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Microalbuminuria In Nondiabetic Acute Ischaemic Stroke

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Introduction

"Cerebrovascular Disease" or "Stroke" is one of the leading causes of mortality and morbidity in adults worldwide, posing serious medical, socio-economic and rehabilitation problems. Stroke also called 'Brain Attack' because it involves an acute insult to the brain, is a major disabling disease. But throughout the world, unfavourable trends in stroke risk factor profile, lack of prevention programs, lack of awareness of stroke risk factors and warning signals by the public and lack of emphasis on preventive training in medical schools, portend high stroke rates and serve to widen the stroke prevention gap.[1] This is unfortunate because stroke is well suited for prevention since it has high prevalence, high burden of illness and economic cost, well defined modifiable risk factors and effective prevention measures.[2]

Hence, there is growing interest in unifying mechanisms in ischemic stroke pathogenesis. Overtime, numerous risk factors have been found to be associated with increased occurrence of stroke. But only one half of the cerebrovascular disease risk could be explained by conventional risk factors. The realization that atherosclerosis is an inflammatory disease[3] has led to a search for new stroke risk factors and treatment.

The markers of inflammation like C-reactive protein, intercellular adhesion molecule-1, lipoprotein associated phospholipase A2, elevated white blood cell count, interleukins, variant endothelial nitric oxide synthase; infectious agents like Chlamydia pneumoniae, Helicobacter pylori and Cytomegalovirus; Homocysteine; Renin angiotensin system; Tissue factor; Fibrinogen; Lipoprotein (a); Small dense LDL; Cytokine transforming growth factor, etc., have been proposed as new risk factors for stroke.[4] One more addition to the growing list is 'Microalbuminuria'.

Microalbuminuria has been associated with many disease entities like diabetic nephropathy, hypertension with left ventricular hypertrophy and renal insufficiency, etc. Microalbuminuria has been associated with clinical risk factors for stroke like diabetes, hypertension, aging, history of myocardial infarction, obesity, smoking and left ventricular hypertrophy. But there was little

information regarding microalbuminuria as an independent risk factor for stroke or as a predictor of stroke outcome. With the availability of sensitive and relatively inexpensive methods for detection of microalbuminuria, many studies were conducted in different parts of the world to determine the potential use of microalbuminuria, as a marker of stroke risk and outcome in non-diabetic population.

Aims and Objectives

- To estimate the incidence of microalbuminuria in non-diabetic acute ischemic stroke patients.
- To evaluate the prognostic significance of microalbuminuria in non-diabetic Acute ischemic stroke patients.

Review of Literature

Ischaemic Stroke Definition

Stroke

WHO defines stroke as "the rapidly developing clinical symptoms and/or signs of local [at times global] disturbance of cerebral functions, with symptoms lasting for more than 24 hours or leading to death with no apparent cause other than that of vascular origin" [Hatano, 1976].[5]

Transient Ischaemic Attack (TIA)

TIA is a clinical syndrome characterized by an acute loss of focal cerebral or monocular function with symptoms lasting less than 24 hours and which is thought to be due to inadequate cerebral or ocular blood supply as a result of arterial thrombosis or embolism associated with arterial, cardiac or hematological disease (Harkey and Warlow, 1994).6 TIA serves as a 'warning signal' for later occurrence of stroke and thus, may form the basis of a 'high risk' prevention strategy.

Reversible Ischaemic Neurological Deficit [RIND]

RIND defines an event characterized by neurological deficits that lasts more than one day but disappears within 7 days.

Stroke in Evolution

It describes a progressive neurological deficit developing over a few hours or days, which evolves to completed stroke after a few hours or days.

Completed Stroke

It is the term applied to the temporal profile of the stroke syndrome in which the deficit is prolonged and often permanent causing demonstrable parenchymal changes.

Small Vessel Stroke

It is the infarction following atherothrombotic or lipohyalinotic occlusion of a small artery [30 - 300 mcm] in the brain [lacunar infarction].

Classification

I. Oxfordshire stroke sub-classification[7]

A. Total Anterior Circulation Syndrome

- Implies a large cortical stroke in middle cerebral or middle and anterior cerebral artery territories.
- It is characterized by a combination of:

a) New higher cerebral dysfunction.

b) Homonymous visual field defect.

c) Ipsilateral motor and/or sensory deficit involving at least two out of three areas of the face, arm and leg.

B. Partial Anterior Circulation Syndrome

- Implies a cortical stroke in middle or anterior cerebral artery territory.
- The patients will have two out of three components of the total anterior circulation syndromes or new higher cerebral dysfunction alone or a motor/sensory deficit more restricted than those classified as total anterior circulation syndromes.

C. Lacunar Syndrome

- Implies a subcortical stroke due to small vessel disease.
- Evidence of higher cortical dysfunction or disturbance of consciousness excludes a lacunar syndrome.

D. Posterior Circulation Syndrome

- Ipsilateral cranial nerve palsy with contralateral motor and / or sensory deficit.
- Bilateral motor and/or sensory deficit.

- Disorder of conjugate eye movement.
- Cerebral dysfunction without ipsilateral long tract involvement.
- Isolated homonymous visual field defects.

II. Hachinske and Norris Classification[8]

A. Presumed Stroke

Presumed TIA

B. Anatomic classification:

a. By vascular supply - Carotid.
Vertebrobasilar.

b. By location

- Supratentorial - Lobar.
  Ganglionic/Thalamic.
- Infratentorial - Cerebellar.
  Brainstem.

C. Etiologic classification:

a. By result

- Cerebral Infarct - Arterial.
  Arteriolar Venous.
- Cerebral hemorrhage - Parenchymal.
  Subarachnoid.

b. By cause

- Ischaemia - Embolism.
  Extra cranial vascular disease.
- Hemorrhage - Hypertension.
  Vascular malformation
  Aneurysm.
  Amyloid Angiopathy.

D. Management classification:

- TIA and minor stroke.
- Major stroke.
- Deteriorating stroke.
- Young stroke.

Epidemiology

Stroke remains the second leading cause of death worldwide[88]. Stroke is also the leading cause of disability in adults worldwide. Worldwide annual incidence of stroke is 0.2-2.5/1000 population.[9] Worldwide prevalence rate of stroke is 500-600/1,00,000 population.[10]

A. Incidence and prevalence of stroke in India

The first population based study in India regarding incidence of stroke was conducted in Vellore in 2 phases. In the first phase (1968-69), a population of 2,58,576 in and around Vellore was surveyed to detect the prevalent cases of hemiplegia. In the second phase (1969-71), the population was kept under surveillance for two years and attempts were made to record all the incidence cases of hemiplegia. The main observations made during this study are:

1. Two year prevalence rate of stroke - 84 per 1,00,000 population.
2. Annual incidence of stroke - 13 per 1,00,000 population.

The second study was carried out as a part of WHO collaborative study in Rohtak, Haryana between 1971 and 1974. The study made the following observations:

1. Crude prevalence rate - 44 per 1,00,000 population.
2. Annual incidence of Stroke - 33 per 1,00,000 population.

Subsequent study done in Gowribidanur in Karnataka in South India found the prevalence rate of stroke to be 52/1,00,000. In Eastern India, a neuroepidemiological study in rural Bengal found prevalence of stroke to be 126/1,00,000 and in Chottanagapur in Bihar it was 103/100,000. The stroke prevalence in Metropolitan city of Mumbai has been reported as high as 245/100,000. In a smaller study in New Delhi, the crude prevalence of stroke has been reported to be 125/100,000 population.

B. Mortality due to stroke

WHO estimated that in 1990, out of a total of 9.4 million deaths in India, 6,19,000 deaths were due to stroke, making the stroke mortality rate of 73 per 100,000.

The estimated number of deaths due to stroke were 22 times than due to Malaria, 1.4 times than due to tuberculosis, 4 times than due to rheumatic heart disease and almost equal to than due to ischemic heart disease.[11]

Risk Factors For Stroke

1. **Age**: It is the strongest risk factor for stroke. Stroke is found to be 25 times more

common in people aged 75-84 years than in people aged 45-54 years.12

2. **Sex**: There is slight male preponderance in middle and old age.12
3. **Blood Pressure**: Increased blood pressure is strongly associated with stroke risk, the risk being present for both systolic and diastolic BP.13,14 The age adjusted relative risk for cerebrovascular disease in hypertension was 3.1 for men and 2.9 for women.15
4. **Smoking**: It is a definite risk factor for stroke with a relative risk of about 1.5. It is established that there is dose-response relationship, affecting both sexes in all age groups. Even passive smoking increases the stroke risk.16
5. **Blood lipids**: The relationship between blood lipids and stroke is much weaker than that for coronary artery disease, but serum lipoprotein (a) is found to be predictive.17
6. **Diabetes Mellitus**: Patients with diabetes have double the risk of stroke compared to non-diabetics.18 Stroke in diabetics is more likely to be fatal.19
7. **Haemostatic variables**: Increased fibrinogen,20 raised plasma factor VII coagulant activity, low blood fibrinolytic activity, raised von Willebr and factor and raised haematocrit are all risk factors for stroke.21,22
8. **Atrial Fibrillation**: AF, especially in patients with the previous embolic event, increasing age, hypertension, diabetes, left ventricular dysfunction, enlarged left atrium etc acts as the most frequent cardiac source of embolism to the brain.23
9. **Alcohol**: Modest consumption of alcohol might be protective for ischemic stroke.24 But alcohol also raises the BP,25 alters blood lipids, causes AF and cardiomyopathy and this may increase stroke risk.
10. **Obesity**: Stroke risk increases particularly if the weight has been gained in middle age or has fluctuated substantially or compounded by hypertension and diabetes.25
11. **Diet**: Omega-3 polyunsaturated fatty acids and less saturated fatty acid consumption may reduce stroke risk.27 Excessive salt intake may increase blood pressure and increases stroke risk.28 High intake of potassium reduces the stroke risk by lowering blood pressure.[29]
12. **Exercise**: It reduces the blood pressure, plasma cholesterol and fibrinogen levels and the risk of NIDDM, thus reducing stroke risk.[30]
13. **Non-stroke Vascular Disease**: Coronary artery disease, asymptomatic peripheral vascular disease and TIA are all associated with increased stroke risk.[31,32]
14. **Genetic Factors**: Various vascular anomalies; connective tissue disorders like Ehler-Darlos Syndrome, Pseudoxanthoma elasticum Marfan's syndrome, Fibromuscular hypoplasia, MVP; hematological diseases like sickle cell disease, anti-thrombin III deficiency, protein deficiency, dysfibrinogenemia; familial hypercholesterolaem-ia; cerebral amyloid angiopathy; homocystei-nemia; Fabry's disease; cardiac myxoma; mitochondrial cytopathy etc are associated with increased risk of stroke.[33]

Causes of Ischemic Stroke[34]

Common causes	Uncommon causes
Thrombosis	**Hypercoagulable disorders**
• Lacunar stroke	• Protein C deficiency
• Large vessel Thrombosis	• Protein S deficiency
• Dehydration	• Anti-thrombin III deficiency
Embolic occlusion	• Anti-phospholipid syndrome
• Artery-to-artery	• Factor V Leiden Mutation
Carotid bifurcation	• Prothrombin G 20210 Mutation
Aortic arch	• Systemic malignancy
Arterial dissection	• Sickle cell anemia
• Cardioembolic	• β – Thalassemia
f Atrial Fibrillation	• Polycythaemia vera
f Mural thrombosis	• Systemic lupus erythematosus
Myocardial infarction	• Homocysteinemia
Dilated cardiomyopathy	• Thrombotic thrombocytopenic purpura
Valvular lesions	• Disseminated intravascular coagulation
Mitral Stenosis	• Dysproteinemias
Mechanical valve	• Nephrotic syndrome
Bacterial Endocarditis	• Inflammatory bowel disease
Paradoxical embolus	• Oral contraceptives
Atrial Septal defect	**Venous sinus thrombosis**
Patent Foramen ovale	**Fibromuscular dysplasia**

Common causes	Uncommon causes
Atrial septal aneurysm	**Vasculitis**
Spontaneous ECHOContrast	• Systemic vasculitis (PAN, Wegener's, Takayasu's, Giant cell arteritis) • Primary CNS vasculitis • Meningitis (Syphilis, tuberculosis, fungal, bacterial, Zoster)
	Cardiogenic
	• Mitral valve calcification
	• Atrial myxoma
	• Intracardiac tumor
	• Marantic endocarditis
	• Libman-Sacks endocarditis
	Subarachnoid hemorrhage vasospasm
	Drugs – cocaine, amphetamine
	Moyamoya Disease
	Eclampsia

Diagnostic Approach In Stroke Patients[35]

- The rapid evaluation of patients is essential for use of time-sensitive treatments such as thrombolysis.
- An adequate history from an observer is essential.
- Once the diagnosis of stroke is made, a brain imaging study is necessary to determine if the cause of stroke is ischemic or hemorrhagic.

