repeats as well as regions homologous to the kringle 5 and protease (P) regions of plasminogen. The kringle 4 type 2 domain (42) is present in multiply repeated copies from 2 to .40 that differ in number between apolipoprotein(a) isoforms.1 Apolipoprotein(a) is linked to apolipoprotein B100 by a single disulfide bond involving an unpaired cysteine residue in kringle 4 type 9.[54,55]

Genetics

Plasma levels of Lp(a) are to a large extent genetically determined via variation in the apolipoprotein(a) gene.[56] This makes the apolipoprotein(a) gene ideal for use in a Mendelian randomization study,[57] examining whether lifelong, genetically elevated levels of plasma Lp(a) cause CVD. By analogy, familial hypercholesterolaemia with mutations in the LDL receptor or apolipoprotein B genes have lifelong, genetically elevated LDL cholesterol levels and premature CVD, a fact that has helped establish that elevated LDL cholesterol levels constitute a direct cause of atherosclerosis and CVD.[55]

A Mendelian randomization study[57] needs three pieces of data to help provide evidence for a causal link between elevated plasma Lp(a) levels and CVD. First, elevated plasma Lp(a) levels should be associated with increased CVD risk, as demonstrated in the previous section on Lp(a) epidemiology. Secondly, genetic variation should exist in human populations that can explain a large fraction of the variation in plasma Lp(a) levels: such genetic variation has been known for many years, most importantly the kringle IV type 2 size polymorphism, resulting in a variable number from 2 to >40 number of a 5.6 kb repeat associated inversely with plasma Lp(a) levels.[55] Thus, the fewer the repeats in the apolipoprotein(a) gene, the higher the plasma levels of Lp(a), which has also been demonstrated in the past.[56] Thirdly, such genetic variation should be linked directly with CVD risk: previous smaller case–control studies ($n < 2400$) have demonstrated an association of kringle IV type 2 genotype [or the associated apolipoprotein(a) isoform size] with risk of CVD, as reviewed previously.[55,56]

Metabolism

It is believed that plasma concentrations of Lp(a) are determined chiefly by rates of hepatic synthesis of apolipoprotein(a): although the site of formation of Lp(a) has not been definitively identified, evidence suggests that apolipoprotein(a) adducts extracellularly and covalently to apolipoprotein B100-containing lipoproteins, predominantly LDL. Apolipoprotein(a) genotype, which determines both the synthetic rate and size of the apolipoprotein(a) moiety of Lp(a), alone accounts for 90% of plasma concentrations of Lp(a). As hepatic secretion rates are lower for large apolipoprotein(a) isoforms, and as most individuals are heterozygous for two different isoforms, the smallest isoform typically predominates in plasma.

Lipoprotein(a) is thought to be catabolized primarily by hepatic and renal pathways, but these metabolic routes do not appear to govern plasma Lp(a) levels.[55]

Pathophysiological mechanisms underlying the atherothrombotic potential of lipoprotein(a)

After transfer from plasma into the arterial intima, Lp(a) may be more avidly retained than LDL as it binds to the extracellular matrix not only through apolipoprotein(a), but also via its apolipoprotein B component,[58] thereby contributing cholesterol to the expanding atherosclerotic plaque. *In vitro*, Lp(a) binds to several extracellular matrix proteins including fibrin[59] and defensins, a family of 29–35 amino acid peptides that are released by neutrophils during inflammation and severe infection.[60] It is likely that defensins, like lipoprotein lipase, provide a bridge between Lp(a) and the extracellular matrix.[55]

Transgenic mice expressing a mutant form of apolipoprotein(a) with greatly reduced ability to bind to fibrin exhibited 20% less atherosclerotic lesion area and less accumulation in the arterial wall compared with transgenic mice expressing wild-type Lp(a).[61] In addition, Lp(a) seems to be retained at sites of mechanical injury;[58] fibrin deposition occurs preferentially at such sites.[55]

Through its apolipoprotein(a) moiety, Lp(a) also interacts with the β2-integrin Mac-1, thereby promoting the adhesion of monocytes and their transendothelial migration.[62] In atherosclerotic coronary arteries, Lp(a) was found to localize in close proximity to Mac-1 on infiltrating mononuclear cells.[55]

Lipoprotein(a) has also been shown to bind pro-inflammatory-oxidized phospholipids[63] and is a preferential carrier of oxidized phospholipids in human

plasma. Lipoprotein(a) also contains lipoprotein-associated phospholipase A2 (equally referred to as Paf-acetylhydrolase), which may cleave oxidized fatty acids at the sn-2 position in oxidized phospholipids to yield short chain fatty acids and lysolecithin.[64]

Apolipoprotein(a), a homologue of the fibrinolytic proenzyme plasminogen, impairs fibrinolysis. Indeed, Lp(a)/apolipoprotein(a) can competitively inhibit tissue-type plasminogen activator-mediated plasminogen activation on fibrin surfaces, although the mechanism of inhibition by apolipoprotein(a) remains controversial. Essential to fibrin clot lysis are a number of plasmin-dependent, positive feedback reactions that enhance the efficiency of plasminogen activation, including the plasmin-mediated conversion of Glu-plasminogen to Lys-plasminogen. It has been observed that the apolipoprotein(a) component of Lp(a) inhibits the key positive feedback step involving conversion of plasmin-mediated Glu-plasminogen to Lys-plasminogen. Lipoprotein(a) may also enhance coagulation by inhibiting the function of tissue factor pathway inhibitor.[55]

Finally, small isoforms of apolipoprotein(a) have been observed to possess elevated potency in inhibiting fibrinolysis and thereby promoting thrombosis. Indeed, a recent meta-analysis demonstrated a two-fold increase in the risk of CHD and ischaemic stroke in subjects with small apolipoprotein(a) phenotypes.[55] Furthermore, prospective findings in the Bruneck study have revealed a significant association specifically between small apolipoprotein(a) phenotypes and advanced atherosclerotic disease involving a component of plaque thrombosis.[65] These data suggest that the determination of apolipoprotein(a) phenotype/genotype may provide

clinicians with additional information by which to evaluate Lp(a)/apolipoprotein(a)-associated atherothrombotic risk.[55]

In summary, elevated Lp(a) levels may promote atherosclerosis via Lp(a)-derived cholesterol entrapment in the intima, via inflammatory cell recruitment, and/or via the binding of pro-inflammatory-oxidized phospholipids. The prothrombotic, anti-fibrinolytic actions of apolipoprotein(a) are expressed on the one hand as inhibition of fibrinolysis with enhancement of clot stabilization and on the other as enhanced coagulation via the inhibition of tissue factor pathway inhibitor.[55]

Measurement

Several types of Lp(a) assays are currently available, some commercially; prominent among them are sandwich enzyme-linked immunosorbent assays (ELISAs), non-competitive ELISAs, latex immunoassays, immunonephelometric assays, and immunoturbidometric and fluorescence assays.[66] In order for clinical laboratories to provide clinicians with Lp(a) values which allow correct cardiovascular risk evaluation when Lp(a) is included in the estimate, the following elements in standardization between Lp(a) assays are critical.[55]

1. Inclusion of antibodies in assay kits whose immunoreactivity with Lp(a) is apolipoprotein(a) isoform-insensitive and fully characterized, and for which there is minor variation between batches over time. In this regard, immunosorbent assays are of considerable interest, as they allow the use of polyclonal antibodies [anti-apolipoprotein(a) capture; anti-apolipoprotein B100] and are isoform-insensitive.

2. Availability of a robust secondary reference Lp(a) preparation at an international level, which has received approval by organizations such as the International Federation of Clinical Chemistry and the World Health Organisation.

3. The widespread use of methodologies which are robust, highly reproducible with inter- and intra-coefficient of variations <10%, economically priced, and accurate.

4. A common resolve, based on the uniformity and widespread availability of an approved and standardized Lp(a) assay, to express Lp(a) concentrations as total Lp(a) protein; point (ii) above is critical to this goal,

5. Standardization of procedures for blood collection, plasma, or serum isolation with a preferential use of fresh samples.

6. Ranges and percentiles for Lp(a) protein levels established for individual ethnicities given present knowledge of race-dependent variation in Lp(a), ultimately leading to race-specific estimates of risk thresholds.[55]

These factors will contribute significantly not only to the reliable diagnosis and classification of subjects presenting with high atherothrombotic risk due to elevation of Lp(a), but also to the success of multicentre clinical trials designed to evaluate pharmacotherapeutic agents targeted to concomitantly reduce elevated Lp(a) levels and CVD risk.[55]

Whom to screen

Lp(a) should be measured once in all subjects at intermediate or high risk of CVD/CHD who present with:

- premature CVD,
- familial hypercholesterolaemia,
- a family history of premature CVD and/or elevated Lp(a),
- recurrent CVD despite statin treatment,
- ≥3% 10-year risk of fatal CVD according to the European guidelines,[67] and
- ≥10% 10-year risk of fatal and/or non-fatal CHD according to the US guidelines[68]

Repeat measurement is only necessary if treatment for high Lp(a) levels is initiated in order to evaluate therapeutic response.

Treatment

Studies using niacin alone or in combination with, for example, statins have shown cardiovascular benefit;[69,70] niacin reduces Lp(a) levels by up to 30–40% in a dose-dependent manner and in addition exerts other potential beneficial effects by reducing LDL cholesterol, total cholesterol, triglycerides, and remnant cholesterol and by raising HDL cholesterol.[71] In a meta-analysis including 11 randomized controlled trials with 2682 patients in the active group and 3934 in the control group, niacin 1–3 g/day reduced major coronary events by 25% (95% CI: 13–35%), stroke by 26% (8–41%), and any cardiovascular event by 27% (15–37%).[69]

However, there have been no randomized, controlled intervention trials with selective reduction in plasma lipoprotein(a) levels aimed to reduce CVD: we urgently need trials demonstrating that selective reduction of Lp(a) in those with Lp(a) above the 80th percentile will benefit clinically with reduced CVD. Until such trials are published, reduction in Lp(a) should mainly be achieved using niacin, as the use of niacin for CVD risk reduction as described above is evidence-based. However, in addition to lowering Lp(a), niacin lowers LDL cholesterol, total cholesterol, triglycerides, and remnant cholesterol and concomitantly increases HDL cholesterol levels. Therefore, the favourable effects of niacin on CVD cannot be ascribed solely to Lp(a) reduction. Nevertheless, these studies clearly demonstrate that the use of niacin for reduction in Lp(a) to the suggested desirable levels (*less than 30 mg/dl*) is safe and in all likelihood beneficial.

