RISK FACTORS, ETIOLOGY, AND PREDICTORS OF OUTCOME IN YOUNG PATIENTS WITH ISCHEMIC STROKE

DR. G BALASWAMY REDDY

DM THESIS

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RISK FACTORS, ETIOLOGY, AND PREDICTORS OF OUTCOME IN YOUNG PATIENTS WITH ISCHEMIC STROKE

A thesis submitted in partial fulfillment of the rules and regulations for DM Degree Examination of Sree Chitra Thirunal Institute for Medical Sciences and Technology

A THESIS SUBMITTED BY

DR. G BALASWAMY REDDY

TO

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IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE AWARD OF

DM NEUROLOGY

2020-2022

DECLARATION

I, **Dr. Balaswamy Reddy**, hereby certify that I had personally carried out the work depicted in the thesis titled, "**RISK FACTORS, ETIOLOGY, AND PREDICTORS OF OUTCOME IN YOUNG PATIENTS WITH ISCHEMIC STROKE",**

No part of this thesis has been submitted for the award of any other degree or diploma before this date.

Signature

Dr. Balaswamy Reddy

Date: 29/07/2022

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

CERTIFICATE BY THE RESEARCH GUIDE

Name of the Guide: **Dr. Sylaja P N**

Department: **NEUROLOGY**

This is to certify that **Dr. G BALASWAMY REDDY**, department of **NEUROLOGY** of this institute has fulfilled the requirements prescribed for the DM degree of the Sree Chitra Thirunal Institute for Medical Sciences and Technology, Trivandrum.

The thesis entitled, **"RISK FACTORS, ETIOLOGY, AND PREDICTORS OF OUTCOME IN YOUNG PATIENTS WITH ISCHEMIC STROKE"** was carried out under my direct supervision. No part of the thesis was submitted for the award of any degree or diploma before this date.

*Clearance was obtained from the Institutional Ethics Committee for carrying out the study.

Signature Sylaja PN
Name of the Guide

Date: 8/8/22

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श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

CERTIFICATE BY THE RESEARCH CO-GUIDE

Name of the Co-Guide: **Dr. SAPNA ERAT SREEDHARAN**

Department: **NEUROLOGY**

This is to certify that **Dr. G BALASWAMY REDDY**, department of **NEUROLOGY** of this institute has fulfilled the requirements prescribed for the DM degree of the Sree Chitra Thirunal Institute for Medical Sciences and Technology, Trivandrum.

The project work under the thesis entitled, **"RISK FACTORS, ETIOLOGY, AND PREDICTORS OF OUTCOME IN YOUNG PATIENTS WITH ISCHEMIC STROKE"**, was carried out under my direct supervision. No part of the thesis was submitted for the award of any degree or diploma before this date.

*Clearance was obtained from the Institutional Ethics Committee for carrying out the study.

Signature

Name of the Co-guide
Sapna Erat Sreedharan

Date: 8/8/2022.

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Forwarded:

This is to certify that thesis entitled "**RISK FACTORS, ETIOLOGY, AND PREDICTORS OF OUTCOME IN YOUNG PATIENTS WITH ISCHEMIC STROKE**" a bonafide research work done by **Dr Balaswamy Reddy**, senior resident, in Department of Neurology in partial fulfillment of the requirement for DM Neurology degree.

Date: 8/8/22

Trivandrum.

Sylaja PN

Dr Sylaja P N

Professor and Head,

Department of Neurology, SCTIMST

SCTIMST, TRIVANDRUM

SCTIMST, TRIVANDRUM

APPROVAL OF THE THESIS

The thesis entitled

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Submitted by

Dr. G BALASWAMY REDDY,

for the degree of

MD/DM/MCh

of

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM

is evaluated and approved by

Dr. Sylaja P N

(Name & Signature of the Guide)

…….

(Name & Signature of thesis examiner)

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LIST OF ABBREVIATIONS

S No	Abbreviation	Full Form
1	APLA	Antiphospholipid antibody syndrome
2	AF	Atrial fibrillation
3	ASD	Atrial septal defect
4	aOR	Adjusted Odd's ratio
5	AHA/ASA	American hear association /American stroke association
6	CVA	Cerebrovascular event
7	CT	Computed Tomography
8	CAD	Coronary artery disease
9	CADASIL	cerebral autosomal dominant arteriopathy with subcortical ischaemic strokes and leukoencephalopathy
10	CHF	Congestive heart failure
11	CE	Cardioembolic
12	DM	Diabetes Mellitus
14	DSA	Digital Subtraction Angiogram
15	GWAS	genome-wide association studies
16	HR	Hazard ratio
17	HTN	Hypertension
18	ICA	Internal carotid artery
19	LAA	Large artery atherosclerotic disease,
20	LAE	Left atrial enlargement

21	LVH	Left ventricular hypertrophy
22	mRS	Modified Rankin's Scale
23	MELAS	mitochondrial encephalopathy with lactic acidosis and stroke-like episodes
24	MI	Myocardial infarction
25	MRI	Magnetic Resonance Imaging
26	MCA	Middle cerebral artery
27	MR	MR Angiogram
28	NIHSS	National Institute of Health Stroke Scale
29	OCPs	Oral contraceptive pill
30	OR	Odd's ratio
31	PVOD	Peripheral vascular occlusive disease
32	PFO	Patent foramen ovale
33	PICA	Posterior inferior cerebellar artery
34	PAR	Population attributed risk
35	PCA	Posterior cerebral artery
36	PACNS	Primary angiitis of the CNS
37	RCT	Randomized controlled trail
38	RWMA	Regional wall motion abnormalities
39	RCVS	reversible cerebral vasoconstriction syndrome
40	RHD	Rheumatic Heart Disease
41	SCA	Superior cerebellar artery
42	SLE	Systemic Lupus Erythematosus

43	SEC	Spontaneous echo contrast
44	SVD	Small vessel disease
45	TCD	Transcranial Doppler
46	TIA	Transient Ischemic Attack
47	TTE	Trans-thoracic echocardiogram
48	TOAST	Trial of Org 10172 in Acute Stroke Treatment
49	TEE	Trans-esophageal echocardiogram
50	WHO	World health organization

SYNOPSIS

RISK FACTORS, ETIOLOGY, AND PREDICTORS OF OUTCOME IN YOUNG PATIENTS WITH ISCHEMIC STROKE

SYNOPSIS

BY

Dr. G BALASWAMY REDDY

for DM Neurology

of

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM

SYNOPSIS

Introduction

Young stroke has devastating effects on patients and families**.** There is limited data on young stroke from low- and middle-income countries, especially regarding etiology and long-term outcomes from India.

This study aims to analyze the risk factors and short-term and long-term outcomes of young [18-50 years] ischemic stroke patients.

Methods

The young patients with first-ever ischemic stroke, between 2011-2020 were included in the study. The clinical, demographic details, and risk factors data were collected. The stroke etiology is classified according to the TOAST classification. The outcome measures included were recurrent vascular events, mortality, and functional outcome at 3 months and one year.

Results

Of the 569 patients, 66.61% were males, with a mean age of 40.70 [SD±7.63] years. Diabetes mellitus (34%), hypertension (40%), and smoking (33%) were the most common risk factors. Cardioembolic stroke was the etiology in 113 (19.8%), specific causes in 139 (23%), and undetermined in 191(33.5%). Among the specific etiologies, arterial dissection was the single most common cause accounting for 15.6%

of all-cause strokes. A good functional outcome (mRS 0-2) seen in 65% at 3 months & 77% at 1 year. Recurrent strokes occurred in 16 (2.81%) patients at 1 year. In multivariate analyses, the baseline stroke severity was the predictor of short-term (OR=15.6, 95%CI=8.18-29) and long-term (OR=11.4, 95%CI=5-26) outcomes. The history of tobacco smoking is the only independent predictor of mortality at 1-year. Diabetes mellitus is the sole independent predictor of recurrent vascular events at 1 year [OR=3.26, 95%CI=1.42-7.44].

Conclusions

Though the risk factors are similar, there is an age-related difference in the etiology of stroke in young adults. The outcome up to 1 year was favorable with low recurrence risk.

INTRODUCTION

INTRODUCTION:

Stroke ranked second among the major causes of death and third among the most frequent causes of disability globally. The total number of people suffering from stroke-related deaths and disability has continued to rise in low- and middle-income (LAMI) countries, primarily driven by an increase in worldwide incidence of stroke at an earlier age over the decades [1–3]. Currently, 15-18% of ischemic strokes are taking place in young adults (18-50 years) [1]. This is partly due to a trend of increasing traditional vascular risk factors at an earlier age. The other is due to an increased prevalence of modifiable lifestyle risk factors such as sedentary lifestyle, changing dietary patterns, and of course improvements in diagnostics over time [4].

Stroke has devastating consequences, especially in young adults, due to potentially serious sequelae such as physical disability, loss of visual fields, and cognitive impairment that may affect their physical mobility, social life, productive job, and quality of life. Overall, an increase in the prevalence of stroke at younger ages has substantial socioeconomic implications, as young adults constitute a major workforce in any society [5–7].

Most of the literature pertinent to stroke focused on elderly adults as well as the management of stroke in the young by and large based on the extrapolated data from stroke among the elderly. Despite an extensive evaluation, the risk factors and etiology of stroke remain mysterious in about one-third of young stroke sufferers [3,4]. This is further compounded by a difference in the risk factor profile between developed and developing countries. For example, preventable infectious causes like rheumatic heart disease, and tuberculosis are largely a problem in underdeveloped nations. Similarly, substance abuse-related strokes are the cause in the developed world. Along similar lines, cardio embolism is a leading cause of young stroke in Europe[1], whereas it is an uncommon cause in a recently concluded large young Chinese cohort[8]; additional factors contain a dearth of literature and secondary knowledge gap from developing countries

including India; another consistent issue is sample size constraints & methodological heterogeneity across scientific literature [8–13].

Above all emphasize an increasing need for clinical research into the various aspects of stroke in young people, particularly putting things from an Indian perspective. This includes differences in their clinical profile of young stroke; risk factors, and factors that determine the outcome. This may translate into various interventions or preventive measures, thereby reducing the recurrences and their associated morbidity and or mortality.

In this study, we attempted to analyze whether the change in the risk factor profile and outcome in the South Indian scenario is identical or different from the western population.

AIMS AND OBJECTIVES

Aims & Objectives:

• To investigate the etiology, risk factors, and short-term (3-months) and long-term (1-year) outcomes of young adult patients with first-ever ischemic stroke.

• To evaluate the risk of recurrent vascular events in young stroke patients.

REVIEW of LITERATURE

Young stroke:

Patients who develop stroke at a younger age must cope with a tremendous impact on their life for the coming decades. This is due to their longer post-stroke survival periods with neurological deficits such as loss of visual fields, physical disability, and often inability to drive, and overall, they may suffer from low quality of life or suffer from a cumulative cognitive deficit [14]. This is because young patients are often at crossroads in their lives with young families, demanding jobs, and social interactions that may remain impaired in coming decades. In addition, the socio-economic strain of stroke in the young due to loss of working years and pricy health-care costs is high, bearing in mind also the number of productive life years lost. Stroke is a major cause of morbidity and mortality worldwide making the enormity of socio-economic implications to nations the huge [9].

What upper age cut-off exactly constitutes the younger adults is an ambiguous topic in the published literature as throughout the timeline. Also, from various geographic regions. For example, it ranged widely between 45 years to 65 years in the published literature during the last 3 decades across the world including analyses of the global burden of diseases by WHO. However, in the past decade, a widely accepted upper cut-off of 50 years has been emerging, and increasingly studies use the range of 18 to 50 years as the pragmatic definition while describing the younger adults who have stroke [4,9,15].

Epidemiology:

Up to 10-15% of first-ever strokes are estimated to occur among younger adults aged between 18-50 years [9]. With an annual stroke incidence of 15 million people around the world, we expect at least 1.5 – 2 million young adults to be suffering from strokes every year globally[16]. In the recently published review article, the incidence of young stroke ranged from 5 to 15 per 1,00,000 person-years in many European studies to 20 per 100000 person-years in most Northern American, Australian, and Asian studies and as many as 40 per 100 000 person-years in certain African countries and Iran[9]. There is a paucity of exact incidence or prevalence data for most African and

Asian countries, and hence a precise global burden of this problem is not known. Add to this, certain methodological issues can impede appropriate comparisons of published incidences, which include the heterogeneity in the definition of young ischemic stroke, regarding age limits used, and the inclusion of other stroke subtypes. There is a wide range of variation in the young stroke prevalence and its sub-types globally. The reasons for this include geographic distribution, race, ethnicity, socioeconomic status, and the prevalence of vascular risk factors.

There is an overall trend of rising in stroke incidence with increases in age. Studies show that octogenarians are at a 2-fold higher risk for stroke and a 3-fold higher death rate than younger adults and thus projected to be lower among young adults. Approximately 10% of all strokes occur under the age of 50 years [15]. However, certain studies showed a steadily increasing trend over the past few decades in the incidence of strokes among the young. For example, one of the largest systematic review studies spanning over three decades on the incidence of stroke among young adults. It analyzed 29 papers published between 1980 and 2009 including 3589 patients. It showed crude rates of first-ever stroke ranging between 5.76 and 39.79 per 100,000 whereas standardized rates ranged between 6.14 and 48.51 per 100,000[3,4,9,16,17]. This study highlighted an increase in absolute numbers and prevalence rates in both ischemic strokes for younger adults between 1990 and 2013. Another study noted a more than 100% rise in the incidence of stroke, from 1970-1979 to 2000-2008[18]. This was done from low- and middle-income nations including the data from India.

Concurrently, certain studies have also shown a drop in strokes in elderly patients. However, there is concern that this overall trend masks an alarming rise in incidence among the young. In this regard, the American Heart Association states that '[t]here is now a large amount of evidence that ischemic stroke incidence is increasing in young adults, and the reasons behind this trend are probably multiple'[19]. Certain factors can contribute to this trend of increasing young stroke incidence over the decades. In contrast, a greater incidence of young strokes in low-income nations is due to variations in the risk factor profile and variations caused across the time points and the lesser recognition and treatment of risk factors due to resource

limitations & financial constraints. Current technological sophistications for example in MR techniques made DWI able to detect even smaller infarctions in patients with symptoms lasting <24 h when combined with ADC image. In addition, the prevalence of cardiovascular disease risk factors has changed over time[2,9]. There is an increased prevalence of diabetes mellitus, dyslipidemia, hypertension, obesity, and increased use of alcohol and illicit drugs in the younger population.

One can notice remarkable sex differences in the incidence of young stroke. The incidence is lower for women than for men under the age of 75 years and males are at greater risk of ischemic stroke when compared to females [2,3]. However, some studies from Europe and the USA demonstrated that women outnumbered men under certain age groups like the age of 30, 35, or 44 years [5]. In contrast, the incidence rates were comparable between both sexes in France (18 to 55 years), and in Spain, the incidence was greater among men (18 to 54 years[9]). From the Asian point of view, a study showed in the Chinese adult population (aged 20 to 49 years), that there was no statistical disparity in the age-standardized prevalence of ischemic strokes between the sexes [9]. The growing incidence of stroke at youthful age varies between men and women. Among the females, a larger number of strokes were under the age of <35 years. In contrast, men had a higher incidence of strokes in the >35 years age group.

