

Original Research Article

Prevalence, risk factors and clinical profile of patients with cardioembolic stroke in South India: a five-year prospective study

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ABSTRACT

Background: Stroke is the second leading cause of mortality and morbidity worldwide. Cardioembolic stroke accounts for 15-30% of Ischemic stroke. There have been very few clinical studies on cardioembolic stroke, especially from India. Our aim was to provide a demographic, risk factor and clinical profile of patients with cardioembolic stroke in South India.

Methods: A prospective study was conducted at the Neurology Inpatient Department over a period of 5 years from January 2013 to January 2018 collecting necessary information and data from all cases diagnosed as cardioembolic stroke.

Results: 651 patients were diagnosed to have acute Ischemic stroke. Of the 76 patients (11.6%) diagnosed with cardioembolic stroke, 35 (46%) were females. Mean age was 53.5±12.2 years. Occurrence of cardioembolic stroke was seen to be higher (71% vs 28.9%, p value<0.0001) in patients of older age group (46 years or more). A significant proportion of patients of the older age group (37%) had hypertension (p value=0.0048). Coronary artery disease (CAD) was the most prevalent cardiac disorder, observed in 42 patients (55.2%), valvular heart disease in 22 patients (28.9%) and atrial fibrillation in 14 patients (18.4%). Limb weakness (84.2%) and Middle Cerebral Artery (MCA) territory (73.6%) infarct were observed in majority of the patients.

Conclusions: Prevalence of cardioembolic stroke in this region is lower than reported worldwide. While male predominance of cardioembolic stroke was noted, old age and hypertension were the major vascular risk factors identified. CAD was the major source of cardioembolism.

Keywords: Cardiac risk factors, Heart, Hyderabad, Stroke

INTRODUCTION

Stroke is one of the major causes of mortality and morbidity across the globe and cardioembolic stroke accounts for 14-30% of all cerebral infarctions worldwide.¹⁻⁵ The severity and recurrence rate of cardioembolic stroke are seen to be much higher than in non-cardioembolic stroke. The hospital based stroke registries from Southern India have shown that cardioembolic stroke is attributed only to 10-15% of

Ischemic stroke.^{6,7} With the overall changes in demographic profile and the increasing life expectancy, risk factors for cardiac embolism have become more common in low and middle-income countries and they are expected to increase three fold by 2050.⁸ Embolism from the heart to the brain occurs from one of the three means: blood stasis and thrombus formation in an enlarged left cardiac chamber; release of material from an abnormal valvular surface; and atrial fibrillation leading to inadequate contraction and stasis marked in left atrial

appendage. While rheumatic heart disease (29%) and ischemic heart disease (27%) are identified as the predominant causes for cardioembolic stroke in India,⁶ atrial fibrillation is the common cardioembolic risk factor worldwide.⁹ Early confirmation of cardioembolic stroke, which is crucial in management can substantially reduce the recurrence of stroke, as cardioembolism causes a more severe stroke and the rate of recurrence is much higher than other subtypes of ischemic stroke.¹⁰ High-risk sources of cardiac embolism are atrial fibrillation or flutter, rheumatic heart disease (RHD), systolic heart failure, mechanical prosthetic valve, left atrial or ventricular thrombus, a recent occurrence of myocardial infarction (<4 weeks), dilated cardiomyopathy, infective endocarditis, regional left ventricular akinesia, atrial myxoma and patent foramen ovale with thrombus in situ. Based on this background, our study aimed to find the demographic and clinical profiles, the prevalence and the risk factors of cardioembolism prevailing among the people belonging to South India, as clinical studies on cardioembolic stroke from India are very limited.

METHODS

Study design

This was a prospective study which included patients diagnosed with cardioembolic stroke admitted to the Department of Neurology from January 2013 to January 2018 at ESIC Super speciality Hospital, Hyderabad. Stroke was defined as an acute onset of focal neurological deficit and confirmed by computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain. Cardioembolic stroke was confirmed by a neurologist based on the presence of a typical clinical presentation and neuroimaging profile, positive evidence of a high-risk cardiac source (based on Echocardiography and Electrocardiogram) and the exclusion of a large-artery plaque. All patients in whom diagnosis of cardioembolism was confirmed, were consecutively recruited after obtaining consent from them or their relatives. Demographic and clinical profiles, vascular risk factors and risk factors for cardioembolism were assessed using a proforma. The details collected were carefully examined and recorded by a qualified neurologist.