Compared with LDL, Lp(a) is relatively refractory to both lifestyle and drug intervention. The data on the effects of statins and fibrates on Lp(a) are limited and highly variable. Overall, statins have, however, been shown to consistently and modestly decrease elevated Lp(a) in patients with heterozygous familial hypercholesterolaemia. Other agents reported to decrease Lp(a) to a minor degree (<10%) include aspirin, l-carnitine, ascorbic acid combined with l-lysine, calcium antagonists, angiotensin-converting enzyme inhibitors, androgens, oestrogen, and its replacements (e.g. tibolone), anti-estrogens (e.g. tamoxifen), and thyroxine replacement in hypothyroid subjects.[55]

Larger studies of longer duration of Lp(a) lowering against background statin therapy in high-risk individuals including diabetics are needed. In the FATS angiographic trial,[72] aggressive lowering of LDL and apolipoprotein B abrogated the

risk due to Lp(a) in patients with established coronary disease. The ongoing AIM-HIGH and HPS2-THRIVE) trials will further evaluate this notion, although the niacin employed in these trials is not selective for Lp(a) lowering as noted above.

It is clear that more detailed studies of the metabolism of Lp(a) are required to aid in the design and development of selective and potent therapies for lowering Lp(a). Given the critical role of Lp(a) synthesis in determining the plasma concentration of Lp(a), targeting either the synthesis of apolipoprotein(a) and/or the formation of Lp(a) would appear worthwhile. Antisense oligonucleotide and thyroid hormone analogue therapies directed at apolipoprotein(a) synthesis may hold particular promise for the future.[55]

Finally, in young or middle-aged patients with evidence of progressive coronary disease and markedly elevated plasma Lp(a), serious consideration should be given to instituting LDL apheresis which removes Lp(a) efficaciously; however, this form of treatment is prohibitively expensive and impractical for most patients and most clinical centres.[55]

Future needs in basic and clinical research on lipoprotein(a) and apolipoprotein(a).[55]

The European Atherosclerosis Society Consensus Panel is convinced that further international effort is required in different ethnicities to assess the atherothrombotic risk due to the Lp(a) particle on the one hand and to apolipoprotein(a) on the other. The potential contribution of Lp(a)-associated phospholipase A2, and equally of Lp(a)-associated oxidized phospholipids, to the pathophysiological mechanisms underlying such elevated risk remains indeterminate.

Both cutting-edge basic research, rigorously designed prospective studies and intervention trials of selective Lp(a) lowering agents are required to attain these goals. Furthermore, it is entirely appropriate that Lp(a), as a causal, independent risk factor, should be integrated into existing treatment algorithms. Finally, randomized, controlled intervention trials with selective reduction in plasma lipoprotein(a) levels to reduce CVD in both primary and secondary prevention settings are urgently needed in order to define more precisely who to treat and to what targets.[55]

In the atherosclerosis risk in communities (ARIC) study, the association of Lp(a) with stroke was investigated in 15 160 participants (4160 blacks and 11 000 whites). In this study, Lp(a) was an independent risk factor for strokes and TIA, in both blacks and whites. The relative risk of Lp(a) associated stroke morbidity was not influenced by race.[73]

VanKooten and colleagues[2] assessed Lp(a) concentrations in 151 consecutive patients admitted because of acute cerebral ischaemia. They found that in about one third of patients Lp(a) values were significantly raised, but this increase was not associated with the cardiovascular risk profile, stroke characteristics, or the prognosis.[74]

In a study by Lindgren et al.[75] determined lipid variables in 131 patients six months after stroke. These patients have higher TG and Lp (a) values and lower TC, LDL, HDL concentrations compared with controls.

In a study by Nagayama M, et al.[76] Lipoprotein(a) and ischemic cerebrovascular disease in young adults stated that higher median Lipoprotein (a) a

levels among stroke/Transient ischaemic attack patients than controls among whites,blacks and Asians.

In a study by Nagaraj SK et al.[6] showed no statistical significant differences in serum lipid and lipoprotein (a) profile between controls and thrombotic stroke patients.

METHODOLOGY

The present study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from January 2015 to December 2015.

Study design and duration

The study design was a hospital based cross-sectional study.

Study period

The present study was done for the period of one year from January 2015 to December 2015.

Place

The present study was carried out in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi a tertiary care teaching hospital attached to Jawaharlal Nehru Medical College, Belagavi.

Source of Data

Patients presenting with ischemic stroke in the Department of General Medicine, and Department of Neuro-Medicine, KLES Dr Prabhakar Kore Hospital and MRC, Belagavi were enrolled

Sample size

A total of 100 patients with ischemic stroke were studied.

Sampling procedure

The sample size was calculated using the following formula as below.

Sample Size (n) = $4PQ/D^2$

Where,

N = Sample size

P = Prevalence of the disease (50%)

Q = 100- P

D = Absolute error considered as 10%

Therefore, $n = 4 \times 50 \times (100 - 50) / 10^2$

$n = 100$

Hence the sample size of 100 was considered for this study.

Selection criteria

Inclusion Criteria

- Newly detected ischemic stroke patients.

Exclusion Criteria

- Patients with following conditions were excluded
    a. Old ischaemic stroke
    b. intra cerebral hemorrhage
    c. Intracranial mass lesions

d. Deranged liver function tests and renal function tests
e. Thyroid function abnormalities
f. Patient on lipid lowering agents
g. Women on hormonal therapy
h. Neuro infections
i. Malignancy.

Ethical clearance

The study was approved by the Institutional Ethics Committee, Jawaharlal Nehru Medical College, Belagavi prior to the commencement.

Informed consent

The patients who fulfilled the selection criteria were informed about the nature of study and a written informed consent was obtained. If in any case patient is unconscious or disoriented consent was obtained from authorised legal representative (Annexure–I).

Data collection

The selected patients / caretakers were interviewed for the history of presenting illness and other comorbid conditions and the demographic data, clinical and systemic examination. These findings were tabulated on a predesigned and pretested proforma (Annexure II).

Investigations

Venous blood samples (10 ml) were collected immediately on admission and were subjected following investigations.

- Lipoprotein (a)
- Lipid profile
- Complete blood picture
- Mini renal
- Liver function tests
- Thyroid function tests
- CT or MRI brain scan

Fasting lipid profile is measured by following methods:

- Cholesterol – Cholesterol Oxidase method.
- HDL – Accelerator Selective Detergent Methodology.
- LDL- Direct Method.
- TGL – Lipase or Glycerol dehydrogenase method.

Based on NCEP (National Cholesterol Education Program) guidelines[77] normal values of lipid parameters were interpreted as;

- Low density lipoprotein < 100 mg/dL.
- High density lipoprotein;
  - Female > 50 mg/dL.
  - Males > 40 mg/dL.
- Total Cholesterol < 200 mg/dL.

- Triglycerides < 150 mg/dL.

Measurement of Lipoprotein (a)

Estimation of lipoprotein (a) was done by Randox immunoturbido- metric immunoassay.[78]

Randox immunoturbido- metric immunoassay

Intended use

For the quantitative in vitro determination of Lipoprotein (a) in human serum or plasma. This product is suitable for use on the Dade Dimension® AR, ES. ARX, XL, RXL, and XPAND analysers. (Cat No. LP 2878)

Clinical significance

The Lipoprotein (a) test system is intended to measure lipoprotein (a) in serum. Lipoprotein (a) measurements are used to evaluate disorders of lipid metabolism and to assess coronary heart disease in specific populations.

Principle

Agglutination occurs due to an antigen-antibody reaction between Lp(a) in a sample and anti-Lp(a) antibody adsorbed to latex particles. This agglutination is detected as an absorbance change at 700 nm proportional to the concentration of Lp(a) in the sample.

Sample collection and storage

Collect serum using standard sampling tubes and plasma using tubes

containing Li heparin, Na heparin, Na EDTA, K EDTA or citrate. The samples should be analysed immediately or stored at -20°C or -70°C for delayed testing. Freeze thaw cycling is not recommended.

Reagent composition

Wells		**Initial concentration**
1 – 2	**Lp (a) Latex Reagent**	
	Suspension of latex particles coated with anti-Lp(a) antibodies	0.5%
	Glycine	0.17M
	Sodium chloride	0.1 M
	Sodium azide	≤ 0.09% w/v
3 – 6	**Lp (a) Assay Buffer**	
	Glycine	0.17 M
	Sodium Chloride	1.08 M
	EDTA disodium salt	0.05 M
	Sodium azide	≤ 0.09% w/v

Calculation of results

The instrument automatically calculates and prints the concentration of Lipoprotein (a) in mg/dL using the calculation scheme illustrated in Dimension System manual.

Normal values

Adults less than 30 mg/dL

Study variables

Patients were evaluated for following parameters

- Lipoprotein (a) levels
- Risk factors
    - Hypertension
    - Diabetes mellitus
- Lipid profile
    - Total Cholesterol
    - HDL
    - LDL- Direct Method.
    - Triglycerides

Statistical methods

The data obtained was coded and entered into Microsoft excel spreadsheet and data was analysed using SPSS version 21. The categorical data was expressed in terms of rates, ratios and percentages and the continuous data was expressed in terms of mean ± standard deviation. The association between the Lipoprotein (a) A and demographic characteristics, lipid profile, risk factors was tested using Chi-square test or Fisher's exact test. Continuous data was compared using independent sample 't' test. At 95% confidence interval, a probability (p) value of ≤ 0.050 was considered as statistically significant.

RESULTS

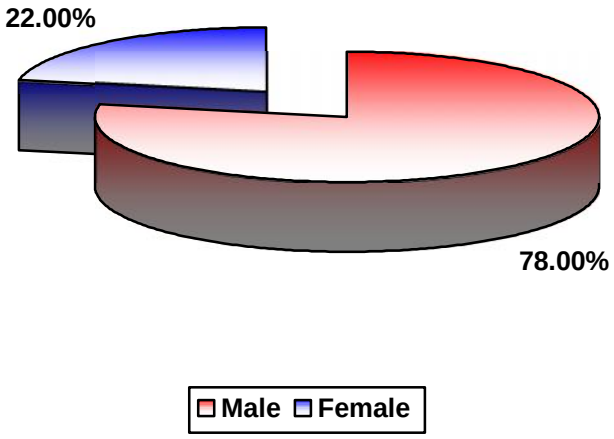
This one year cross-sectional study was conducted from January 2015 to December 2015. A total of 100 patients presenting with CVA-Acute ischemic stroke to the department of medicine and department of Neurology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi were studied.

