

# **Research Article**



# Prevalence and Outcome of Cardio-Embolic Stroke Patients Admitted at Referral Neurology Hospital in Bangladesh

S K Jakaria Been Sayeed1\*, AKM Mahmudul Haque1, Md. Moniruzzaman1, Reaz Mahmud2, Subir Chandra Das1, Mohammad Bazlur Rashid<sup>1</sup>, Sabrina Rahman<sup>2</sup>, Golam Mostafa<sup>1</sup>, Abu Nayeem<sup>1</sup>, MS Jahirul Hoque Chowdhury<sup>1</sup>, Md. Mujibur Rahman<sup>3</sup>

# **Abstract**

Background: Among ischemic stroke, cardio-embolic has both higher severity and mortality.

Objective: To find out clinical outcomes and determine predictors of mortality related to cardio-embolic stroke.

Methodology: This prospective cohort study was conducted among patients of acute ischemic stroke of cardiac origin. Patients were kept under follow-up to 90 days from discharge. A multivariate regression analysis was done to find out factors associated with mortality.

Results: A total of 689 ischemic stroke patients were screened, 156 had confirmed Cardio-embolic stroke, and hospital frequency of cardioembolic stroke was 22.64%. NIH Stroke scale score (median, IQR) during admission was 13 [7-19]. Overall mortality was 47 (29.9%). Modified Rankin score at 90 days was 2 [min 0, max 5] those who survived. Factors associated with mortality (odds ratio, [95% CI], p value) were acute myocardial infarction (1.6 [1.14 - 2.52], 0.04), reduced ejection fraction (3.4 [2.17-5.27], <0.001), hypotension (3.1 [2.07-4.68], <0.001), chronic kidney disease (1.8 [1.06 - 3.10], 0.04), raised Creatinine (2.4 [1.52 - 3.84], 0.01), raised blood sugar (1.8 [1.14 - 2.89], 0.02), severe stroke (4.5 [3.57]) -7.03], <0.001), large infarct (5.7 [4.59 - 7.47], < 0.001), hemorrhagic transformation (4.43 [2.89 - 6.84], < 0.001) and aspiration pneumonia (1.9[1.28-2.39], 0.01).

Conclusions: Overall frequency, severity, functional disability, and mortality in cardio-embolic stroke are higher. Acute myocardial infarction, severe stroke, presence of hyperglycemia, hypotension, renal impairment, low ejection fraction, large infarct, hemorrhagic transformations, and aspiration pneumonia are both clinically and statistically significantly associated with mortality in cardio-embolic stroke.

Keywords: Cardio-Embolic Stroke; Frequency; Outcomes; Predictors of Mortality

Abbreviations: AF- Atrial Fibrillation; COPD- Chronic Obstructive Pulmonary Disease; CRHD- Chronic Rheumatic Heart Disease; ECG-Electrocardiogram; IHD- Ischemic Heart Disease; ICH- Intra Cerebral Hemorrhage; MRS- Modified Rankin Score; MI- Myocardial Infarction; NIHSS- National Institute of Health Stroke Scale; TIA- Transient Ischemic Attack; TSH- Thyroid Stimulating Hormone.

# Affiliation:

<sup>1</sup>Stroke Unit, National Institute of Neurosciences and Hospital, Dhaka, Bangladesh

<sup>2</sup>Department of Neurology, Dhaka Medical College Hospital, Dhaka, Bangladesh

<sup>3</sup>Department of Medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

# Corresponding author:

S K Jakaria Been Sayeed, Stroke Unit, National Institute of Neurosciences and Hospital, Dhaka, Bangladesh.

Citation: S K Jakaria Been Sayeed, AKM Mahmudul Haque, Md. Moniruzzaman, Reaz Mahmud, Subir Chandra Das, Mohammad Bazlur Rashid, Sabrina Rahman, Golam Mostafa, Abu Nayeem, MS Jahirul Hoque Chowdhury, Md. Mujibur Rahman. Prevalence and Outcome of Cardio-Embolic Stroke Patients Admitted at Referral Neurology Hospital in Bangladesh. Cardiology and Cardiovascular Medicine 6 (2022): 480-486.