Participants

Out of the 651 ischemic stroke patients, 76 patients with a diagnosis of cardioembolic stroke were included in the study (Figure 1). Patients included in the study were those with age more than 18 years with diagnosis of cardioembolic stroke whose work up was complete. Patients or their relatives who did not give consent were excluded from the study, children and pregnant ladies were also excluded. Information regarding reliable variables comprising demographic details, vascular risk factors and co-morbid illnesses, associated cardiac illnesses, clinical features and echocardiographic findings were collected using a structured proforma. General

information included the patient's age, sex, and duration of hospital stay. Information concerning the medical history of diabetes mellitus, hypertension, heart disease, prior stroke, migraine, thyroid disorder and any other medical illness were collected. Laboratory parameters such as fasting lipid profile and glycosylated haemoglobin were included. Habitual history, if any, of smoking, alcohol use or tobacco chewing was also taken into consideration. Details regarding territory of stroke, cortical or subcortical, haemorrhagic conversion of infarct were collected. The requirement of triple therapy (double antiplatelet and oral anticoagulant) versus only anticoagulant was also confirmed. The study was approved by the Institutional Ethical Committee.

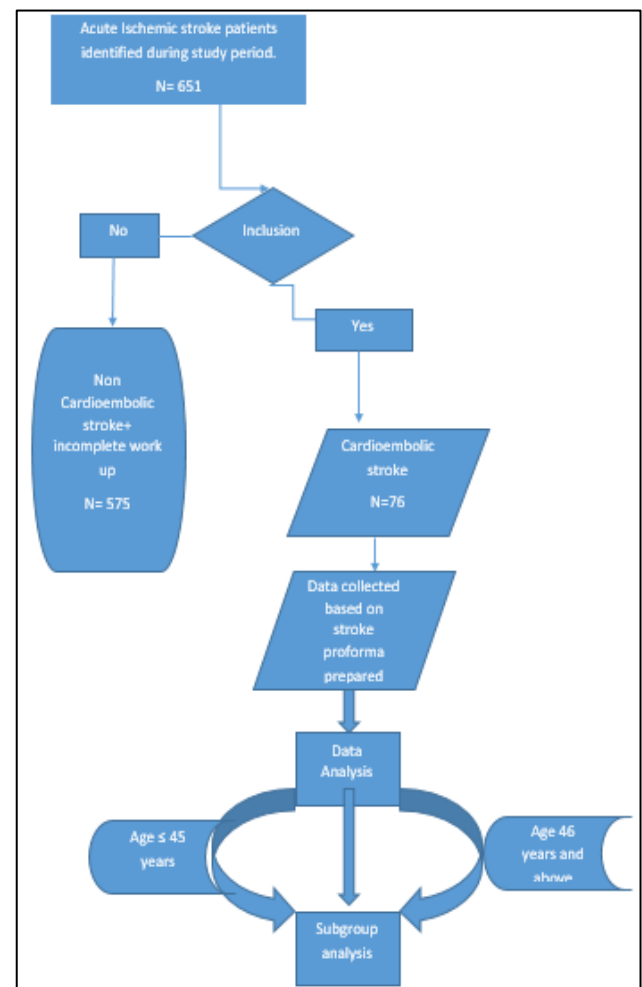


Figure 1: Flow chart of study design.

Definition of study variable

Diagnosis of cardioembolic stroke

Confirmation of the presence of a typical clinical feature, a potential major cardiac source of embolism and a neuroimaging profile in the absence of arterial disease remain the mainstay of clinical diagnosis of Cardioembolic stroke.