Data obtained was analysed and the observations and interpretations were tabulated as below.

Table 1. Distribution of study population according to the sex

Sex	Distribution (n=100)	
	Number	**Percentage**
Male	78	78.00
Female	22	22.00
Total	**100**	**100.00**

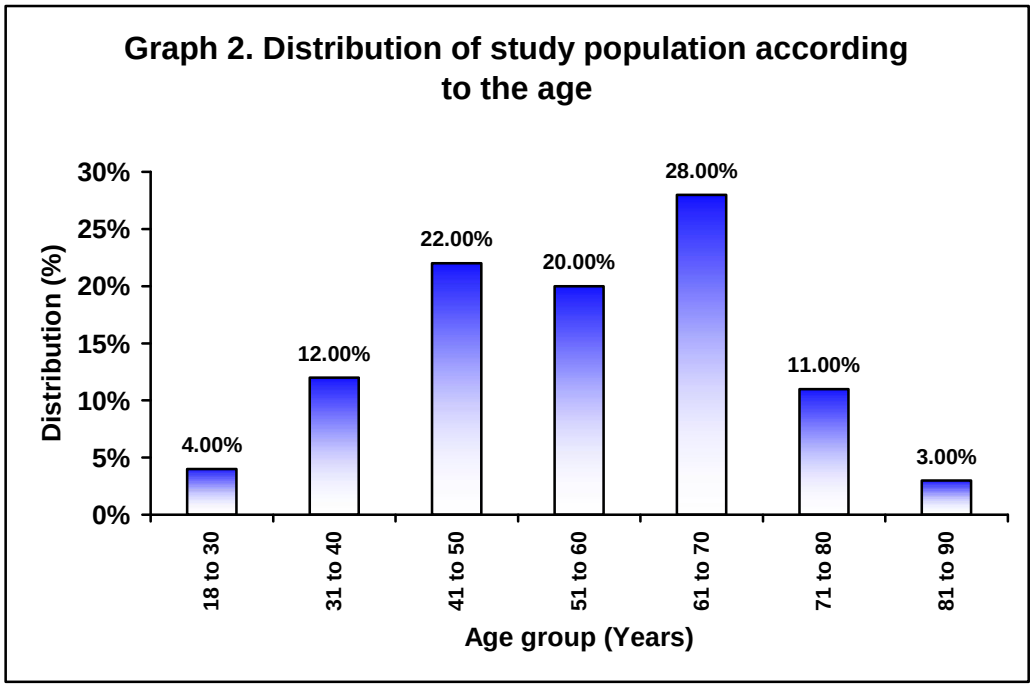
Graph 1. Distribution of study population according to the sex



In the present study majority of the patients were males (78%). The male to female ratio was 3.54:1.

Table 2. Distribution of study population according to the age

Age group (Years)	Distribution (n=100)	
	Number	**Percentage**
18 to 30	4	4.00
31 to 40	12	12.00
41 to 50	22	22.00
51 to 60	20	20.00
61 to 70	28	28.00
71 to 80	11	11.00
81 to 90	3	3.00
Total	**100**	**100.00**

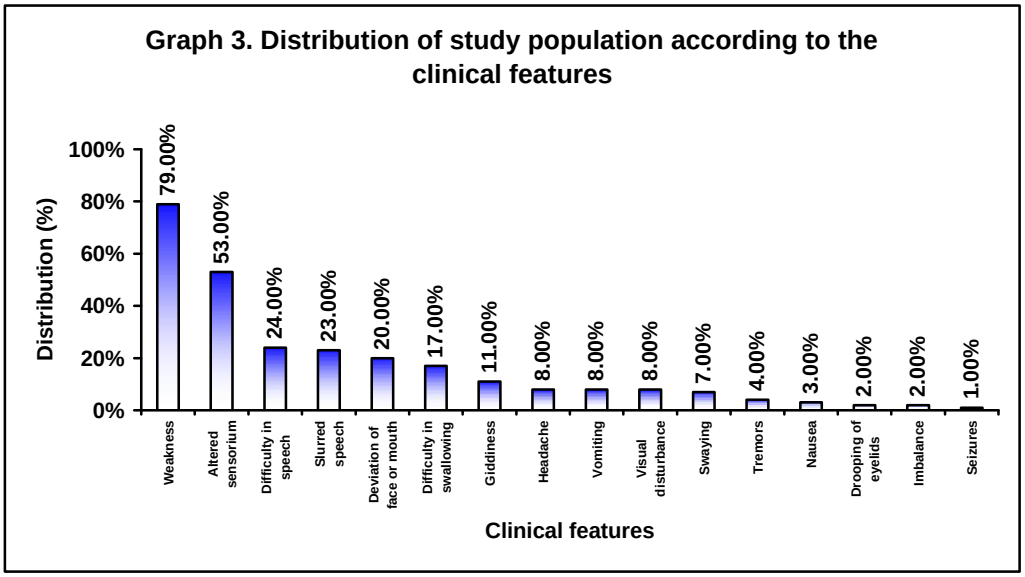


In this study most of the patients that is, 28% were aged between 61 to 70 years followed by 41 to 50 years (22%) and 51 to 60 years (20%). The mean age was 55.64 ±15.11 years

Table 3. Distribution of study population according to the clinical features

Clinical features	Distribution (n=100)	
	Number	Percentage
Weakness	79	79.00
Altered sensorium	53	53.00
Difficulty in speech	24	24.00
Slurred speech	23	23.00
Deviation of face or mouth	20	20.00
Difficulty in swallowing	17	17.00
Giddiness	11	11.00
Headache	8	8.00
Vomiting	8	8.00
Visual disturbance	8	8.00
Swaying	7	7.00
Tremors	4	4.00
Nausea	3	3.00
Drooping of eyelids	2	2.00
Imbalance	2	2.00
Seizures	1	1.00

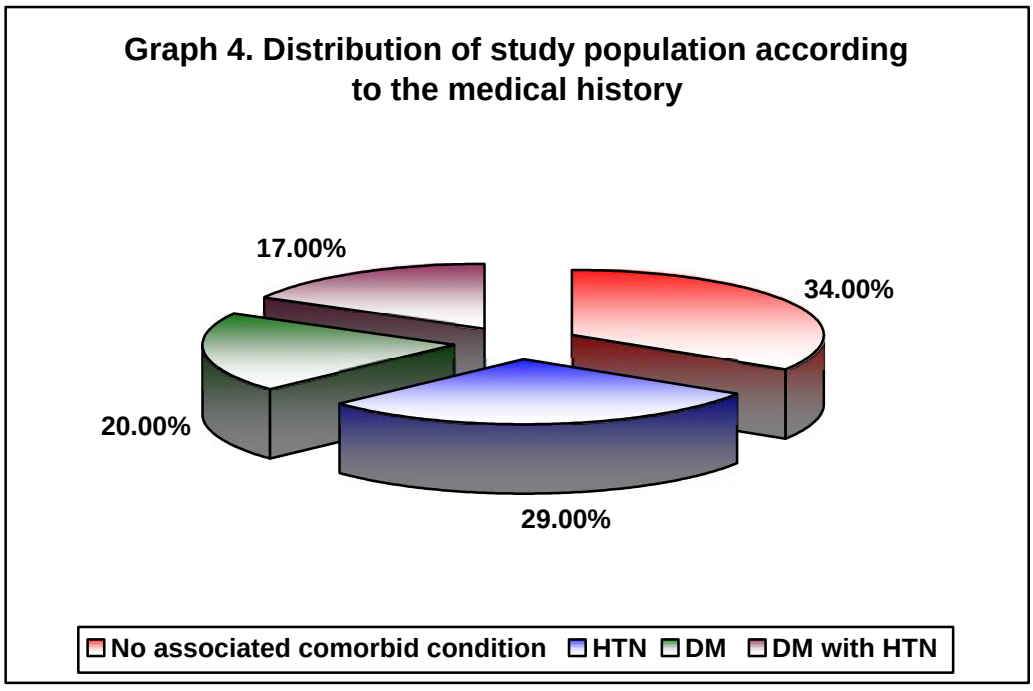
Multiple features hence total not shown



In this study most of the patients presented with weakness (79%) followed by altered sensorium (53%), difficulty in speech (24%) and deviation of face or mouth (20%).

Table 4. Distribution of study population according to the medical history

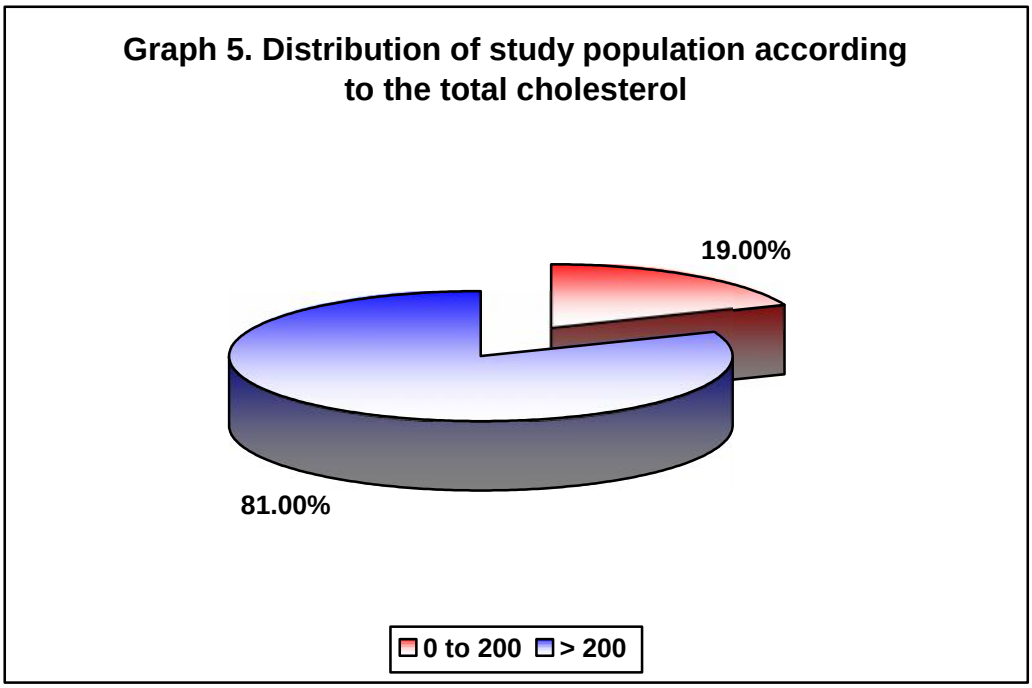
Medical history	Distribution (n=100)	
	Number	**Percentage**
No associated comorbid condition	34	34.00
HTN	29	29.00
DM	20	20.00
DM with HTN	17	17.00
Total	**100**	**100.00**



In the present study 29% of the patients had hypertension, 20% had diabetes mellitus and 17% had both diabetes mellitus and hypertension.