Received: August 25, 2022 Accepted: September 06, 2022 Published: September 22, 2022



## Introduction

Each year twenty-six million people worldwide experience a stroke and it is the second-leading cause of mortality and a leading cause of long-term disability. One-third of strokes represent intracerebral or subarachnoid hemorrhage, whereas two-thirds represent cerebral ischemia [1]. The reported prevalence of stroke in Bangladesh is 0.3 -1% [2, 3]. Approximately one in four ischemic strokes is of cardioembolic origin [4]. Atherosclerosis of the cerebral circulation, occlusion of cerebral small vessels, and cardiac embolism are the major causes of ischemic stroke [5]. According to Stroke Data Bank and Registries divided the potential cardiac causes of stroke into strong sources (prosthetic valves, atrial fibrillation, sick sinus syndrome, ventricular aneurysm, akinetic segments, mural thrombi, cardiomyopathy, and diffuse ventricular hypokinesia) and weak sources (myocardial infarct in earlier months, aortic and mitral stenosis, aortic, and mitral regurgitation, congestive heart failure, mitral valve prolapse, mitral annulus calcification, and hypokinetic ventricular segments) [6, 7]. Cryptogenic stroke accounts for 25% of all ischemic strokes, the majority of which are likely to be of embolic origin [8]. Cardio-embolic stroke has been increasing in number not only in the developed country but also in low to middle-income countries whereas the overall incidence of stroke is decreasing due to adequate treatment and prevention strategies against hypertension, and dyslipidemia [9, 10, 11]. In Bangladesh, chronic rheumatic heart disease is one of the common causes of cardio-embolic stroke, prevalence of rheumatic heart disease is 0.9 per 1000 [12]. The risk of recurrence in cardio-embolic stroke is highest (around 10%) in the first weeks after the stroke which drops to 5% in the following 12 months, however, the risk of early embolic recurrence varies between 1 to 10% [13]. Cardioembolic stroke is known to cause more severe stroke and higher mortality [14] than other stroke subtypes. However, in Bangladesh prevalence of cardio-embolic stroke is not adequately evaluated, there is a lack of sufficient information regarding clinical & laboratory characteristics. Moreover, information regarding neurological and cardiac outcomes is still not known. Nevertheless, the effect & outcome of anticoagulant therapy especially in myocardial infarction, rheumatic heart disease, or atrial fibrillation with ischemic stroke in our country still inadequately described. For this reason, we have conducted this prospective study to describe hospital prevalence, and clinical and anticoagulant treatment outcomes among patients who were admitted to the National Institute of Neurosciences & Hospital. It is obvious that the study result will help the clinicians as well as policymakers to identify the original statistics and plan of management of this group of patients.

#### **Methods**

## **Study Settings and Populations**

This was a prospective study, conducted at the National

Institute of Neurosciences, the largest neurology referral hospital in Bangladesh. All acute ischemic stroke patients due to cardio-embolism admitted for the first time in NINS were enrolled.

#### **Inclusion Criteria**

Patients, more than 18 years of age with acute ischemic stroke (new case) diagnosed by CT or MRI within 1 week of index events due to cardiac (Arrhythmia, Acute MI, CRHD, Left ventricular aneurysm, prosthetic heart valve, atrial myxoma or any thrombus or vegetation in the cardiac chamber or valve surface) causes diagnosed by electrocardiogram, echocardiography was included in the study.

#### **Exclusion Criteria**

Patients with intracranial hemorrhage or infection or tumor, transient ischemic attack, ischemic stroke due to neck vessels thrombus/ disease, severe organ dysfunction (renal and liver Injury), and other causes of cerebral infarction (Coagulopathy, Vasculitis, and tumor) were excluded.

