

## Frequency of Ischemic Stroke Subtypes Based on Toast Classification at a Tertiary Care Center in Pakistan

### Abstract

**Background:** The purpose of this study was to determine the frequency of ischemic stroke subtypes based on Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification at a tertiary care center in Pakistan. **Materials and Methods:** A cross-sectional study was conducted in Stroke Unit of Shifa International Hospital, Islamabad. We included 145 patients who presented to us from November 2015 to February 2016 with radiological confirmed neurological deficits consistent with ischemic stroke. The causes of ischemic stroke were classified according to TOAST criteria. Regression analysis and Chi-square test were used to compute *P* value. **Results:** Among the 145 patients diagnosed with ischemic stroke, there were 54.1% males and 45.9% females with a mean age of  $65 \pm 14$  years. Nearly 62.7% patients had hypertension (HTN) as the most common risk factor, followed by 38.6% diabetes mellitus (DM), 27.5% heart failure, 19.3% valvular disease, 18.6% previous stroke, 16.4% smoking, 15.1% dyslipidemia, 13.7% ischemic heart disease, and 13.1% atrial fibrillation. HTN was significantly associated with large vessel disease ( $P = 0.028$ ). DM was significantly associated with small vessel disease ( $P = 0.001$ ). Smoking and atrial fibrillation both were associated with unknown etiology of stroke ( $P = 0.001$  and  $P = 0.039$ , respectively). Most common etiology of stroke was cardioembolism (40%), and atrial fibrillation is found to be the most common cause of cardioembolic stroke with 30.6% incidence. **Conclusion:** Our study concludes that cardioembolic stroke is the most common cause of acute ischemic stroke in our stroke unit. Atrial fibrillation is found to be the most common cause of cardioembolic stroke.

**Keywords:** Atrial fibrillation, cardioembolism, stroke

### Introduction

Stroke is the second leading cause of death that mostly affects middle-aged and older individuals. About 5.7 million deaths were attributed to stroke in 2008 according to the World Health Organization, and 85% of these deaths occurred in developing countries.<sup>[1]</sup> Burden of this disease in Asian countries is going to increase according to literature.<sup>[2]</sup> Race and ethnicity are important determinants of etiology of stroke. Lacunar stroke was found to be the most common subtype of stroke in the population of Pakistan in contrast to the Western studies that report cardioembolic stroke as the most frequent subtype.<sup>[3,4]</sup> Acute large vessel occlusions document 28.7% of incidence according to studies performed globally.<sup>[5]</sup> Approximately, one in four ischemic strokes is of cardioembolic origin.<sup>[6,7]</sup> Kaul *et al.* and Hart *et al.* reported 16% of patients with lacunar infarction and about 25% of ischemic strokes of cryptogenic origin,

respectively.<sup>[8]</sup> Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification introduced in 1993 is still an effective and convenient system that is used in stroke studies globally. The systems of classification used previously were often incomplete and difficult to apply in routine clinical settings.<sup>[9]</sup> The TOAST classification system has worldwide acceptance and has moderate inter-rater reliability.<sup>[10,11]</sup> The rationale of our study is to compare the frequency of stroke subtypes in a tertiary care hospital of Pakistan setup and to improve long-term management that includes prevention, diagnosis, treatment, and follow-up. Classifying it according to TOAST classification helped us to know causes of different subtypes of strokes which altered our management strategy. Carotid endarterectomy is the treatment of choice in large-vessel disease, whereas anticoagulation is primarily performed in cardioembolic stroke and risk factor

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prevention helps majorly in small vessel disease. Stroke recurrence can also be prevented by better risk factor control.

There are other reports of stroke, subtypes of stroke, or studying risk factors in Pakistan. Syed *et al.* found that small vessel disease is the most common stroke subtype in Pakistani population.<sup>[3]</sup> Wasay *et al.* studied stroke subtypes in South Asian Countries and documented increased prevalence of large vessel disease in India and lacunar infarcts in Pakistan. Cardioembolic stroke is reported to be less prevalent in South Asia than in Western countries.<sup>[12]</sup> According to our study results, cardioembolic stroke has been found to be the most common stroke subtype in north of Pakistan that is distinct from the regional studies' results; a probable reason could be that the above-mentioned studies were done in South of Pakistan and our study was conducted in North of Pakistan. The peculiar genetic makeup could be a reason and should be further investigated.