Socioeconomic conditions and lifestyles might be confounding factors to account for such gender-based differences in prevalence. In another aspect, these differences are partially explained by female-specific risk factor and their causes. For example, oral contraceptives, pregnancy and puerperium, and the greater incidence of migraine, and auto-immune disorders among women. The landmark TOAST study found a male predominance in etiologies such as large arterial disease (LAA) and small-vessel disease (SVD), while female predominance was seen in specific etiologies [9]. Tobacco abuse and diabetes mellitus have been associated with stroke among both sexes. The relationship of ischaemic stroke with cardiovascular disease (the presence of coronary heart disease, heart failure, or peripheral arterial disease), diabetes mellitus type 2, hypertension, positive family history, and low HDL-cholesterol were significant only among the men in the recent Finnish study[4,9]. The population attributable risks (PARs) of high blood pressure, diabetes mellitus, tobacco

abuse, and alcohol intake were higher among men than in women. In contrast, the PARs of a sedentary lifestyle and overweight/obesity was greater for women than for men.

Geographically there is variation in the incidence of strokes in a young population. It ranges from 5 to 10% under 45 years in western nations. This was from 19 to 30% in the developing world [3]. For example, in one study from the developed world, a high yearly incidence rate of 7–17 per 100,000 for populations 45 years reported whereas contemporary Indian data showed that 20% of patients diagnosed with first-ever strokes hospitalized were younger than 40 years. Certain evidence also shows that the median age of patients with stroke in the developing world is 15 years younger than their peers in developed countries.

In this regard, the largest dataset from the Global Burden of Disease study between 1990 and 2010 showed the age-normalized incidence of stroke significantly decreased by 12% in the western countries, whereas it increased by 12% in LAMI countries [3,18]. Despite the overall decline in stroke incidence reported in high-income countries, certain epidemiological surveys from the USA reported a progressive increase in young strokes. For example, ~30,000 young stroke hospitalizations occurred in 2013 alone which is significantly higher than in 2003. Although the trend of increased incidence of a stroke may also be partly due to changes in diagnostic classification systems, the true effect of improved diagnostic tools such as the use of magnetic resonance imaging (MRI), and better reporting mechanisms in recent years, maybe no longer as significant as one may expect [19].

The marked ethnic and racial inequalities with a greater risk of strokes in the black and Hispanic populations when compared to the White population in the USA. For example, in the USA, the stroke incidence among Black people and Hispanics (both eleven for each 100 000 persons/year) was found more than in whites (7 per 100 000 persons/year) [9]. The disparity in incidence rates between Black people and whites in the USA is highest between the third and fourth decade of age. For both Black people and whites, there is a growing incidence of stroke among young adults outlined over time. This disparity might be attributable to the high prevalence of hypertension in Black people and diabetes among Hispanics when compared to the White population

groups. Concerning the high rate of stroke in Asians, a Taiwanese study attributes it to the high rate of certain vascular risk factors associated with Asian populations like hyperlipidemia, tobacco use, and high blood pressure than their counterparts. Similarly, a population study in Australia reported on stroke differences between the Indigenous and Torres Strait Islanders compared with the total Australian population. Natives had twice the risk for strokes as the non-Native populations (with an incidence ratio of 2.4; p=0.06) [3]. The availability of such data on socio-ethnographic variations from developing nations is scarce.

1. Risk factors:

There are two kinds of risk factors that contribute to stroke. 1) Non-modifiable risk factors that include - gender, age, race, ethnicity, and different genetic factors [20,21]. 2) modifiable risk factors: diabetes mellitus (DM), high blood pressure, atrial fibrillation (AF), smoking, etc comes under this category. These are preventable or modifiable in nature. Around 80% of ischemic strokes in the young are known for modifiable or traditional risk factors. Globally the prevalence of modifiable risk factors among young stroke continues to grow over decades. There exists a gender-based variation in their distribution. For example, certain traditional risk factors (high blood pressure, diabetes mellitus, tobacco smoking, and alcohol consumption) are more common in young men than in younger women whereas others (low exercise and high BMI), are more represented in young women. The above risk factors not only contribute to the pathogenesis of stroke but also affect recovery from stroke. As the nature of risk factors varies in young stroke patients, studying them and their variations in contrast to the elderly would be of paramount importance.

Many studies have shown that young stroke patients have an elevated prevalence of having multiple vascular risk factors. Also, the nature of the risk factor could differ; for example, among traditional vascular risk factors occurrence of hypertension shows a growing trend with increases in age whereas smoking is much less common in older people than in younger adults. Even there is emerging evidence showing that the PAR of certain traditional vascular risk factors in the young stroke is significantly different from that of stroke among the elderly. Another aspect is concerning the number of risk factors I.e., young stroke patients have double the number of risk factors than counterparts with stroke as shown in a study. A multi-centric study conducted in Europe and USA has shown an absolute rise in the prevalence of high blood pressure (4–11%), dyslipidemia (12–21%), diabetes mellitus (4–7%), smoking (5–16%), and obesity (4–9%) over the last few decades [9]. As the prevalence of prospective recurrent vascular events will be determined by multiple vascular risk factors an individual has,

the possession of multiple risk factors among young stroke patients is particularly concerning.

Among the modifiable risk factors diabetes {for type-1 diabetes OR = 6.72 (95% CI 3.15 to 14.33) to type-2 diabetes 2.31 (1.35 to 3.95)}, sedentary lifestyle {OR = 5.9 (95% CI 5.1 to 6.7)} found to have greater odd ratios followed by current smoking status, hypertension, and obesity respectively; however, concerning PAR, it was highest in sedentary lifestyle {59.8 (56.2 to 63.4)} followed by hypertension {19.9 (14.8 to 23.9)}, current smoking status, obesity, followed by diabetes in the descending order [9].

Following is a brief literature review on certain common and unusual risk factors for ischemic stroke in young.

Non-modifiable risk factors:

1. **Monogenic causes:**

Seven percent of strokes in the young are explained by this category. Although recent progress in genetic testing led to the identification of several monogenic disorders as causes of young strokes, still AHA/ASA guidelines do not routinely recommend screening of genetic factors on a routine basis [9]. A significant proportion of them is mediated by the cerebral small-vessel disease only. This particularly is suspected when (recurrent) lacunar infarctions occur with accompanying severe, confluent white matter hyper-intensities without any known vascular risk factors. As clinico-radiological symptoms and signs are not often specific to any single underlying genetic cause, genetic testing often would be prudent [22].

Sickle cell anemia:

This disease is caused by a genetic mutation in the hemoglobin gene. Resultantly there is an abnormal viscous nature of blood contributing to strokes. The most serious form has been homozygous hemoglobin S (HbSS) mutation. Certain studies have shown its association with ischaemic stroke. In the USA, there

has been an increase in the incidence rate of ischaemic stroke among populations suffering from sickle cell anemia i.e., it increased with age; ~740 for every 100 000 person-years in the 35-64 years age group, which is thrice greater than in general population. In its heterozygote form sickle cell disease carries a less severe risk develop a stroke. Though the sickle-cell disease is a well-known monogenic disorder with stroke as a possible primary manifestation, among African Americans, a recent meta-analysis did not prove an association between sickle cell trait and ischaemic stroke. It may suggest other alternative mechanisms in pathogenesis. Enormous differences exist in the worldwide distribution of this disease. For example, in the African area, it represents as high as 75%, followed by Southeast Asia where it accounted for 15% of the worldwide burden. In contrast, the European continent accounted for 1.3% while in the USA it was 4.6% of neonatal disease burden [9,14,17].

Although rare, metabolic disorders, such as **Fabry** disease also be linked to stroke in young adults up to 1% in a survey of 5023 patients with young strokes. Thus, routine genetic testing used for Fabry disease is not required yet.

In most instances, genetic components are a part of a multifactorial predisposition to stroke, for which individual genetic variations are responsible for a small increase in risk. Thus, therefore, routine genetic testing was not warranted yet. For example, a common genetic variant in a single intron of the PHACTR1 gene has been linked to a modest increase in risk for fibromuscular dysplasia as well as cervical dissection. This was explored in the initial genome-wide association studies (GWAS). The GWAS is restricted to young people with a stroke that remains in its early stages of development [23]. Just one genome-wide association signal has been identified, near HABP2, which encodes a serine protease that regulates coagulation, fibrinolysis, and inflammatory pathways and is expressed in high concentrations in young people with stroke. Studies with larger sample sizes are ongoing to confirm and expand this finding.

The modifiable-risk factors: common ones

1. **Systemic hypertension:**

WHO reports the supreme prevalence of systematic hypertension in Africa [46%], whereas it is lowest in the north and South Americas [35%]. Hypertension is the most frequent risk factor in ischemic strokes. Studies in young patients with ischemic stroke have shown up to 35% prevalence of systemic hypertension. A newly published large young stroke cohort from Chinese showed a high prevalence of 55.3%. For hypertension PAR was higher in the Southeast Asian region [54.8%] compared to European countries [40.7%]. Lower PAR [12.2%] has been found in populations such as Finland's young stroke cohort. In this context Indian cohorts showed a prevalence of 17%; however, this was up to 23% in certain age groups in the fourth decade & early fifth decade [3,9].

2. **Dyslipidemia**

50-60% of young stroke sufferers have lipid anomalies in multiple cohorts consistently. This trend is particularly noted in certain etiological categories of young strokes including large artery atherosclerotic disease and small vessel disease. This was not common in the cardioembolic strata. Despite being very prevalent, dyslipidemia has not shown a significant increase in PAR for all cause-stroke (PAR of −2.1%; 95%CI −6.7 to 2.6 and OR=0.9; 95%CI 0.8 to 1.1). However, this discrepancy is explained in part by the presence of diverse risk factors associated with young stroke causation, and for certain of them, dyslipidemia is not a direct risk factor. The contrary explanation would be large artery atherosclerotic disease and small vessel disease most often found in the elderly. For both above conditions, dyslipidemia is a common risk factor. Certain methodological flaws also need consideration while interpreting this over-representation but less PAR; it is the rarity of large studies looking at each lipid variable and their relationship with a stroke rather than the most often used high LDL & low HDL method. For example, a Brazilian study reported an association of apolipoprotein B (ApoB)/apolipoprotein A-I (ApoA-I) (ApoB/ApoA-I) ratio

with the ischemic stroke (OR=4.03; 95%CI 1.62 to 10.03). Whereas another study from Finland did not find any connection between LP (a) and early atherosclerosis, though the latter did not explore the association with cerebrovascular accidents [3,9,24].

3. Diabetes mellitus

Up to 10% of young stroke patients are detected to have this risk factor. Generally, PAR for diabetes in young adults would be around 5%, whereas diabetes association with young stroke was with an OR of 2. Due to the growing prevalence of diabetes globally, particularly in the Asian part of the world, it is a significant risk factor in preventive measures. Currently, India is among the top 3 world nations with the highest prevalence of diabetes. Also, PAR for diabetes is much higher in Asians [28.6%] than in the western world [3.5%]. There is also gender-based variation I.e., type -1 diabetes has a greater association with the female gender.

From the Indian perspective a previous study from our center published in 1997 showed a prevalence of 7% for diabetes, and 18% for hypertension. Data is scarce from rest of the India to study the regional variation [3,9].

4. Smoking

The proportion of people having active smoking is high among patients with young stroke; a review has shown a prevalence of up to 50%. Smoking contributes to young stroke with high PAR or around 20%. Also, over recent decades data has shown that smoking is becoming more prevalent among young cohorts of ischemic stroke. Between tobacco smoking and young ischemic stroke, there exists a dose of exposure-harm relationship. In the published literature higher prevalence can be seen in the European countries [28.7%] & in Southeast Asia whereas lower prevalence has been observed in studies from the African countries [13.9%]. The PAR also ranges from 4.5% in African patients whereas it is as much as 18% in Western Europe. In those studies, it has been demonstrated that the prevalence of smoking was elevated in South Asia and certain western and Central European countries. Concerning the gender-based variation, the high prevalence of smoking

among females is evident in western and central European countries. Also, a racial predilection was observed in whites [3,6,9].

The risk increased with the duration and dosages of the exposure, which ranges from an OR of 2·2 (1·5–3·3) for one to ten cigarettes use per day up to an OR of 9·1 (3·2–26·0) for 40 or more cigarettes use per day. A substantial proportion of smokers in young ischemic strokes comes from certain developing countries, which is a key concern [25–28].

5. Alcohol abuse

Though no specific studies directly, across all studies globally shown that alcohol consumption, in general, raises the risk of ischemic strokes. There are certain geographical differences in alcohol abuse. The prevalence was likely to be higher among high-income countries in comparison to low-income countries. Also, there is gender-based variation i.e., males are found to have a higher prevalence of binge drinking than females. Studies from European centers demonstrated that binge alcohol drinking can increase the risk for young stroke at high PAR [17.3%, 95% CI 14.2-20.5; OR=2.2; 95% CI=1.9-2.5] [6,8,9,29].

6. Obesity:

Obesity is becoming the largest global health epidemic. The increasing BMI seen among children and adolescents puts them at increased risk for cardiovascular complications, including stroke at an early age. These trends are disturbing. It warrants better primary prevention. This includes lifestyle adjustments, such as dietary therapy, quitting smoking, increased exercise, and early screening for identifying and treating these risk factors [2,8,9,30–32]. Despite sedentary lifestyles being the primary risk factor most often in western countries than in developing nations.

Less common modifiable risk factors:

Migraine: Various case-control studies showed that patients suffering from migraines with aura are at an elevated stroke risk among young females under 40 years of age. This relative risk seems close to three. Too high OR of 34-35 was reported in the group of young women who have a history of smoking, using the OCP, and

experiencing migraines with aura. The mechanism of stroke in this condition is yet to be elucidated. Proposed mechanisms were by having an impact on the posterior cerebral artery territory, single and multiple infarcts of any size and locations reported in the literature. Also, the frequency of strokes is too low to illustrate the risk of stroke in migraineurs. Other potential mechanisms could be an association of migraine with known or unknown causes or risk factors associated with stroke (e.g., PFO, dissection). Other mechanism includes increased platelet activation, the secretion of serotonin, and increased aggregation of platelet during an acute attack. Certain disorders such as MELAS, CADASIL, or conditions such as essential thrombocythemia can also contribute to stroke and consistently demonstrated an association with migraine. The presence of cerebral infarcts among the migraineurs warrants thorough investigation along the same lines as done for any ischemic strokes among young people and, the term migrainous stroke the diagnosis of exclusion [2,23,25,33].

In different series, a variable percentage of women ranging from 7%- 45% give a history of **oral contraceptive** use. The stroke risk increased by four times for women receiving pills high in estrogen and is doubled for those who take pills with low estrogen content. This risk is truer for women with a concomitant history of migraine headaches and or prothrombotic states. Oral birth-control pills exclusively containing progesterone do not seem to raise the risk of stroke [2,33–36].

During pregnancy the risk of ischemic stroke increases in the 3rd trimester, and within the 1st six weeks following delivery. However, an overall pregnancy-complicated stroke is rare. It is an enigma that whether a hyper-coagulable state related to pregnancy or certain gestational changes in vessel walls contributes to the increasing incidence of these cryptogenic ischaemic strokes is unclear. Eclampsia is the major pregnancy-specific disorder that may be associated with conditions such as reversible cerebral vasoconstriction syndrome (RCVS) and with stroke mimicking episodes [1,2,37,38].

I**llicit drug abuse** though conventionally considered primarily a problem in the western world is no longer true and it is a growing trend in the developing world, particularly in South Asian countries [2,3,39].