## **Outcomes Measure**

The primary outcome was to determine predictors of mortality at 90 days after the index event. Secondary outcomes were assessing functional status by modified ranking scale score (mRS), and recurrent stroke (ischemic or hemorrhagic) at 90 days after the index event. Moreover, we also determined the hospital frequency, measured stroke severity by using NIHSS (National Institute of Health Stroke Score) during admission and before discharge, and anticoagulant induced hemorrhage especially intracranial hemorrhage at 90 days.

# **Investigations & Follow Up**

For, each patient's baseline investigations like CBC, Urine R/E, Creatinine, SGPT, RBS, HbA1C, Electrolyte with special investigations like (Coagulation profile, D-dimer, Troponin I, Fasting lipid profile, TSH, ANA, ANCA if needed) were done. 12 lead ECG, 24 hours halter (if applicable), Echocardiography (2D, M mode, color Doppler), and CT / MR angiogram of Brain and Neck vessels were done where necessary. Here, all investigations were done at NINS. We kept discharged patients under regular follow-up for up to 90 days from the index event. After discharge 1st follow-up was given 1 month from the index event, thereafter 2nd followup 1 month from 1st follow-up, again 3rd follow-up was given 1 month from 2nd follow-up. As the COVID situation is ongoing we had maintained follow-up using social media like what's app, messenger, imo and viber (video conference) whatever is available. Two trained doctors were allocated for data collection, and follow-up schedule maintenance. Those who suffered a further stroke were admitted to the same institute for evaluation and management.



## **Statistical Analysis**

As cardio-embolic stroke prevalence in Bangladesh is 4.9% according to Bhowmik NB et al. [15]. Therefore, we assume 72 will be the size according to the prevalence equation. However, we enrolled 156 cardio-embolic stroke patients among 689 acute ischemic stroke patients as per inclusion criteria. The Sampling technique was purposive & consecutive. All data had been analyzed in SPSS 24 version. Continuous variable had been expressed with number, mean and standard deviation (SD) while value with skewed deviation expressed as IQR (Interquartile Range). Comparison between groups (Group A- alive, Group B- dead) with mortality & functional outcome were analyzed by Pearson chi-square test for categorical variables. For continuous variable independent student's t (normally distributed) or Mann Whitney U test for skewed data were applied. For assessing predictors of mortality, multivariate logistic regression analysis was done. Predictors have expressed with an odds ratio with 95% confidence interval which was adjusted with age and sex.

#### **Ethical Issues**

This study was conducted in full conformance with the ICH E6 guideline for Good Clinical Practice (ICH-GCP) and the principles of the Declaration of Helsinki and ethical clearance from the respective institutional review boards [ERC No- NINS 24-120-21]. This article has been posted in medRxiv. https://doi.org/10.1101/2022.02.16.22271069

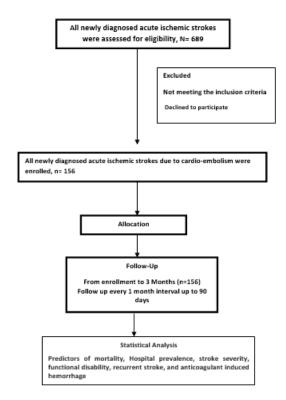


Figure 1: Schematic flow chart of research work.