Investigations of TIA and stroke

Investigation sequence	Clinical Presentation TIA or Minor stroke				Reason for investigation
	Lacunar	Hemispheric	Brain Stem	Severe Stroke	
CT at presentation (not enhanced)	Yes	Yes	Yes	Yes	To differentiate infarction from hemorrhage, tumor, subdural hematoma.
U/S scan of carotid arteries, MRI/MRA or both	No	Yes if good recovery	No	No	To assess patency of vessels.
Echocardiogram	No	Yes if carotid MRA normal	Yes if clinical evidence of cardiac stroke	No	To see for cardiac source of embolism
Intra-arterial DSA	No	Yes, if U/S,MRA shows significant stenosis	Usually No	No	More precise evaluation of intracranial and extracranial vessels
Repeat CT at day 7-10or MRA even earlier	Yes if CT	Yes, if earlier CT normal	Yes, if earlier CT normal	Yes, if earlierCT	For topography of infarct mechanism and progression

TREATMENT[34]

1. Medical support

- Protection of airway to avoid obstruction, hypoventilation and aspiration.
- Maintenance of body temperature to prevent hyperthermia.
- Maintenance of blood glucose less than 200 mg/dl and BP around 150 mmHg.
- Maintenance of nutritional status and fluid requirement.
- Watch for brain edema and treat it with mannitol.
- Bowel and bladder care, prevention of pressure sores and infections.

2. Thrombolysis

IV rtPA at a dose of 0.9 mg/kg within 3 hours of stroke onset seems to have a role in the treatment of acute ischaemic stroke.

Administration of intravenous Recombinant Tissue Plasminogen Activator (rtPA) for acute ischemic stroke

Indication	Contraindications
• Clinical diagnosis of stroke. • Onset of symptoms to time of drug administration < 3 hrs. • CT scan showing no hemorrhage or significant edema. • Age > 18 years. • Consent by patient or surrogate.	• Sustained BP >185/110 mm Hg. • Platelets < 100,000; Hct <25%. Glucose < 50 or > 400 Mg%. • Use of heparin within 48 hr and prolonged PTT. • Rapidly improving symptoms. • Prior stroke or head injury within 3 months: prior intracerebral haemorrhage. • Major surgery in preceding 14 days. • Minor stroke symptoms. • Gastrointestinal bleeding in preceding 21 days. • Recent myocardial infarction. • Coma or stupor.

3. Anti-platelet drugs: Use of aspirin within 48 hrs of stroke onset reduced both stroke recurrence and mortality minimally. Agents that act at glycoprotein II b/III receptors are under trial.

4. Anti-coagulation: Trials do not support the use of heparin or other anticoagulants for patients with atherothrombotic stroke. But inspite of absence of evidence, heparin is still used frequently in the treatment of stroke.

5. Neuroprotection: It is the concept of providing a treatment that prolongs the brain's tolerance to ischemia. Hypothermia, excitatory amino acid pathway blockers etc., are under trial.

6. Rehabilitation: It includes early physical, occupational and speech therapy.

Primary and Secondary Prevention

- ***General principles***
- Life style modification.
- Evaluation of patients clinical risk profile and control of risk factors like hypertension, hyperlipidemia, diabetes etc.
- Use of alternate day aspirin in high risk patients.

2. Atherosclerotic Risk factors

- Use of Angiotensin converting enzyme inhibitors and angiotensin receptor blockers.
- Use of statins.

3. Anti-platelet drugs

Aspirin, Clopidogrel and combination of Aspirin and dypridamole are used.

4. Anti-coagulation therapy:

Used in embolic stroke to maintain INR 2-3.

Prognostification in Acute Stroke [36]

The survival, recovery and ultimate outcome of an individual who has sustained in acute stroke may be influenced by many variables:

1. Demographic variables

Includes age, gender and race. Survival is found to be significantly better in men than women, young than in old, married than in the single, rural areas than urban areas and in those discharged home than in those transferred to long term care hospitals.

2. General Medical Characteristics

Hypertension, diabetes mellitus, heart disease, atrial fibrillation, hyperlipidemia, obesity, past history of stroke, physical inactivity, estrogen therapy, high alcohol consumption and smoking are associated with increased likelihood of recurrent stroke and thereby would influence long term survival. Comorbidities like heart disease, COPD, peripheral vascular disease, Parkinson's disease, polyneuropathy, osteoarthritis etc have a direct effect on functional recovery and compound the patient's disabilities.

Lesion related variables

Survival is better in infarction than in hemorrhage and in subarachnoid hemorrhage than in intracerebral hemorrhage. Anterior circulation infarcts have higher risk of death and so also intracerebral or subarachnoid hemorrhage. Occurrence of coma at stroke onset reflects severity and is an important predictor of 30-day survival. Bilateral pyramidal signs, generalized seizures, abnormal respiratory pattern etc reflect brain stem dysfunction and in combination are related to a very high risk of early death. Severity of paralysis, urinary and bowel incontinence also adversely influence the outcome.

3. Specific therapy intervention

Better management of respiratory and cardiac problems in acute phase may result in decreased mortality.

4. Biochemical variables

Hyperglycemia at stroke onset even in non-diabetic patients is an adverse prognostic factor. Protein C and S have been found to be decreased in some patients with ischemic stroke and predict adverse outcome. Lipoprotein (a) is found to be an independent risk factor for arteriovascular disease. Recent studies have suggested that presence of microalbuminuria is associated with poor stroke outcome.

Outcome Prediction in Individual Patients[34]

Several multivariate scoring systems have been developed with the aim of predicting stroke outcome. Important among these are:

1. National Institute of Health Stroke Scale.
2. Canadian Stroke Scale.
3. Scandinavian Stroke Scale.
4. Orpington Prognostic Scale.
5. Fugl-Meyer Assessment.
6. Barthel Index.
7. Communication Index.

Of these, the features of the scoring system used in this study is:

Scandinavian Stroke Scale[37]

Function	Score	Prognostic score	Long term score
Consciousness:			
• Fully conscious.	6		
• Somnolent can be awaked to full consciousness.	4		
• Reacts to verbal command, but not fully conscious.	2		
Eye movement			
• No gaze palsy.	4		
• Gaze palsy present.	2		
• Conjugate eye deviation.	0		
Arm, motor power			
• Raises arm with normal strength.	6		
• Raises arm with reduced strength.	5		
• Raises arm with flexion in elbow.	4		
• Can move, but not against gravity.	2		
• Paralysis.	0		
Leg, Motor power			
• Normal strength.	6		
• Raises straight leg with reduced strength.	5		
• Raises leg with flexion of knee.	4		
• Can move, but not against gravity.	2		
• Paralysis.	0		
Orientation			
• Correct for time, place and person.	6		
• Two of these.	4		
• One of these.	2		
• Completely disorientated.	0		
Speech			
• No aphasia.	10		
• Limited vocabulary or incoherent speech.	6		
• More than yes / no, but not longer sentences.	3		
• Only yes/no or less.	0		
Facial palsy			
• None/dubious.	2		
• Present.	0		
Gait			
• Walks 5 M without aids.	12		
• Walks with aids.	9		
• Walks with help of another person.	6		
• Sits without support.	3		
• Bedridden / wheel chair.	0		
Maximal Score			

Microalbuminuria

Definition

Microalbuminuria or dipstick negative albuminuria is conventionally defined as urinary albumin excretion between 30-300 mg/24 hour for timed 24 hours urine collections and between 20-200 mg/L for untimed samples.[39]

Mechanism

The intimate relationship between low-level albumin excretion and vascular permeability makes urinary albumin excretion highly sensitive to the presence of any inflammatory process including cerebrovascular disease.

The kidney is ideally placed to amplify any small changes in the systemic vascular permeability. The glomeruli receive 25% of the cardiac output. Of the 70 kg of albumin that pass through the kidneys every 24 hours, less than 0.01% reaches the glomerular ultra filtrate (i.e., less than 7g/24 hour) and hence enters the renal tubules. Almost all the filtered albumin is absorbed by the proximal tubule via a high affinity, low capacity endocytotic mechanism, with only 10-30 mg/24 hr appearing in the urine. Assuming that 7 gm of

albumin is filtered every 24 hour, 1% increase in systemic vascular permeability in response to an inflammatory stimulus would result in an additional 70 mg of albumin passing into the filtrate. Since tubular mechanisms for albumin reabsorption are near saturation, urinary albumin excretion would increase from a maximum of 30 to approximately 100 mg/24 hour.[40]

lomerular permeability to albumin is dependent on endothelial charge selectivity as well as size selectivity. The negative charge conferred on the glomerular membrane by its consistent glycoprotein plays a role in restricting the permeability of anionic proteins. Loss of glomerular charge selectivity has been found in both diabetic and non-diabetic population with microalbuminuria.[41]

Other possible mechanisms of microalbuminuria include the following:

1. Systemic transvascular albumin leakage: Transcapillary escape rate of albumin (TERalb) is defined as the fraction of the intravascular mass of albumin (IVMA) going through the vascular bed per unit time. The transcapillary escape rate of albumin is an overall measure of macromolecular permeability of the vascular bed in vivo. As microalbuminuria reflects systemic transvascular leakiness for albumin, which may also allow for a higher degree of lipid insudation into the large vessel wall, this may link microalbuminuria to atherogenesis.[42]

2. Role of sialic acid: Sialic acid has been reported to affect several haematological factors, transvascular permeability and accumulation of lipid in the arterial wall. Studies showed that in subjects without diabetes mellitus, an elevated serum concentration of sialic acid is predictive of atherosclerotic vascular disease in presence of concomitant elevation of urinary albumin excretion.[43]

3. Impaired arterial dilatory capacity: Slightly elevated urinary albumin excretion is associated with impaired conduit arterial dilatory capacity in clinically healthy subjects, and this impairment may be explained by a reduced dilatory response to nitric oxide of both endogenous and exogenous origin. Impaired arterial dilatory capacity may contribute to the increased cardiovascular risk in subjects with elevated UAE.[49]

4. Elevated VWF concentrations and other prothrombotic factors: Studies showed that prothrombotic factors like fibrinogen and factor VII C, Von Willebrand Factor antigen (VWF) are elevated in patients with type 1 diabetes complicated by microalbuminuria, so also in hypertensive patients. These were considered a potential markers of endothelial dysfunction.[45,46]

5. Hyperinsulinaemia: In vitro, insulin has been shown to cause smooth muscle cell proliferation; stimulate LDL binding to smooth muscle cells, fibroblasts and monocytes; and stimulate cholesterol synthesis in monocytes.[47]

Hyperinsulinaemia and microalbuminuria are components of metabolic syndrome and are associated with a highly abnormal cardiovascular risk factor pattern.

6. Hyperhomocysteinaemia: The enhanced risk of cardio and cerebrovascular disease with microalbuminuria may also be due in part to an association with hyperhomocysteinaemia, a risk factor for atherosclerosis.[48]

Significance Of Microalbuminuria

"Microalbuminuria signifies abnormal vascular permeability and its presence may be considered as kidney's notice for markedly enhanced cerebrovascular risk."[49]

The importance of microalbuminuria was first appreciated in the early 1980s when two landmark studies in London and Denmark independently reported that it was predictive of development of overt diabetic nephropathy and progressive renal failure.[50,51]

Since then, various studies have established the significance of microalbuminuria in several conditions:

1. Several studies have shown that microalbuminuria in diabetic patients predicts diabetic nephropathy as well as increased cardiovascular and overall mortality.[52]

Persistent microalbuminuria in these patients also correlates with the presence of hypertension, obesity and dyslipidemia.[53] American Diabetes Association has adopted cut off values for diagnosis of diabetic nephropathy.[54]

ADA guidelines for Diabetic Nephropathy

Stages	Albuminuria cut-off values	Clinical characters
Microalbuminuria	*20 - 199 mcg/min.	• Abnormal nocturnal fall in BP and rise in BP level.
	* 30 - 200 mcg/24 hours.	• Increased Triglyceride, total and LDL cholesterol. • Increased frequency of metabolic syndrome component.
	* 30 - 299 mg/gm.	
		• Endothelial dysfunction.
		•Association with diabetic retinopathy, amputation and CVD.
Macroalbuminuria	≥200 mcg/min.	• Hypertension.
	≥300 mg/24 hr.	• Increased triglycerides, total and LDL cholesterol.
	>300 mg/gm.	• Asymptomatic Myocardial ischemia.
		• Progressive GFR decline.