2. Etiology:

The etiology of ischemic stroke is more heterogenous for the younger populations than the elderly. It represents up to 1/5th of cases in some cohorts. Prevalence data of the etiological strata comes from a large Baltimore (USA) cohort published in 1998. It showed that large artery atherosclerosis was present in only 2% of cases, whereas cardio embolism in 15%, small vessel disease in 10%, specific causes in 35%, and the etiology was undetermined in 38% of cohort [40]. Comparison this with a European study (2009) published ten years later reveals similar pattern: LAA (7.5%); SVD (13.8%); cardio embolism (19.6%); specific causes (26%); and cryptogenic in 31% [3]. The **Helsinki stroke registry** is shown as follows: LAA (8.4%); cardio embolism (18.7%); SCD (13.9%); among the specific causes dissection alone contributes to an overall frequency of 15.5%; and cryptogenic strokes were 33.1% [41].

In the Indian context, early studies mention that 21-48% of young strokes occur due to large artery atherosclerosis, 10-33% due to non-atherosclerotic arteriopathies, 13-35% due to cardio embolism, 3-18% attributed to lacunar etiology whereas the remaining 4-15% attributed to specific causes. Also, they noted the very presence of conventional vascular risk factors like hypertension, diabetes, and hyperlipidemia were seen more often in patients with large artery atherosclerotic disease or small vessel occlusive disease [7].

A 2007 study on the young stroke from SCTIMST showed the prevalence of cardioembolic stroke at 25.2%; large artery atherosclerosis at 12.6%; lacunar infarcts at 7.5% and Strokes due to other determined etiology in the remaining 11.2%. Among the specific etiology, dissection was the most frequent observation [10]. The table below is a brief review of the etiological data published from the Indian context. Besides those mentioned in the table, other studies from the north-eastern part of India, Karnataka, and Kerala published the data on young stroke etiology. A few of them did not classify the etiology in a standard way and or had certain methodological shortcomings hence they could not be mentioned [12,42–44]. (Table 3.1, 3.2)

Table 3.1: Etiology of stroke from studies published across the world

Study	**Age group**	**Patient no**	**LAA**	**SVD**	**CE**	**ODE**	**UDE**
Nayak et al[45] ***(India) 1997***	**15–45**	**177**	**12.6**	**7.5**	**25.2%**	**11. 2%**	**43**
Kittner et al.,1998 (Baltimore, USA) [40]	**15–44**	**428**	**2**	**10**	**15**	**35**	**38**
Leys et al., (France) 2002 [46]	**15-45**	**287**	**8.4**	**1.7**	**5.2**	**22.3**	**62.5**
Lipska et al., (India) 2007 [10]	**15–45**	**214**	**12.6**	**7.5**	**25.2**	**11.2**	**43.5**
Putaala et al., (Finland) 2009. Helsinki Young Stroke Registry [41]	**15-49**	**1008**	**7.5**	**13.8**	**19.6**	**26**	**31**
Wasay M., Kaul S, et al (Asian centres) 2010 [47]	15–45	958	24	15	19	**NM**	**NM**
Jiao Jiao, et al (China), 2019 [8]	**15-49**	**956**	**43.7**	**39**	**5.1**	6.3	5.9

LAA: Large artery atherosclerotic disease, SVD: Small vessel occlusive disease, CE: Cardioembolic, ODE: Other determined etiology, UDE: Undetermined etiology

Table 3.2: Indian literature on the etiology of stroke

Indian study and year	Age group (In years)	No. of patients	LAA (%)	CE (%)	SVD (%)	Cryptogenic (%)
Bansal et al[7]; 1973	15-45	177	24	17	-	36
Nayak et al[45]; 1997	15-45	177	24	17	8.2	36
Lipska et al[10]; 2007	15-45	214	7.9	25.2	7.5	43.5
Masaraf et al[43]; 2018	15-45	76	51.31	15.78	-	21.05

1. Large artery atherosclerosis

Usually, as age increases in young adults, the incidence of conventional vascular risk factors adds to the well-established risk factors for atherosclerotic disease, thereby higher prevalence seen in higher age groups among the young. Therefore, it is more common by the late '40s [2,25,48–52].

Extra- or intracranial large-vessel arterial atherosclerotic disease is an unusual cause of stroke in young patients but other pathologies such as arteritis (especially Takayasu arteritis) are not uncommon, especially in Asians. In addition, Moyamoya disease is also an important etiological consideration.

Depending on local availability and experience, various investigative modalities such as CTA, MRA, DSA, or neck vessel Doppler in conjunction with TCD [34,35,12] may be of use in the evaluation of extracranial or intracranial arterial disease or arterial occlusion.

2. Cardioembolic

Compared to the other etiologies this group causes more serious strokes. Common causes come under this category include diseases of cardiac valves, congenital structural heart defects, cardiomyopathies, patent foramen ovale which can cause

paradoxical embolism, and most importantly cardiac rhythm disorders, especially atrial fibrillation.

Among the cardioembolic strokes mitral valve disease is the most common. In certain cohorts, rheumatic heart disease prevalence varies between 40% to as much as 70%. Rheumatic heart disease (RHD) is an autoinflammatory condition caused by an aberrant immune reaction to untreated streptococcal infections caused by group A species. It causes valvular damage thus increasing the odds of a cardio-embolic stroke due to their diverse secondary complications. The RHD prevalence among young strokes ranges from 1.8-2.0% in the European continent and Northern America whereas it ranged from 3.4-23.2% in Asia. RHD is most frequently seen in LAMI countries in comparison to western countries. For instance, in Iran, it was 32%. In contrast, it was far less frequent in the Helsinki stroke registry due to the virtual absence of rheumatic fever in that part of the world. Similarly, DCM is more common in South American countries owing to Chagas' disease, also due to the high prevalence of alcohol abuse in certain regions of the world. Atrial fibrillation represents a small but significant fraction of cases in several studies i.e., 4-17%, most often it is associated with RHD. In the absence of RHD, nonvalvular atrial fibrillation is responsible for a much smaller number of cases. Other potential causes in the cardioembolic category would be myocardial infarction, SABE; rarely aortic valve disease, and LV clot[2,33,41].

Investigative work up to detect this category include ECG, TTE, TEE, Holter monitoring, and cardiac MRI which may reveal specific etiology in most patients, and correction of which often significantly reduce the future stroke risk[53,54]. In young patients, high-risk sources of embolism detected using echocardiography include those develop on mechanical prosthetic valves, and in conditions such as mitral stenosis, endocarditis (infective and non-infective), dilated cardiomyopathies, and intracardiac thrombus, and associated with intra cardiac tumors.

PFO as well as atrial septal aneurysm, akinetic or dyskinetic segments of the ventricular wall, and redundant mitral valve prolapse are the common sources of often cryptogenic strokes. In this technique usually, agitated saline will be injected into the antecubital vein. Then transcranial doppler monitoring of bilateral middle cerebral

arteries will be done to detect a right-to-left shunt. One can provide grading of shunt intensity also [14,33,55].

The foramen ovale is a remnant of fetal life. It remains patent in about one-fourth of the general population. TEE with a bubble contrast study is the more sensitive diagnostic test. Suggested mechanisms of stroke with PFO include - a shunt via a PFO that might allow passage of thrombotic material from the veins into the arterial circulation (paradoxical embolism); direct embolization of thrombi formed in situ and paroxysmal arrhythmia. One should note that PFO is a common finding in the normal population and an incidental finding in about a third of patients with ischaemic stroke. Few strokes consequently misattributed to a PFO [14,56].

PFO and its relationship with young ischemic stroke is a complex topic, though seen in a small number of cases. A meta-analysis of 566 young strokes including nine cohorts, showed that the PFO had an OR of 6.0 for young stroke among the cryptogenic etiology compared to young patients with a known etiology of stroke. Having a PFO has an OR of 3 for the stroke. Studies regarding the large septal defects yielded conflicting results in the published literature.

Though arrhythmias such as atrial fibrillation, and atrial flutter are important in the etiology of stroke [57,58], most often a problem of elderly rather than young strokes [49,59–62].

3. Small vessel disease

Also called lacunar stroke, this entity denotes the occlusion of a small-vessel perforator usually produces a tiny (<15 mm diameter) deep hemispherical or brainstem stroke. Most considered etiologies were high blood pressure and diabetic state. However other causes such as infection, vasculitis, Fabry's disease, and CADASIL also can produce such tiny lacunar infarcts. These patients are often incidental silent lacunar infarcts, leukoaraiosis, deep or periventricular white matter lesions on T2-weighted and FLAIR MRI, or micro-bleeds on GRE/SWI sequences. However, before labeling a patient with lacunar stroke, two common pitfalls need to be avoided: (1) proximal arterial or cardiac embolic source also produces a small deep infarct and must not be missed, and (2) cholesterol plaque

on the wall of a large vessel may encroach ostium of the perforator vessel. Therefore, it may cause a lacunar infarct. These should be adequately investigated and excluded [2,14,63].

4. Specific causes:

Dissection

The most significant single cause of young ischaemic strokes is arterial dissection. This constitutes ~15% of all young strokes in specific populations. Due to financial constraints, poorer countries may not at all thoroughly investigate with a neck CT angiogram or doppler study often. Most often imaging is available only for intracranial vessels. In Europe, extracranial artery dissections are more frequent whereas in Asia intracranial dissections are more common. The most frequent location affected is the extracranial vertebral arteries. Most occur spontaneously. However, in certain instances, patients give a medical history of associated triggers such as coughing, vomiting, sudden head movement during road-traffic accidents, chiropractic manipulation, or sexual intercourse. Other predisposing factors include migraine, recent infection, pregnancy, and OCP use. In a few studies, overweight and dyslipidemia may be protective against spontaneous cervical artery dissection. Among the genetic etiologies most often found associations are with Ehler-Danlos type IV, Marfan syndrome as well as Pseudoxanthoma elasticum [14,23]. In this, a tear in the vascular intima leads to thrombus formation, which can potentially cause an artery-to-artery embolism. This hypothesis forms the basis for theories of the rationale of early anticoagulation. Unless an extension into the aorta, ischemic strokes due to cervical arterial dissections usually are not contraindicated for iv thrombolysis. Regarding the outcome in such cases, a study reported that 9% of cases developed recurrent dissection during the first month of the index event. Seven percent of recurrent dissections are seen after 1 month following a stroke. A pragmatic multicenter randomized control trial showed much of the recurrent strokes after extra cranial cervical artery dissection occurs during the first 10 days after stroke, although a small percentage (1%) [22].

In the extracranial ICA dissection typically begins just inches after the

common carotid bifurcation, or in the vertebral artery after it enters the intervertebral canal or as its exit from the intervertebral canal and just before piercing the dura. In one-fourth of cases, extracranial dissection occurs in multiple vessels. Dissection usually occurs subintimal and the resultant bleed may cause long, irregular stenosis or even occlusion of the affected vessel. Occasionally dissection may occur subadventitial; in such cases, it forms the pseudo-aneurysm. Clinical features suggestive of dissection include the history of head or neck trauma (even minor), headache or neck pain, and local signs (such as Horner's syndrome or cranial nerve palsies), in addition to or without other symptoms of cerebral ischemia [2,38].

Vasculitis

Primary systemic vasculitis such as SLE and Takayasu's disease stroke is common and often perhaps the presenting feature. Other vasculitic strokes include Churg-Strauss, Granulomatosis with Polyangiitis vasculitis, polyarteritis nodosa, cryoglobulinemia, Behçet's disease, etc. Sneddon's syndrome is an uncommon condition featuring widespread generalized livedo reticularis and multiple strokes which may occur in isolation or combination with antiphospholipid syndrome. Though rare incidence-wise primary angiitis of the CNS is another major cause of young strokes [64].

In this category, most patients suffer from encephalopathy, cognitive decline, and headaches. Lumbar puncture tests frequently show lymphocytic pleocytosis, and CT angiography either shows signs that suggest vasculitis or is normal. Confirmation of the diagnosis will often require an invasive procedure like meningocortical biopsy despite it might be often negative or inconclusive (sensitivity: 50–60%). Cerebral vasculitis needs distinctions from RCVS. In the latter various segmental stenosis of the intracranial vessels disappear on follow-up angiograms after a couple of weeks and CSF tests are usually normal[2,33].

Moyamoya disease:

Moyamoya disease presents 6 – 15% of non- atherosclerotic vasculopathies among the young. It has a predilection for Asians; however, it is not unusual in whites and for those of African descent among the specific causes of stroke. It has a

characteristic DSA feature, the so-called 'puff of smoke' from which the term 'Moyamoya" derived from bilateral intracranial carotid artery stenosis/occlusion with associated dilatation of lenticulostriate arteries[9,65]. Moyamoya disease is characterized by progressive stenosis of the ICA, eventually leading to occlusion. The prevalence rate of Moyamoya disease is higher in children and adolescents than in those aged 50 years or more besides a geographical variation. Across non-Asian countries, the true prevalence of Moyamoya is yet to be studied. From published literature, the highest prevalence was observed in certain Asian countries i.e., ~10.5 for each 100 000 persons in Japan. It was 16.1 for each 100 000 persons in the Korean peninsula. Up to 4% seen for each 100 000 persons in China. Whereas lower prevalence is seen from the limited available data of Western countries; most exact numbers are unknown. Corresponding to prevalence, a high incidence was found in Japan (9.4 for each million population), South Korea (23 for each million population), and China (4.3 for each million population), while the incidence in Washington and California (0.86 for each million population) is much lower. Accurate epidemiological data on Moyamoya disease in other areas are lacking [2,65,66].

Other miscellaneous causes include **RCVS** which accounts for <5% of all young strokes and is an increasingly recognized condition over recent years. Reasons for the under-diagnosis are its reversible aspect. This can occur usually in postpartum but is also common in conjunction with cervical arterial dissection. Radiologically this entity is marked by a diffuse segmental cerebral arterial constriction with resolution at third-month follow-up. Sometimes associated with cerebral Convexity SAHs.

Other rare non-inflammatory arteriopathies:

Nonatherosclerotic arteriopathies: Various conditions such as dissection, migraine, vasculitis, infections, radiation vasculopathy, CADASIL, MELAS, RCVS, Moyamoya, Sneddon's syndrome, malignancy, and Fabry's disease comes under the rubric of nonatherosclerotic arteriopathies. A lot of these causes are influenced by racial, ethnic, geographic, and genetic linkages. For example, Moyamoya is mostly seen in Asians; similarly, Takayasu arteritis is seen exclusively in Asian female populations. Among the infections, varicella or TB can cause secondary vasculitic infarcts which are most seen in LAMI countries or HIV populations. Another rare

cause of PACNS more prevalent in middle-aged men, RCVS and Sneddon's syndrome were frequently seen in females. CADASIL can occur both as sporadic and familial. Published literature showed among this dissection is the most common occurrence. In certain studies, up to 20-25% were followed by infection-related vasculitis in up to 7% of cases. Moyamoya is particularly seen in Asians up to 6-15% of patients. Migraine as a risk factor in young strokes seen in 1-5% of the patient population in large cohorts. Whereas all other remaining causes among the above constitute another 7-25% of cases which also include cases of CAD, migraine, Moyamoya, and infections each of them accounts for ~1% of cases [2,3,33].

Other arteriopathies include radiation arteriopathy, fibromuscular dysplasia, and moyamoya syndrome [95,96]. The rare causes of young stroke include retinocerebral or retinocochlearcerebral arteriopathy, and other rarer causes include- Eale's disease (retinopathy with neoangiogenesis), Susac's syndrome (encephalopathy, hearing impairment, and the retina artery branch obstructions) [3].