## Results

A total of 689 ischemic stroke patients were screened, 156 had confirmed Cardio-embolic stroke and the hospital frequency of cardio-embolic stroke is 22.64%. Overall, the male-to-female ratio was 1.3:1, mean age of 63 ( $\pm$  15) years. The most commonly affected age group is 61-70, 45 (28.8%). Sixty-six (42.3%), 17 (12.1%) used to smoke & drinks alcohol accordingly. Hypertension 119 (76.3%), Atrial fibrillation 107 (68.6%) and ischemic heart disease 61 (39.1%) were most common risk factors. However, it is worthwhile to mention that 56 (35.9%) had acute myocardial infarction as important risk factor. Interestingly, we found only 23 (14.7%) patients with chronic rheumatic heart diseases, and 11 (7.5%) had hyperthyroidism. Duration of hospital stay was 7 days (minimum 3, maximum 17) in group A while in group B it was 2 days (minimum 1 and maximum 21 days). For Group A, NIH stroke scoring during admission was 9 (minimum 2, maximum 26), while on discharge it was 4 (minimum 0, maximum 11). For Group B, NIH stroke scoring during admission was 21 (minimum 7, maximum 29), while on discharge it was 8 (minimum 4, maximum 11). Most of the cardio-embolic stroke had moderate severity 56 (35.9 %) in Group A while for Group B it was severe 25 (16.1%) (Table 1). Regarding ECG observation, atrial fibrillation was seen in 107 (68.6%) followed by acute myocardial infarction in 56 (35.9%). However, in the echocardiogram ejection fraction was reduced in 39 (24.8%) although wall motion hypokinesia was present in 47 (30.1%) (Table 2). The most commonly involved lobe in cardio-embolic stroke was parietal 50 (32.1%) but interestingly parieto-frontal involvement was also common 42 (26.9%). The middle cerebral artery was the most frequently involved vascular territory 116 (74.4%) (Table 3). 90 days clinical outcome was variable as the modified Rankin score (disability scoring) was 3 (minimum 0, maximum 5), had some symptoms 37 (29.1%), and minor disability 31 (24.4 %) among 109 patients. Hemorrhagic infarct occurred in 29 (18.5%) patients; among them 5 (3.2%) had developed after starting anticoagulant. Only 8 (7.3%) patients developed recurrent ischemic stroke even though on anticoagulants (CHADVAS score  $5 \pm 1$ , Rivaroxaban 10 mg) & beta blockers while only 7 (4.5%) suffered a hemorrhagic stroke (5 of them on Warfarin). Overall mortality was 47 (29.9%), among them 30 (19.2%) died on 24-48 hours of hospital admission while 17 (10.9%) within 90 days of hospital discharge (Table 4). Risk factors associated with mortality were acute myocardial infarction OR 1.6 [1.14 - 2.52] p =0.04, severe stroke OR 4.5 [3.57 - 7.03], p <0.001, hypotension OR 3.12 [2.07 -4.68], p < 0.001, raised Troponin-I OR 1.89 [1.16-2.99], p < 0.01, raised blood sugar OR 1.82 [1.14 - 2.89], p < 0.02, raised Creatinine OR 2.41 [1.52 -3.84] p < 0.01, low ejection fraction OR 3.38 [2.17-5.27] p < 0.001, large infarct OR 5.7 [4.59 - 7.47] p < 0.001, hemorrhagic infarction OR 4.43 [2.89] -6.84] p< 0.001 and aspiration pneumonia OR 1.9 [1.28-[2.39] p = 0.01. (Table 5).



Table 1: Demographic Characteristics and severity of Cardio-embolic Patients (n= 156).