Clinical presentation in cardioembolic stroke

Clinical features that support the diagnosis of cardioembolic stroke include sudden onset to maximal deficit (<5 min) and decreased level of consciousness at onset rapid regression of symptoms (the spectacular shrinking deficit syndrome) and the onset of symptoms after a Valsalva-provoking activity (coughing, bending, etc.).¹¹⁻¹⁴ Wernicke's aphasia or global aphasia without hemiparesis, visual-field abnormalities, neglect, and aphasia are common secondary symptoms of cardioembolism.^{15,16}

Neuroimaging profile in cardioembolic stroke

Neuroimaging data supporting cardioembolic stroke includes simultaneous or sequential strokes in different arterial territories (predominating in the middle cerebral artery and carotid distributions), haemorrhagic transformation of an ischemic infarct and early recanalization of an occluded intracranial vessel radiological location of lesions in a cortical territory and vascular imaging of the intracranial circulation showing an abrupt vessel cut-off without significant atherosclerotic narrowing of the upstream vessel.^{1-3,14,16-18}

Young age onset stroke

Patients having acquired stroke at less than or equal to 45 years of age, old age onset stroke, patients having acquired stroke 46 years or more of age.¹⁹

Statistical analysis

Data obtained in the study were subjected to statistical analysis with SPSS (version 18.0). Categorical variables were summarized as counts (percentage) and continuous variables as means or medians. Unpaired t test was used to compare between quantitative variables. Bivariate analysis was done using 2x2 Fisher's exact test for significance. A two tailed probability value <0.05 was considered significant. All confidence intervals (CI) were set at 95%.

RESULTS

Out of the 651 acute Ischemic stroke patients, 76 (11.6%) were diagnosed to have suffered cardioembolic stroke during the past 5 years.

Baseline characteristics

Mean age of patients with cardioembolic stroke was 53.5±12.2 years (range 30-81), 41 (53.9%) patients were male, and 35 (46 %) patients were female. Male to female ratio was 1.17:1. 22 (28.9%) patients had early occurrence of stroke (age ≤45 years), while 54 (71%) patients had old age stroke. The rate of occurrence of cardioembolic stroke was noted to be higher in patients of older age group (46 years or more) and this association

was statistically significant (p value<0.0001). There was no significant differences in the age of onset of cardioembolic stroke among men (mean age=53±12 years) and women (54.2±12.5). Hypertension (57.8%) was the most common vascular risk factor among patients with cardioembolism (Table 1).

Table 1: Baseline characteristics of patients with cardio-embolic stroke.

Variables	N (%)
Male	41 (53.9)
Age group (years)	
≤45	22 (28.9)
>45	54 (71)
Smoking	26 (34.2)
Alcohol use	23 (30.2)
Diabetes mellitus	31 (40.7)
Hypertension	44 (57.8)
Prior stroke	5 (6.5)
Thyroid disease	4(5.2)
Hyperlipidemia	28 (36.8)

Risk factors for cardioembolic stroke

The most common cardiac disorder associated with cardioembolism observed in the present study was CAD. Around 42 patients (55.2%) had CAD, followed by valvular heart disease in 22 patients (28.9%) (Table 2).

Further subgroup analysis was done with two groups based on their age of onset of stroke, the young being ≤45 years and the old being 46 years or more. A higher proportion of patients with older age (46 years or more) had hypertension than the younger group and this difference was statistically significant (p-value=0.0048). Also, a higher proportion of the older age group had CAD (61.1%) and cardiomyopathy (22.2%) when compared to the young with an early onset of cardioembolic stroke. But this difference was not statistically significant. Valvular heart disease (40.9%) and Left ventricle apical clot (22.7%) were notably higher in the young than in the older age group (Table 4).

Table 2: Cardiac disorders observed in study group.

Cardiological abnormalities	N (%)
Coronary artery disease	42 (55.2)
Valvular heart disease	22 (28.9)
Cardiomyopathy	14 (18.4)
Arrhythmia	15 (19.7)

Among patients with CAD, left ventricular (LV) dysfunction with low ejection fraction (ejection fraction of less than 55%) was found to be the major source of cardioembolism. 22 (52.3%) patients had LV dysfunction with low ejection fraction and the lowest ejection fraction was 28.6% (Table 3). Among specific cardiac disorders, Chronic Rheumatic Heart Disease (CRHD) and atrial

fibrillation turned out to be potential causes for high source cardiac embolism (Table 3). CRHD accounted for 21% while atrial fibrillation accounted for 18.4% of cardioembolic stroke.