Hematological disorders:

APLA syndrome: Certain studies have found an association between young ischemic stroke and the anti-LAC and ACL antibodies. In a large cohort of criteria proven APLA syndrome prevalence of stroke was 13%, whereas TIA occurrence was around 7%. Other systemic conditions such as the Systemic Lupus Erythematosus (SLE) exhibit an association with young stroke via APLA antibodies, however independently also they can cause ischemic stroke via conventional risk factors [1,2,25,33,63,67].

Apart from sickle-cell anemia, certain other hematological diseases affect young patients and are often complicated by an ischemic stroke. Paroxysmal nocturnal hemoglobinuria, thrombotic thrombocytopenic purpura, erythrocytosis, leukemia, and intravascular lymphoma were a few among them[1,25].

Infections:

Preventable **infectious** causes of stroke are uncommon in developed nations but are still frequently seen in developing nations. In addition, in most affluent countries because of the comprehensive diagnostic evaluation, a reliable etiology of a stroke may be determined. However, in idiopathic strokes, a patient's travel history is the

component most often that may go unnoticed or underreported. It has very important in a selected scenario of infection-associated strokes. Two of those examples of infectious etiology particularly seen in low-income nations are rheumatic heart diseases and Chagas sickness. They contribute to cardioembolic strokes in certain high-prevalence geographical regions such as Africa, the Middle East, and Southeast Asia [9,33,36].

Chagas sickness is a parasitic illness caused by a tropical Protista. It has an estimated prevalence of 6.6million people, mostly in Central and South American countries [2,9,14,57,58,68,69]. Unawareness of the infection among affected patients is the common reason for its enigmatic incidence. Chagas disease has been one of the common infectious causes of cardiomyopathy. It has an associated higher risk of young stroke (OR 2.10, 95% CI 1.17 to 3.78) and is treatable i.e., effectively managed by benznidazole and nifurtimox [9,25].

Other infections associated with an elevated risk of ischaemic stroke are HIV, neurocysticercosis, and tuberculosis. Particularly Sub-Saharan Africa reports a large seroprevalence of HIV often to the tune of carrying two-thirds of the world's HIV burden in conservative estimates. In those specific regions, often stroke could be an initial manifestation of the underlying HIV infection. In one systematic review, ~90% of young stroke sufferers from sub-Saharan Africa had HIV. It causes mostly ischaemic strokes. HIV patients with strokes often had coagulopathy and more severe strokes in comparison to those young without HIV infection. Studies from other developing nations also produced similar findings. Even after adjusting for the contribution of vascular risk factors, there was an increased odds of stroke among patients with HIV found in both gender people. Mechanisms of stroke in HIV- patients are alterations in the coagulation state, cardio-embolism, HIV- linked vasculitis & vasculopathies, as well as mycotic aneurysms [9,17].

Neurocysticercosis is an infectious opportunistic illness caused by cerebral cysts of tapeworms found in pigs. The inflammatory process surrounding the cerebral cysts has the potential to induce infarcts. Mechanisms explained were progressive stenosis and blockage of smaller and larger vessels around those inflammatory zones. Poor hygiene & local cultural customs have been known to associate with it. It frequently

occurs in rural areas, particularly those in Latin American countries, sub-Saharan Africa, and Asia. Tuberculosis is associated with an increased risk of ischaemic stroke that results from vasculitis or intimal proliferation causing thrombosis. Stroke in tuberculosis occurs in 15% to 57% of tuberculosis meningitis cases, especially in the severe ones. Approximately 8% of young strokes are attributed to infectious causes such as tuberculosis in countries such as India. The incidence rates of tuberculosis vary among nations. The highest rates were seen in nations from Africa and Asia [9,25,70].

5. Undetermined

In one-third of patients, the etiology of stroke cannot be identified despite the comprehensive initial aetiological work up till a decade ago; However, in recent studies, this percentage has dropped to 20-25% or a mere one-fourth of cases. This is also by and large due to advancements and the wide accessibility of diagnostics. Certain patients have conventional vascular risk factors, but they do not show evidence of either large atherosclerotic disease or small vessel arterial disease features. A frequent avoidable error while diagnosing cryptogenic stroke is an incomplete or delayed etiological workup. This misdiagnosis is of particular importance in the case of dissection, where dissection can resolve quickly; in the intracardiac thrombus, thrombus may either resolve or fragment or embolise. Similarly, outcomes of specific laboratory tests (eg, APLA syndrome) may fluctuate over time, and necessitate a repeated assessment. Along the same lines, repeated or extended Holter monitoring might be necessary to detect paroxysmal atrial fibrillation; a follow-up angiography distinguishes between reversible cerebral vasoconstriction syndrome, and vasculitis, atherosclerosis, or other vasculopathies of intracranial arteries, where the narrowing persist or even progress over the time [49,55,56,63].

The term ‘embolic stroke of undetermined source’ (ESUS), is reserved for a subgroup of cryptogenic strokes with radiological evidence of cerebral arterial territory infarcts thought to be due to cardiac emboli after exclusion of an arteriopathy, though no definitive proof of cardioembolic source established. Certain retrospective chart reviews showed that 9-25% of young ischemic strokes are thought to be ESUS. This is one of the areas in young stroke undergoing active investigation [2,15,56]. For example,

preliminary evidence showed that the use of anticoagulation in this group would fare better than anti platelets. Published studies investigated Rivaroxaban vs. aspirin so far for the management of this entity [57].

3. Outcome:

Short term:

In the cryptogenic ethology of stroke, few recent studies focused on imaging-based biomarkers in the prediction of short-term outcomes; for example, in a large study among 2732 patients with first-ever ischemic strokes, the presence of severe WMH independently predicted high long-term mortality (HR 3.11, 95% CI, 1.29–7.50) exclusively in younger adults and poor short-term functional outcome as assessed by 3 month - mRS scores (OR 5.25, 95% CI, 2.07–13.31). However, the limitations of that study would be the underlying concomitant substenotic atherosclerotic disease as acknowledged by the authors; of course, a primary objective of that study was different[49,71].

Limited available Indian literature is showing favorable outcomes in comparison to the western data. An Indian study published in 1997 showed a short-term good functional outcome in 75% of patients; among them 55% achieved recovery[13].

Long term:

In Asia, a study from Thailand (2013) published long-term (1 year) outcomes among young ischemic stroke survivors. It found overall a favorable outcome and certain factors such as cardio embolism and alcohol were associated with poor functional outcomes assessed at 1 year[36].

A negative long-term outlook was emphasized in a study from a Canadian longitudinal cohort (2019); it showed that young stroke survivors, even after adjustment for vascular comorbidities were at a 7-fold increased hazard of the composite outcome (including recurrent strokes, MI, all-cause hospitalizations) than controls matched at 1

year. In the same study even at 5-year and 5-year, piecewise hazard remained more than 5-fold higher[72].

Mortality:

A 20-year longitudinal study showed that cumulative mortality after stroke in young adults was 4-fold higher than the age-matched controls[2].

In this aspect, a 2017 published study from Eastern Europe showed higher short-term and long-term mortality among young strokes. It showed that among young ischemic stroke patients, higher mortality was predicted by stroke severity, presence of structural cardiac disease, and post-stroke infections. In that study cumulative mortality at 30 days and 5 years was 4.5% and 16.8% respectively. Among the deceased vascular causes were present in 87.9% at 30 days and 54.6% at the fifth-year follow-up [4,73]. In Western Europe (Netherlands) another study highest mortality was predicted by cardio emboli cholesterol etiology of stroke, whereas Baltic nations have shown large artery atherosclerosis as the highest contributor of mortality [66,74].

Regarding the cause of death, all-vascular causes have been attributed in 47-57% of cases in various published papers. A lot of them did not find any gender differences. Concerning individual causes of death, over the long-term general medical conditions are on the rise as evidenced by a South Korean study (at fifth-year follow-up) despite its significant contribution in the first 30 days following stroke [30,75,76]. Another European cohort found the association of post-depression in the mortality after stroke in the young, though the association between post-stroke depression and mortality is strongly and with higher odds established in the elderly cohorts with stroke[76].

In the USA, the length of hospital stay was found longest in Hispanics compared with Black people and whites. In Black people, the hospital stay was longer than in whites. This can partially be due to the greater frequency of medical complications (eg, pneumonia, deep venous thrombosis, or urinary tract infections) among Afro-Americans compared with the people who come from European American lineage. Afro-Americans are more likely discharged to a rehabilitation facility, skilled nursing facility, or a long-term-care hospital compared with people of European-American lineage. Also, mortality was found to be higher among people of

African ancestry when compared to those who migrated from Europe to the USA. Hispanics ethnics found to have a lower early mortality risk. An international multicentre collaborative study investigated young stroke patients' data from certain prospective databases maintained in the USA, Europe, and Asia. It concluded the existence of differences in hospitalization patterns, functional outcomes, and mortality. This study found that Asians (denoted by a median National Institute of Health Stroke scale (NIHSS) score of 8 (IQR: 5 to 14)) had significantly higher stroke severity at admission than Black people (median NIHSS score of 7 (IQR: 3 to 12)) and whites (median NIHSS score of 3 (IQR: 1 to 9) ($p<0.001$)). In addition, early mortality was found to be lower in Asians compared with Black people and whites. A population study in Australia reported on stroke differences between the Aboriginal tribes and Torres Strait Island people in comparison to the general Australian population. In the general group, they did not report any differences in the crude mortality due to all-cause strokes, studied at 1-year follow-up [9].

In India, a study showed a short-term mortality rate of 1.2% whereas in certain developed nations short-term mortality ranges from 2 to 12.7% [13].

Functional recovery:

A review on this reported that >50% of patients are unable to return to work after stroke in the young. A topical review mentioned that young patient after recovery from stroke were found to have certain cognitive domains affected on formal neuropsychological assessments and this persisted even at the 11th-year follow-up after a stroke, though this group fares better than the elderly in the overall-cognitive prognosis. Post-stroke fatigue was one of the common symptoms contributing to morbidity and poor functional outcome [9,21,22]. A Dutch study investigated the retention rates of employment following young strokes; it found that around 29% remained unemployed even 8 years after a stroke. Another Danish study found an unemployment rate of 33% at a second-year follow-up.

From the Indian context, literature is scarce regarding the functional recovery and employment levels among young patients who survive strokes in the long term.

Recurrence of vascular events:

When men compared to women in the propensity to develop recurrent strokes, few studies found evidence for higher mortality rates and risk to develop recurrent vascular events exclusively among men than women. The first one-month period after a stroke is considered the period with the highest risk to develop recurrent vascular events. This was consistent across all the age strata [4,50,52,73,77,78].

Usually, patients who develop strokes due to cardio embolic or large artery atherosclerotic etiology are at an elevated risk to develop recurrences, in comparison to the other classes of TOAST etiological classification.

The largest Italian cohort had shown that the risk of developing recurrent vascular events among young strokes is most often influenced by certain age-specific modifiable risk factors such as the positivity of antiphospholipid antibodies, migraine with aura, and poor drug adherence at discharge after stroke. There was also such an association with the risk factors for stroke.

From the western countries' perspective, another large prospective cohort from the Netherlands titled ‘Observational Dutch Young Symptomatic StrokE studY (ODYSSEY)’ initiated in 2014 addresses the mortality and recurrent vascular events, though it did not provide details on the functional outcome, recovery rates & employment levels at short-term and long-term follow-ups. It included the 18-49 years age strata and awaits completion [21].

From India in this aspect literature is scarce. Selected studies that provide data on mortality and the functional outcome often indirectly, as their main objectives were different, the employed methodologies were heterogeneous, and at times not standardized, hence needs consideration as a rough guide.

MATERIALS AND METHODS

Design:

A retrospective observational study.

Subject/Participant selection

All consecutive patients admitted to stroke unit/seen in stroke clinic aged 18 to 50 years with ischemic stroke from January 2011 to December 2020.

Inclusion criteria

1) Patients with acute ischemic stroke within 1 month of onset

2) Age group between 18 to 50 years

3) Patients with first-ever ischemic stroke

Exclusion Criteria

1) Intracerebral bleed, cerebral venous sinus thrombosis, and subarachnoid hemorrhage

2) Baseline modified Rankin scale more than or equal to 3.

Methods:

All patients who fulfilled the inclusion and exclusion criteria were included in the study. The risk factors of stroke were reviewed in detail. The various risk factors included hypertension, diabetes mellitus, dyslipidemia, smoking, alcoholism, illicit drug abuse, oral contraceptive exposure, as well as cardiac diseases like Rheumatic heart disease, atrial fibrillation, valvular heart diseases, coronary artery disease, congestive heart failure, congenital structural heart disease, and thrombogenic blood diseases.

The objective measure used to assess the severity of the stroke in this study is the National Institute of Health Stroke Scale (NIHSS) [79]. This NIHSS contains a total of 11 items. Each specific item score ranges from 0 to 4. The maximum possible score is 42 and the minimum score is 0. The severity was classified as mild if NIHSS is <5; moderate if NIHSS is between 6-14; and severe if NIHSS is >15.

The etiology of the stroke was classified as per the TOAST classification [80] into large artery atherosclerosis, cardio embolism, lacunar stroke, and undetermined and specific causes. The primary outcome was a 3-month functional disability. This was assessed using the modified Rankin scale (mRS) [81]. This scale contains 6 items with a total possible score of 6. In that score 0 indicates no symptoms whereas a score of 6 denotes death. A good outcome is defined as mRS less than or equal to 2. The details of secondary prevention medication were collected. The secondary outcome measures were recurrent vascular events and mortality due to such vascular events. The recurrent cerebral vascular events included transient ischemic events, ischemic stroke, and hemorrhagic stroke. The cardiac events included angina, myocardial infarction, and revascularization procedures like PTCA, and CABG.

Size:

The calculated sample size was 312, using Open Epi (Kelsey method) with the alpha error level at 0.05 and power of detection at 80%, ii) Based on previous studies it was found that common risk factors and major etiological categories were significant

among patients with stroke in the age group of 18 to 50 years, with this sample size (Dean AG et al, 2013).

Statistical Analysis:

Statistical analysis was done by standard software (Stata package 15.1). Ordinal data were assessed by a non-parametric test. Dichotomous and categorical variables were compared with the chi-square test. Whereas continuous variables were compared with the unpaired t-test.

Demographic, risk factors, and clinical variables of the patients were described using univariate analysis like frequencies, mean, standard deviation, median, and interquartile range.

Univariate analysis between the demographic, risk factors, clinical variables, and outcome measures according to age groups 18-40 years and 40-50 years. Functional outcomes based on the mRS score will be divided into good (0to 2) and poor (>2) outcomes.

Pearson's Chi-squared test and Fisher's exact test were used to comparing categorical variables across groups and Student's t-test was used to compare means. Numerical values with non-normal distribution were shown as the median (interquartile range, IQR) and a non- parametric test was used to compare differences between the two groups. A two-tailed probability value P of <0.05 was considered significant.

In addition, exploratory analyses were performed to determine the predictors associated with outcome variables such as mRS groups (good mRS versus poor mRS), mortality, and recurrent vascular events. Large sample chi-square tests were performed to determine the association between the above binomial outcome groups. Further, we performed regression analysis using multiple logistic regression techniques for the multiple unrelated groups. This was done to identify the independent predictors of outcome parameters [45].

RESULTS

Descriptive analysis:

We enrolled 569 patients (379 Males and 190 females). The mean age of the study population was 40.70 (S.D. 7.63, range 18 - 50). The mean age in male patients was 41.10 (S.D.=7.27) while in female patients it was 39.91 (S.D.=8.23).