1. In 1998 ADA included positive microalbuminuria as risk factor for coronary artery disease in diabetic subjects.[55]
2. Studies have shown that the prevalence of microalbuminuria is enhanced in hypertensive subjects, in particular in those with blood pressure characteristics that are associated with enhanced cardiovascular risk, such as salt sensitivity and an abnormal diurnal blood pressure rhythm. Microalbum-inuria possibly identifies at an early stage, hypertensive patients with an enhanced risk of developing the well-known renal and cardio vascular hypertensive complications.[56]
3. Studies have documented the relationship between the presence of microalbuminuria and other atherosclerotic risk factors such as hypertension, dyslipidaemia and smoking in the general population. Studies have revealed the significance of microalbuminuria as predictor of increased mortality in elderly persons.[57]
4. Microalbuminuria is detected early in the course of Acute Myocardial Infarction and is considered as an independent predictor of early mortality in this condition. Microalb-uminuria has been found to be proportional to the size of the infarct. Gosling et al suggested that early rise in urinary albumin concentration is useful in distingue-ishing myocardial infarct from Angina.[58] Spyridon K et al found that microalbuminuria is a strong indepen-dent predictor of 3 year adverse prognosis in patients who has sustain-ned acute myocardial infarction.[59]
5. Roine et al demonstrated that microalbuminuria distinguished bacterial meningitis from aseptic meningitis with specificity of 94%.[50]
6. Shearman et al found that microalbuminuria peaked 36 hours after admission in patients with acute pancreatitis and that serious complications developed later, only in

those with the higher values of microalbuminuria.[61]

7. Pallister et al found that microalbuminuria levels 8 hours after admission in trauma victims predicted the development of ARDS with a positive predictive value of 85% and a negative predictive value of 95%.[62]
8. Microalbuminuria has been found to be associated with wide variety of inflammatory conditions like rheumatoid arthritis, inflammatory bowel disorder, and surgery etc.[63-65]
9. Highly significant association between microalbuminuria and carotid artery intima-media thickness has been reported - a finding which suggests that microalbuminuria may be a marker for early development of carotid artery atherosclerosis and points to a possible linkage between microalbuminuria and atherothrombotic stroke mechanism.[66]

Studies Relating Microalbuminuria And Ischaemic Stroke

Although microalbuminuria is associated with clinical risk factors for stroke including diabetes, hypertension, aging, history of myocardial infarction and left ventricular hypertrophy there was little information regarding microalbuminuria being independent risk factor for stroke or as predictor of stroke outcome. But in recent times, several studies have been conducted to ascertain any relationship between microalbuminuria and ischaemic stroke.

1. Damsgaard EM et al followed 216 people who had been selected as control subjects for diabetics during a systematic screening for diabetes mellitus among all people aged between 60-74 years, living in municipality of Fredericia, Denmark, between Feb 1981 and Dec 1987. Extensive clinical and biochemical examination found median urinary albumin excretion rate of 7.52 mcg/ min. 8 of those with a rate below the median died compared to 23 with a rate equal to or greater than the median. The median albumin excretion rate in the 31 who died was 15 mcg/min and cardiovascular disease was the main cause of death in both groups.[67]
2. Yudkin et al used Islington Diabetes Survey in 1988 to study urinary albumin excretion and found that urinary albumin excretion had skewed distribution with maximum rate of 191.9 mcg/min. There was significant correlation between albumin excretion rate and systolic BP, diastolic BP and 2 hour blood glucose, but not with age, sex or body mass index.68
3. Heikke Miettinen et al followed up cohorts of non-diabetics [n=1375] and NIDDM [n=1056] subjects in Finland between 1982 and 1990 and found elevated urinary albumin excretion in 25% non-diabetics and 58% of NIDDM patients. All case mortality was higher both in non-diabetic and NIDDM subjects with borderline or clinical proteinuria, than in those without proteinuria.[69]
4. Mlacak B et al studied the frequency of albuminuria in patients with and without diabetes (138/160) randomly selected from a stratified sample comparable with known diabetes by age, sex and profession in Metlika country, Slovenia between 1994 to 1998. The groups were examined in the same way and mortality was followed over 5 years. Albuminuria was significantly high in diabetics, peripheral arterial disease, hypertension, coronary heart disease and hyperlipidemia. The albuminuria

was frequent in those who died in the observed 5 year period.[70]

5. Nancy B. Beamer et al conducted a study in Portland Veterans Administration and Oregon Health Sciences University Hospital in Portland around 1999 and found that microalbuminuria was 3 times more prevalent in patients with recent stroke (29%) than in those with clinical risk factors for stroke (10%) and was undetectable in healthy elderly controls. During follow up period of 1.5±0.9 years, 20% of patients with recent stroke, 14% with risk factors for stroke and 0% of healthy elderly volunteers had vascular end points with events being as frequent in patients with microalbuminuria (32%) as in patients with macroalbuminuria (33%).[71]
6. Yuyun MF et al conducted a population based prospective cohort study in British population consisting of 23,630 individuals between 40-79 years, and followed them up for 7 years (1993 - 1997), with baseline albuminuria tested. A total of 246 stroke events occurred. Age adjusted incidence of stroke increased significantly across categories of baseline albuminuria. They concluded that microalbuminuria is independently associated with approximately 50% increased risk of stroke in the general population.[72]
7. Hans. L. Hillege et al conducted PREVEND (Prevention of Renal and Vascular End Stage Disease) study in Groningen, Netherlands around 2001 and found that increased level of albuminuria was more frequent with advanced age, male sex, diabetes, hypertension, hyperlipidemia, smoking etc. Although micro and macroalbuminuria was found more frequently in diabetic and hypertensive sub group, microalbuminuria was still prevalent in 6 (6%) of the non-diabetic, non-hypertensive subjects and independently associated with cardiovascular risk factors and morbidity.[73]
8. Turaj W et al conducted a study on 52 patients in stroke unit of Neurological Department in Jagiellonian University, Caracow, Poland within 24 hours after stroke onset (2001). Microalbuminuria was found in 24 of 52 stroke patients (46.1%) and in 5 of 37 controls (13.5%) ($p<0.05$). The 90 day mortality was higher in patients with microalbuminuria as compared to patients without microalbuminuria (45.8% Vs. 7.1%). Patients with microalbuminuria scored lower on the Scandinavian stroke scale than patients without microalbuminuria, both on admission and later.[74,83]
9. Słowik A et al studied patients admitted within 24 h of their first ischemic stroke, 50 patients with a history of ischemic stroke, and 30 control subjects without known cerebrovascular diseases in 2002. Neurological deficit was assessed by the Scandinavian Stroke Scale (SSS) on admission and on days 1, 7, 14, and 30. Urinary albumin excretion was measured, with 24-hour collections performed on day 2. Outcome was assessed by 30-day, 90-day and 1-year mortality. Microalbuminuria was found in 46.7% of patients with acute stroke, 16% of subjects with a history of stroke, and 16.7% of controls. On admission, acute stroke patients with microalbuminuria had more severe neurological deficit (median of SSS score on admission was 28 vs. 40, and on day 1, 22 vs. 39, both $p < 0.05$) and

more often had a decreased level of consciousness (32 vs. 10%, p < 0.05). Mortality was higher in the group of patients with microalbuminuria in acute stroke (21 vs. 3% after 30 days, 39 vs. 6% after 90 days and 50 vs. 9% after 1 year, p < 0.05). In logistic regression analysis, microalbuminuria was found to be an independent predictor of 1-year mortality after ischemic stroke[82] .

10. Mathur P.C. et al studied 50 patients of nondiabetic acute ischaemic stroke within 24 hours of onset of symptoms for MA by dipstick urinalysis in 2005 in India .The incidence of MA was 68% (34 patients). Of all the traditional risk factors for stroke- age, male gender, hypertension, dyslipidaemia, smoking, obesity - only age of patients (>60 years) showed a positive correlation with the presence of MA (<0.05). Patients with MA had more severe neurological deficit (Scandinavian Stroke Scale {SSS} < 30 vs. > 30; mean+S.D=24.3+8.66 vs. 30.3+10.3, p<0.03) and more severe depressed levels of consciousness {SSS < 4 vs. SSS > 6, 82.35 vs. 17.6, p<0.05). The incidence of MA in Indians with nondiabetic acute ischaemic stroke is significantly higher than that of western populations. Patients with MA in the first 24 hours after the onset of stroke have more severe neurological deficit and depressed levels of consciousness than patients without MA[84].

11. Lima H.N et al evaluated and followed for at least 7 months patients with first-ever stroke or transient ischemic attack admitted to a prospective cohort from March 2005 to December 2007. analyzed traditional CV risk factors, albumin-to-creatinine ratio and eGFR (ml/min/1.73 m2) as predictors of mortality or recurrence.From a total of 185 patients included, 38 patients suffered from a recurrent stroke or died, with a mean follow-up of 25.1 ± 8.7 months. AUr (≧30 mg/g) was found in 50.2% (93/185), and 38.9% (72/185) presented an eGFR <60. In univariate analysis, age >65 years, eGFR ≤50, atrial fibrillation (AF), no alcohol intake and AUr >17 mg/g were associated with the composite endpoint. In a multivariate analysis, AF and AUr >17 mg/g were independent predictors of the composite endpoints, but eGFR ≤50 was not. The presence of AUr >17 mg/g is independently associated with death or recurrence after stroke[85].

12. Yoko Watanabe et al divided into 3 groups 166 consecutive patients with acute ischemic stroke who were admitted to their Stroke Center in 2011, 1) those with proteinuria (n=47), 2) those with microalbuminuria alone (n=43), and 3) those without microalbuminuria or proteinuria (n=76). analyzed the relationship of each group to the subtype of ischemic stroke, the National Institutes of Health Stroke Scale scores (NIHSS) on admission and at discharge, risk factors for ischemic stroke (hypertension, diabetic mellitus, dyslipidemia, previous stroke, and smoking), plasma levels of high-sensitivity C-reactive protein (hs- CRP), and cerebral white matter lesions (periventricular hyperintensity; PVH, and deep white matter hyperintensity; DWMH) on brain magnetic resonance imaging (MRI).Patients with proteinuria or microalbuminuria had higher NIHSS scores on admission and at discharge than patients without proteinuria or

microalbuminuria. In groups with proteinuria or microalbuminuria, the incidence of cerebral white matter lesions was high[86].

13. Gumbinger C et al included Patients with acute ischemic stroke admitted to stroke unit in this study. Clinical history and vascular risk factors were recorded. Severity of stroke and outcome were assessed by NIHSS and modified Rankin scale (mRS) upon admission and discharge. Urinary albumin excretion was measured in 24-h urine samples. multivariate analysis was performed to investigate predictors of poor outcome. MA was found in 43% of 138 patients and was associated with elevated levels of C-reactive protein (CRP), glucose at baseline, and HbA1c; higher rates of diabetes mellitus and atrial fibrillation; higher systolic blood pressure; greater age; and higher premorbid mRS, NIHSS upon admission/discharge, and mRS upon discharge. In a multivariate analysis, MA, premorbid mRS, and NIHSS upon admission were indepe-ndent predictors of poor outcome upon discharge. MA was frequently found in acute ischemic stroke patients. It was associated with severe neurological deficit upon admission and severe functional impairment upon discharge. MA in the acute phase was shown to be an independent predictor of poor outcome[87].

Tests for Microalbuminuria

In 1963, Keen and Chlouveraskis described the first specific radioimmunoassay (RIA) for albumin in urine.75 Since then several methods have been described for measurement of urinary albumin excretion with emphasis on unexpensive, easy to apply, rapid tests which can be used on a large scale population. The various methods used are:

Dipstick method

Semi quantitative method.

• Chemical precipitation (Sulphosalicyclic acid trichloroacetic acid)

• Immuno precipitation (Micral Test).

3. Photometric method.

4. Nephelometric method.

5. Sensitive Quantitative methods

• Radio immunoassay.

• Cellulose acetate, agarose gel electrophoresis.