Table 3: Specific cardiac disorder observed in study population.

Variables	Number (n=76) (%)
Atrial fibrillation (AF)	14 (18.4)
Valvular AF	9 (64.2)
Non-valvular AF	5 (35.7)
Junctional rhythm	1 (1.3)
Chronic Rheumatic Heart disease (CRHD)	16 (21)
Prosthetic valve replacement done	10 (62.5)
No valve replacement	6 (37.5)
Recent Myocardial Infarction (MI)	12 (15.7)
Anteroseptal MI	6 (50)
Inferior wall MI	3 (25)
Anterolateral MI	3 (25)
Dilated cardiomyopathy	12 (15.7)
Alcoholic	6 (50)
Ischemic	4 (33.3)
Combined	2 (16.6)
Restricted cardiomyopathy	2 (2.6)
Non Rheumatic valvular disease	6 (7.8)
Ischemic	4 (66.6)
Sclerotic valvular disease	2 (33.3)
Left ventricle apical clot	9 (11.8)
Left ventricular dysfunction and low ejection fraction (<55%)	22 (28.9)

Clinical characteristics

Limb weakness (focal deficit) was the most common clinical presentation. Hemiparesis occurred in 61.8% patients, hemiplegia in 22.3% and aphasia in 11.8% patients (Figure 2). Mean duration of hospital stay was 11±6 days. A sizeable number of patients (50%) had Modified Rankin Score of 4 at admission.

The present study found that cardioembolic infarction was predominate in anterior circulation. Neuroimaging revealed Middle cerebral artery infarct (MCA) in 56 (73.6%) patients and multiple artery infarcts in 6 (7.8%) patients. Among those with MCA territory infarcts, right MCA territory infarct (non-dominant) was found to have occurred in 32 (57.1%) patients. While majority of patients had multiple infarcts in MCA, a few had single large striatocapsular and capsuloganglionic infarcts. Multiple artery infarcts included combined anterior circulation (MCA and Anterior cerebral artery (ACA), combined anterior circulation and posterior circulation (MCA, Posterior with cerebral artery (PCA), and cerebellar infarcts). Baseline haemorrhagic transformation occurred in 8 (10.5%) patients. The vast

majority of these cardioembolic strokes involved lesions in a cortical territory as observed in 59 (77.6%) patients (Table 5).

Table 4: Comparison between patients of young and older age onset cardioembolic stroke.

Study variables	Older age (46 years and more) n=54 (%)	Young age (≤45 years) n=22	P value
Mean age	59.6±7.9	38.1±5.1	<0.0001
Male	29 (53.7)	12 (54.5)	1
female	25 (46.2)	10 (45.4)	1
Hypertension	37 (68.5)	7 (31.8)	0.0048
Diabetes mellitus	25 (46.2)	6 (27.2)	0.19
Smoking/tobacco use	20 (37)	6 (27.2)	0.59
Alcohol use	18 (33.3)	5 (22.7)	0.42
CAD	33 (61.1)	9 (40.9)	0.13
Valvular heart disease	10 (18.5)	9 (40.9)	0.07
Cardio-myopathy	12 (22.2)	1 (4.5)	0.09
Atrial fibrillation	10 (18.5)	3 (13.6)	0.7
LV apical clot	5 (9.2)	5 (22.7)	0.14

CAD-Coronary artery disease, LV- Left ventricle

Table 5: Neuroimaging profile of patients with cardioembolic stroke.