We classified the study population into 2 age groups (18-39 and 40-50 years). 35% were between 18-39 years and 65% were between 40-50 years group. (Table 4.1)

Table 4.1: Gender, and age distribution of the study group:

Mean Age years [SD]	40.70 [SD=7.63]
Age groups	<40 y = 35%. >40 y = 65%
Gender	Males = 66%. Females = 33%
Males	Mean age- 41.10 (SD=7.27). Median- 43
Females	Mean age- 39.91 (SD=8.23). Median- 42

The frequencies of risk factors were shown in Table 4.2.

Table 4.2: Risk factor profile of patients:

Risk Factor	Number	*Percent (%)*
Hypertension	229	***40.25***
Diabetes	195	***34.27***
Dyslipidemia	140	***24.6***
History of smoking	189	***33.22***
Current smoking	163	***28.6***
Alcohol	164	***28.82***
OCP use/Exposure to any hormone	4	***0.70***
Coronary artery disease	52	***9.14***
Valvular heart disease	62	***10.90***
Non valvular atrial fibrillation	8	***1.41***
Valvular atrial fibrillation	25	***4.39***
Congestive heart failure	23	***4.04***
Congenital heart disease	14	***2.46***
Peripheral vascular occlusive disease	5	***0.88***
Connective tissue diseases	26	***4.57***
Hematological & prothrombotic states	12	***2.11***
Migraine	29	***5.10***
History of prior TIA	32	***5.62***

The mean time from symptom onset to admission to the hospital was 5.39 days (S.D.=7.85. Range: 0-31). A total of 325 (57.11%) patients presented within 24 hours of symptom onset or were last seen normal.

In 366 (64.32%) patients, ECG was normal while other abnormalities found in ECGs were left ventricular hypertrophy (LVH), Left atrial enlargement, and recent myocardial infarction (defined as acute myocardial infarction presenting after 24 hours from symptom onset) or old myocardial infarction (defined as an electrocardiographic finding of pathologic Q waves, without evidence of current or ongoing acute infarction) [82]. Echocardiogram was normal in 458 (80.49%) patients while LV Dysfunction in 34 (5.97%) patients, left ventricular thrombus in 16 (2.81%) patients, Valve disease in 33 (5.79%) patients, and infective endocarditis (IE) in 1 (0.17%) patient were noted (Table 4.3). In addition, Patent foramen ovale (PFO) was noticed in 20 (3.51%), out of which a clinically significant PFO defined as the presence of atrial septal aneurysm and right to left shunt on Valsalva within the first 3 breaths was demonstrable in only 20 patients, who subsequently underwent PFO closure. Holter monitoring was performed in 193 (34%) patients, but the diagnostic yield was poor, only 9 patients had tachyarrhythmias leading to a change in treatment modality.

Serum ANA was positive in 25 (4.39%) patients, dsDNA positive in 8 (1%) patients, ANCA in 2 (0.35%) patients, APLA in 15 (2.64%) patients; the homocysteine levels were elevated in 91 (36.25%) patients.

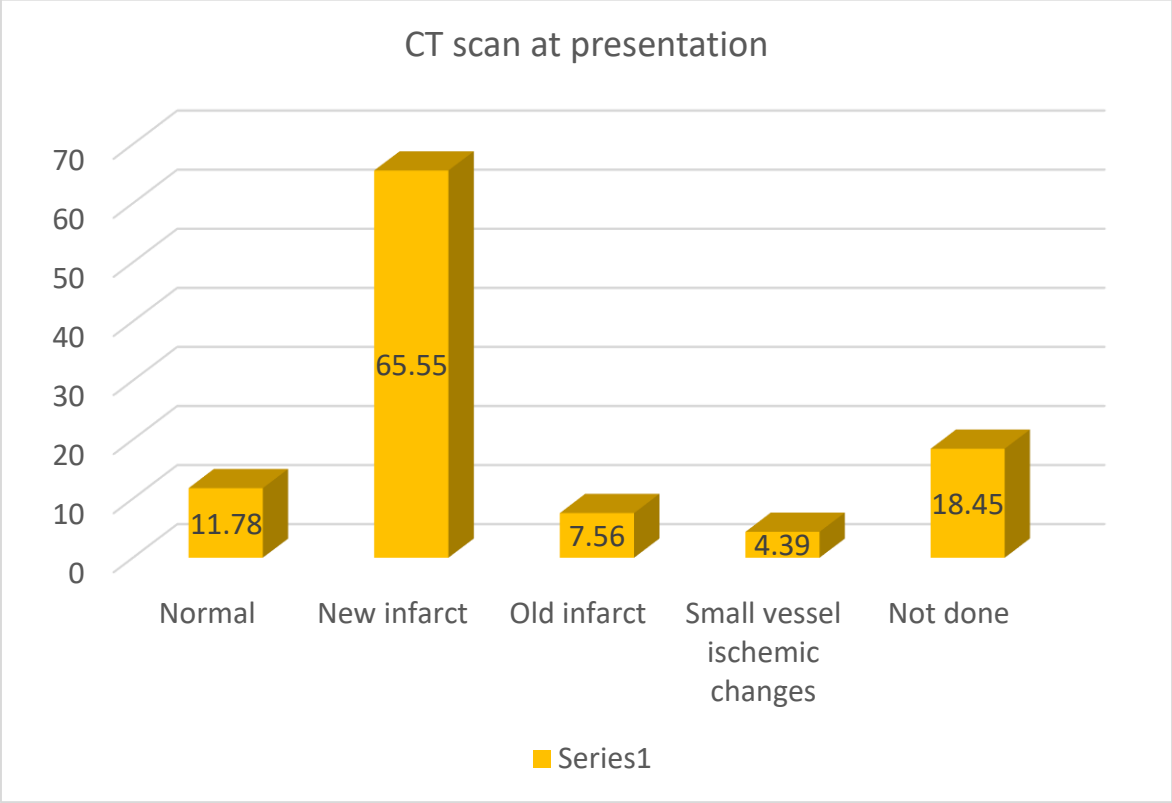
Table 4.3: Frequencies of echocardiogram abnormalities

Echocardiography Changes	**Number**	**Percent (%)**
Normal	458	**80.49**
Left ventricular dysfunction	34	**5.97**
Left ventricular clot	16	**2.81**
Spontaneous echo contrast	6	**1.05**
Valvular abnormalities	33	**5.79**
Patent foramen ovale	20	**3.51**
Infective endocarditis	1	**0.17**
Atrial septal defect	**1**	**0.17**

The mean NIHSS of the study population was 8.46. A total of 240 (42.18%) patients had mild strokes, 210 (36.90%) patients had moderate strokes, and the remaining 119 (20.91%) patients had severe strokes.

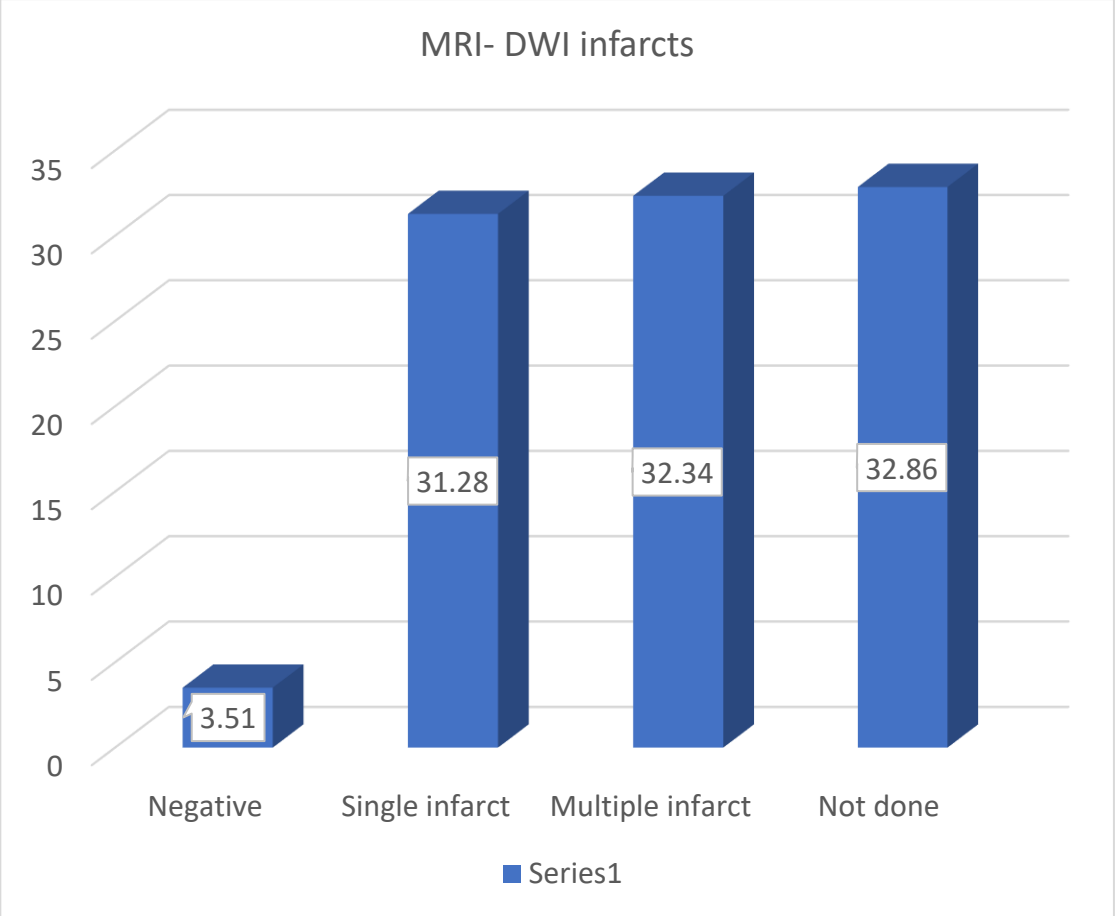
At presentation, CT-Brain was done on 464 (81.54%) patients. New infarcts were seen in 373 (65.55%) patients while in 67 (11.78%) patients it was normal. (Figure 4.1)

*Figure **4.1:** Frequencies of admission CT scan abnormalities*



MRI-DWI imaging showed a single acute infarct in 178 (31.28%) patients, whereas multiple acute infarcts were seen in 184 (32.34%) patients. MRI was negative in a total of 20 (3.51%) patients and not done in 187 (32.86%) patients. (Figure 4.2)

Fig 4.2: DWI abnormality at presentation



Admission CT scan showed the frequency of infarcts-location as follows – (Table 4.4). Around 197 (34%) patients had infarcts involving the whole MCA territory, whereas only 33 (~5.8%) patients had infarcts involving the M2 branch territory.

Dense vessel signs were seen in the initial CT scan in 34 (5.97%) patients, and almost all of them were seen in the MCA, and only one additional patient had hyperdense basilar artery.

Table 4.4: *Territory of acute infarct on CT scan*

Territory of acute infarct by CT scan	**Percentage**
ICA *(Internal carotid artery)*	**4.8**
ACA *(Anterior cerebral artery)*	**2.1**
MCA *(Middle cerebral artery)* ***complete***	**34.62**
MCA Superior division	**3.16**
MCA inferior division	**2.63**
MCA subcortical	**11.77**
Posterior circulation	**12.47**
Normal	**34.97**

Table-4.5:- *Frequencies of the affected vessel status*

	Normal	**Moderate stenosis (50-69%)**	**Severe stenosis**	**Arterial dissection**	**Vessel occlusion**
Final impression on vessel status	**212 (37.25%)**	**26 (4.68%)**	**28 (5.04%)**	**81 (14.57%)**	**209 (37.59%)**

The territory of stroke was in the anterior circulation in 498 (87.53%) patients while posterior circulation strokes occurred in 71 (12.47%) patients. In anterior circulation, the frequency of stroke in descending order is as follows: MCA complete, MCA subcortical, MCA superior division, ICA, MCA inferior division, and ACA. Dense – artery-sign which signify an occlusion of the affected artery was seen in 5.97% of the case, out of which the majority were in MCA followed by basilar and ICA.

As mentioned in table 4.5, symptomatic vessels were completely normal in approx.

37.25% of cases. The major abnormality noticed was vessel occlusion followed by dissection. The rest of the vessels showed mild to moderate or severe stenosis. The frequency of affected arteries is shown in table 4.6. The most common arteries affected were the MCA-M1 segment followed by the extracranial internal carotid artery.

In 44.66% of the patients, strokes occurred on the right cerebral hemisphere whereas in 45.75% they occurred on the left; another 9.59% of the patients had infarcts in the either basilar system or bilateral cerebral hemispheres.

Table 4.6: Frequency of arteries involved

Vessel involved	**Frequency**	**Percentage**
Extracranial ICA *(Internal carotid artery)*	112	**19.68**
Intracranial ICA	32	**5.62**
MCA-M1 segment	116	**20.39**
MCA-M2 segments	35	**6.15**
ACA *(Middle cerebral artery)*	13	**2.28**
Basilar	14	**2.46**
Vertebral	40	**7.03**
PCA *(Posterior cerebral artery)*	15	**2.64**
SCA *(Superior cerebellar artery)*	2	**0.35**
PICA *(Posterior inferior cerebellar artery)*	14	**2.46**
AICA *(Anterior inferior cerebellar artery)*	1	**0.18**

Of the etiology of stroke, large artery atherosclerosis constituted 13%, cardioembolic 19.8%, specific causes 23%, undetermined 33%, and lacunar stroke was 10.19%.

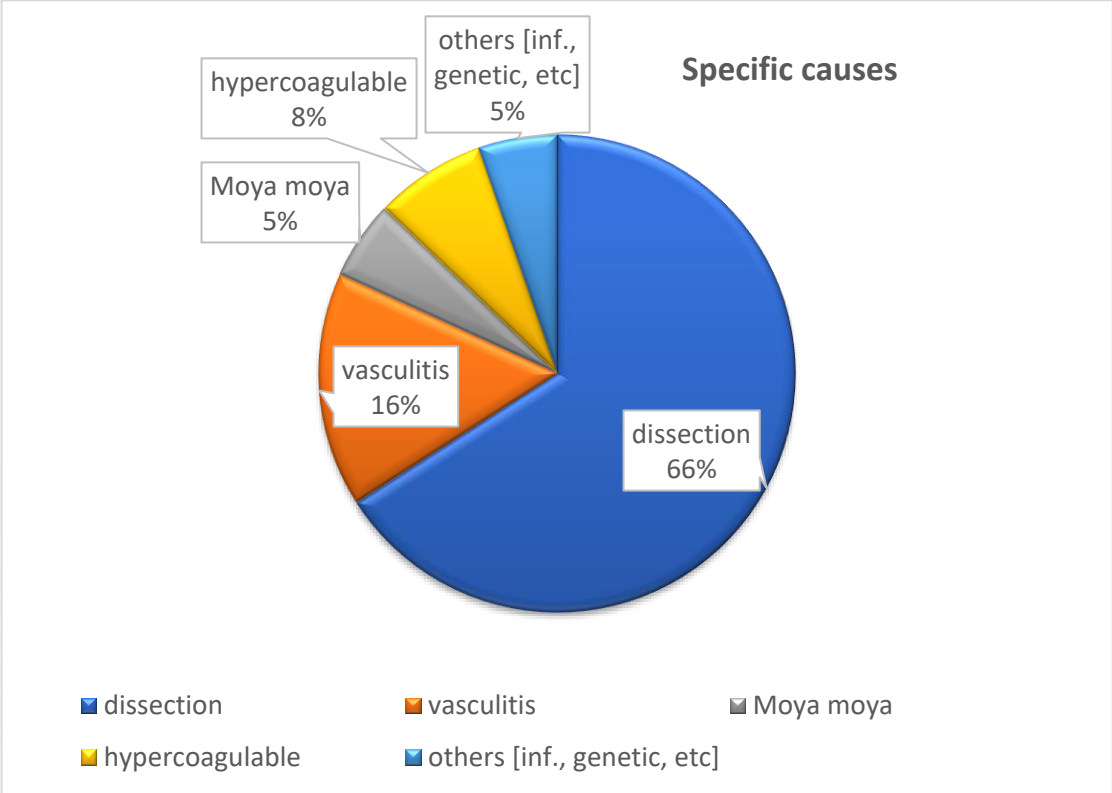
Of the cardioembolic strokes, rheumatic heart disease (RHD) accounted for 9.49% (n=54) of cases followed by PFO 3.16% (n=18); cardiomyopathy 1.23% (n=7), and severe LV dysfunction 3.3% (n=19).