Characteristics		Results	
	Group A- Alive (109)	Group B- Death (47)	Total (156)
Age ( Mean, SD)	61.7 ± 16.6	66.7 ± 13.8	63.2 ± 15.9
Age Group (Years, frequency, percentage)			
21-30	2 (1.3)	1 (0.6)	3 (1.9)
31-40	12 (7.7)	1 (0.6)	13 (8.3)
41-50	12 (7.7)	1 (0.6)	13 (8.3)
51-60	26 (16.7)	13 (8.3)	39 (25)
61-70	29 (18.6)	16 (10.2)	45 (28.8)
71-80	16 (10.2)	8 (5.1)	24 (15.3)
81-90	8 (5.1)	5 (3.2)	13 (8.3)
91-100	4 (2.6)	2 (1.3)	6 (3.8)
Sex			
Male	57 (36.5)	30 (19.2)	87 (55.8)
Female	52 (33.3)	17 (10.9)	69 (44.2)
Smoker	45(28.8)	21 (13.5)	66 (42.3)
Alcoholic	12 (7.7)	5 (3.2)	17 (10.9)
Family H/O Stroke or Heart Disease	59 (37.8)	20 (12.8)	79 (50.6)
Co-morbidities (frequency, percentage)			
Hypertension	79 (50.6)	40 (25.6)	119 (76.3)
Atrial Fibrillation	78 (50)	29 (18.6)	107 (68.6)
Dyslipidemia	30 (19.2)	13 (8.3)	43 (27.5)
Acute Myocardial Infarction	34 (21.8)	22 (14.1)	56 (35.9)
Diabetes	39 (25)	24 (15.4)	63 (40.4)
Ischemic Heart Disease	40 (25.6)	21 (13.5)	61 (39.1)
Chronic Rheumatic Heart Disease	17 (10.9)	6 (3.8)	23 (14.7)
Chronic Kidney Disease	9 (5.8)	9 (5.8)	18 (11.6)
Hyperthyroidism	11(7.5)	0	11 (7.5)
Asthma	4 (2.6)	0	8 (5.1)
COPD	3 (1.9)	1(0.7)	4 (2.6)
Prosthetic Heart Valve	3 (1.9)	1(0.7)	4 (2.6)
Hospital stay, Median [IQR]	7 [min 3, max 17]	2 [ min 1, max 21]	7 [5-9]
NIHSS Score on admission, Median [IQR]	9 [ min 2, max 26]	21 [min 7, max 29]	13 [ 7- 19]
NIHSS Score on discharge, Median [IQR]	4 [ min 0, max 11]	8 [min 4, max 11]	5 [3-7]

NIHSS Severity			
Mild	13 (8.3)	0	13 (8.3)
Moderate	56 (35.9)	4 (2.6)	60 (38.5)
Moderate to severe	27 (17.3)	18 (11.5)	45 (28.8)
Severe	13 (8.3)	25 (16.1)	38 (24.4)
On Anticoagulant therapy	106 (67.9)	37 (23.7)	143 (91.7)
On Beta Blocker	103 (66)	33 (21.1)	136 (87.1)

Table 2: Cardiac Abnormality observed in Electrocardiography and Echocardiography (n = 156).

Findings	Frequency (%)
Atrial Fibrillation	107 (68.6)
Left Ventricular Hypertrophy	26 (16.7)
STEMI	33 (21.2)
IHD	31 (12.1)
NSTEMI	23 (19.9)
Variable AV Block	9 (5.7)
Atrial Flutter	5 (3.2)
Echocardiography	
Rhythm Abnormality	113 (72.4)
Concentric Hypertrophy	31 (19.8)
Valvular Heart disease	23 (14.7)
Valve Replacement	4 (2.6)
Wall Hypokinesia	47 (30.1)
Reduced EF	39 (24.8)
Preserved EF	116 (75.2)
Left atrial thrombus	11(8.3)
Left Ventricular thrombus	2(1.3)

STEMI- ST Elevated Myocardial Infarction; NSTEMI- Non ST Elevated Myocardial Infarction; IHD- Ischemic Heart Disease; AV-Atrio-Ventricular; EF- Ejection Fraction.

Table 3: Site of Infarction with involved vascular territory in Brain (n=156).