Khealani *et al.*, Shah *et al.*, Taj *et al.*, and Kamal *et al.* have already mentioned risk factors associated with stroke,<sup>[13-16]</sup> as we were reviewing retrospective data, we also highlighted the risk factors but that was not our elementary goal, and more or less similar risk factors were identified.

## Materials and Methods

We conducted a cross-sectional study in stroke unit of Shifa International Hospital, Islamabad, Pakistan including 145 male and female patients aged  $\geq 18$  years, who presented with neurological deficits consistent with radiological confirmed ischemic stroke from November 2015 to August 2016. Patients with incomplete data, those who refused to give consent, and patients with intracranial bleed or dural sinus thrombosis were excluded from the study. Ischemic stroke was classified according to TOAST criteria [Table 1].

Hypertension (HTN) was defined as the patient with known HTN before stroke (whether taking treatment or not) or patient with clinical or radiological evidence of HTN. Diabetics were defined as patients with labeled diabetes or persistent high glucose level requiring treatment during hospital stay. Dyslipidemia was defined as a history of impaired lipid profile, especially cholesterol and low-density lipoprotein or impaired lipid profile during hospital stay. Patients were labeled having cardiac disease presenting with cardiac arrhythmia, ischemic heart disease, valvular heart disease, i.e., mitral stenosis, and congestive cardiac failure. Workup included computed tomography (CT) scan and magnetic resonance imaging (MRI), carotid Doppler, CT angiography where carotid Doppler was inconclusive, electrocardiogram, transthoracic echocardiography, transesophageal echocardiography, Holter monitoring, coagulation profile, complete blood picture with differential

**Table 1: Trial of Org 10172 in Acute Stroke Treatment classification of stroke**

Large artery atherosclerosis: infarcts size $>1.5$ cm on CT/MRI brain, stenosis $>50\%$ of an appropriate artery (intracranial or extracranial)
Cardioembolism: Comprising a cardiac source for an embolus, for example, atrial fibrillation, prosthetic valves, infective endocarditis
Small vessel occlusion: Diameter $<1.5$ cm, history of diabetes, and HTN
Stroke of other determined etiologies: Nonatherosclerotic vasculopathies, hypercoagulable states, hematologic disorders
Stroke of undetermined etiology includes
Two or more causes identified, i.e., both cardioembolic and large vessel atherosclerosis found simultaneously in a patient
Negative evaluation, i.e., no cause found after workup
Incomplete evaluation - patient workup not completely done, like in our study due to affordability issues or the patient expired
MRI – Magnetic resonance imaging; CT – Computed tomography; HTN – Hypertension

count, serum blood glucose, serum electrolytes, renal function tests, hemoglobin A1c, and fasting lipid profile. Stroke workup including protein C, protein S, antithrombin III, complement levels (C3 and C4), lupus anticoagulant, anticardiolipin antibody, antinuclear antibody, antineutrophil cytoplasmic antibody, anti-double-stranded DNA, serology for syphilis, and an erythrocyte sedimentation rate was performed in selected cases. Patients who fulfilled the inclusion criteria were evaluated by a consultant neurologist, and the data were recorded by neurology resident on a standardized form.

The data were collected during the patient's hospital stay. The data were entered and analyzed using SPSS 16 (IBM Corporation, NY, USA) for Windows. Mean and standard deviation were calculated for the age of the patient, systolic blood pressure, diastolic blood pressure, and random blood sugar. The frequencies and percentages were calculated for risk factors and subtypes. Chi-square ( $\chi^2$ ) test of proportion was applied for the significance of patients with risk factors.  $P < 0.05$  was considered statistically significant. Nominal regression analysis and Pearson's Chi-square test were performed to evaluate risk factors' distribution in various etiologies of stroke.