Of the specific causes: arterial dissection which accounted for 66% of all specific causes I.e., n=87 patients and 15.67% of all causes followed by vasculitis is-which accounted for 3.52% (n=21) of all-cause strokes; others include- Moyamoya disease, prothrombotic states, sickle cell disease, infectious strokes and rare genetic causes such as CADASIL. (Table 4.7, Figure 4.3)

Table 4.7: Etiology of stroke as per TOAST classification

Etiology of Stroke	Percentage
Large artery atherosclerotic disease	**13.18**
Cardioembolic	**19.86**
Rheumatic heart disease	9.49
Patent foramen ovale	3.16
Severe left ventricular dysfunction	3.3
Nonvalvular atrial fibrillation	0.17
Infective Endocarditis	0.35
Cardiomyopathy, Endomyocardial fibrosis, etc	1.23
Other specific causes	**23.20**
Dissection	15.67
Antiphospholipi**d** antibody syndrome	0.18
Vasculitis	3.52
Moyamoya disease	1.23
Prothrombotic states	1.41
Secondary vasculitis [eg- Behcet]	0.35
Aneurysm	0.35
Infective vasculitis	0.35
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy	0.18
Undetermined	**33.57**
Lacunar	**10.19**

Figure 4.3: Etiologies among the category of specific causes of stroke:



At discharge, 366 (64.32%) were on dual antiplatelet agents, 451 (79.26%) patients were on Aspirin, 271 (47.62%) on clopidogrel, and 106 (18.80%) on Warfarin. A total of 69 (12.13%) patients received acute interventions either iv thrombolysis or mechanical thrombectomy. Of them, 30 (5.27%) patients received iv thrombolysis, 36 (6.33%) patients received mechanical thrombectomy, and 9 (1.58%) patients received bridging iv thrombolysis before the mechanical thrombectomy. On a follow-up, a total of 9 (1.58%) patients were treated with carotid endarterectomy whereas 4 (0.7%) patients had undergone Moyamoya revascularisation surgery. Another 13 (2.28%) patients underwent closure for patent foramen ovale whereas an overall of 33 (5.80%)

patients in this cohort underwent decompressive craniectomy.

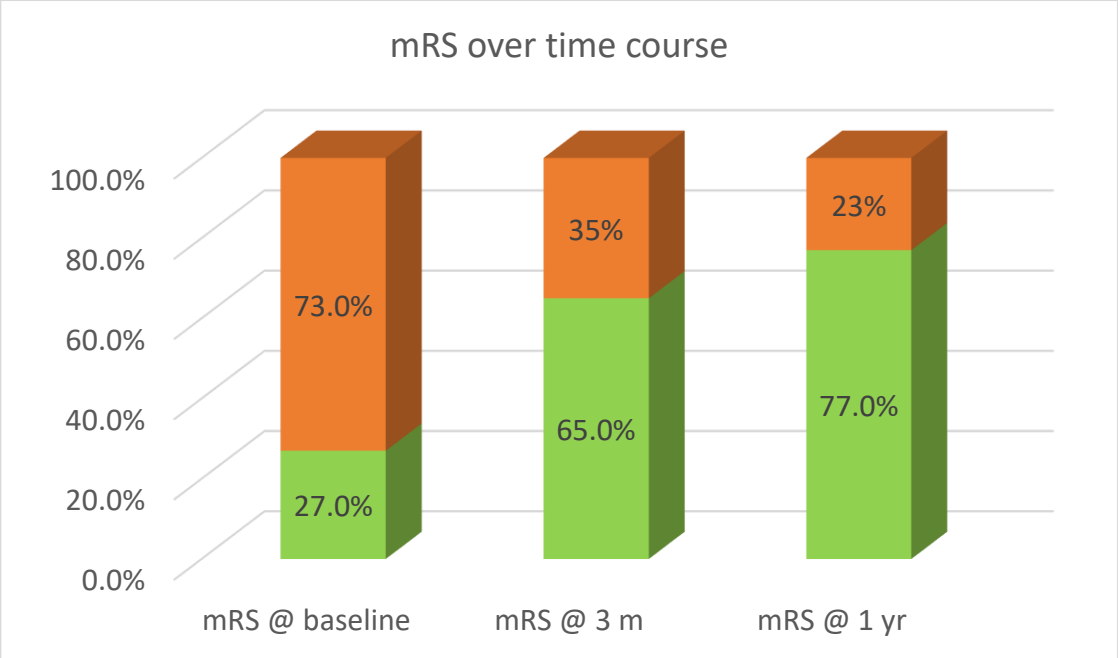
The in-hospital mortality was 2.81% (n=16). The cause of death was stroke in 10 patients and other vascular-related complications in 6 patients.

At 3 months, 369 (65%) patients had good (mRS <3) outcome and stroke recurrence occurred in 1.58% (n=9).

At 1 year 438 (77%) patients had a good outcome and recurrent strokes occurred in 14 (2.46%) patients. (Figure 4.4)

On cumulative, **16 (2.81%) patients developed recurrent strokes** at annual follow-up.

Figure 4.4: mRS scores comparison at different time points (green color denotes good outcome):



Out of 21 (3.69%) **deaths** in this cohort, 11 deaths were due to strokes, whereas 10 deaths were due to other vascular causes such as CAD, and peripheral vascular

occlusive disease (PVOD). Among them, 16 (2.81%) patients expired in-hospital, whereas 3 and 2 deaths occurred at the 3rd month and 1st year follow up respectively.

A total of 12 (2.10%) patients had **recurrent vascular events** at the 3rd-month follow-up. Whereas a total of 18 (3.16%) patients developed recurrent vascular events at the end of 1-year. The most common other vascular event is coronary artery disease. Less common causes include- traumatic SDH and peripheral arterial occlusive disease.

At 3rd month follow-up, out of 12 vascular events, 9 were strokes and 3 were other vascular events. Among the strokes (n=9; 1.58%) three patients had TIAs, one patient had posterior circulation stroke, two were ACA strokes, and the rest all were MCA strokes. Other vascular events reported were deep venous thrombosis (DVT), new onset congestive heart failure (CHF), and PVOD each in 1 patient respectively.

Out of 18 (3.16%) recurrent vascular events recorded **at 1-year follow-up**, 14 events were due to stroke (n=14; 2.46%) and 4 patients developed other vascular events. Among the stroke-related causes 4 patients had TIAs only, 3 patients developed intracranial bleeds, and the remaining patients developed either anterior or posterior circulation strokes (n=7; 1.23%). Among the other vascular events, 3 were coronary events, and one was CHF.

Predictors of outcome:

We investigated the predictors of **3-month (short-term) mRS** outcomes. In an exploratory analysis, a poor 3-month mRS outcome was associated with baseline moderate to severe strokes (NIHSS 6-14 & >15 respectively), presence of significant stenosis/occlusion of the symptomatic vessel, MCA-M1 occlusion, and anterior circulation strokes. (Table 4.8)

However, after multiple logistic regression, **only** the baseline moderate to severe strokes ($p<0.001$) predicted the poor 3-month mRS outcome. None of the other parameters such as age, gender, risk factors, etiology of the stroke, symptomatic vessel status, the territory of stroke, or the affected artery predicted the 3-month mRS outcome. (Table 4.9)

Table 4.8: Predictors of Short-term (3-month) mRS outcome

Variable	mRS ≤ 2 (%)	mRS > 2 (%)	OR (95% CI)	P value
Age ≥ 40 years	212 (61.27)	134 (38.73)	1.56 (1.06-2.31)*	0.023
Gender: males	227 (64.12)	127 (35.88)	1.08 (0.73-1.58)	0.689
Diabetes mellitus	106 (59.22)	73 (40.78)	1.43 (0.98-2.07)	0.059
Smoking	104 (59.09)	72 (40.91)	1.43 (0.98-2.09)	0.056
Large artery atherosclerotic etiology	33 (47.83)	36 (52.17)	0.53 (0.31-0.88)	0.015
Cardioembolic etiology	64 (59.81)	43 (40.19)	0.61 (0.33-1.13)	0.120
Specific etiology	76 (63.33)	44 (36.67)	0.53 (0.29-0.96)	0.039
Undetermined etiology	123 (70.29)	52 (29.71)	0.38 (0.21-0.68)	0.001

Lacunar etiology	45 (80.36)	11 (19.64)	0.22 (0.09-0.50)	<0.001
Moderate (6-14) baseline NIHSS score	98 (50.26)	97 (49.74)	15.05 (8.18-27.69)*	<0.001
Severe (>15) baseline NIHSS score	30 (28.57)	75 (71.43)	38.03 (19.13-75.59)*	<0.001
Vessel status (presence of stenosis/dissection/occlusion)	170 (54.31)	143 (45.69)	3.87 (2.53-5.92)*	<0.001
MCA-M1 involvement	52 (49.52)	53 (50.48)	2.21 (1.43-3.41)*	<0.001
Anterior circulation strokes	131 (50.97)	126 (49.03)	3.36 (2.30-4.90)*	<0.001
Posterior circulation strokes	54 (73.97)	19 (26.03)	0.60 (0.34-1.05)	0.076
IV thrombolysis	22 (75.86)	7 (24.14)	0.56 (0.23-1.35)	0.201
Mechanical thrombectomy	20 (57.14)	15 (42.86)	1.40 (0.70-2.82)	0.334

Table 4.9: Multiple logistic regression of the predictors of Short-term (3-month) mRS outcome

Variable	**OR (95% CI)**	**P value**
Age ≥ 40 years	1.23 (0.73-2.06)	0.430
Moderate (6-14) baseline NIHSS score	15.63 (8.18-29.84) *	<0.001
Severe (>15) baseline NIHSS score	32.40 (15.33-68.46) *	<0.001
Vessel status (presence of stenosis/dissection/occlusion)	4.63 (1.37-15.61)	0.13
Anterior circulation strokes	0.56 (0.16-1.89)	0.352

A poor **1-year (long-term) mRS** outcome was found to have a statistically significant association with the age group of ≥ 40 years, smoking tobacco, moderate to severe baseline severity of stroke (assessed by NIHSS), presence of symptomatic vessel stenosis/occlusion/dissection, MCA-M1 segment involvement, and anterior circulation strokes. (Table 4.10)

However, after multiple logistic regression **only** the age ≥40 years, moderate to severe baseline strokes, and male gender were found to be independently predicted the poor 1-year mRS outcome. (Table 4.11)

Even though, gender did not affect the outcome either in the short-term (3 months) or over the long-term (at 1 year), an intriguing observation is that after multiple logistic regression, the male gender was found to independently predict a poor 1-year mRS outcome, whereas no such trend seen at 3rd month. For this, OR was 1.92 (CI: 1.04-3.53, P=0.035).

Table 4.10: Predictors of Long-term (1-year) mRS outcome

Variable	mRS ≤ 2 (%)	mRS > 2 (%)	OR (95% CI)	P value
Age ≥ 40 years	191 (68.46)	88 (31.54)	2.03 (1.24-3.34) *	0.004
Gender: males	204 (71.33)	82 (28.67)	1.28 (0.79-2.05)	0.303
Smoking	88 (63.77)	50 (36.23)	1.93 (1.24-3.02) *	0.003
Dyslipidemia	84 (79.25)	22 (20.75)	0.63 (0.37-1.07)	0.088
Alcohol abuse	80 (66.67)	40 (33.33)	1.52 (0.96-2.42)	0.072
Valvular heart disease	30 (61.22)	19 (38.78)	1.84 (0.98-3.42)	0.051
Large artery atherosclerotic etiology	32 (57.14)	24 (42.86)	0.75 (0.44-1.27)	0.287
Cardioembolic etiology	54 (64.29)	30 (35.71)	0.74 (0.37-1.48)	0.396

Specific etiology	73 (75.26)	24 (24.74)	0.43 (0.21-0.88)	0.021
Undetermined etiology	111 (78.17)	31 (21.83)	0.37 (0.19-0.72)	0.003
Lacunar etiology	36 (87.80)	5 (12.20)	0.18 (0.06-0.54)	0.002
Moderate (6-14) baseline NIHSS score	90 (63.38)	52 (36.62)	13 (5.92-28.53) *	<0.001
Severe (>15) baseline NIHSS score	36 (40)	54 (60)	33.75 (14.80-76.95)*	<0.001
Vessel status (presence of stenosis/dissection/occlusion)	167 (65.23)	89 (34.77)	3.40 (2.00-5.76)*	<0.001
MCA-M1 involvement	53 (60.23)	35 (39.77)	2.11 (1.28-3.47) *	0.003
Anterior circulation strokes	126 (60.58)	82 (39.42)	3.67 (2.17-6.20) *	<0.001
Posterior circulation strokes	48 (84.21)	9 (15.79)	1.05 (0.45-2.45)	0.892
IV thrombolysis	19 (76)	6 (24)	0.83 (0.32-2.15)	0.716
Mechanical thrombectomy	21 (70)	9 (30)	1.16 (0.51-2.62)	0.715

Table 4.11: Multiple logistic regression of the predictors of Long-term (1-year) mRS outcome

Variable	**OR (95% CI)**	**P value**
Age ≥ 40 years	1.93 (1.02-3.65) *	0.042
Moderate (6-14) baseline NIHSS score	11.48 (5.05-26.07) *	<0.001
Severe (>15) baseline NIHSS score	26.05 (10.73-63.27) *	<0.001
Vessel status (presence of stenosis/dissection/occlusion)	2.50 (0.65-9.59)	0.179
Anterior circulation strokes	0.91 (0.23-3.55)	0.895

Out of 21 cumulative deaths recorded in our study, only 3 occurred in the 3rd month and 2 per 1-year, and a multiple logistic regression model could not be performed for several important vascular risk factors such as valvular heart disease, diabetes, atrial fibrillation, imaging-based parameters such as final status of the symptomatic vessel, and the arteries affected, as they did not have entries to perform the analysis. Hence only the predictors of cumulative mortality were analyzed.