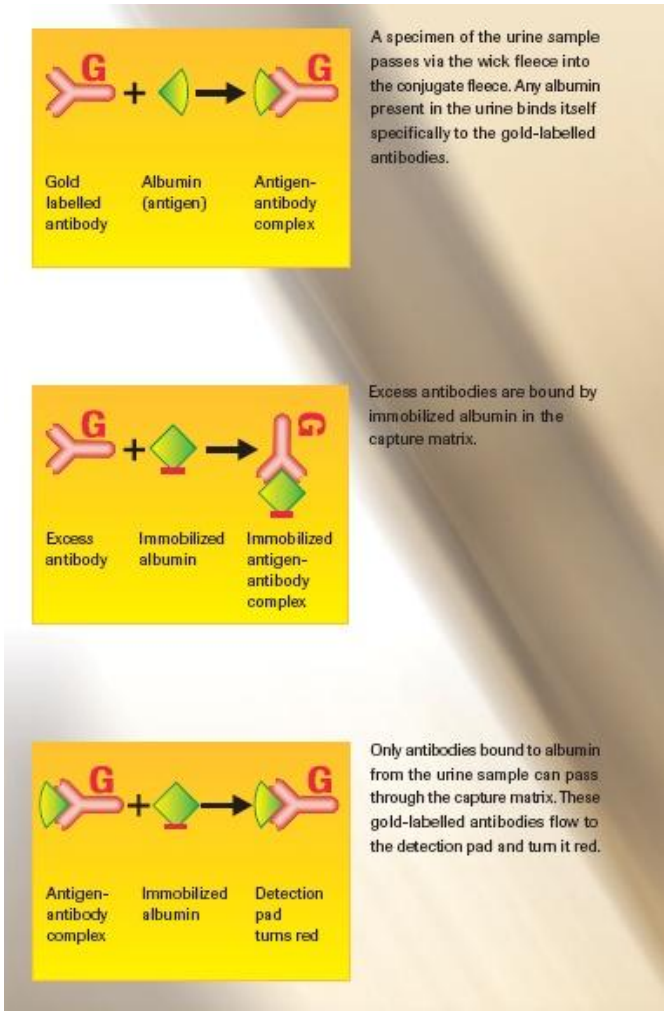
The procedures of various important methods include the following:

1. Dipstick method: Chemically impregnated dipstick contains methyl red and bromophenol blue with buffering salts. The later dissolve on contact with urine and protein in the urine lowers the pH turning it green. It was traditionally known to detect albuminuria >300 mg/L and hence not advocated for screening for microalbuminuria. But in a study by Alfredo Pegoraro et al, they found that the combination of sulfosalicylic acid testing and chemstrips was as good as and less expensive than Micral-Test in ruling out microalbuminuria.[76]

2. Chemical precipitation (Sulphosalicylic acid test): 5 drops of 20% Sulphosalicylic acid is added to 3 ml of urine in one test tube. This test tube is compared with test tube of untreated urine held against a dark background, immediately and turbidity is taken to indicate proteinuria.77

3. Immunoprecipitation (Micral test): It is based on color shift of monoclonal antibody to human albumin labelled with gold. Here Gold Labelled Optically Read Immuno Assay detects microalbuminuria. A specimen of the urine sample passes via the wick fleece into the conjugate fleece. Any albumin present in the urine binds itself specifically to the gold labelled antibodies. Excess antibodies are bound by immobilized albumin in the capture matrix. Only antibodies bound to albumin from the urine sample can pass through the capture matrix.

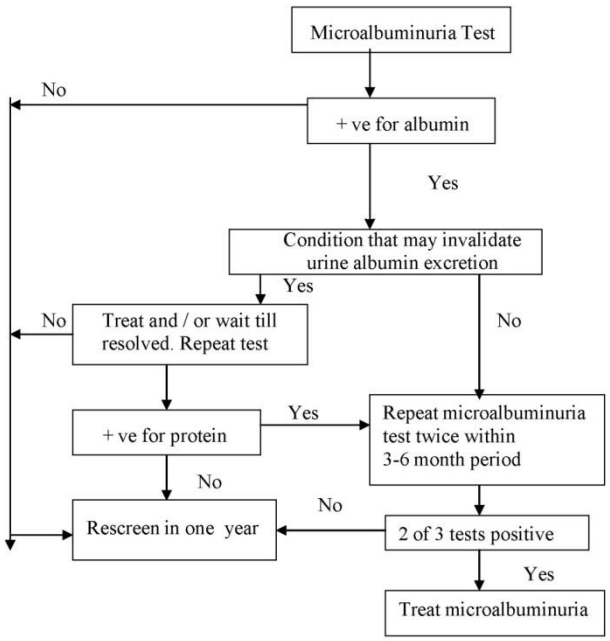
These gold-labelled antibodies flow to the detection pad and turn it red. Test is performed on early morning random urine sample by immersing the strip for 5 sec and reading the result at 2 min, visually comparing with color blocks on vial (0 mg/l, 20mg/l, 50 mg/l and 100 mg/l albumin).77



Principle of Micral Test

4. Radioimmuno assay: It is the "gold standard" for estimation of albuminuria. It is a double antibody technique where albumin in the sample has to compete with the fixed amount of 125I. Labelled albumin for the binding sites of the specific antibodies. Bound and free albumin is separated by addition of a second antibody immuno absorbent followed by centrifugation and decanting. The radio activity in the pellet is measured with a C-counter, Albumin concent-ration in the sample is inversely proportional to the radioactivity. The sensitivity for RIA method was 0.3 mg/l.

An algorithm for screening of microalbuminuria



Treatment of Microalbuminuria

1. Control of Blood pressure: Systolic BP is one of the most relevant determinants of microalbuminuria. Studies of secondary prevention have shown that blood pressure reduction effectively reduces the albumin excretion rate. Among anti- hypertensives, ACE inhibitors and Angiotensin receptor blockers seem to be particularly effective.78 The target BP should be < 140/90 mmHg in non-diabetics and < 130/80 mmHg in diabetic patients.

2. Glycemic control: Intensive diabetic therapy can significantly reduce the risk of development of microalbuminuria and overt nephropathy in people with diabetes.79

3. Treatment of Dyslipidaemia: Statins modify endothelial dysfunction, inflammatory response, plaque vulnerability and thrombus formation. Their usage is known to slow progression of microalbuminuria and is associated with stabilization of UAE.80

4. Smoking cessation: Smoking should be strongly discouraged in patients with microalbuminuria not only to retard the progression of microalbuminuria but also to guard against cardiovascular disease.

5. Protein restriction: Animal studies have shown that restriction of dietary proteins intake reduces hyper filtration and intraglomerular pressure hence retarding the progression of microalbuminuria. The general consensus is to prescribe a protein intake of 0.8 g/mg/day in patients with overt nephropathy.

Microalbuminuria: A Practical Perspective

Several pathways may link microalbuminuria and vascular disease. Several factors that cluster with microalbuminuria include insulin resistance, central obesity, low levels of high-density lipoprotein, cholesterol, high triglyceride levels, systolic hypertension, lack of nocturnal dip in blood pressure on 24 hour monitoring, salt sensitivity, endothelial dysfunction, hypercoagul-ability, impaired fibrinolysis and renal dysfunction. This provides enough proof to support the role of microalbuminuria as a predictor or vascular events in high-risk population. Hence, screening for microalbuminuria on a regular basis may help to identify a subgroup of patients who are at high risk for cerebrovascular disease and need more intensive therapy and closer follow-up because they could benefit from early intervention and treatment.81

Materials and Methods

Source of data

- The proposed study is conducted in the Department of Medicine, S.R.N. Hospital, Allahabad.

Inclusion criteria

- It include patients diagnosed with ischemic stroke irrespective of age and sex confirmed by CT scan brain, within 24 hours after the onset of symptoms.
- The severity of neurological deficit will be measured by the Scandinavian Stroke Scale (SSS).
- The albumin excretion rate will be measured using spot urine collection by Micral Test.

Exclusion criteria

a) Patients with hemorrhagic stroke.
b) Patients with diabetes, defined as fasting plasma glucose > 126 mg/dl or 2-hour plasma glucose > 200 mg/dl during an oral glucose tolerance test or use of antidiabetic drugs.
c) Patients with hypertension, defined as systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg or the use of anti-hypertensive medication.
d) Systemic infection including bacterial meningitis.
e) Nephropathy and abnormal urinalysis.
f) Major trauma and surgery.

- •Detailed history, clinical examination and relevant laboratory investigation were done as per the proforma.
- The severity of stroke was assessed using Scandinavian Stroke Scale.

In the selected patients, the following investigations were done.

1. CT scan brain (plain) to establish the ischemic lesion.
2. Urinalysis, to exclude hematuria, leucocyturia, glucosuria and proteinuria.
3. Serum glucose levels, blood urea, serum creatinine and fasting lipid profile were estimated.
4. ECG, chest x-ray and echocardiogram were done to assess the cardiac status.
5. The albumin excretion rate was assessed using Micral test on early morning urine sample and expressed as --------- mg/L.

- 60 age and sex matched healthy controls were selected.
- The controls were screened for stroke risk factors and assessed for urinary albumin excretion rate using Micral test,

urea,creatinine, serum glucose, WBC count, total cholesterol, LDL, HDL and triglycerides.

Method of Statistical Analysis

The data was collected and entered in Microsoft excel. The graphs and tables were generated using Microsoft Word and Excel. The analysis of the data was done using the statistical Software namely SPSS 11.0 and Systat 8.0. Chi-square and Fisher Exact Test were used to test the significance of proportions of predisposing Factors and presence of microalbuminuria between cases and controls. Similar tests were used to find the significance of proportion of presenting factors and age between the microalbuminuria positive and negative patients. Student t test (Two tailed) was used to test the significance of mean pattern of parameters between cases and controls and microalbuminuria positivity and negativity.

1. Chi. Square Test

$X2 = \Sigma (Oi - Ei)2$ where Oi is observed frequency and Ei is expected

Ei frequency.

2. Fisher Exact Test

	Class 1	**Class 2**	
Sample 1	A	B	a+b
Sample 2	C	D	c+d
Total	a+c	b+d	A

$$\text{Fisher Exact Test statistic} = \Sigma P = \frac{(a+b)!\,(c+d)!\,(a+c)!\,(b+d)!}{n!} \cdot \frac{1}{\Sigma a!b!c!d!}$$

3. Student t test (Independent)

Objective: To investigate the significance between the means of two populations

$$t = \frac{(x_1 - x_2) - (\mu_1 - \mu_2)}{\sqrt{s^2\,(1/n1 + 1/n2)}}$$

$$\text{Where } s^2 = \frac{(n1-1)\sum_{i-1}^{n1}(x1 - x1)^2 + (n2-1)\sum_{i-1}^{n^2}(x2 - x2)^2}{n1 + n2 - 2}$$

.

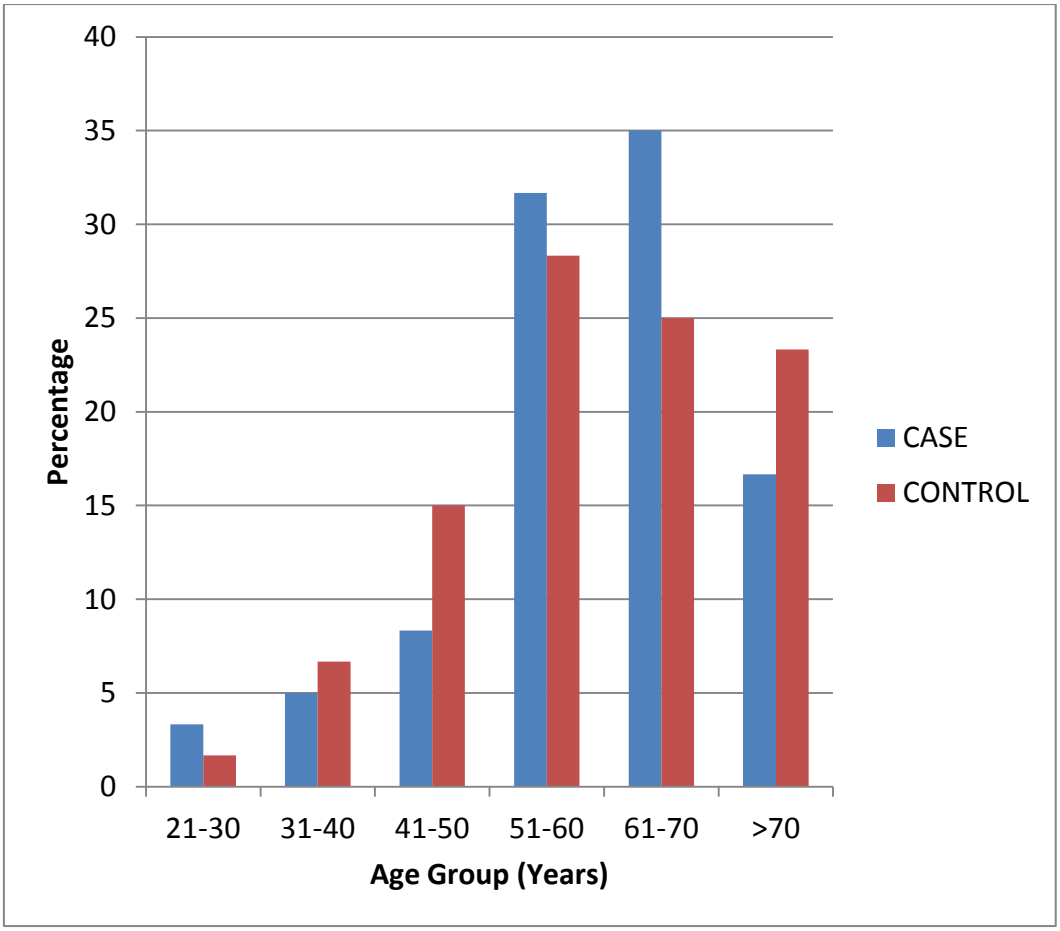
Observations

Study Design: This comparative study consisting of 60 non-diabetic acute ischemic stroke patients as cases and 60 healthy individuals as controls had the following findings.