Table 5. Distribution of study population according to the total cholesterol

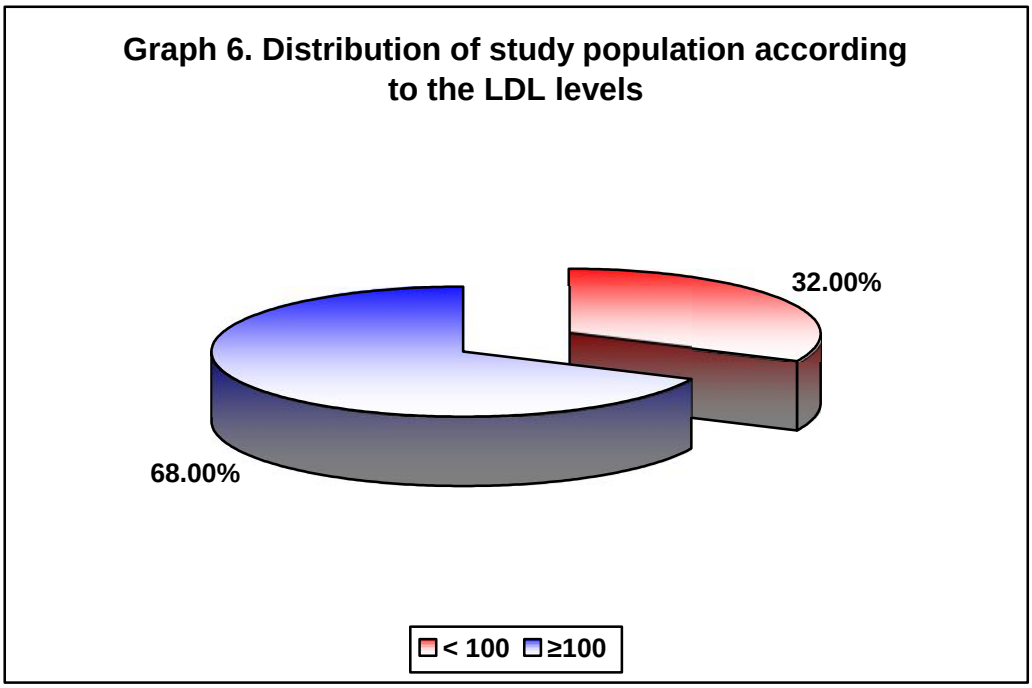
Total cholesterol (mg/dL)	Distribution (n=100)	
	Number	**Percentage**
0 to 200	19	19.00
> 200	81	81.00
Total	**100**	**100.00**



In the present study majority of the patients (81%) had raised cholesterol levels (> 200 mg/dL).

Table 6. Distribution of study population according to the LDL levels

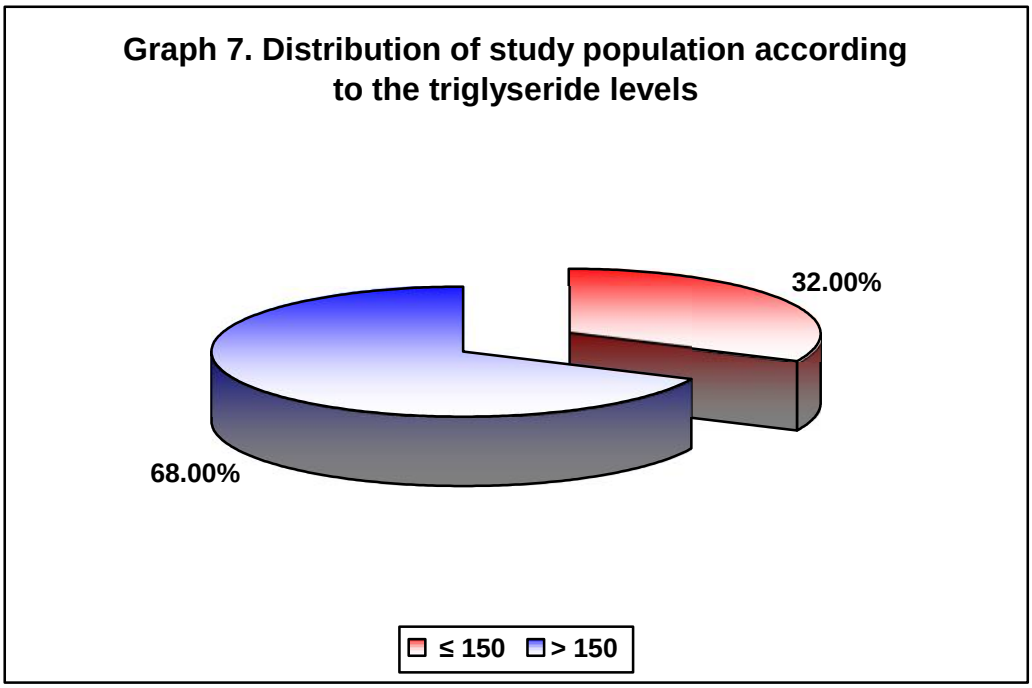
Low density lipoprotein (mg/dL)	Distribution (n=100)	
	Number	**Percentage**
< 100	32	32.00
≥100	68	68.00
Total	**100**	**100.00**



In this study 68% of the patients had raised low density lipoprotein levels (≥100 mg/dL).

Table 7. Distribution of study population according to the triglyceride levels

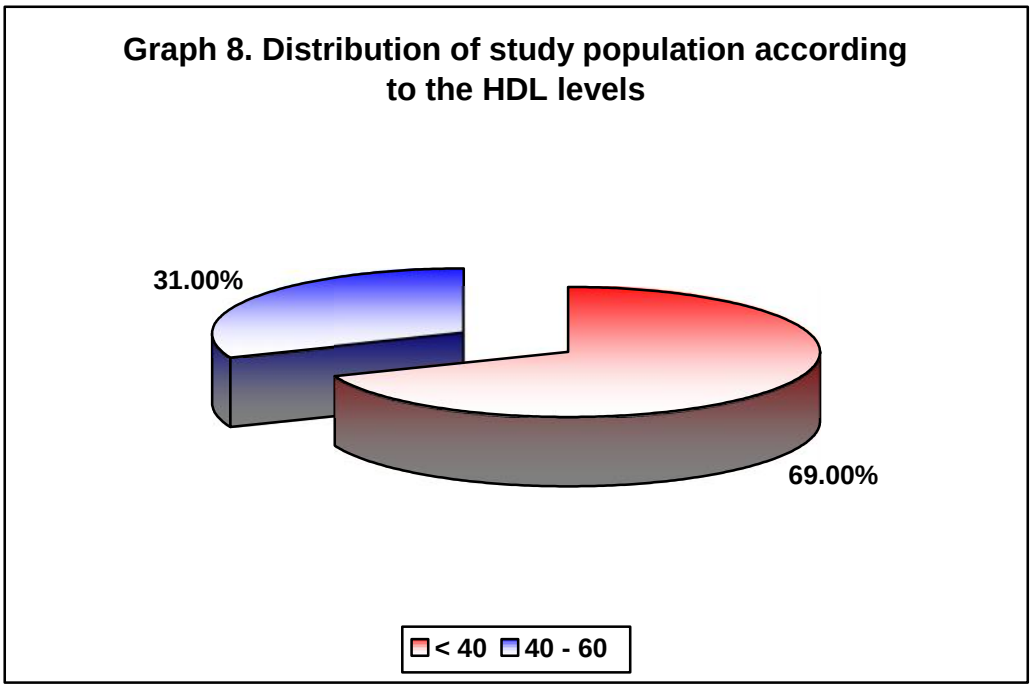
Triglyceride (mg/dL)	Distribution (n=100)	
	Number	**Percentage**
≤ 150	32	32.00
> 150	68	68.00
Total	**100**	**100.00**



In the present study 68% of the patients had raised triglyceride levels (>150 mg/dL).

Table 8. Distribution of study population according to the HDL levels

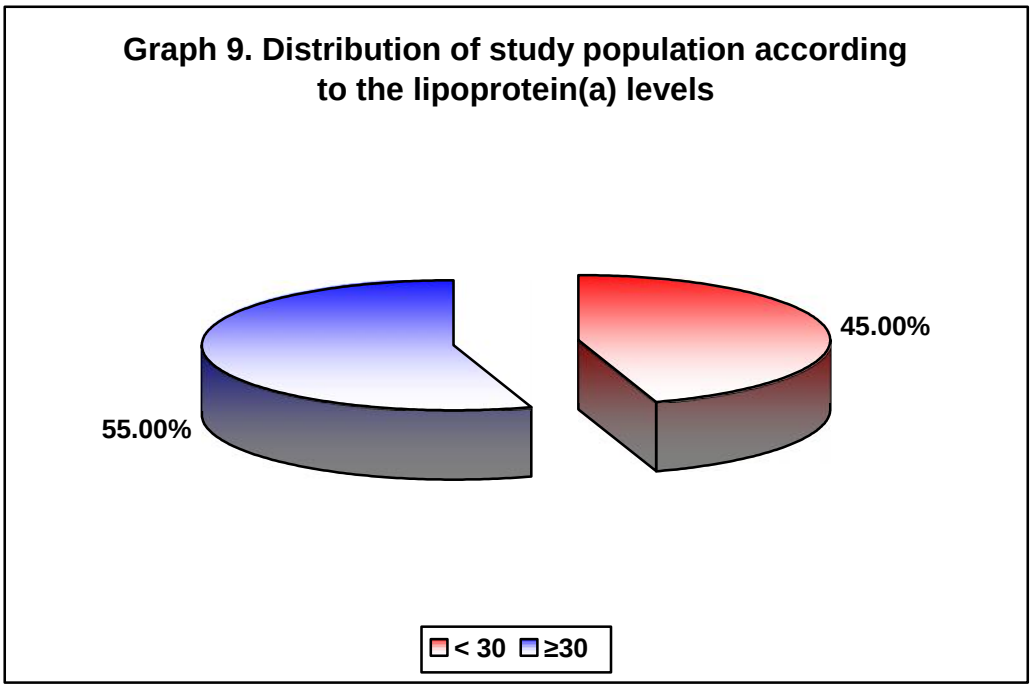
High density lipoprotein (mg/dL)	Distribution (n=100)	
	Number	**Percentage**
< 40	69	69.00
40-60	31	31.00
Total	**100**	**100.00**



In this study most of the patients (69%) had low high density lipoprotein levels (< 40 mg/dL).