On bivariate analyses, **mortality** was predicted by current smoking status, valvular heart disease, severe baseline stroke, presence of symptomatic vessel stenosis/occlusion/dissection, and anterior circulation strokes. (Table 4.12)

However, after logistic regression, **only** current smoking alone independently predicted a poor long-term outcome. (Table 4.13)

*Table 4.12: Predictors of **mortality***

Variable	Deaths (%)	OR (95% CI)	P value
Age ≥ 40 years	18 (6.45)	3.17 (0.91-10.95)	0.068
Gender – male	10 (3.50)	0.40 (0.16-0.97)	0.045
Hypertension	8 (4.65)	0.88 (0.35-2.17)	0.784
Diabetes mellitus	9 (6.47)	1.55 (0.63-3.77)	0.332
Dyslipidemia	1 (0.94)	0.14 (0.01-1.05)	0.057
Current smokers	3 (15.79)	10.68 (1.65-68.93)*	0.013
Alcohol abuse	3 (2.50)	0.40 (0.11-1.38)	0.149
Valvular heart disease	7 (14.29)	2.95 (1.62-11.12)*	0.003
Large artery atherosclerotic etiology	3 (5.36)	1.08 (0.30-3.82)	0.895
Cardioembolic etiology	12 (14.29)	2.94 (0.79-10.95)	0.107
Specific etiology	1 (1.03)	0.18 (0.01-1.81)	0.147

Undetermined etiology	4 (2.82)	0.51 (0.11-2.36)	0.391
Lacunar etiology	1 (2.44)	0.44 (0.04-4.40)	0.486
Moderate (6-14) baseline NIHSS score	6 (4.23)	4.10 (0.81-20.63)	0.087
Severe (>15) baseline NIHSS score	13 (14.44)	15.70 (3.46-71.23)*	<0.001
Vessel status (presence of stenosis/dissection/occlusion)	18 (7.03)	4.35 (1.32-25.28)*	0.02
Anterior circulation strokes	16 (7.62)	4.16 (1.19-14.56)*	0.025
Posterior circulation strokes	2 (3.39)	0.63 (0.14-2.78)	0.543

Table 4.13: Multiple logistic regression analyses of the predictors of mortality

Variable	OR (95% CI)	P value
Current smoking	11.53 (1.73-76.86)*	0.011
Moderate (6-14) baseline NIHSS score	2.37 (0.19-28.88)	0.498
Severe (>15) baseline NIHSS score	32.09 (0.35-57.02)	0.247

Bivariate analyses showed **vascular recurrence** at 1 year was predicted by diabetes, CAD, and valvular heart disease. None of the other factors such as risk factors of stroke, stroke severity, symptomatic vessel status or artery involved, or territory of stroke had a significant association. (Table 4.14)

A best fit logistic regression model could be applied only to select variables such as the age ≥40 years, diabetes, and coronary artery disease (CAD) due to the

above reasons i.e., all other remaining variables do not have an entry to apply the model.

Multiple logistic regression showed that diabetes mellitus was the **only** independent predictor of recurrent vascular events at 1-year. (Table 4.15)

*Table 4.15: Predictors **of Recurrent vascular events***

Variable	Recurrent vascular events (%)	OR (95% CI)	P value
Age ≥ 40 years	21 (6.34)	1.61 (0.67-3.88)	0.283
Gender– male	17 (4.93)	0.70 (0.32-1.53)	0.376
Hypertension	12 (5.74)	1.10 (0.51-2.38)	0.801
Diabetes Mellitus	16 (9.14)	2.66 (1.23-5.77)*	0.013
Dyslipidemia	7 (5.38)	0.95 (0.39-2.31)	0.092
Smoking	7 (4.09)	0.63 (0.26-1.52)	0.311
Alcohol abuse	6 (4.05)	0.64 (0.25-1.62)	0.349
Coronary artery disease	6 (12.77)	2.90 (1.11-7.55)*	0.029
Valvular heart disease	8 (16)	4.14 (1.72-9.97)*	0.002
Nonvalvular atrial fibrillation	3 (15)	3.27 (0.89-11.81)	0.073
Large artery atherosclerotic etiology	5 (7.6)	1.45 (0.53-3.96)	0.463
Cardioembolic etiology	9 (9.78)	3.05 (1.27-7.28)	0.012
Specific etiology	6 (5.08)	0.88 (0.35-2.24)	0.803
Undetermined etiology	6 (3.51)	0.51 (0.20-1.29)	0.159

Lacunar etiology	2 (3.51)	0.59 (0.13-2.55)	0.480
Vessel status (presence of stenosis/dissection/occlusion)	13 (4.45)	0.62 (0.28-1.36)	0.237
Anterior circulation strokes	13 (5.46)	0.70 (0.32-1.52)	0.377

Table 4.14: Multiple logistic regression analyses of the predictors of recurrent vascular events

Variable	OR (95% CI)	P value
Age ≥ 40 years	1.10 (0.43-2.80)	0.838
Diabetes mellitus	2.43 (1.07-5.50)*	0.033
Coronary artery disease	2.50 (0.94-6.68)	0.066

DISCUSSION

Discussion

We investigated the etiology, risk factors, and outcome among young stroke patients with first-ever ischemic stroke. The most common risk factors found in our study were hypertension (40.2%), diabetes (34%), tobacco smoking (33%), alcohol abuse (28.8%), and dyslipidemia (24.6%). Other important risk factors were rheumatic heart disease (RHD) (10.9%), coronary artery disease (CAD) (9.1%), prior transient ischemic attack (TIA) (5.6%), congestive heart failure (4%), and finally connective tissue diseases (4.5%) in the descending order. Being a tertiary care cardiology center performing large volumes of cardiac valve replacement & interventions may be a reason for the high prevalence of rheumatic heart disease and coronary artery disease seen in our study. Atrial fibrillation was seen in fewer patients (1.4%) in our study, which is usually common in the elderly or among patients >50 years old. The higher prevalence of connective tissue diseases, prothrombotic conditions, and congenital heart diseases seen in our study may be attributed to a comprehensive investigatory protocol we employ while managing stroke patients. Prevalence of migraine (5.1%) and OCPs (0.7%) seems to be negligible and did not influence the risk of stroke in our cohort. A higher prevalence of classical risk factors seen in our study than in the previous work published here is however less than that of the western world, and it may be due to the changes in dietary patterns and lifestyle changes. From the above studies, it also appears that the risk factor profile resembles the older population with increasing age in the young. This change was evident at a median age of 44 years. Various studies report a high rate of diabetes, hypertension, smoking, and alcoholism

in the range of 30-40% as is the presence of multiple risk factors [11,13]. However, dyslipidemia was reported to be less among those patients I.e., ~20% only [10,44]. Over the past few decades, the prevalence of certain modifiable risk factors is probably increasing when one observes the prevalence against the timeline of publications from India including our study. This could be due to the phenomenon of the epidemiological transition occurring in this part of the world [10,12,13,43–45]. For example, in a 1997 study [45], the prevalence of hypertension was 18%, diabetes at 7%, and smoking (only in males) at 69%; in contrast, a study published in 2011 [11,44] showed a prevalence of hypertension in the tune of 44%, alcoholism in 31%, and diabetes in 31%; our study a representative sample of the previous 10 years, also shows a similar prevalence of hypertension (41%), diabetes (34%), smoking (33%), and alcoholism (28.8%). In summary, the prevalence of risk factors shown in our study findings did not significantly differ from the Indian data. Global data on the prevalence of risk factors also appeared similar. For example, a Southeast Asian study [83], showed hyperlipidemia (53.1%), tobacco abuse (~50%), hypertension (46%), and a family history of stroke (29%) as the most common risk factors. In that study hyperlipidemia and hypertension were more commonly seen in patients with small vessel occlusion, large artery atherosclerosis, and stroke due to unknown etiology. However, it was seen less commonly in cardioembolic strokes. Analysis of the risk factor prevalence from the western context reveals the prevalence of hypertension in the range of 20-60%. In Baltimore Study [84] examining 296 incident stroke cases in Black and White adults, hypertension was present in 61% of Blacks; The prevalence of smoking was 40-57%. In the Helsinki Young Stroke Registry, a study examined 1008 young stroke patients,

the most common risk factors identified were hypertension, tobacco abuse, and dyslipidemia with high total cholesterol. The prevalence of hypertension increased with increasing age. It was seen in 28.3% of patients in the 15–44year age group [84]. Whereas the same figure was 51.7% of the patients belong to the 45 to 49-years of age strata. Gender-wise, a male preponderance is seen across the published work from India and western countries, ranging from a 3:1 ratio in a previous paper published from our center ~24 years ago [45] to 2:1 as shown in another study from here ten years ago [10]. The current study also follows the same trend. If we analyze the pattern of the risk factors from the Indian context, a comparative analysis of two papers published in south India more than 2 decades ago is noteworthy. The first study [85] showed that elderly people have more diabetes, hypertension, and dyslipidemia whereas younger people more often have had substance abuse (alcohol, tobacco). The second study was done from our center [45] showed that though atherothrombogenic vascular risk factors are more often seen in the elderly like the above, certain factors such as alcohol abuse, and cardioembolism did not differ significantly between the elderly and the young. In contrast, recent studies have shown that atrial fibrillation (AF) shares a consistent stronger association in the young than the elderly, often with an aOR value of 6 [12], which was independent of the high alcoholism, and RHD seen in those cohorts. Diabetes shares a conflicting association with young stroke as shown in two important studies published from south India a decade ago; one was from Mangalore, India [44] and the other one from our center by Lipska et al [10]; in the latter diabetes was found to be not a risk factor for stroke when compared with hospital-based controls. From the above, it also appears that the risk factor profile becomes like the older population with

increasing age in the young. This change was evident at a median age of 44 years.

In our cohort of 569 first-ever ischemic young strokes, we found following etiologies of stroke: Large artery atherosclerotic disease (LAA) (14.4%), Cardioembolic (19.8%) [RHD - 9.4%, patent foramen ovale-3.1%, CAD - 3.3%, Atrial fibrillation - 0.17%, Infective Endocarditis - 0.35%, cardiomyopathy/ Endomyocardial fibrosis - 1.2%], Specific causes (23.2%) [Dissection 15.6, Prothrombotic 1.4%; Vasculitis 3.6%, Moyamoya 1.1%, Hematological 1.4%]; Lacunar (10.2%), and undetermined (33.5%). The LAA is usually a common etiology in the elderly and presents less often among the young. In certain European countries, 21–48% of young strokes were due to LAA. A recently published largest Chinese cohort, which included 787 first-ever ischemic strokes and 167 recurrent young strokes, showed a very high prevalence of LAA (43.7%) like that seen in western countries. It was not only due to its overall higher prevalence of conventional vascular risk factors (in the range of 50-70%) [I.e., hypertension (60.0%), dyslipidemia (55.3%), smoking (54.1%), and alcohol consumption (49.6%)] but also due to its inclusion of recurrent strokes. In contrast, the prevalence of LAA seen was comparable to a previous study from here [45] which showed LAA in 12.6% and is like studies from Southeast Asia, and earlier cohorts from the USA & Western Europe as well. Overall, a higher prevalence of cardioembolic strokes seen from our center was due to RHD, and CAD may be partly attributed to a referral bias. Despite, the reduction over time in the frequency (25.2%→19.8%) [45] in comparison to prior reports published here may be due to a general decreasing trend of RHD over the last 15 years in this part of the world due to better preventive strategies. The most important etiology seen in our study is specific

causes (23.2%), of which arterial dissection accounted for 15% of all-cause strokes. This may be due to vascular imaging of either CT angiogram or MR angiogram being available in most of our patients and the neck & intracranial vascular imaging was available. A previous study from our center[45], also showed specific etiologies in 11. 2% (7% arterial dissection) [10]. Cervical artery dissection was one of the relatively common causes of stroke in the western series, with a reported prevalence of 6–15%. While the data from European countries showed non-atherosclerotic large artery occlusive disease in 10– 33% of cases, of which dissections have comprised 10–20%. Among them, a Swedish study [41] reported as high as 59% of specific etiology, with arterial dissection as the most common single etiology. Among 155 patients with dissection seen in that study, 80 had vertebral artery dissection and 67 had internal carotid artery dissection. The range of specific etiologies mentioned in the Indian studies was 3-22%. Among the other studies APLA syndrome, ANA positivity, SLE, fibromuscular dysplasia, migraine-related stroke, and miscellaneous vasculitis were observed only in 1–2% of patients, whereas in our study higher frequencies were noticed for other specific causes like vasculitis, prothrombotic states, and Moyamoya disease. For the latter s higher representation, a possible explanation could be being a leading center of revascularisation surgery for Moyamoya patients with a wider catchment area spanning across the country, there could be a referral bias. Being a comprehensive stroke care center and a tertiary referral center may be the reason for more patients with vasculitis being seen in our cohort. After an initial evaluation etiology may remain undetermined in 7–40% of the cases in several studies [3,9]. We also found similar frequencies, though less than that seen in a previous study from here

[10].

Our study shown a favorable functional outcome (measured in mRS) in 65% & 77% of patients at 3-months & 1-year respectively. There was a progressive improvement in mRS from admission to discharge in all. At the end of 1 year, 47.38% of our patients achieved m-RS of 0, while only 4% of patients remained as mRS 4 & 5 at 1 year. It suggests an excellent recovery in the younger population with aggressive management and continuous rehabilitative measures. Similarly, if we look at NIHSS, severe strokes (>15) present at admission in 20.9% of patients improved to 6.9% at the time of discharge. Earlier reported literature from India has certain limitations such as the usage of heterogenous and non-standardized measures of outcome while reporting. From our center Nayak et al [45], reported at a mean follow-up of 7 months (range 1-62 months), functional independence or only mildly disability in 75% of patients, whereas a study of 272 patients by Varona et al [86], at a mean follow-up of 12.3 years, showed ADL independence in 90% patients, and 53% of them rejoined work; however in contrast to our study their patients achieved an mRS of 0 in only 27% of instances. Other than these there is a scarcity of data using standardized methodology from India [7,11,12,43,44]. In contrast, several western studies examined standardized functional outcome measures based on mRS, mortality, and recurrent strokes. A study by Leys et al [46], comprising 272 young strokes, showed high functional independence (mRS 0-2) in 94%. One study examined the association between the etiology of stroke with functional outcome and turned out to be negative I.e., found neither lacunar nor cardioembolic etiologies predicted the mRS outcome at long-term follow-up [87].

Mortality was seen only in 3.6% of patients in our study. This was at the end of a

one-year follow-up. Further, ~95% of all mortality occurred during the first 92 days following a stroke or ~85% during the first 45 days after a stroke. An Indian study reported 7.3% of mortality in this context [44], whereas it ranges from 4.5% at 1 month after stroke to ~17% at 5th-year follow-up in European studies [4]. We report recurrent vascular events in 4.9% (n = 21) of patients at 1-year follow-up, whereas among them recurrent-strokes accounted for only 3.1% (n = 16). The oldest Baltimore study found a low occurrence of 0.9%, whereas, in an Italian study published around the same time, it was 3.3%. However, few other studies particularly from the Eastern Europe & Scandinavian regions provide a pessimistic view with a remarkably high recurrence rate. For example, the largest multi-centric study [88] showed a high recurrent rate of 14% at 4th-year follow-up; they report age and diabetes mellitus as the only independent predictors of recurrent strokes. Certain other studies published subsequently also provide recurrence rates ranging from 9% to as high as 25.4% [88–92]. In contrast, a single study from South-Eastern Asia reported a favorable outcome [36]. Like the western literature, we found a favorable functional outcome in both at short-term and long-term. However, unlike the Eastern European data, we found a low rate of stroke recurrences which is like the south-east Asian study. A more recent study from China (2017)[92] found that the only independent predictor of stroke recurrence at 1-year was baseline stroke severity. Regarding the predictors of recurrence, our findings were like the Estonian study [73] I.e., diabetes alone independently predicted stroke recurrences in the long-term. However, in our study unlike the Chinese cohort [8] , baseline stroke severity did not increase the odds of recurrence of vascular events.