Trait	Frequency (%)
Lobe	
Parietal	50 (32.1)
Frontal	19 ( 12.2)
Temporal	2 (1.3)
Occipital	3 (1.9)
Cerebellar	11 (3.6)
Fronto-parietal	42 (7.1)
Parieto-temporal	10 (6.4)
Parieto-Occipital	2 (1.3)
Multiple	17 (10.8)
Vascular Territory	
Anterior Cerebral Artery	21 (13.5)
Middle Cerebral Artery	116 (74.4)
Posterior Cerebral Artery	19 (12.1)

Citation: S K Jakaria Been Sayeed, AKM Mahmudul Haque, Md. Moniruzzaman, Reaz Mahmud, Subir Chandra Das, Mohammad Bazlur Rashid, Sabrina Rahman, Golam Mostafa, Abu Nayeem, MS Jahirul Hoque Chowdhury, Md. Mujibur Rahman. Prevalence and Outcome of Cardio-Embolic Stroke Patients Admitted at Referral Neurology Hospital in Bangladesh. Cardiology and Cardiovascular Medicine 6 (2022): 480-486.



**Table 4:** Outcome of cardio-embolic stroke patients at 90 days of enrollment in study (n=156).

Outcomes			Results
	Group A- alive	Group B-death	
MRS ( Modified Rankin Score) Median [IQR] At 3 months	2 [min 0, max 5] 3 [ 2-3]	6	
MRS Severity at 90 days			
No limitations	16 (12.6)	0	16 (12.6)
Some Symptoms	37 (29.1)	0	37 (29.1)
Minor disability	31 (24.4)	0	31 (24.4)
Moderate disability	21 (16.5)	0	21 (16.5)
Severe disability	5 (3.9)	0	5 (3.9)
Death		17 (13.4)	17 (13.4)
Hemorrhagic Infarct	6 (3.8)	23 (14.7)	29 (18.5)
Anticoagulant induced hemorrrhage	2 (1.3)	3 (1.9)	5 (3.2)
Recurrent Stroke within 90 days			
Ischemic	6 (3.8)	2 (1.3)	8 (7.3)
Hemorrhagic	3 (1.9)	4 (2.6)	7 (4.5)
Death			47 (29.9)

Table 5: Risk factors associated with mortality among cardio-embolic stroke patients.

Risk Factors	Odds Ratio [ 95% CI ]	P value
Age	0.98 [0.95-1.01]	0.08
Sex	1.40 [0.85-2.32]	0.25
Smoker	1.1 [0.68-1.77]	0.83
Diabetes	1.50 [0.96-2.48]	0.11
Hypertension	1.7 [0.87-3.63]	0.14
Ischemic heart disease	1.26 [0.78-2.02]	0.45
Chronic kidney disease	1.82 [1.06 - 3.10]	0.04
Chronic rheumatic heart Disease	0.85 [0.41 -1.76]	0.83
Atrial fibrillation	0.74 [0.46-1.45]	0.3
Acute Myocardial infarction	1.6 [1.14 – 2.52]	0.04
Raised Troponin	1.89 [1.16-2.99]	0.01
Raised Blood Sugar	1.82 [1.14 - 2.89]	0.02
Raised Creatinine	2.41 [1.52 -3.84]	0.001
Hypotension	3.12 [2.07 – 4.68]	<0.001
Severe Stroke	4.5 [3.57 – 7.03]	<0.001
Low Ejection fraction	3.38 [2.17-5.27]	<0.001
Large Infarct	5.7 [4.59 - 7.47]	<0.001
Hemorrhagic Infarction	4.43 [2.89 – 6.84]	< 0.001
Aspiration Pneumonia	1.9 [1.28-2.39]	0.01

For factor analysis, multivariate regression model was used to find out association with mortality. Predictors were expressed with odds ratio with 95% confidence interval which was adjusted with age, sex.