Table 9. Distribution of study population according to the lipoprotein (a) levels

Lipoprotein (a) (mg/dL)	Distribution (n=100)	
	Number	**Percentage**
< 30	45	45.00
≥ 30	55	55.00
Total	**100**	**100.00**

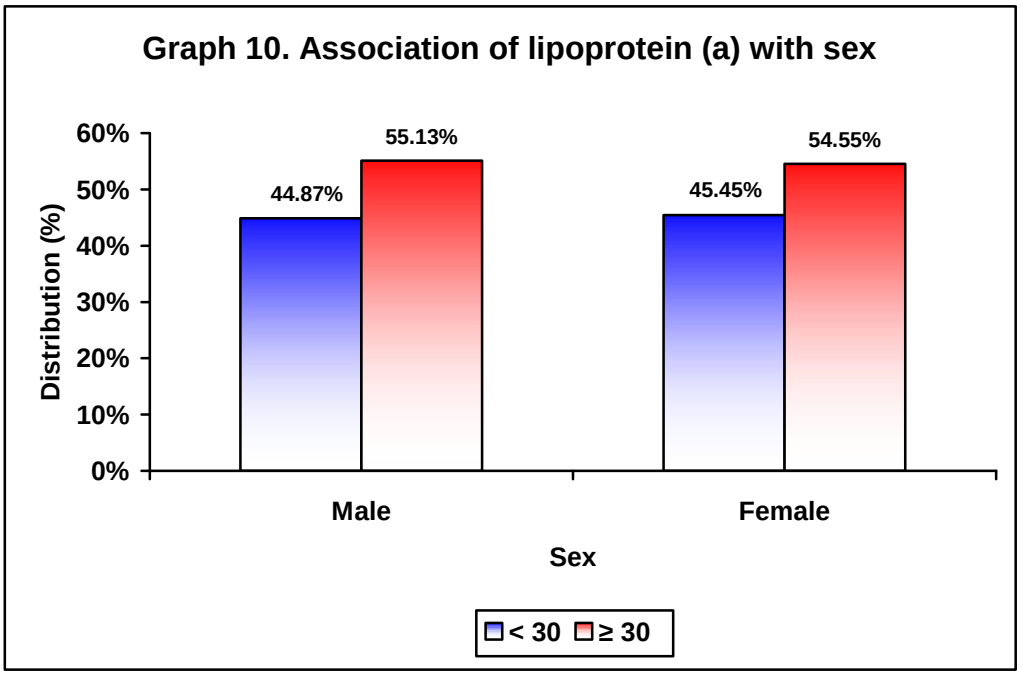


In this study (55%) of the patients had raised lipoprotein (a) levels (≥30 mg/dL).

Table 10. Association of lipoprotein (a) with sex

Sex	Lipoprotein (a)				Total (n=100)	
	< 30		≥ 30			
	No	%	No	%	No	%
Male	35	44.87	43	55.13	78	100.00
Female	10	45.45	12	54.55	22	100.00
Total	**45**	**45.00**	**55**	**55.00**	**100**	**100.00**

p = 0.961

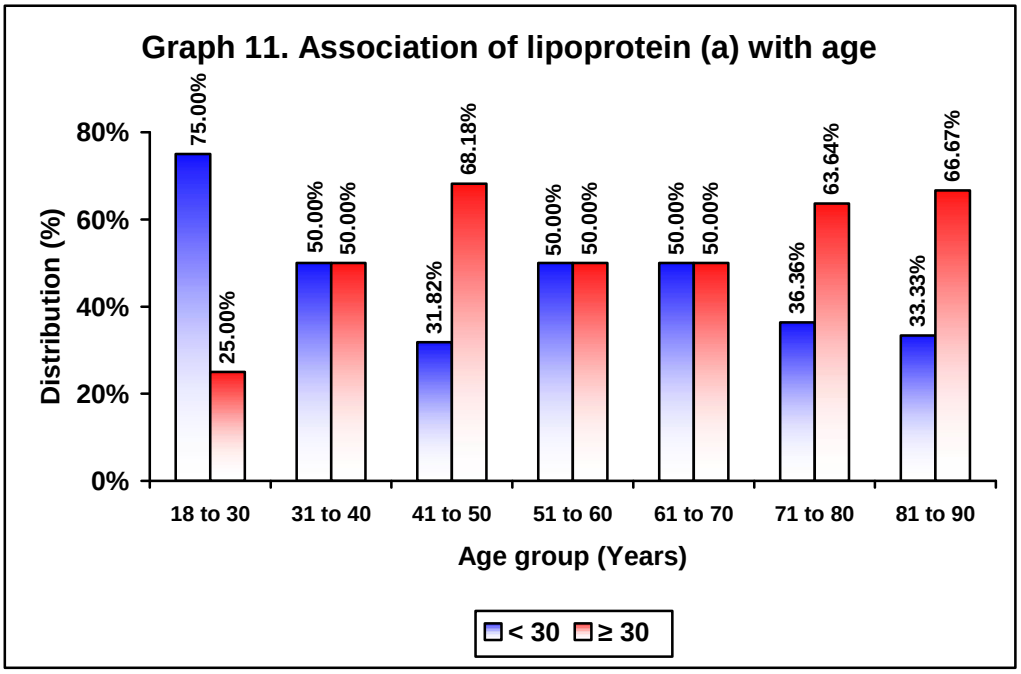


In this study no association was found between raised lipoprotein (a) with sex (p=0.961) .

Table 11. Association of lipoprotein (a) with age

Age group (Years)	Lipoprotein (a)				Total (n=100)	
	< 30		≥30			
	No	%	No	%	No	%
18 to 30	3	75.00	1	25.00	4	100.00
31 to 40	6	50.00	6	50.00	12	100.00
41 to 50	7	31.82	15	68.18	22	100.00
51 to 60	10	50.00	10	50.00	20	100.00
61to 70	14	50.00	14	50.00	28	100.00
71 to 80	4	36.36	7	63.64	11	100.00
81 to 90	1	33.33	2	66.67	3	100.00
Total	**45**	**45.00**	**55**	**55.00**	**100**	**100.00**

p = 0.690

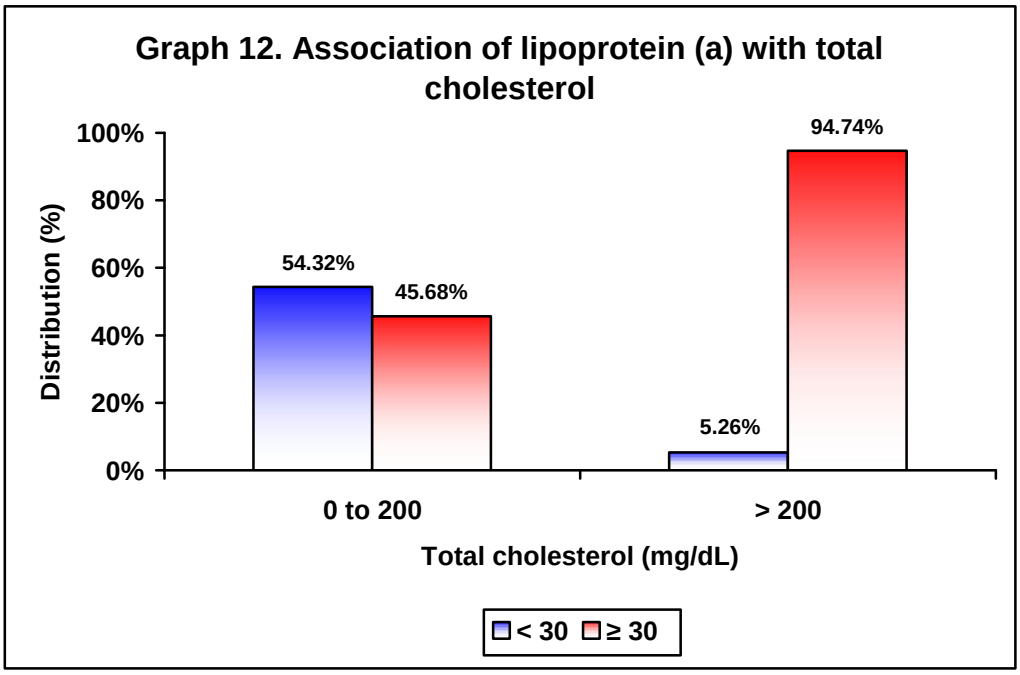


In the present study maximum patients with age between 41 to 50 years (68.18%) had raised Lp (a) levels followed by 81 to 90 years (66.67%) but the same was not true statistically (p=0.690).