Radiological variables	Number (%)
MCA territory infarct	56 (73.6)
ACA territory infarct	3 (3.9)
PCA territory infarct	2 (2.6)
Multiple artery infarcts	6 (7.8)
Cerebellar infarcts	4 (5.2)
Cortical infarcts	59 (77.6)
Subcortical infarcts	9 (11.8)
Baseline haemorrhagic transformation	8 (10.5)

MCA- Middle cerebral artery, ACA-Anterior cerebral artery, PCA-Posterior cerebral artery

Majority of patients were treated initially with low molecular weight heparin (LMWH) followed by bridging oral anticoagulant. The following treatment regimen was observed: Oral anticoagulant therapy alone in 28 patients (36.8%), double antiplatelets in 27 (35.5%) patients, triple regime (oral anticoagulant and double antiplatelets therapy) in 11 (14.4%) patients, oral anticoagulant and single antiplatelet (ecospin 150 mg) in 9 (11.8%) patients and single antiplatelet in 2 (2.6%) patients. Only one patient was administered newer oral anticoagulant. Decisions on different regimes were based on CHADS2

score (acronym for congestive heart failure, hypertension, age, diabetes mellitus and stroke) and haemorrhagic (intracranial and extracranial) manifestation.

DISCUSSION

The prevalence of cardioembolic stroke in India is less when compared to western report (10-15% vs 15-30%).³⁻⁷ In present study 76 patients had cardioembolic stroke among 651 cases of ischemic stroke, which account to 11.6%. Prevalence is similar to previous reports from India. One reason for low prevalence can be due to lack of utilization of transoesophageal echocardiography and Holter monitoring in all cases in view of limited available resources. Patients with cardioembolic stroke are susceptible to early and long-term recurrence. Therefore early confirmation and diagnosis of cardioembolic infarction are extremely important in the initiation of anticoagulation therapy for an adequate secondary prevention. Oral anticoagulant therapy can prevent upto 70% of strokes in patients with the most common cardioembolic risk factor, namely atrial fibrillation (AF).²⁰ Till date, there has been no gold standard or definite diagnostic criteria for cardioembolic stroke. The diagnosis mostly depends on typical clinical features, neuroimaging profile, and establishment of cardioembolic source and exclusion of large vessel disease plaque.^{18,21,22} There exists very limited data regarding cardioembolic stroke in South Asian countries. Hence, a study assessing the prevalence, vascular risk factors, clinical profile and cardiac source of embolism would definitely provide a deeper insight into stroke risk in this sub group of people from South India.

As per our study, cardioembolic stroke accounted for 11.6% of ischemic strokes. This is similar to the majority of hospital-based studies from Hyderabad in South India and the rest of Asia.^{6,7,23,24} Registries from the Western world including North America, the United Kingdom, and Europe report a higher frequency (15-30%).^{3-5,25} In a recent Indo-US Collaborative Stroke Project, a comparatively larger proportion (24.9%) of cardioembolic stroke was reported from India.²⁶

As for the limitations of our study, it is indeed possible that some cases of cardioembolism might have remained undetected in our cohort. Extensive investigations including continuous ECG recording, Holter monitoring and transoesophageal echocardiography could have detected a significantly higher proportion of cardioembolic stroke among the undetermined groups.²⁷ Another constraint for the study was the generally low prevalence of cardioembolic stroke in Hyderabad. Though earlier studies from this region showed a prevalence rate similar to that of other regions, racial and ethnic factors vary from region to region altering the pattern of ischemic stroke subtypes.

In our cohort, the risk factor profile demonstrated hypertension as the predominate risk factor associated

with cardioembolic stroke. This association was statistically significant (p value<0.0001) in patients of older age group when compared to the young. Hypertension is undoubtedly the most common condition affecting humans and one in every eight Indian suffers from high blood pressure according to the National Family Health Survey, which screened 22.5 million adults across 100 districts in India in 2017. Cardiac involvement usually occurs in patients with hypertension. Recent reviews have demonstrated that treatment of increased blood pressure with administration of angiotensin convertase enzyme (ACE) inhibitors and angiotensin 1 (AT1) receptor blocker may abolish the incidence of cardiac arrhythmia and markedly atrial fibrillation, when compared to other antihypertensive regimes.²⁸ Hence early identification and treatment of hypertension is crucial in the prevention of cardioembolic stroke in this sub group of population from South India.