Table-1: Age distribution

Age in years	Cases		Controls	
	Number	%	Number	%
≤ 20	-	-	-	-
21-30	2	3.33	1	1.67
31-40	3	5.00	4	6.67
41-50	5	8.33	9	15.00
51-60	19	31.67	17	28.33
61-70	21	35.00	15	25.00
>70	10	16.67	14	23.33
Total	60	100.00	60	100.00
Mean ± SD	60.77±13.02		59.88±13.10	
Inference	Two samples are age matched with p=0.7096			

Figure-1: Age distribution



Among the cases, the youngest patient was 22 years old and the oldest patient 90 years. The mean age was 60.77±13.02 years.

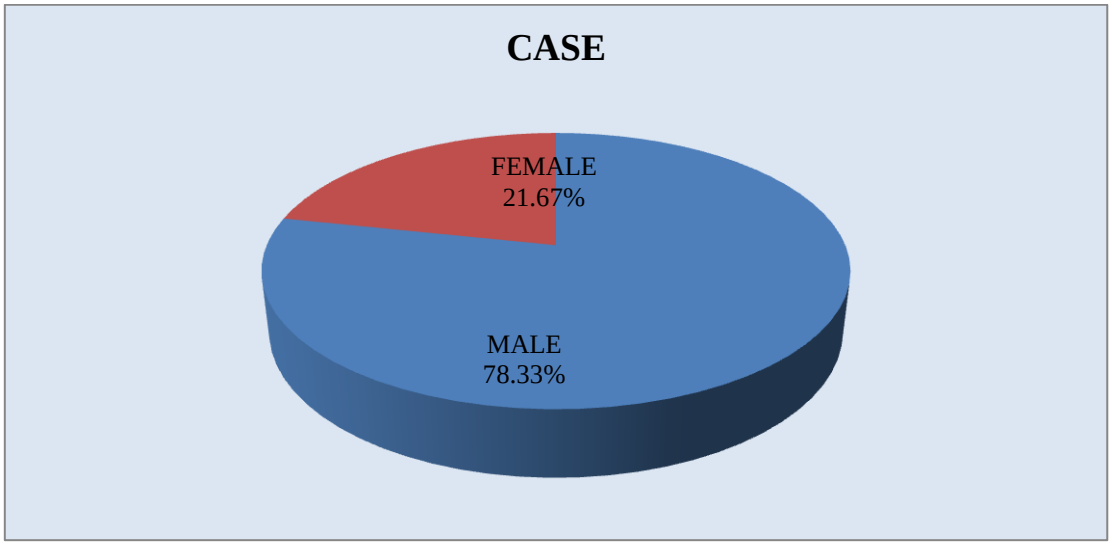
Among the controls, the youngest patient was 26 years and oldest patient was 85 years. The mean age was 59.88±13.10 years.

Hence the cases and controls were age matched with p=0. 7096

Table-2: Sex distribution

Age in years	Cases (n=60)		Controls (n=60)	
	Number	%	Number	%
Male	47	78.33	44	73.33
Female	13	21.67	16	26.67

Figure-2 : Sex distribution



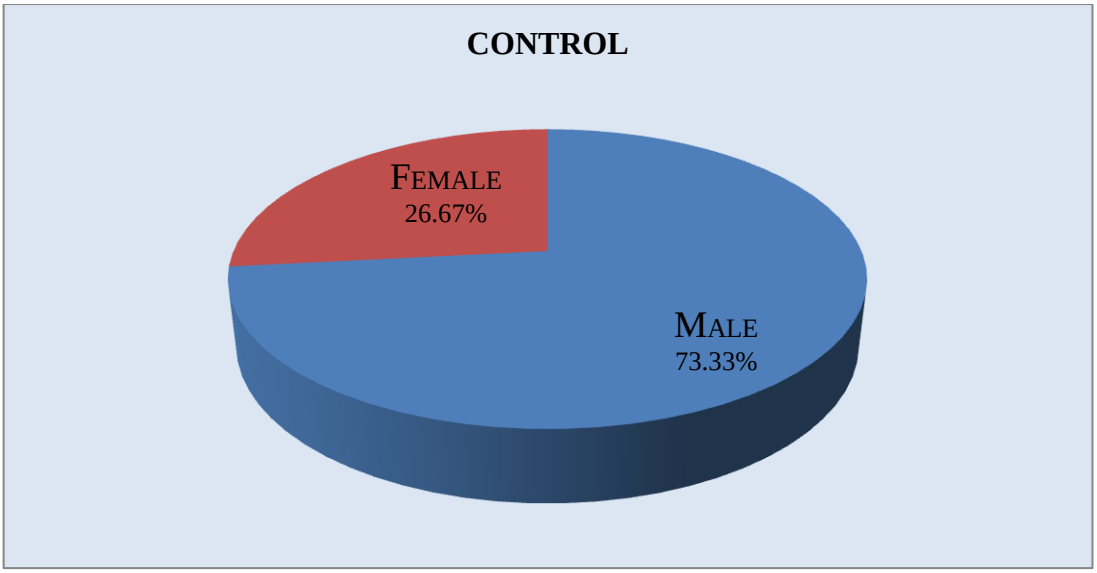
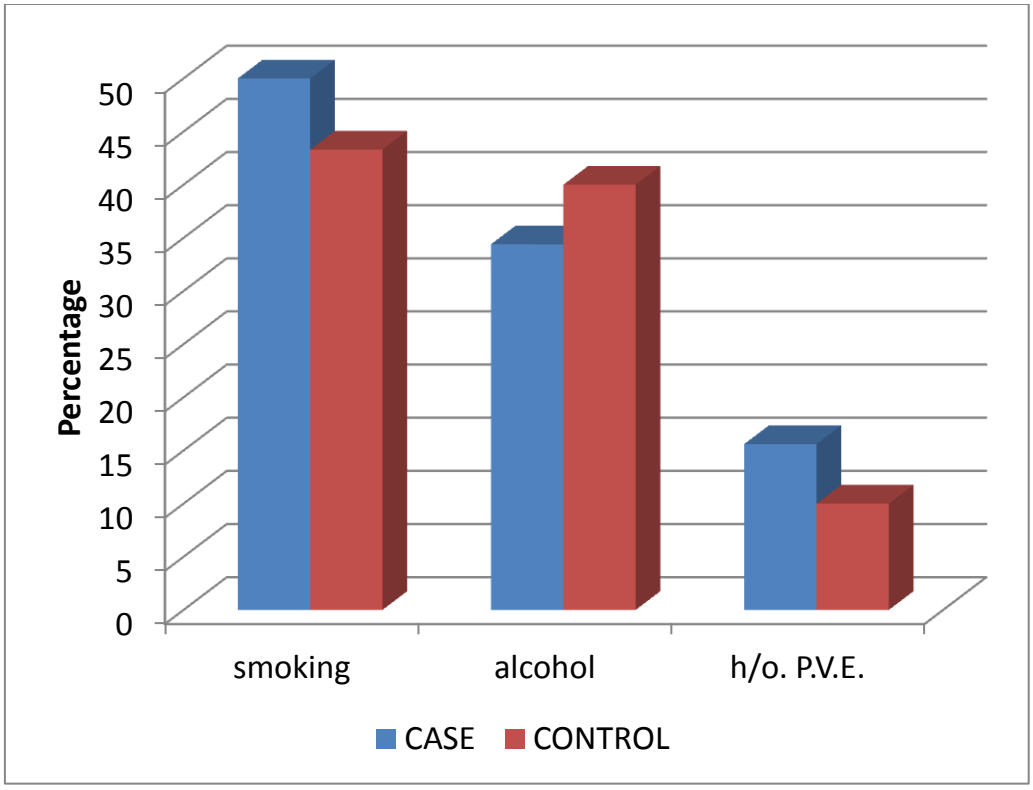


Table -3: Predisposing factors

Predisposing factors	Cases(n=60)	Control(n=60)	P value
smoking	30(50.0%)	26(43.3%)	0.599
alcohol	21(35.0%)	24(40.0%)	0.647
History of previous vascular events (h/o PVE)	9(15.0%)	6(10.0%)	0.709
inference	The predisposing factors are statistically similar between two groups (p>0.05)		

Figure-3 : Predisposing factors



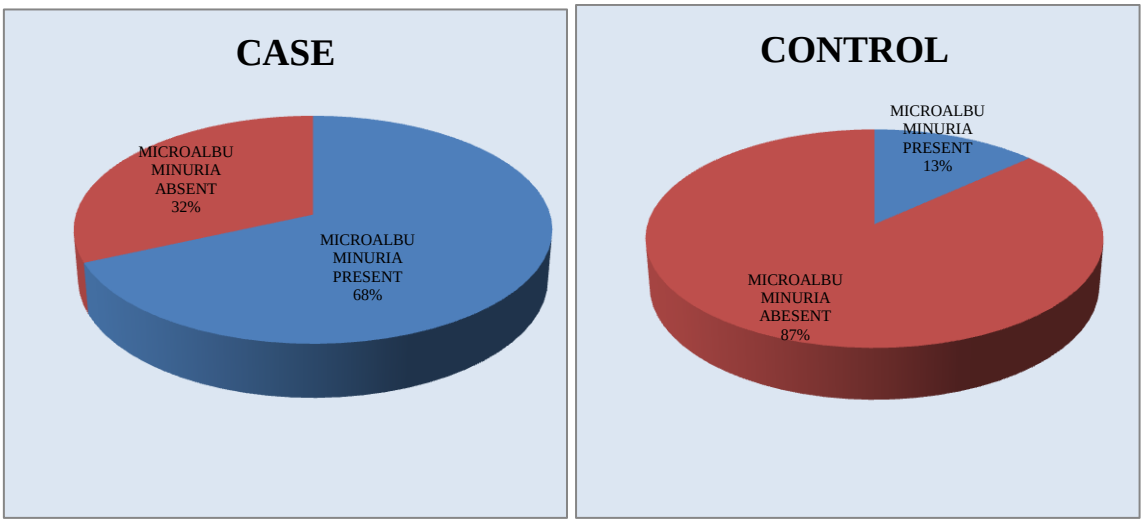
In the study population, the predisposing factors included smoking being 30 (50%) in cases and 26 (43.3%) in controls and alcoholism being 21 (35.0%) in cases and 24 (40%) in controls.

The history of previous vascular events including ischemic heart disease and peripheral vascular disease was found in 9(15.0%) of cases and 6(10.0%) of controls. The predisposing factors were thus statistically similar between two groups.

Table - 4: Incidence of microalbuminuria among study population

Microalbuminuria	Cases (n=60)	Controls (n=60)
Absent	19(31.67%)	52(86.67%)
Present	41(68.33%)	8(13.33%)
Inference	Patients with acute ischemic stroke are 5.125 times more likely to have microalbuminuria with P =o.ooo1	

Figure -4: Incidence of microalbuminuria among study population



Microalbuminuria was found in 41 (68.33%) patients with acute ischemic stroke while only 8 (13.33%) controls. Thus patients with acute ischemic stroke were 5.125 times more like to have microalbuminuria when compared to the controls.

Table -5: Association of age / sex with the presence of microalbuminuria

	Microalbuminuria		p value
	Absent	**Present**	
Age in years (Mean± SD)	56.70±14.45	63.18±11.66	0.066
Sex	Male=13(65%) Female=7(35%)	Male=32(80%) Female=8(20%)	>0.05
Inference	Age and sex are not statistically associated with the presence of microalbuminuria (p>0.05).		