Table 12. Association of lipoprotein (a) with total cholesterol

Total cholesterol (mg/dL)	Lipoprotein (a)				Total (n=100)	
	< 30		≥ 30			
	No	%	No	%	No	%
0 to 200	44	54.32	37	45.68	81	100.00
> 200	1	5.26	18	94.74	19	100.00
Total	**45**	**45.00**	**55**	**55.00**	**100**	**100.00**

p<0.001

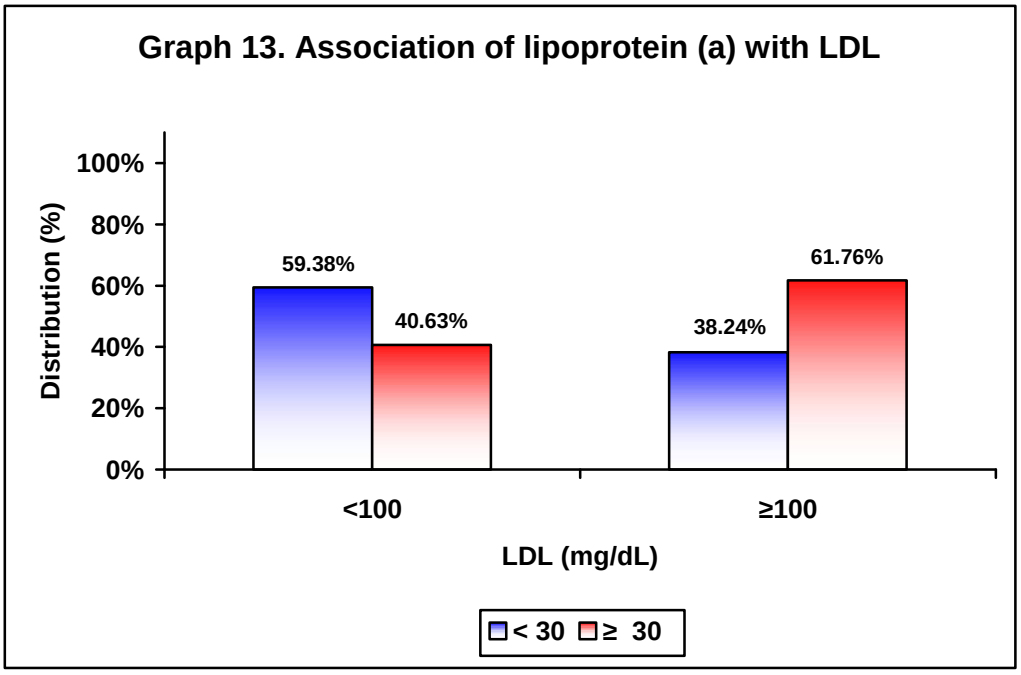


In this study significantly higher number of patients with total cholesterol levels of > 200 mg/dL had raised lipoprotein (a) levels (97.74%) (p<0.001).

Table 13. Association of lipoprotein (a) with LDL

LDL (mg/dL)	lipoprotein (a)				Total (n=100)	
	< 30		≥ 30			
	No	**%**	**No**	**%**	**No**	**%**
< 100	19	59.38	13	40.63	32	100.00
≥100	26	38.24	42	61.76	68	100.00
Total	**45**	**45.00**	**55**	**55.00**	**100**	**100.00**

p = 0.047

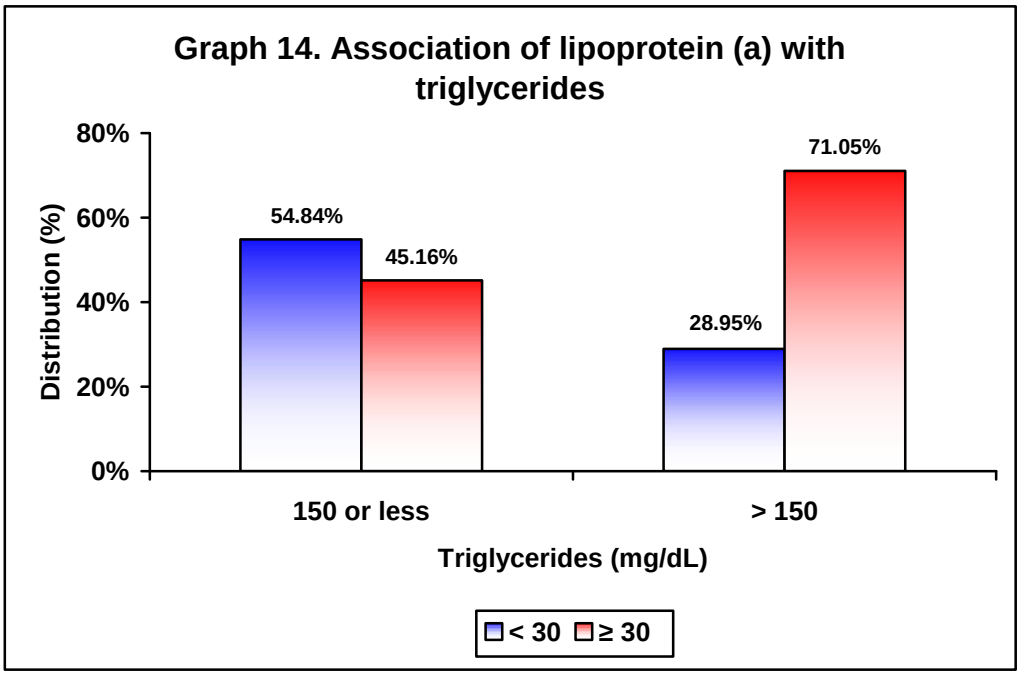


In the present study significantly higher number of patients with LDL levels of ≥100 mg/dL had raised lipoprotein (a) levels (61.76%) (p=0.047).

Table 14. Association of lipoprotein (a) with triglycerides

Triglycerides (mg/dL)	Lipoprotein (a)				Total (n=100)	
	< 30		≥ 30			
	No	%	No	%	No	%
150 or less	34	54.84	28	45.16	62	100.00
> 150	11	28.95	27	71.05	38	100.00
Total	**45**	**45.00**	**55**	**55.00**	**100**	**100.00**

p = 0.021

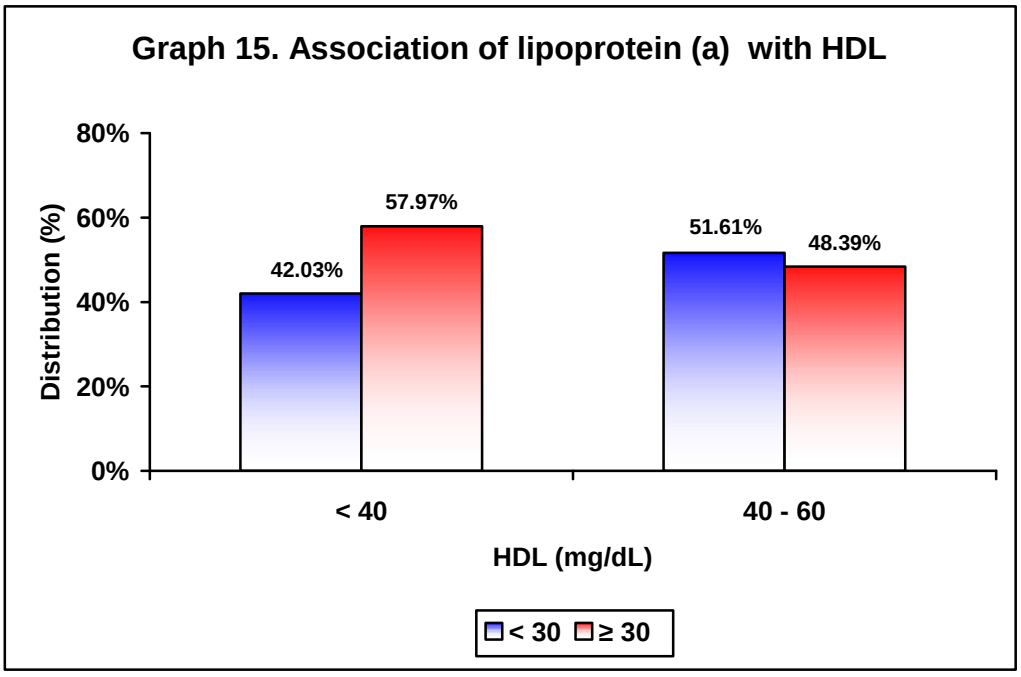


In the present study significantly higher number of patients with raised triglycerides (71.05%) had raised lipoprotein (a) levels (p=0.021).

Table 15. Association of lipoprotein (a) with HDL

HDL (mg/dL)	lipoprotein (a)				Total (n=100)	
	< 30		≥ 30			
	No	%	No	%	No	%
< 40	29	42.03	40	57.97	69	100.00
40 - 60	16	51.61	15	48.39	31	100.00
Total	**45**	**45.00**	**55**	**55.00**	**100**	**100.00**

p = 0.373

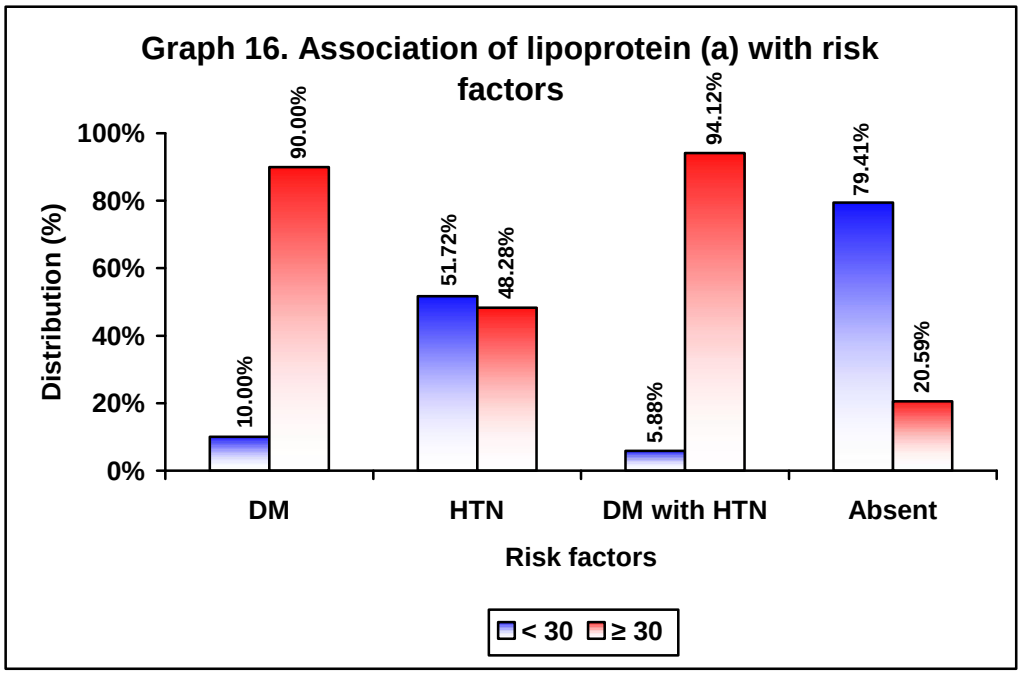


In this study most of the patients with HDL levels of < 40 mg/dL (57.97%) had raised lipoprotein (a) levels compared to 48.39% with HDL levels of 40 to 60 mg/dL, but this difference was statistically not significant (p=0.373).