## Results

During the 1-year period, 145 patients with acute ischemic stroke confirmed by either CT scan or MRI findings were included in the study. It enrolled patients from acute stroke data bank of Shifa International Hospital, Islamabad. The mean age at presentation of patients with acute ischemic stroke was  $65.1 \pm 13.7$  years with 66 (45.5%) females and 79 (54.1%) males. Overall 101/145 (69.6%) patients were admitted in neuro step down unit compared to 44/145 (30.4%) patients in other wards. Tissue plasminogen activator injection was only needed in 14/145 (9.6%)

patients who presented within window of 4.5 h after the appearance of symptoms of stroke. Anterior, posterior, and border zone strokes with specified vessels involved have been shown in Table 2. Stroke etiologies based on TOAST classification had been mentioned. Most common etiologies or causes of ischemic stroke were cardioembolism in 58/145 (40%), followed by 38/145 (26.89%) undetermined etiologies, 25/145 (17.24%) small vessel disease, 19/145 (13.79%) large vessel disease, and 5/145 (3.4%) with other etiologies [Figure 1].

Risk factors' distribution in various etiologies of stroke was documented [Table 3]. HTN was significantly associated with large vessel disease ( $P = 0.028$ ). Diabetes mellitus (DM) was significantly associated with small vessel disease ( $P = 0.001$ ). Smoking and atrial fibrillation both were associated with unknown etiologies of stroke ( $P = 0.001$  and  $P = 0.039$ , respectively). Cardiac dysfunction (systolic + diastolic) was associated with cardioembolic stroke ( $P = 0.015$ ) and small vessel disease ( $P = 0.006$ ). Similarly, valvular heart disease was significantly associated with both cardioembolic and small vessel disease etiologies ( $P = 0.0001$  and  $P = 0.039$ , respectively). Chronic kidney disease was

associated with strokes of other etiology ( $P = 0.019$ ). Previous stroke history was associated with small vessel disease ( $P = 0.038$ ) and stroke of other etiologies ( $P = 0.030$ ). On the other hand, risk factors such as dyslipidemia, alcohol, ischemic heart disease, and hypercoagulable state were not associated with any other etiologies of stroke ( $P = 0.005$ ).

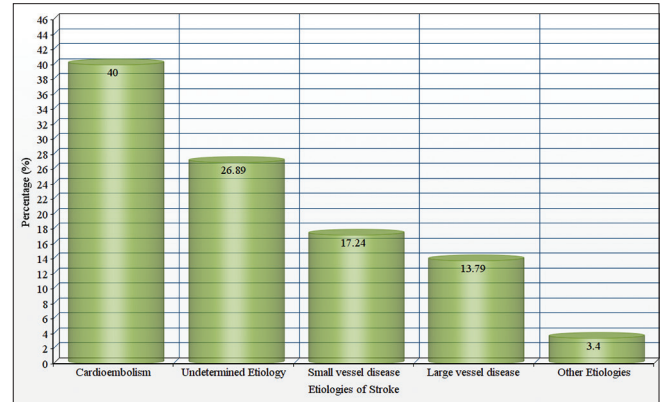


Figure 1: Trial of Org 10172 in Acute Stroke Treatment classification -etiologies of stroke

Table 2: Distribution of stroke based on vessels involved (n=145)

Anterior stroke	Frequency (%)	Posterior stroke	Frequency (%)	Border zone stroke	Frequency (%)
Left anterior cerebral artery	1 (0.68)	Anterior inferior cerebellar artery	1 (0.68)	Basal ganglia watershed area	1 (0.68)
Left middle cerebral artery	56 (38.6)	Basilar	4 (2.7)	R-pontine stroke	2 (1.3)
Right anterior cerebral artery	2 (1.3)	Cerebellar	5 (3.4)	-	-
Right middle cerebral artery	49 (33.7)	Posterior cerebral artery	-	-	-
-	-	Posterior inferior cerebellar artery	-	-	-