Figure-5: Association of age with the presence of microalbuminuria

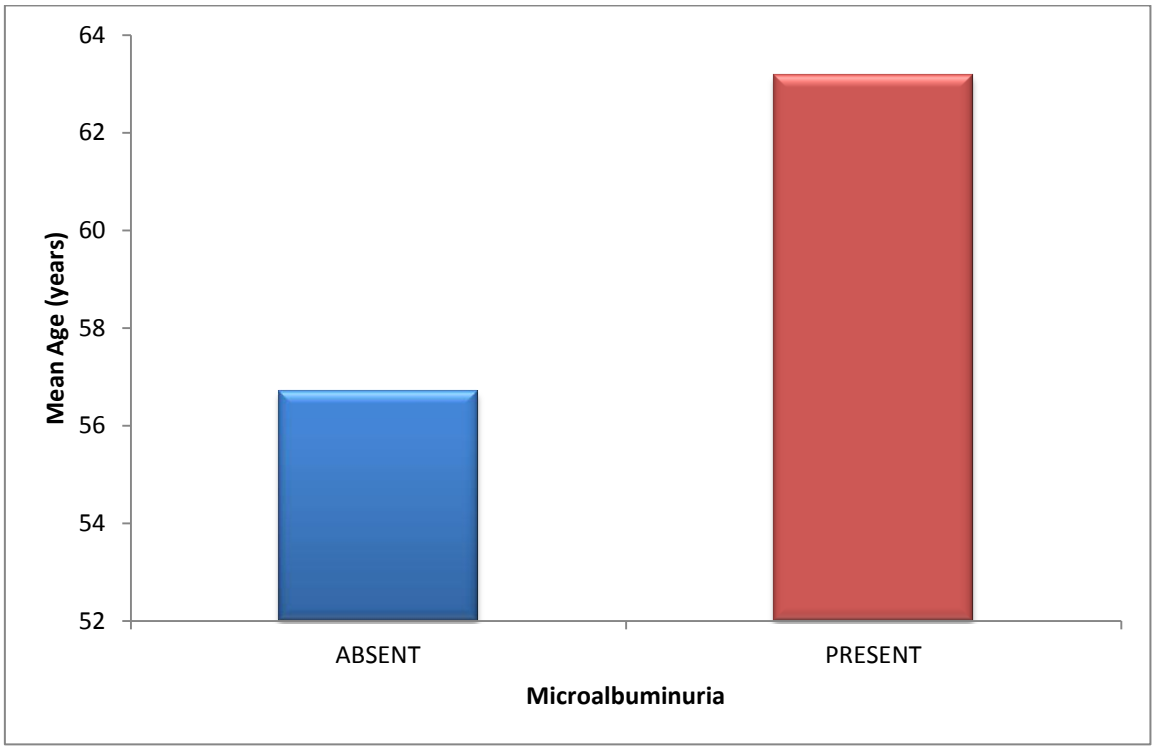
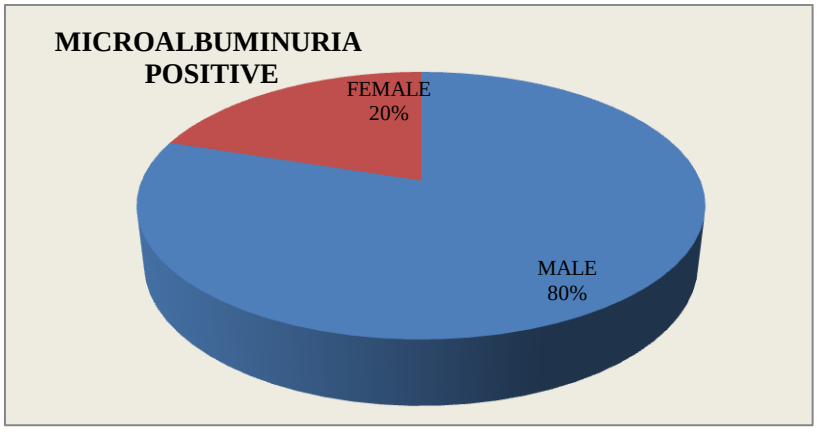
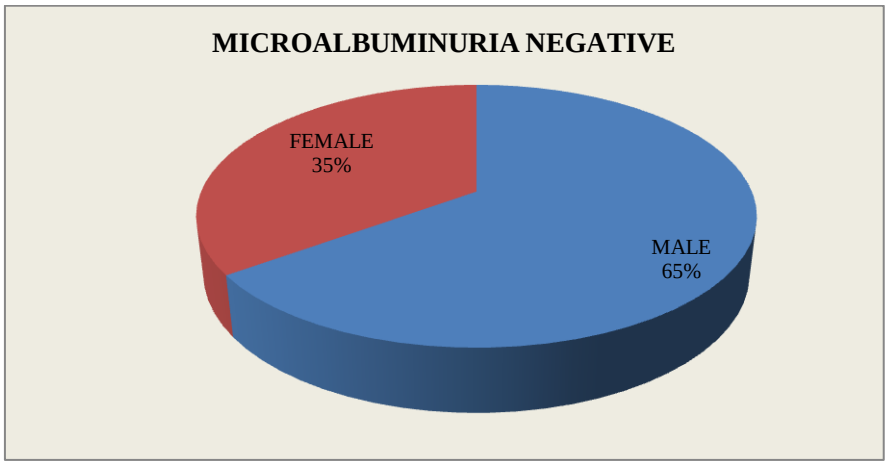


Figure-6: Association of sex with the presence of microalbuminuria





Of the 40 patients with microalbuminuria, 31 patients were above the age of 50 years but age was not statistically associated with presence of microalbuminuria(63.18±11.66 Vs. 56.70±14.45).

Among the patients with microalbuminuria 32 were male and 8 female. gender was not statistically associated with presence of microalbuminuria.

Table -6: Mean pattern of parameters

Parameters (Mean±SD)	Cases (n=60)	Controls (n=60)	P value
SBP mm Hg	125.10±10.84	127.43±15.75	0.3471
DBP mm Hg	77.93±6.71	76.67±5.58	0.2657
RBS in g/dl	107.11±20.51	93.76±22.72	0.0010
Blood urea in mg/dl	43.99±16.04	38.85±15.08	0.0731
Serum Creatinine in mg/dl	1.06±0.36	1.01±0.35	0.4420

Figure-7: Mean pattern of SBP & DBP

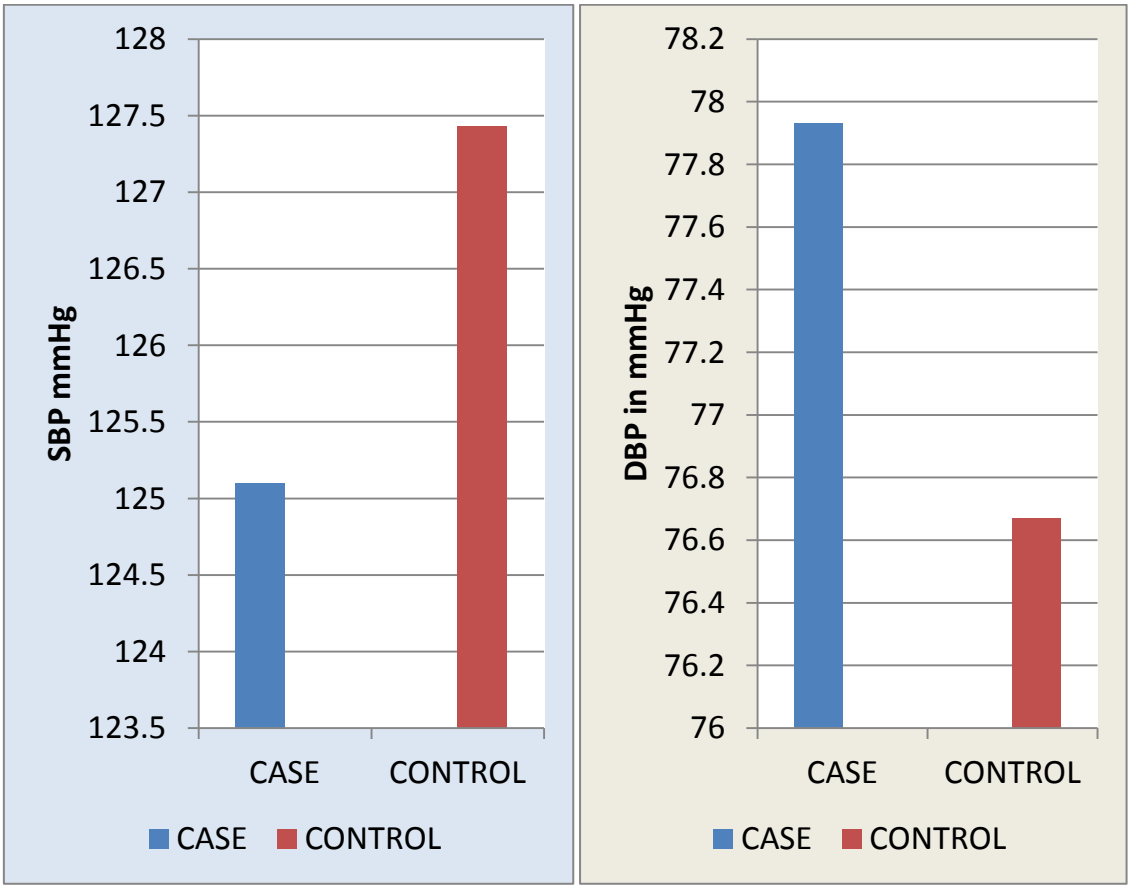


Figure-8: Mean pattern of RBS

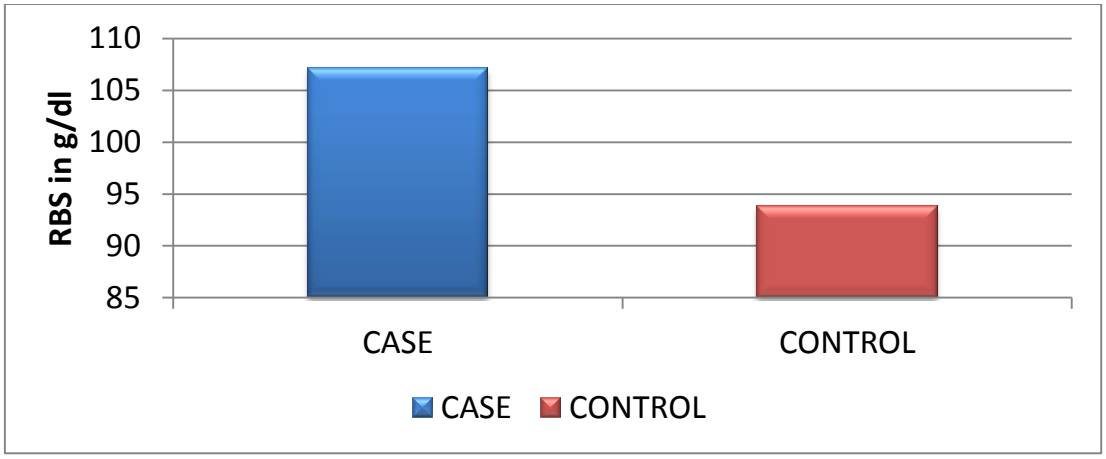
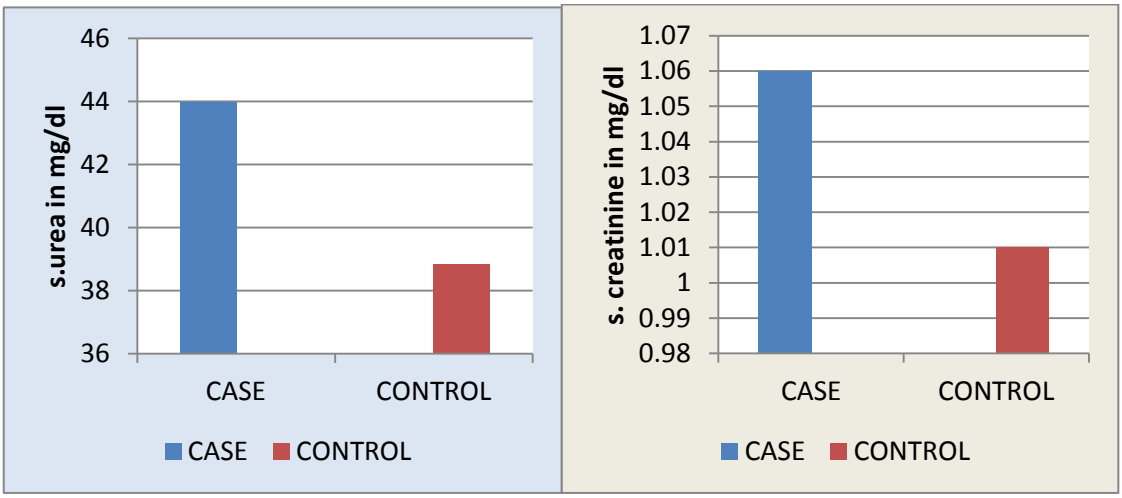


Figure-9: Mean pattern of S.Urea & S. Creatinine



Blood pressure was found to be similar between cases and controls.