Conclusions

Conclusions:

1. Males are at increased risk for stroke in comparison to females in the young population.
2. The risk factors like hypertension, diabetes mellitus, smoking, and alcoholism are important in the younger population and are seen increasing in the young population in comparison to previous studies which may be related to a change in lifestyle and dietary habits.
3. The most important etiology of stroke were specific causes and cardioembolic strokes. Of the specific causes, arterial dissection was an important cause of stroke.
4. Young strokes had an excellent outcome and less risk of stroke recurrence compared to the older population.
5. Stroke severity was the most important factor which predicted a 3-month functional outcome.
6. History of tobacco smoking was the only independent predictor of mortality at 1 year, whereas the presence of diabetes mellitus predicted recurrent vascular events at 1 year.

Limitation of Study:

1. Being a hospital-based study and tertiary care center, referral bias and admission bias cannot be eliminated.
2. Since it is a retrospective study, the recurrence of stroke and other vascular events may have been missed.

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ANNEXURE –I

Proforma for Stroke in young, risk factors, etiology, and factors affecting the outcome

1. Particulars about the patient and general information

1.1. Serial No.:

1.2. Age: 1.3. Sex: 1. Male 2.Female

1.4. Time and date of symptom onset

1.5. Date and Time of admission 1.6. Date saw in opd

1.7. Date of discharge 1.8. The total duration of hospital stay

2. *Risk factors:* (1. Yes 2. No)

2.1: HTN Duration

2.2: DM Type of DM Duration of DM

End organ dysfunction due to DM/HTN:

(if any, mention the type and duration……)

2.3: Smoking: Current Reformed Stopped…….yrs back

Exposure (In pack years):

2.4a: Drug addiction:

2.4b: Alcoholism:

2.4c: OCPs/Hormonal replacement therapy:

2.5: Cardiac Disease: Y:1,N:2 Type Duration

a. Coronary artery disease

b. Valvular heart disease

c. Congenital heart disease

d. Cardiac rhythm disorder

e. Congestive cardiac failure

2.6: Peripheral vascular disease

2.7: Connective tissue disorder

2.8: Haematological disorder

2.9: History of Migraine

2.10a: History of prior TIA

2.10b: Known carotid disease

2.11: Patient on treatment:

Type of treatment:

a. Ecospirin

b. Clopidogrel

c. Oral anticoagulation

2.12: Family history of TIA/CAD

2.13: Any specific comment

3. Symptoms and Signs:

Vital:

3.1: 1. Regular, 2.Irregular

3.2: BP:(First recorded blood pressure): RBS

at presentation:

3.3Cardiac Auscultation:

3.4aCarotids: Weak: 1. Yes 2. No 3.4b:Bruit: 1. Yes 2. No

Symptoms:

3.5: Headache

3.6: Vomiting

3.7: Seizure

3.8 ***Signs*** as per NIHSS: Score

LOC:

1a.

1b.

1c.

3.8.2Vision:

3.8.3Gaze:

3.8.4Facial:

3.8.5Motor arm:

3.8.6Motor leg:

3.8.7Ataxia:

3.8.8Best language:

3.8.9Dysarthria:

3.8.10Sensory:

3.8.11Extinction:

3.8.12Other signs/symptoms not included in NIHSS:

3.9NIHSS at presentation:

3.10GCS AT presentation:

3.11MRS at presentation:

4. Investigations:

4.1.1: Biochemical:

4.1.1.aFBS

4.1.1.bPLBS

4.1.1.cLipid profile: Total CH…….LDL……HDL……..TGs……VLDL……

4.1.1.dBUN……Creatinine……

4.2: Immunological (1. Positive, 2. Negative 3. Not done)

4.2.aANA……..ds DNA…….

4.2.bRA factor

4.2.cANCA

4.2.dAPLA

4.3: Prothrombotic

4.3.1Homocystine: If done then value:

4.3.2Prothrombotic w/u: Pls specify:

4.4: Cardiac:

4.4.1ECG: 1. Normal 2. LVH 3. LAE 4. Old MI 5.Recent Ischemic changes 6.Not done

4.4.2 2D Echo: 1. Normal 2.LV dysfunction 3. Thrombus 4. SEC 5.Valve disease 6.PFO 7.Infective Endocarditis 8. Not done

4.4.3Holter: 1. Normal 2.Atrial fibrillation 3.Atrial flutter 4. Heart block 5.Other rhythm disturbance 6.Not done

4.5: Imaging:

a. CT Scan: ……..1.Normal 2.New infarct 3.old infarct 4.small vessel ischemic changes 5.Not done

a1: If infarct then any spontaneous hemorrhagic transformation…….1. yes 2.no

If yes then ……1.HI-1, 2.HI2, 3.PH1, 4.PH2.

a2: Territory: ……..1. ICA 2. ACA 3. MCA Complete 4. MCA superior div 5. MCA inferior div 6. MCA subcortical 7. Posterior circulation

a3: Dense artery sign: 1. MCA 2.PCA 3. Basilar 4. ACA 5.ICA 6.Absent.

a4: CT-Angio Neck: …….1. Normal. 2. Abnormal. 3. Not done.

If abnormal specify:

a5: CT-angi intracranial: …….1. Normal 2. Abnormal. 3. Not done.

If abnormal specify:

a6: CT-Perfusion: ……1. Mismatch 2. No mismatch 3. Not done.

b. MRI Scan:

b1: DWI:……1. Negative 2.Positive single lesion 3. Multiple lesion 4. Not done.

b2: Arterial territory of acute infarct: …….1. ICA 2. ACA 3. MCA Complete 4. MCA superior div 5. MCA inferior div 6. MCA subcortical 7. Posterior circulation.

Describe finding if required:

b3: T2/FLAIR:(Old infarct): 1. Normal 2. Single lesion 3. Multiple lesion 4. Not done.

b4: Describe periventricular lesion as per Fazekas scale:……

0: No lesion 1. Caps or thin line 2. Smooth halo 3. Extension into the white matter.

b5: Describe white matter lesion as per Fazekas scale:……

0: No lesion 1. Punctate foci 2. Beginning confluence of foci 4. Large confluent area.

Describe finding if required:

b6: MR Perfusion: …….1. Mismatch 2. No mismatch 3. Not done.

b7: SWI: ……1. Microbleeds 2. Hemorrhagic transformation of infarct 3. Negative 4.Not done

b7.1: No. of microbleeds.

b7.2: 1.HI-1, 2.HI2, 3.PH1, 4.PH2. …….

b8: MRA Neck: ……1. Normal 2.Abnormal 3. Not done.

If abnormal specify:

b9: MRA intracranial: …….1. Normal 2. Abnormal. 3. Not done.

If abnormal specify:

c: Carotid Doppler: ……..1.Normal. 2. Abnormal 3. Not done.

If abnormal specify:

d: DSA……1.Normal. 2. Abnormal 3. Not done.

If abnormal specify:

e: Final impression of vessel status:(Symptomatic vessel): …….1. <50% stenosis 2. Moderate stenosis (50-69%)

3. Severe stenosis 4. Arterial dissection 5. Vessel occlusion 6. Normal.

f: Vessels involved: ……..1. Extracranial ICA. 2. Intracranial ICA .3. MCA M1. 4. MCA M2. 5. ACA 6. BA 7. VA 8. PCA 9. SCA 10.PICA

g: Side of involvement of vessel:……1.Right 2. Left 3. Bilateral

h: Stroke subtype: ……

(TOAST criteria) 1. Large artery atherosclerotic 2. Cardioembolic 3. Other specific causes 4. Undertermined. 5. Lacunar.

h.1: if cardioembolic mention cause:……

h.2: If specific cause: ……1.Dissection. 2. Prothrombotic. 3. Vasculitis. 4. Moyamoya. 5. Hematological 6. Drug-induced.

5: Thrombolysis:

5.1: If thrombolysed: ……1.Yes, 2. No

5.2: If Yes……...1. Intravenous. 2. Intraarterial 3. Bridging.

5.3: If SICH after t-PA :……1. Yes 2. No

6. *Management*:

6.1: Medical : 6.1a: Ecospirin. 6.1b: Clopidogrel. 6.1c: Dipyridamole. 6.1d: Warf:

6.1e: Statins: 6.1f: Anti Hypertensive:

6.2: Interventions: 1. Yes 2. No.

6.2a: Stenting:……. Date of stenting……..

If Yes……1. Carotid 2. Vertebral 3. Basilar

1. Intracranial…….2. Extracranial…….

6.2b: Carotid endarterectomy: ……Date of surgery: ……

6.2c: Moyamoya revascularization……Date of surgery:…….

6.2d: PFO Closure:……Date of surgery…….

6.2e: Hemicranietomy……Date of surgery……

7. Outcome:

7.1: ……1. Discharge 2. Death.

7.1.2: If death, cause of death related to CVA……..1. Yes 2. No.

Specify cause of death:

7.3: Final Diagnosis……..1. Definite TIA 2. Probable TIA. 3. Ischemic stroke.

7.4: New event……..1. before discharge 2. After discharge.

7.4.2:…….Mention new event: ……..1. No. 2. Ischemic stroke. 3. Hemorrhagic stroke. 4. MI 5. CCF 6. Recurrent TIA. 7. Death.

7.4.2.a: Date of new event……

7.4.2.b(If a new event is a stroke): Vessels involved: ……..1. Extracranial ICA. 2. Intracranial ICA .3. MCA M1. 4. MCA M2. 5. ACA 6. BA 7. VA 8. PCA 9. SCA 10.PICA

7.5: Side of involvement of vessel:……1.Right 2. Left 3. Bilateral.

7.6: NIHSS at discharge:

7.7: MRS at discharge:

7.8: Complication in hospital……..1. Pneumonia. 2. MI 3. DVT 4. UTI 5. Bedsore 6. Pulmonary embolism 7. No complications.

7.9: 3 Month outcome:(New event):……. 1. No. 2. Ischemic stroke. 3. Hemorrhagic stroke. 4. MI 5. CCF 6. Recurrent TIA. 7. Death.

7.10: MRS at 3 months:

7.11: NIHSS at 3 months:

7.12: Outcome at 6 months:
MRS…….NIHSS……Death……..Other events……..

7.13: Outcome at 1 year:
MRS…….NIHSS……Death……..Other events……..

7.14: Outcome at 2 years:
MRS…….NIHSS……Death……..Other events…….

7.15: Outcome at 3 years:
MRS…….NIHSS……Death……..Other events……..

7.16: Outcome at 5 years:
MRS…….NIHSS……Death……..Other events……..

7.17: Outcome at 10 years:
MRS…….NIHSS……Death……..Other events……..

7.18: Outcome, at last, follow up:
MRS…….NIHSS……Death……..Other events……..

7.19:If Other events……then specify……

ANNEXURE –II:

NIHSS scale:

1a. Level of Consciousness:

0= **Alert;** keenly responsive.
1= **Not alert**, but arousable by minor stimulation to obey, answer, or respond.
2= **Not alert**; requires repeated stimulation to attend.
3 = Response only with reflex motor or autonomic effects or unresponsive, flaccid, and areflexic.

1b. LOC Questions:

0 = **Answers** both questions correctly. 1 = **Answers** one question correctly.
2 = **Answers** neither question correctly.

1c. LOC Commands:

0 = **Performs** both tasks correctly. 1 = **Performs** one task correctly. 2= **Performs** neither task correctly.

2. Best Gaze:

0= Normal. 1= Partial gaze palsy; 2= Forced deviation,

3. Visual:

0 = No visual loss. 1 = Partial hemianopia. 2 = **Complete hemianopia.**
3= Bilateral hemianopia (blind including cortical blindness).

4. Facial Palsy:

0 = **Normal** symmetrical movements.
1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling).
2 = **Partial paralysis** (total or near-total paralysis of the lower face).
3= **Complete paralysis**.

5. Motor Arm:

0 = No drift;
1 = Drift;.
2 = Some effort against gravity.
3 = **No effort against gravity;**
4 = No movement. UN = **Amputation** or joint fusion

6. Motor Leg:

0 = No drift;
1 = Drift; .
2 = Some effort against gravity;
3 = No effort against gravity;
4 = No movement.
UN = **Amputation** or joint fusion

7. Limb Ataxia:

0 = Absent. 1= Present in one limb. 2= Present in two limbs.

8. Sensory:

0 = **Normal;** no sensory loss.
1= **Mild-to-moderate sensory loss;** 2= **Severe to total sensory loss;**

9. Best Language:

0 = No aphasia; normal. 1 = Mild-to-moderate aphasia;
2 = Severe aphasia; 3 = Mute, global aphasia;

10. Dysarthria:

0 = Normal. 1 = Mild-to-moderate dysarthria;
2 = **Severe dysarthria;**

11. Extinction and Inattention (formerly Neglect):

0 = No abnormality.
1 = Visual, tactile, auditory, spatial, or personal inattention
2 = Profound Hemi-inattention **or extinction to more than one modality**

ANNEXURE –III

MODIFIED RANKIN SCALE (mRS)

Score Description

0 = No symptoms at all

1 = No significant disability despite symptoms; able to carry out all usual duties and activities

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

3 = Moderate disability; requiring some help, but able to walk without assistance

4 = Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

5 = Severe disability; bedridden, incontinent, and requiring constant nursing care and attention

6 = Dead

ANNEXURE –IV

TOAST Classification of Subtypes of Acute Ischemic Stroke

(TOAST, Trial of Org 10172 in Acute Stroke Treatment.)

1. Large-artery atherosclerosis
2. Cardio embolism
3. Lacunar
4. Stroke of other determined etiology
5. Stroke of undetermined etiology

Annexure V:

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेंद्रम - 695 011, केरल, भारत
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY
TRIVANDRUM - 695 011, KERALA, INDIA
(एक राष्ट्रीय महत्व का संस्थान, विज्ञान एवं प्रौद्योगिकी विभाग, भारत सरकार)
(An Institution of National Importance, Department of Science and Technology, Government of India)
टेलीफॉन नं./Telephone No.: 0471-2443152 फैक्स/Fax: 0471-2446433, 2550728
ई-मेल/E-mail: sct@sctimst.ac.in वेबसाइट/Website: www.sctimst.ac.in

Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

SCT/IEC/1600 /NOVEMBER-2020 28.12.2020

Dr. G Balaswamy Reddy
Senior Resident
Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. G Balaswamy Reddy,

Thank you for submitting documents related to your proposal titled "(**ISCHAEMIC STROKE IN YOUNG ADULTS: RISK FACTORS, ETIOLOGY, AND OUTCOME (**IEC/1600)" to the IEC for review.

The following documents were reviewed:

1. Check list
2. Proposal
3. IEC Application Form
4. Covering letter addressed to the Chairperson, IEC, SCTIMST dated 03.09.2020 by the Co-PI
5. Covering letter addressed to the Chairperson, IEC, SCTIMST dated 03.09.2020 by the HOD in charge
6. Proforma
7. TAC Approval Letter
8. CV of Dr. Balaswamy Reddy with APMC number
9. CV of Dr. Sylaja P.N TCMC number
10. CV of Dr. Sapna Sreedharan, with TCMC number
11. Covering letter addressed to the Chairperson, IEC, SCTIMST dated 03.09.2020 by the PI

The following members of the Students Sub-Committee of the Institutional Ethics Committee participated in the discussions held between August 23-October 29, 2020 at the offices and residences of the members

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. R V G Menon	M Tech, PhD	Male	Lay Person (Chairman)	No
2.	Dr. Harikrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
3.	Dr. Kala Kesavan. P	MBBS, MD	Female	Basic Medical Scientist	No
4.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
5.	Dr. Rema M. N	MD	Female	Basic Medical Scientist	No
6.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
7.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

IEC Decision
The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC

Annexure V: Plagiarism check:

Plagiarism Checker X - Report

Originality Assessment

Overall Similarity: **0%**

Date: Aug 16, 2022

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