Table 3: Risk factor distribution in various etiologies of stroke

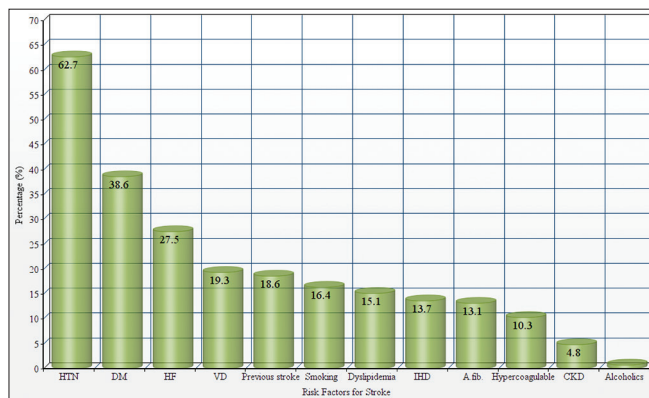
Risk factors	Cardioembolism		Small vessel disease		Large vessel disease		Unknown etiology		Other etiology	
	n	P*	n	P	n	P	n	P	n	P
HTN	30	0.231	78	0.098	14	0.028	11	0.437	3	0.174
DM	19	0.349	22	0.001	7	0.638	5	0.15	1	0.857
Dyslipidemia	4	0.208	5	0.55	1	0.296	3	0.57	0	0.461
IHD	9	0.101	2	0.883	3	0.533	3	0.219	0	0.486
Atrial fibrillation	10	0.17	0	0.101	2	0.948	5	0.039	0	0.498
Smoking	6	0.601	2	0.652	2	0.652	17	0.001	1	0.425
SDF	7	0.015	0	0.006	4	0.378	4	0.382	0	0.523
DDF	7		6		2		2		1	
Alcoholic	0	0.517	1	0.725	0	0.725	0	0.923	1	0.884
Valvular heart disease	20	0.0001	0	0.039	1	0.164	4	0.421	0	0.394
CKD	2	0.958	1	0.773	1	0.773	1	0.242	1	0.019
Hypercoagulable state	3	0.397	15	0.151	3	0.237	7		0	0.554
Previous stroke history	9	0.624	6	0.038	3	0.978	3	0.983	2	0.030

\*Chi-square test=Highlighted P values with statistical significance of ( $P < 0.05$ ). SDF – Systolic dysfunction; DDF – Diastolic dysfunction; n – Number. HTN – Hypertension; DM – Diabetes mellitus; IHD – Ischemic heart disease; CKD – Chronic kidney disease

Age, gender, and ejection fraction based associations with etiologies and causes of stroke were also determined. Overall mean ejection fraction, i.e., 52.71% ± 10.98% was significantly associated with 40/145 cases of cardiac dysfunction that included 20 patients of each systolic and diastolic heart failure ( $P = 0.0001$ ). Out of total 15 cases of undetermined etiology, 6/15 patients were at age  $\geq 45$  years compared to 9/15 cases of undetermined etiology within 25 and 55 years of age ( $P = 0.001$ ). No gender-based associations were found with etiologies of stroke and ejection fraction ( $P > 0.05$ ). HTN was the most common risk factor in 91/145 (62.7%) patients, followed by DM in 56/145 (38.6%), cardiac dysfunction 40/145 (27.5%) including both systolic failure 20/145 (13.7%) and diastolic failure 20/145 (13.7%), valvular disease 28/145 (19.3%), previous history of stroke 27/145 (18.6%), smoking 24/145 (16.4%), dyslipidemia 22/145 (15.1%), ischemic heart disease 20 (13.7%), atrial fibrillation 19/145 (13.1%), hypercoagulable state 15/145 (10.3%), chronic kidney disease 7/145 (4.8%), and alcoholics 1/145 (0.7%) [Figure 2].

### Discussion

Stroke unit in Shifa International Hospital, Islamabad, is a five-bedded unit, well equipped with all modern facilities such as monitoring beds, early rehabilitation assessment, fluid management, speech therapy, physiotherapy, physiological management, dysphagia management (swallowing screened on admission), early mobilization, physiological management, and skilled stroke nursing. It was anecdotal experience in our stroke unit that we see cardioembolic stroke subtype more than any other subtypes of ischemic stroke. Syed *et al.* documented lacunar stroke was found to be the most common subtype of stroke in Pakistani population in the city of Karachi which is in contrast to our results where cardioembolic stroke is the most common subtype in Islamabad, Pakistan.<sup>[3]</sup> According to Western data, cardioembolic stroke is the most frequent