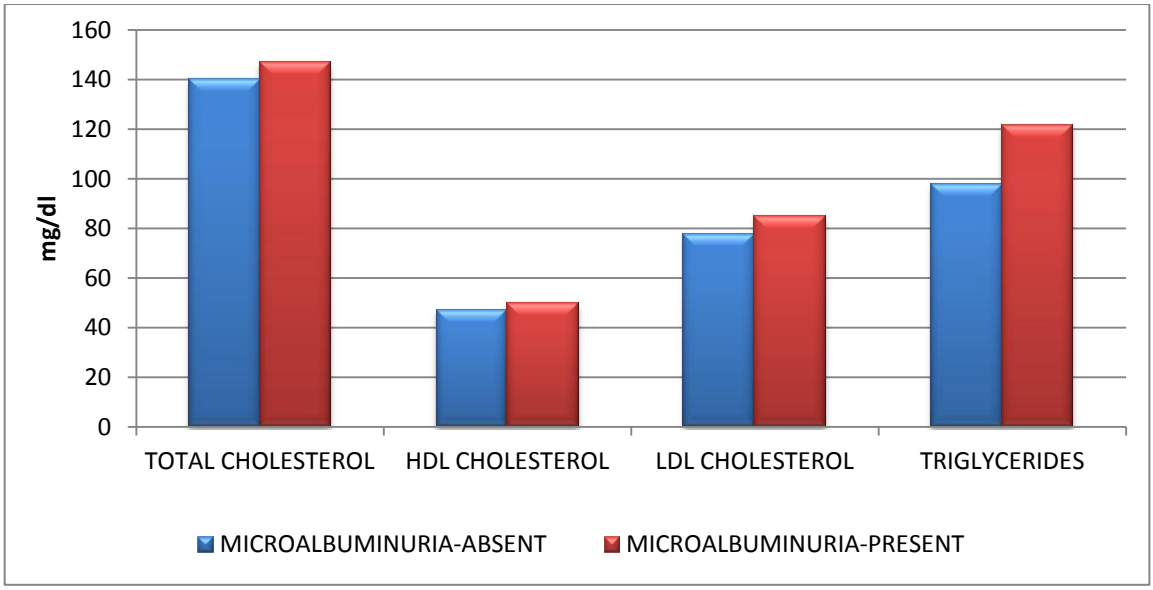
Blood Sugar was 107.11±20.51 among cases while 93.76±22.72 among controls and was statistically significant.

Among cases, blood urea was 43.99±16.04, serum creatinine was 1.06±0.36 while in controls, it was 38.85±15.08 and 1.01±0.35 respectively.

Table-7: Mean pattern of lipid parameters in cases

Lipid Parameters (Mean ± SD)	**Microalbuminuria**		**p value**
	Absent (n=20)	**Present (n=40)**	
Total Cholesterol	140.23±37.65	147±42.64	0.5443
HDL –Cholesterol	46.96±10.19	49.59±10.25	0.3518
LDL-Cholesterol	77.46±33.92	84.79±35.38	0.4464
Triglycerides	97.83±28.26	121.89±46.88	0.0395

Figure- 10: Mean pattern of lipid parameters in cases

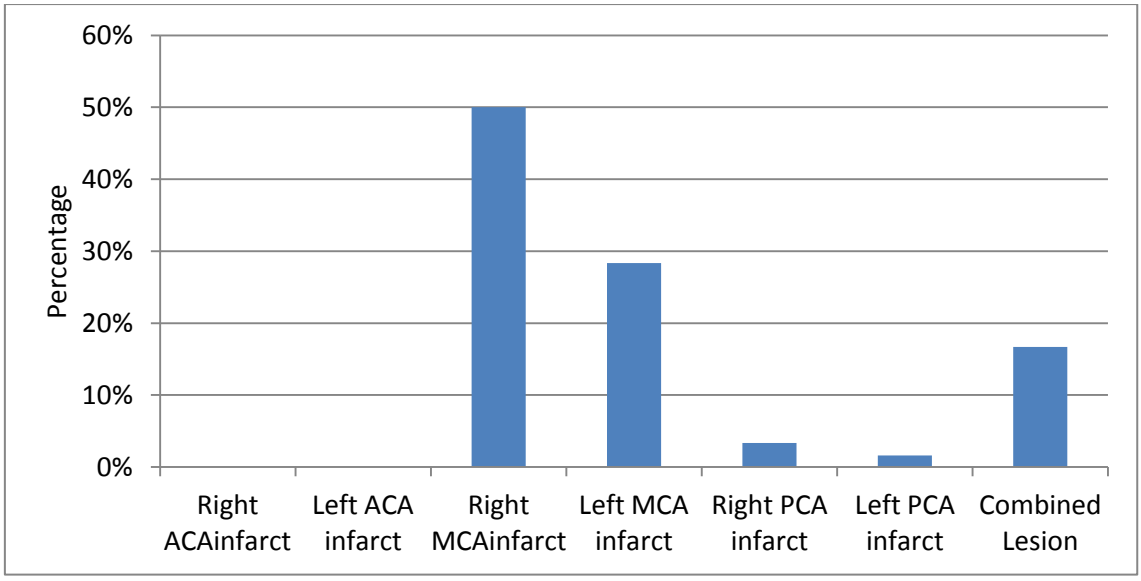


Total cholesterol (147±42.64 Vs. 140.23±37.65), LDL cholesterol (84.79±35.38 Vs 77.46±33.92) and Triglycerides(121.89±46.88 Vs 97.83±28.26) was higher in patients with microalbuminuria but the difference was found to be statistically significant only in case of Triglycerides.

Table -8: CT scan results

CT scan results	Number (n=60)	%
1.Right ACA infarct	-	-
2.Left ACA infarct	-	-
3.Right MCA infarct	30	50
4.Left MCA infarct	17	28.33
5.Right PCA infarct	2	3.33
6.Left PCA infarct	1	1.6
7.Combined Lesion	10	16.67

Figure -11: CT scan results

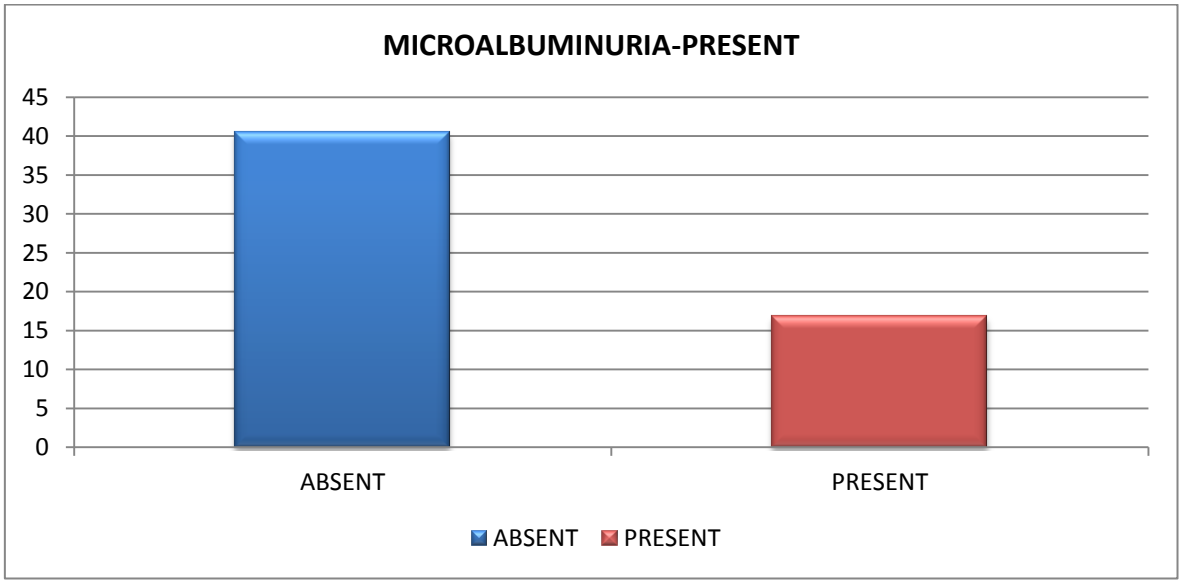


MCA infarct was the commonest lesion found in our study population (Rt 50% Vs Lt 28.33%). Combined lesion was found in (16.67%) patients. Right PCA infarct was found in (3.33%) patients and left PCA infarct was found in (1.6%) patients.

Table -9: Mean Pattern of Scandinavian Stroke Scale(SSS) in presence of Microalbuminuria

Scandinavian Stroke Scale (SSS)	Microalbuminuria		Total (n=60)
	Absent (n=20)	Present (n=40)	
Range	31-49	4-48	4-49
Mean ± SD	40.4±5.09	16.85±10.87	24.7±15.17
Inference	SSS is significantly decreased in the presence of Microalbuminuria with p<0.0001		

Figure -12: Mean Pattern of SSS in presence of Microalbuminuria

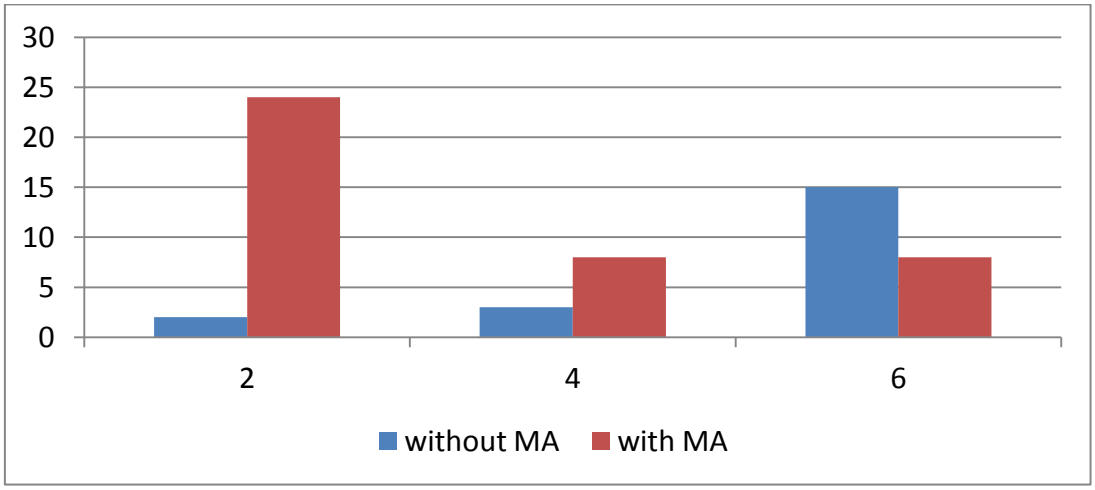


The severity of stroke was assessed by Scandinavian Stroke Scale and was found to significantly lower in presence of microalbuminuria (4-48 with mean of 16.85±10.87) than without microalbuminuria (31-49 with mean of 40.4±5.09).

Table-10: Correlation of Level of Consciousness by SSS and MA

Level of consciousness	Number of patients without microalbuminuria (MA)	Number of patients with microalbuminuria(MA)
2	2	24
4	3	8
6	15	8

Fig. 13 Correlation of Level of Consciousness by SSS and MA

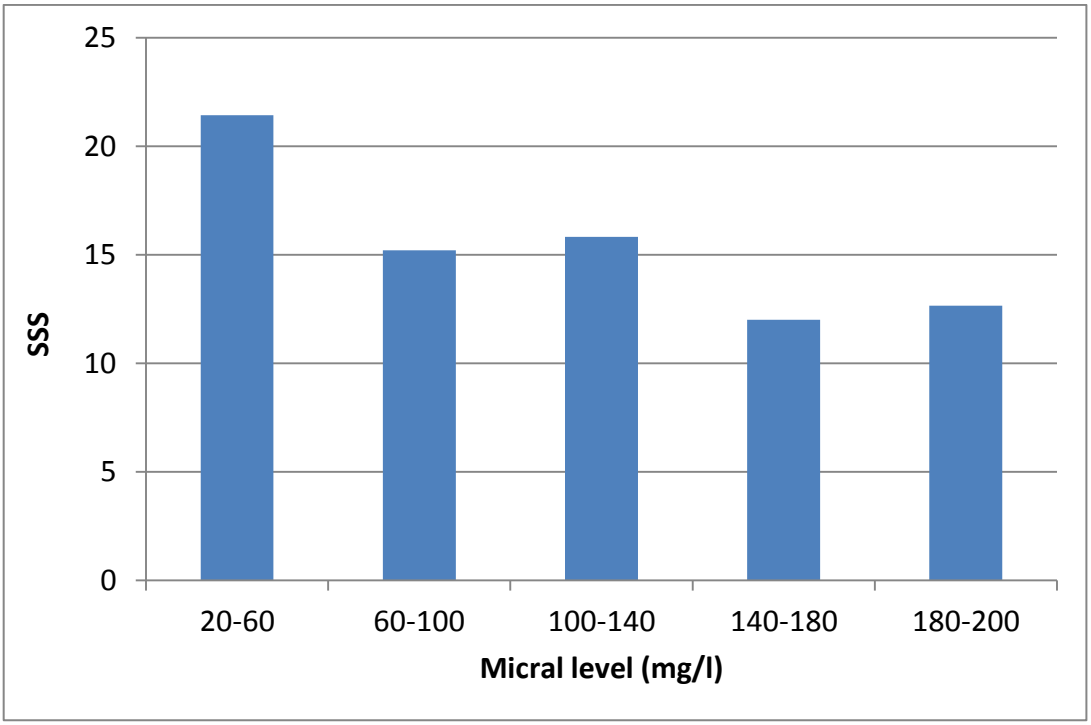


The Patients with MA had more severe depressed levels of consciousness, 60% of patients with MA had level of consciousness 2, whereas 10% of patients without MA had level of consciousness 2.