CAD and valvular heart disease were the major cardiac sources of embolism observed in our cohort and this was similar to the report by Kaul et al, from South India. 55.2% of patients had a history of CAD or recently detected CAD. Recent Myocardial infarction was noted in 15.7% patients.⁶ It has been well documented that 2.5% of patients with acute myocardial infarction experience a stroke within 2 to 4 weeks of the infarction. LV dysfunction with low ejection fraction (ejection fraction of less than 55%), left ventricular aneurysm or thrombus, and associated arrhythmias such as atrial fibrillation are the factors attributed to cardioembolic stroke in CAD patient.^{3,4} In our cohort, LV dysfunction with low ejection fraction (52.3%) contributed the major source of cardioembolism in patients with CAD. This highlights the need to establish preventive strategies targeting patients with CAD and to arrange proper anticoagulation and medical follow-up for these groups.

Valvular heart disease (28.9%) was the second cardiac risk factor observed in the present study where a majority of patients had CRHD. 21% of patients were diagnosed to have CRHD and for the remaining patients valvular involvement was secondary to ischemic heart disease and sclerotic valvular disease. Studies from India have reported that CRHD and prosthetic valves contribute to almost 66% of all cardioembolic stroke in young adults.²⁹ Similar findings were observed in the present study where valvular heart disease was found to be higher in the young and CAD in older patients with cardioembolic stroke. This is in contrast to studies reported from developed countries where only 2.5% of cardiac risk factor is attributed to valvular heart disease, in cardioembolism.³⁰

The majority of arterial embolic stroke originates in the left heart secondary to structural or functional abnormalities. Artery to artery embolism originates from arterial tree itself and occurs as a manifestation of atherosclerosis. In artery to artery embolism cholesterol and other lipids are accumulated in the intimal-medial

layer of the artery with secondary inflammations, fibrous tissue deposition, luminal surface erosions and appearance of often mobile thrombi protruding into the lumen of the major artery (aorta, carotids).³¹ These can be differentiated from cardioembolic stroke by the presence of atherosclerotic plaque in major vessel, either by MR angiogram or CT angiogram of brain and neck vessels extending upto aorta. Presence of cardiac abnormality either structural or functional clues towards cardioembolism, as both embolism share a common clinical presentations. Atherosclerotic plaques formed in carotids are far more likely to embolize to brain causing stroke or TIA. In our study neck vessel Doppler and MR angiogram brain and neck and 2D Echo helped to lineate cardioembolic stroke from artery to artery embolism.

Cardiac emboli arising from the cardiac chambers are often large and cause severe stroke, disability and mortality. They also have high chances of early as well as late embolic recurrences. Hence, early identification of cardioembolic stroke is crucial for planning the appropriate treatment mode (anticoagulation) and prevention strategies.

However, the current study is not without its own limitations. Firstly, all patients did not undergo transoesophageal echocardiography and Holter monitoring. Secondly, follow up was done only till discharge, hence recurrence and mortality at 90 days were not established. Thirdly, the study being hospital-based, results were not inferred from a general population. Yet, despite the drawbacks, the present study, to the best of our knowledge, is the first ever single-centre prospective study, evaluated over a period of 5 years focussing on patients diagnosed with cardioembolic stroke from South Asia. The study highlights hypertension and CAD as major factors leading to cardioembolism. Hence, there is an urgent need for identification of the risk factors by a comprehensive evaluation of every patient to establish a diagnosis of cardioembolic stroke.

CONCLUSION

The present study from a hospital-based registry in South India has successfully created a database on cardioembolic stroke in this region. Prevalence of cardioembolic stroke was found to be consistent with other South Asian Countries, but lower than that reported from the Western stroke registry. Higher frequency of old age onset and male predominance were observed in cardioembolic stroke. Hypertension remained the major vascular risk factor and CAD was the major cardiac risk factor in the cohort. Awareness of these risk factors will be crucial in establishing and determining strategies for appropriate management of cardioembolic stroke and formulation of health care systems in South India.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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