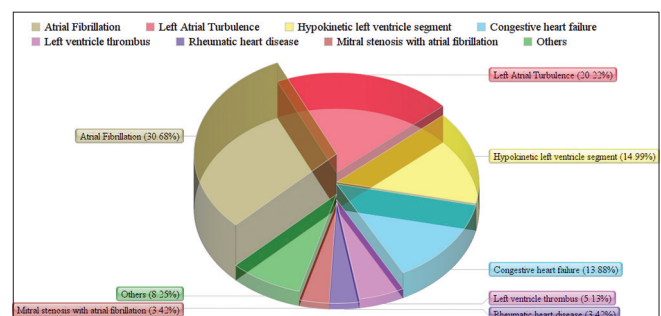


**Figure 2: Distribution of risk factors for stroke.** HTN – Hypertension; DM – Diabetes mellitus; VD – Valvular disease; IHD – Ischemic heart disease; A.Fib. – Atrial fibrillation; HF – Heart failure (systolic + diastolic); CKD – Chronic kidney disease

subtype.<sup>[4]</sup> A study done in Korea by Kim and Kim demonstrated that cardioembolic stroke subtype is common in Western populations, whereas small vessel disease is more common in Asians.<sup>[17]</sup>

According to TOAST classification, sources of cardioembolism are divided into high and medium risk. High-risk sources include mechanical prosthetic valve, mitral stenosis with atrial fibrillation, atrial fibrillation (other than lone atrial fibrillation), left atrial thrombus, and recent myocardial infarction (<4 weeks), whereas medium-risk sources include mitral valve prolapse or annulus calcification and left atrial turbulence.<sup>[18]</sup> In our study, we used echocardiography (transthoracic and transesophageal) and Holter monitoring first to diagnose cardioembolism. We found atrial fibrillation to be the most common cause of cardioembolic stroke, i.e., atrial fibrillation 30.6%, left atrial thrombus 20.2%, hypokinetic left ventricle 14.9%, congestive heart failure 30.2%, left ventricle thrombus 5.1%, rheumatic heart disease 3.4%, mitral stenosis with atrial fibrillation 3.4%, and others 8.2% [Figure 3].

In literature, atrial fibrillation is documented as a potent predictor of recurrent stroke. In developed countries, nonvalvular atrial fibrillation, left ventricular thrombus, and valvular heart disease are found in half, one-third, and one-fourth cases of cardioembolic stroke, respectively.<sup>[19]</sup> Second most documented ischemic stroke subtype in current analysis was stroke of undetermined etiology. Out of 38/145 (17.24%) patients with stroke of undetermined etiology, 17/39 (43.5%) were those in which two or more causes were found. About 11/39 (28.2%) patients were having both large-artery atherosclerosis and cardioembolism, and in these type of cases, it is difficult to decide between carotid endarterectomy and anticoagulation, so decision was based on individual preferences. Cardioembolism along with increase homocysteine levels was found in three (7.6%) patients, and cardioembolism with small vessel disease was found in two (5.1%) patients. Large artery atherosclerosis along with hypercoagulability was found in one (2.5%) patient. Twenty-three patients with either negative or incomplete evaluation were discharged on request or expired before complete workup.



**Figure 3: Causes of cardioembolism**

Third and fourth most common stroke subtypes were small vessel and large vessel diseases with long-standing HTN and diabetes as predispositions to these types of stroke. Syed *et al.* found that small vessel disease is the most common stroke subtype in Pakistani population.<sup>[3]</sup> Higher frequency of small vessel disease found to be present in Asian populations compared to Caucasian population.<sup>[17]</sup> Almost 13.7% all small and large vessel disease patients had >50% carotid artery stenosis and >1.5 cm infarct size. These patients were offered carotid endarterectomy. HTN was the most reported risk factor for ischemic stroke in the current analysis. HTN is an important risk factor for stroke that can be modified.<sup>[20-23]</sup> Our data regarding HTN are comparable to stroke patients in other Southeast Asian countries including Pakistan. We can prevent stroke recurrence by better control of risk factors such as HTN, dyslipidemia, and diabetes.

The limitation of our study was that it was a single-center experience, so results cannot be generalized. The low-middle-income and low-income group patients usually do not come to private hospitals for diagnostic testing. As the burden of stroke is increasing day by day, we should take effective measures to manage it in a better way and to prevent stroke recurrence.

## Conclusion

Our study concludes that cardioembolic stroke is the most common cause of acute ischemic strokes in our stroke unit; our results are different from other studies found in literature where small vessel disease with lacunar infarcts was found to be most common causes of ischemic stroke in Asian population including Pakistan. Atrial fibrillation is found to be the most common cause of cardioembolic stroke.

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## Conflicts of interest

There are no conflicts of interest.

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