Table 16. Association of lipoprotein (a) with risk factors

Risk factors	lipoprotein (a)				Total (n=100)	
	< 30		≥ 30			
	No	**%**	**No**	**%**	**No**	**%**
DM	2	10.00	18	90.00	20	100.00
HTN	15	51.72	14	48.28	29	100.00
DM with HTN	1	5.88	16	94.12	17	100.00
Absent	27	79.41	7	20.59	34	100.00
Total	**45**	**45.00**	**55**	**55.00**	**100**	**100.00**

p = <0.001



In this study significantly higher number of patients with diabetes mellitus (90%), both diabetes mellitus and hypertension (94.12%) had raised lipoprotein (a) levels (p<0.001).

DISCUSSION

Stroke is one of the leading causes of death in developed countries and constitutes a major source of disability in persons older than age 60 years. The relation between serum lipids and lipoprotein(a) in ischemic cerebrovascular disease (ICVD) is not as clear-cut as in coronary heart disease (CHD).[79,80] Studies in subjects with average lipid profiles indicate that raised lipoprotein(a)[Lp(a)] concentrations are associated with myocardial infarction, coronary artery disease, peripheral atherosclerosis and cerebral ischemia.[29]

Lipoprotein(a) is considered as an independent risk factor for atherosclerosis. Due to unique structural homology with plasminogen, it interferes with the function of plasminogen thus increasing thrombotic risk. Several studies have evaluated the association between Lp(a)and ischemic stroke. Several cross sectional studies and a few prospective studies provide contradictory findings regarding Lp(a) as a predictor of ischemic stroke.[20] The meager reports[6,29] available in Indian patients who have different social, living and dietary habits compared to western population which prompted us to evaluate the role of lipoprotein (a) as a marker for ischaemic stroke.[29]

The present one year hospital based cross-sectional study was done from January 2015 to December 2015 in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi. A total of 100 patients presenting with ischemic stroke from Department of General Medicine, and Department of Neuro-Medicine, KLES Dr Prabhakar Kore Hospital and MRC, Belagavi were studied.

The male sex has been listed as a risk factor for stroke.[81] The same was true in the present study as males (78%) outnumbered females (22%) with male to female ratio of 3.45:1 suggesting male preponderance in patients with ischaemic stroke.

In this study most of the patients that is, 28% presented with age between 61 to 70 years. While least that 4% were aged between 18 to 30 years. The mean age was 55.64 ± 15.11 years suggesting that, ischemic stroke in this study was common among elderly age group. Age is an important non-modifiable risk factor for stroke. The mean age of stroke onset in the South Asian region (for example, 63 years in India and 59 years in Pakistan) is lower than in Western countries (for example, 68 years in the USA and 71 years in Italy).[38]

Multiple risk factors are associated with cerebral infraction. Risk factor profile for ischaemic stroke differs and is variable in young and elderly patients. Various proatherothrombotic processes leading to macrovascular complications are well known. Diabetes mellitus, hypertension, smoking, alcoholism and dyslipidemia are some of the prominent modifiable risk factors for atherothrombotic ischaemic stroke. Other risk factors of stroke are raised homocystein, obesity, inadequate physical activity, migraine, oral contraceptives and hormonal supplements, fibrinogen and clotting factors, vasculitis, collagen vascular diseases and cardiac disorders to name a few. Age, gender, ethnic and geographical background, genetic inheritance and familial predisposition are some of the non-modifiable risk factors of ischaemic stroke. In spite of the adequate control of these conventional risk factors, the incidence of cerebral infarction is not curbed, emphasizing a need to look into novel and unrecognized risk factors.[82] In this study hypertension was the commonest risk factor (29%) followed by diabetes

mellitus (20%) and combined diabetes mellitus and hypertension were reported by 17% of the patients. A similar study by Nagraj SK et al.[6] from Karnataka conducted study on 20 participants in 2011 to find the association of lipoprotein (a) and lipid profile in thrombotic stroke patients reported diabetes in 24% of the patients and hypertension in 43% of the patients and both diabetes and hypertension in 27.77% of the patients.[6]

In the present study lipoprtotein A levels ranged between 12.2 to as high as 86.2 mg/dL and mean lipoprtotein A levels were 32.95 ± 15.24 mg/dL. More than half of the study population (55%) presented with raised Lipoprotein (a) levels (≥30 mg/dL). That is, almost every second patients with ischaemic stroke had raised Lipoprotein (a) A levels. These findings suggest that, the Lipoprotein (a) A levels tend to be profoundly high in patients with ischarmic stroke. These findings were consistent with the several other studies in the literature by Van Kooten et al.,[74] Milionis, HJ. et al.,[20] The Atherosclerosis Risk in Communities (ARIC) study,[73] Rigal et al.

A recent meta-analysis by Smolders B et al.[83] tried to combine the data from the available literature in order to define the possible association of Lp(a) with stroke. The data analysis from 31 studies with 56010 subjects and >4,609 stroke events concluded that Lp(a) is a risk factor for cerebrovascular disease (CeVD).

Van Kooten et al.[74] measured Lp(a) concentration in plasma from 151 patients with acute ischemic stroke and followed them up for a mean period of 2.5 +/- 1.2 years. The results showed that Lp(a) is increased in about one third of

patients with acute ischemic stroke, but it is not associated with the cardiovascular risk profile, stroke characteristics or the prognosis of these patients.

A population-based case-control study by Milionis, HJ et al.[84] compared Lp(a) plasma concentration of 163 patients with first-ever-in-alifetime acute ischemic non-embolic stroke and 166 healthy subjects and concluded that stroke patients exhibited higher Lp(a) concentrations ($p<0.001$) associated with a higher prevalence of small apo (a) isoforms.

In a prospective study by Wiberg B et al.[85] with a follow up period of 32 years, 2,313 men were enrolled at the age of 50. At the end of the follow up period 421 incidence stroke had occurred. The analysis of Lp(a) plasma concentration concluded that Lp(a) constitutes an independent risk factor for stroke.

The Atherosclerosis Risk in Communities (ARIC) study[86] enrolled 14,221 subjects of both sexes and after a follow-up period of 13.5 years, there were 496 incident ischemic strokes. The analysis of the baseline levels of Lp(a) concluded that participants with Lp(a) >300µg/ml had a 79% increased age, sex, and race-adjusted hazard ratio of ischemic stroke than did those with Lp(a) <100µg/ml. There was an association of Lp(a) with the incidence of ischemic stroke in black and white women and in black men, but not in white men.

Rigal et al.[87] compared Lp(a) levels between 100 patients with acute ischemic stroke and 100 healthy subjects and noted that even a slight elevation in Lp(a) plasma concentration was strongly and independently associated with ischemic stroke in men, but not in women.

In the present study with regard to lipid profile, majority of the patients (81%) had raised cholesterol levels (>200 mg/dL). Raised Low density lipoprotein levels (>100 mg/dL) were noted in 68% of the patients. Raised (150mg/dL) Triglyceride levels were noted in 68% of the patients. Most of the patients had (69%) lower high density lipoprotein levels (< 40 mg/dL). Furthermore the mean total cholestereol levels (175 ± 40.88 mg/dL) were suggestive of hypercholesterolaemia and mean LDL (124 ± 44.90 mg/dL) levels were also high while mean HDL levels were low (34.5 ± 9.51 mg/dL) but mean triglyceride levels were normal (134.1 ± 56.97 mg/dL). Data from prospective studies in male patients have shown that in the presence of total serum cholesterol values > 240 to 270 mg/dL, there is an increase in the rates of ischemic stroke.[82,88] The risk of ischemic stroke in both genders is clearly related with dyslipidemia. In men, low HDL level is a risk factor for cerebral ischemia but data in women are inconclusive. Because high levels of LDL are clearly related with a higher cardiovascular risk, adequate control of LDL cholesterol is recommended (*e.g.*, National Cholesterol Education Program III guidelines) in subjects without history of cerebrovascular accident.[77] High triglyceride levels are a component of the metabolic syndrome. In a study of 11117 patients with coronary heart disease, cerebral infarctions were significantly associated with high serum levels of triglycerides and low levels of HDL cholesterol.[89]

In this study almost equal number of males (55.13%) and females (54.55%) had raised Lipoprotein (a) levels (p=0.961) suggesting lack of association between raised Lipoprotein (a) levels with sex. In contrast to these observations, The Cardiovascular Health Study, conducted among 3972 elderly people, showed that higher

Lp(a) levels were independently associated with increased risk of stroke in men but not in women.[12] Another prospective study of 11335 middle-aged whites reported significant positive associations between Lp(a) and stroke/ TIA incidence in men but not in women.[90] On the other hand, the Framingham Heart Study showed that elevated plasma Lp(a) was an independent predictor of stroke/TIA in 3103 middle-aged women.[91]

In the present study Maximum patients with age between 81 to 90 years had raised lipoprotein (a) levels (66.67%) while 25% of the patients aged between 18 to 30 years had raised lipoprotein (a) levels but this difference was statistically not significant (p=0.646). these findings suggest lack of association between raised lipoprotein (a) levels and age. These findings were consistent with observations made by Wityk RJ et al. who measured Lp(a) levels of 110 young women (15-44 years of age) with cerebral infarction and 216 age-matched controls and showed no association of Lp(a) plasma concentration with stroke in this population group.[92] Another study by Abucher JF et al.[93] compared Lp(a) levels of 94 patients aged 15-45 years with acute ischemic stroke, with 111 age matched controls and did not find any differences. It is of interest that in this study a very low rate of angiographically evident atherosclerosis was detected (3.2%). The findings of the present study were consistent with observations made by Wityk RJ et al.[92] and Abucher JF et al.[93] however, these studies were conducted with case control control design hence the findings of this study could be compared with the studies by Wityk RJ et al.[92] and Abucher JF et al.[93]

In this study significantly higher number of patients (94.74%) with cholesterol levels of >200 mg/dL had raised lipoprotein (a) levels compared to

45.68% of the patients who has cholesterol levels of < 200 mg/dL ($p<0.001$) suggesting strong association between raised lipoprotein (a) levels with hypercholesterolaemia in patients with ischaemic stroke.