Table-11: Scandinavian Stroke Scale (SSS) with increasing level of Microalbuminuria

Microalbuminuria (mg/l)	Scandinavian Stroke Scale. (Mean)
20-60	21.42±13.06
60-100	15.2±7.01
100-140	15.83±9.84
140-180	12.0±5.66
>180	12.66±10.48

Figure-14: Scandinavian Stroke Scale (SSS) with increasing level of Microalbuminuria



With increasing level of MA, the Scandinavian Stroke Scale (SSS) score decreases indicating poor prognosis with increase in MA level.

Discussion

The present study is a comparative study consisting of 60 Acute ischemic stroke patients as cases and 60 Healthy individual as controls undertaken to investigate:

1. The incidence of microalbuminuria in Acute ischemic stroke patients.
2. The difference in laboratory parameters in patients with and without microalbuminuria.
3. The correlation between Scandinavian Stroke Scale and presence of microalbuminuria.

Incidence of microalbuminuria

	MA in cases	MA in controls
Turaj et al	46.1%	13.5%
Beamer et al	29%	10%
Slowik A et al	46.7%	16.7%
Present study	68.33%	13.33%

Our study found that among age and sex matched cases and controls with similar predisposing factors, patients with acute ischemic stroke were 5.125 times more likely to have microalbuminuria. The finding was similar to that of other studies including Turaj et al[74] , Beamer et al[71] and Slowik A et al.[82]

The incidence of microalbuminuria in cases found greater in Indian population as compared to western population.

Age and microalbuminuria

	With MA	Without MA	Controls
Turaj et al	73.3±11.6	66.0±12.4	65.2±5.5
Beamer et al	69±7	65±8	66±8
Present study	63.18±11.66	56.70±14.45	59.88±13.1

The studies including Turaj et al[74] and Beamer et al[71] had found statistically significant correlation and attributed this to the phenomenon of older patients having a worse neurological deficit. Our study found correlation between age and presence of microalbuminuria but it didn't reach statistically significant level.

Gender and Microalbuminuria

	With MA	Without MA
Turaj et al		
Males	12 (50%)	14 (50%)
Females	12 (50%)	14 (50%)
Present study		
Males	32(80%)	13(77.3%)
Females	8(20%)	7 (22.7%)

The study did not reveal any difference in gender distribution between patients with or without microalbuminuria. This was consistent with study by Turaj et al.[74]

Loss of consciousness and microalbuminuria

	With MA	Without MA	p value
Turaj et al	35.5%	14.3%	< 0.05
Present study	60%	10%	<0.05

Our study found statistically significant correlation between diminished consciousness between patients with and without microalbuminuria. The study by Turaj et al[74] also had similar findings. Hence, presence of microalbuminuria was found to correlate with the severity of stroke.

Gumbinger C et al study show that MA was frequently found in acute ischemic stroke patients. It was associated with severe neurological deficit upon admission. MA in the acute phase was shown to be an independent predictor of poor outcome[87]

Our study also found similar results The Scandinavian Stroke Scale was low in patient with microalbuminuria (16.85±10.87) when compared to patients without microalbuminuria (40.4±5.09). Hence significant correlation was found between microalbuminuria and the severity of the neurological deficit. The Patients with MA had more severe depressed levels of consciousness {SSS < 4 vs. SSS > 6, 80% vs. 20%). In patients with acute ischemic stroke, 41 pts (68.33%) had microalbuminuria. Hence patients with acute ischemic stroke incidence is significantly higher.

Mathur P.C. et al studied 50 patients of nondiabetic acute ischaemic stroke within 24 hours of onset of symptoms for MA by dipstick urinalysis in 2005 in India .The incidence of MA was 68% (34 patients). Of all the traditional risk factors for stroke-age, male gender, hypertension, dyslipidaemia, smoking, obesity - only age of patients (>60 years) showed a positive correlation

with the presence of MA (<0.05). Patients with MA had more severe neurological deficit (Scandinavian Stroke Scale {SSS} < 30 vs. > 30; mean+S.D=24.3+8.66 vs. 30.3+10.3, p<0.03) and more severe depressed levels of consciousness {SSS < 4 vs. SSS > 6, 82.35 vs. 17.6, p<0.05). The incidence of MA in Indians with nondiabetic acute ischaemic stroke is significantly higher than that of western populations. Patients with MA in the first 24 hours after the onset of stroke have more severe neurological deficit and depressed levels of consciousness than patients without MA[84].

In our study incidence of MA is 68.33%(41 patients), The Scandinavian Stroke Scale was low in patient with microalbuminuria (16.85±10.87) when compared to patients without microalbuminuria (40.4±5.09). Hence significant correlation was found between microalbuminuria and the severity of the neurological deficit. The Patients with MA had more severe depressed levels of consciousness {SSS < 4 vs. SSS > 6, 80% vs. 20%). Patients with MA in the first 24 hours after the onset of stroke have more severe neurological deficit and depressed levels of consciousness than patients without MA. Results are similar.

Limitations of the Study

1. To assess the incidence of Microalbuminuria with nondiabetic acute ischaemic stroke requires further studies with large sample size.
2. For long term prognosis in non-diabetic acute stroke patients required a longer follow up study.

Summary

1. The study population consisted of 60 acute ischemic stroke patients of age 60.77±13.02 years with 47 males (78.33%) and 13 females (21.67%).
2. The controls included 60 age and sex matched individuals.
3. The cases and controls were matched for predisposing factors that included smoking and alcohol.
4. Among the cases, 18 (30%) had right hemiparesis, 32 (53.3%) had left hemi paresis while 10(16.67%) had no focal deficits.
5. CT scan results revealed that middle cerebral artery infarct predominated the study population (right and left 78.33%).
6. The blood sugar levels were higher in cases (107.11±20.51) compared to controls (93.76±22.72) despite being in non-diabetic range and were statistically significant. Other parameters like blood pressure, blood urea and serum creatinine were similar among cases and controls.
7. In patients with Acute ischemic stroke, 41pts (68.33%) had microalbuminuria while among controls only 8 patients (13.33%) had microalbuminuria. Hence patients with recent ischemic stroke were 5.125 times more likely to have microalbuminuria with p= 0.0001.
8. 24/60 patients with microalbuminuria (60%) had altered consciousness while 2/20 patients without microalbuminuria (10%) had altered consciousness. Hence microalbuminuria was found to be associated with more severe stroke.
9. The mean age of patients with microalbuminuria was 63.18±11.66 years while that of patients without MA was 56.70±14.45 years. Hence presence of microalbuminuria was found to increase with age but not to the statistically significant level.
10. In patients with microalbuminuria, total cholesterol was 147±42.64, HDL was 49.59±10.25, LDL was 84.79±35.38 and 121.89±46.88 triglycerides while in patients without microalbuminuria, total cholesterol was 140.23±37.65, HDL 46.96±10.19, LDL 77.46±33.92 and 97.83±28.26 triglycerides . The difference

was not statistically significant except in case of triglycerides.

11. The Scandinavian Stroke Scale was low in patients with microalbuminuria (16.85±10.87) when compared to patients without microalbuminuria (40.4±5.09). Hence significant correlation was found between microalbuminuria and the severity of the neurological deficit.
12. The Patients with MA had more severe depressed levels of consciousness {SSS < 4 vs. SSS > 6, 80% vs. 20%).
13. In patients with acute ischemic stroke, 41 pts (68.33%) had microalbuminuria. Hence patients with acute ischemic stroke incidence is significantly higher than that of western populations.

Conclusion

- Various clinical studies have documented microalbuminuria as a risk factor for acute ischemic stroke. The present study found microalbuminuria in 68.33% of non-diabetic acute ischemic stroke patients.
- The incidence of MA in Indians with nondiabetic acute ischaemic stroke is significantly higher than that of western populations.
- Patients with MA in the first 24 hours after the onset of stroke have more severe neurological deficit and depressed levels of consciousness than patients without MA.

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Annexure - 1: Proforma

PATIENT PROFILE:

NAME: OP/IP NO:

AGE: DOA: SEX: DOD: OCCUPATION: ADDRESS:

PRESENTING COMPLAINTS:

1. Paucity of movements of one side of the body
• Yes / No –
• Duration –
2. Loss of consciousness
• Yes / No –
• Duration –
3. Aphasia
• Yes / No –
• Duration –
4. Seizures
• Yes / No –
• Duration –
• Type –
5. Other Symptoms

PAST HISTORY

• HTN -
• Diabetes mellitus -
• Liver disorder -
• Renal insufficiency -
• History of vascular events –

FAMILY HISTORY

• HTN –
• Diabetes mellitus –
• Cerebrovascular accidents –

PERSONAL HISTORY

• Diet -
• Appetite -
• Sleep -
• Bowel movement -
• Bladder movement -
• Alcohol intake -
• Smoking -

OBSTETRIC HISTORY

(In Females)

GENERAL PHYSICAL EXAMINATION

• Built – Poor/ Moderate / Well
• Nourishment – Poor / Moderate / Well
• Pallor -

• Icterus -
• Cyanosis -
• Clubbing -
• Lymphadenopathy -
• Oral cavity -
• Oedema -
• Weight -
• Height -
• Pulse -
• B.P. -
• Temperature -
• JVP -
• RR -

SYSTEMIC EXAMINATION

1. CNS - Scandinavian Stroke Scale

Function	Score	Prognostic score	Long term score
Consciousness:			
• Fully conscious.	6		
• Somnolent can be awaked to full consciousness.	4		
• Reacts to verbal command, but not fully conscious.	2		
Eye movement			
• No gaze palsy.	4		
• Gaze palsy present.	2		
• Conjugate eye deviation.	0		
Arm, motor power			
• Raises arm with normal strength.	6		
• Raises arm with reduced strength.	5		
• Raises arm with flexion in elbow.	4		
• Can move, but not against gravity.	2		
• Paralysis.	0		
Leg, Motor power			
• Normal strength.	6		
• Raises straight leg with reduced strength.	5		
• Raises leg with flexion of knee.	4		
• Can move, but not against gravity.	2		
• Paralysis.	0		
Orientation			
• Correct for time, place and person.	6		
• Two of these.	4		
• One of these.	2		
• Completely disorientated.	0		
Speech			
• No aphasia.	10		
• Limited vocabulary or incoherent speech.	6		
• More than yes / no, but not longer sentences.	3		
• Only yes/no or less.	0		
Facial palsy			
• None/dubious.	2		
• Present.	0		
Gait			
• Walks 5 M without aids.	12		
• Walks with aids.	9		
• Walks with help of another person.	6		

• Sits without support.	3		
• Bedridden / wheel chair.	0		
Maximal Score			

2. Cardiovascular system

• Inspection -
• Palpation -
• Percussion -
• Auscultation -

3. Respiratory System

Inspection
Palpation
Percussion
Auscultation

INVESTIGATIONS

1. Urine Analysis

• Sugar
• Albumin
• Microscopy

2. Complete Haemogram

• Hb% -
• TC -
• DC -
• ESR -

3. RBS

4. Blood Urea -

5. Serum Creatinine -

6. Fasting Lipid Profile

• TC -
• HDL -
• LDL -
• TG -

7. Chest X-ray PA view

8. 12 lead ECG

9. Echocardiogram

10. C.T Scan Brain

11. Micral test for Microalbuminuria