In the present study raised LDL levels were strongly associated with raised lipoprotein (a) levels as significantly higher number of patients (61.76%) with LDL levels of > 100 mg/dL had raised lipoprotein (a) levels ($p=0.047$).

In this study 57.97% of the patients with HDL levels of <40 mg/dL had raised lipoprotein (a) levels compared to 48.39% of the patients with HDL levels of 40 to 60 mg/dL. This difference was statically not significant ($p=0.373$).

In the present study significantly higher number of patients with (71.05%) hypertriglyceridemia had raised lipoprotein (a) levels ($p=0.021$) indicating strong association between hypertriglyceridemia and raised lipoprotein (a) levels.

Overall these findings postulate strong association between hypercholesterolaemia, raised LDL levels and hypertriglyceridemia with raised lipoprotein (a) levels. These findings are consistent with the studies by Jurgens et al. and Muralidhar L. et al.

Jurgens et al.[94] in their study on lipoprotein (a) and other lipid factors on ischemic vascular disease found significant correlation between LDL cholesterol and ischemic stroke. These observations were consistent with the present study despite of methodological differences.

Recently Muralidhar L. et al.[29] in India found statistically positive correlation between serum Total cholesterol, Triglycerides, LDL levels and the risk of stroke. Elevated serum Lp(a) was an independent risk factor of ischemic stroke.

In this study significantly higher number of patients with risk factors of diabetes mellitus (90%), both diabetes mellitus and hypertension (94.12%) had raised lipoprotein A levels ($p<0.001$) compared to those who did not had any risk factoras (20.59%). These findings suggest that, patients presenting ischamic stroke having history of diabetes mellitus are likely to have raised lipoprotein (a) levels. In contrast to these observations de Almeida-Holanda MM et al.[95] in 2005 showed that there were no significant differences between diabetic and non-diabetic patients` serum Lp(a) levels, and elevated Lp(a) levels were associated with ischemic stroke, irrespective of the presence of type 2 diabetes mellitus (type 2 DM).

Overall the present study showed that, the lipoprotein (a) levels are raised in patients presenting with ischaemic stroke. The Potential limitation of this study was the study design that is, cross-sectional study which limited us to ascertain the relative risk in patients with raised lipoprotein levels. While, the case control study deign would have yielded relative risk of stroke. Furthermore small sample size and single centre study limit us to generalize these observations to the entire population. Further case control studies involving different types of stroke with large sample size may elaborate the precise role of lipoprotein A in patients with stroke.

CONCLUSION

Based on the findings of this study it may be concluded that, lipoprotein (a) is raised in patients with ischaemic stroke. The rise in lipoprotein (a) levels is associated with risk factors of stroke that is, hypercholesterolaemia, raised LDL levels and hypertriglyceridemia. The rise in lipoprotein (a) levels is also associated with diabetes mellitus and both diabetes mellitus and hypertension. However, the rise in lipoprotein (a) levels is not influenced by sex and age.

SUMMARY

Lipoprotein(a) is considered as an independent risk factor for atherosclerosis. Few prospective studies provide contradictory findings regarding Lp(a) as a predictor of ischemic stroke. The present study was aimed to evaluate the role of lipoprotein(a) as a marker for ischaemic stroke.

The present one year cross-sectional study was conducted from January 2015 to December 2015. A total of 100 patients presenting with Iscahemic stroke in the Department of Medicine and Department of Neuro-Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi were studied. All the patients were investigated for Lipoprotein(a) levels. The salient findings of the study are as summarised below.

- Majority of the patients were males (78%) and male female ratio was 3.45:1.
- The most common age group was 61 to 70 years (28%) and the mean age was 56.04 ± 14.02 years.
- The most common clinical presentation was weakness (79%) followed by altered sensorium (53%), difficulty in speech (23%) and deviation of face or mouth (20%).
- Hypertension (29%), was the most common risk factor followed by diabetes mellitus (20%) while both diabetes mellitus and hypertension (17%).

- More than half of the study population (55%) had raised Lipoprotein A levels (≥30 mg/dL). The mean lipoprotein(a) levels were 32.95 ± 15.24 mg/dL.

- Majority of the patients (81%) had raised cholesterol levels (> 200 mg/dL). The mean cholesterol levels were 175 ±40.88 mg/dL.

- Most of the patients had raised Low density lipoprotein levels (68%) (>100 mg/dL). The mean LDL levels were 124 ±44.8 mg/dL.

- 68% of the patients had raised (150mg/dL) Triglyceride levels. The mean triglyceride levels were noted in as 134.1 ±56.97 mg/dL.

- Raised lipoprotein(a) levels were associated with hypercholesteolaemia ($p<0.001$), LDL ($p=0.047$) and raised triglycerides levels ($p=0.021$). Also significant association was noted with risk factors viz. diabetes mellitus, and both diabetes mellitus and hypertension ($p<0.001$).

- However raised lipoprotein(a) was independent of sex ($p=0.961$), age ($p=0.646$) and HDL levels ($p=0.373$).

Hence it may be concluded that, lipoprotein (a) is raised in patients with ischaemic stroke. Furthermore, the rise in lipoprotein a levels is associated with hypercholesterolaemia, raised LDL levels, hypertriglyceridemia and diabetes mellitus. However, the rise in lipoprotein (a) levels are not influenced by sex, age and HDL.

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ANNEXURE I – CONSENT FORM

Title of research study: ESTIMATION OF LIPOPROTEIN (a) IN ACUTE ISCHEMIC STROKE

Principal investigator:
Dr. ** ***** ********
Post graduate student,
Department of general medicine,
Jawaharlal Nehru Medical College,
Belagavi – 590 010

Introduction and purpose

Strokes (cerebrovascular accidents) are considered to be one of the most common causes of life threatening neurological disease, causing mortality and long term severe disability in people. It continues to be the third leading cause of death after heart disease and cancer.

The burden of stroke is quite significant and its prevalence is increasing in younger age groups.

Since in many patients, a stroke event cannot be explained on the basis of conventional risk factors, for the last 8-10 years, newer risk factors for stroke are being studied and need for further research on serum lipoprotein(a) and its relationship to ischemic stroke in Indian population in particular and to find novel methods for its prevention and management.

Procedure

If you agree to be part of the research study, you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood, urine and need of CT/MRI brain scans are the necessary investigations.

Risks and benefits

The only risk and possible discomfort you might get is while taking blood samples for the investigations. It may cause swelling, pain, redness bruising or infection (rarely happens) at the site from where the samples are drawn. Benefit is recognizing the well defined precipitating factors / novel markers for ischemic stroke to prevent mortality.

Alternatives

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

Privacy and confidentiality

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

Institution/sponsors/compensation

In case of any injury related to the study, treatment will be made available at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi. There is no compensation or payment for such medical treatment by law.

Financial incentives for participants

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

Authorisation to publish the results

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

Questions/contact details

In case of the queries during study you may contact following persons.

1**) Dr. **** ***** ********
Investigator,
Post Graduate in General Medicine,
Jawaharlal Nehru Medical College,
Belagavi – 590 010
Phone no: ****** ******

2) **Dr. **** *******
Professor and Head of Department
Dept. of General Medicine,
Jawaharlal Nehru Medical College,
Belagavi – 590 010
Phone no: **** *******

In case of any queries regarding your rights as participant you can contact the following person.

3) DR. * ******, Chairman,**
Jawaharlal Nehru Medical College,
Ethical committee for human research
Phone no: **** *****
Extn: ****

CONSENT STATEMENT RELATIVE

I voluntarily agree for the participation of my _____ to take part in this study by signing below. I may withdraw my_____ at any time. I am not giving up any of my _____ legal rights by signing this form. My signature below indicates that I have read, or it has been read to me, this consent form, and have had all the questions answered.

Name of the participant :

Signature/Thumb print :

Name of the legal representative :

Signature/Thumb print :

Investigator name :

Signature :

Date :

Place :

ANNEXURE II – PROFORMA

Case No :

In Patient Number :

Name :

Age/Sex :

Address :

Occupation :

Complaints at Presentation

Past History

Treatment History

Physical Examination

General Condition

Pallor : Yes/No

Icterus : Yes/No

Lymphadenopathy : Yes/No

Cyanosis : Yes/No

Clubbing : Yes/No

Edema : Yes/No

Vitals

Temperature :

Pulse :

Respiratory rate :

Blood pressure :

Systemic examination

Respiratory system :

Cardiovascular system :

Per abdomen :

Central nervous system :

Investigations

ANNEXURE III – KEY TO MASTER CHART

ACA	-	Anterior cerebral artery
B/L	-	Bilateral
BP	-	Blood pressure
CCB	-	Calcium channel blocker
Co	-	Conscious
CT	-	Computed tomography
CVA	-	Cerebrovascular accident
DM	-	Diabetes mellitus
Doc	-	Doctor
E1M2VT	-	GSC scale (Eye/Motor/Verbal)
F	-	Female
F.P	-	Frontol parietal
F.P.O	-	Fronto parieto occipital
GTCS	-	Generalised tonic clonic seizures
H.W	-	House wife
H/O	-	History of
HDL	-	High density lipoprotein
HTN	-	Hypertension
Inj	-	Injection
L	-	Left
LDL	-	Low density lipoprotein
LL	-	Lower limb
LOC	-	Loss of consciousness

Lp(a)	-	Lipoprotien A
M	-	Male
MCA	-	Middle cerebral artery
mg	-	miligram
mg/dL	-	milligram per deciliter
mmHg	-	Millimeters of mercury
MRI	-	Magnetic resonance imaging
NVBS	-	Normal vesicular breath sound
OHA	-	Oral hypoglycaemic agents
P.T	-	Parieto temporal
PCA	-	Posterior cerebral artery
R U.L	-	Right upper limb
R	-	Right
R.F.P.L	-	Right facial palsy
R.H Pr	-	Right hemiparesis
Rt.	-	Right
Rtd	-	Retired
T.	-	Tablet
T.P	-	Temporo parieto
T.P.O	-	Temporo parieto occipital
TSH	-	Thyroid stimulating hormone
UL	-	Upper limb
UMN	-	Upper motor neuron
VBI	-	Vertebro basilar insufficiency

Chapter 9

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