# **Discussion**

Cardio-embolic stroke prevalence has been increasing for the last few decades, especially among the elderly. Approximately one in four ischemic strokes is of cardioembolic origin [3], exerting a profound societal impact, association with greater disability, higher mortality rates, and higher treatment costs as compared to patients with strokes from other causes [16,17]. To the best of our knowledge, this is the 1st prospective cohort study that evaluates hospital frequency, clinical outcome, and risk factors determination for mortality among cardio-embolic stroke patients admitted to the largest neurological hospital in Bangladesh. Bhowmik NB et al. described hospital frequency of cardio-embolic stroke as 4.9% but failed to confirm in 17.2% [16], those who were suspected cases of cardio-embolic stroke. Manorenj S et al. [18] observed 11.6% in a prospective study from south India. However, we have observed frequency is 22.05%, and it's obvious there is a significant difference. As we have a large sample size, an ambulatory 24-hour ECG facility, and a portable echocardiogram that helped us for better identification. The prevalence of cardio-embolic stroke in Bangladesh is compatible to the western report of 15-30% [19]. In our cohort study, risk factors profile demonstrated hypertension followed by atrial fibrillation are the predominant factors associated with cardio-embolic stroke, very similar to the observation of Manorenj S et al. but different from Henninger N et al who found atrial fibrillation as the predominant factor [18, 20]. Hypertension is certainly the most common condition affecting humans and one in every five Bangladeshi suffers from high blood pressure according to Rahman M et al. from Bangladesh [21]. Cardiac involvement usually occurs in patients with hypertension and can lead to the development of atrial fibrillation & stroke [22]. Recent myocardial infarction with left ventricular dysfunction causes an aneurysm or thrombus in the heart that can cause cardio-embolic stroke [23]. We do have a similar observation as (28.6%) of our patients suffered acute MI, and a majority had a low ejection fraction (23.5%) before the development of stroke, like MacDougall NJJ et al [23]. To identify whether ischemic stroke was due to cardio-embolic or thromboembolic we went for an MR angiogram of neck vessels and the brain in almost every suspicious case along with an MRI of the Brain. Most of the embolic strokes in the present cohort involved predominantly the left middle cerebral artery with the parietal lobe of the brain which means the source of embolus was the heart. Manorenj S et al., Henninger N et al. & Hart RG had also observed similar vascular & site of brain involvement [18,20, 24]. 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 cardio-embolic stroke is crucial



for planning the appropriate treatment mode (anticoagulation) and prevention strategies. In our cohort, the majority (45.7%) suffered moderate to severe stroke according to NIHSS grading. Twenty-four (17.1%) patients out of 40 died within 24 hours of hospital admission. Probably large infarcts with severe stroke with acute STEMI (ST elevated myocardial infarction) with low ejection fraction (EF < 40%) and delayed referral to specialized stroke unit were the responsible factors behind in-hospital mortality. It is worthwhile to mention that 24 (17.1%) patient's died during hospital stays whereas Arboix A & Alió J. mentioned in-hospital mortality in their study was 27.3% [25]. Modified Rankin Score (MRS≥ 3) at 90 days was not favorable for those who are alive because most of them have minor to moderate disabilities. Henninger N et al. in the study also observed an unfavorable 90day functional status among cardio-embolic patients [20]. Occluded intracranial vessels with early recanalization and ischemic infarct with hemorrhagic transformations are suggestive of a cardiac-embolic stroke [26]. We observed 21.4% cases of hemorrhagic infarction mostly due to the disease process. However, we also observed anticoagulantinduced hemorrhage in the brain, especially those who were on warfarin, had chronic kidney disease, high blood pressure, atrial fibrillation, and elderly and labile INR. Hart RG also mentioned those risk factors causing intracerebral hemorrhage in patients who were on warfarin [27]. Nevertheless, even after adequate anticoagulation, few of our patients suffered a recurrent ischemic stroke. Seiffge DJ et al. described during the follow-up of 6128 patients with acute ischemic stroke with atrial fibrillation on anticoagulant therapy, 289 patients had a further acute ischemic stroke (4.7% per year), 90 patients had ICH (1.5% per year), and 624 patients died (10.2% per year) while on an anticoagulant [28]. Anticoagulation therapy is not enough to prevent recurrent ischemic stroke. That's why further study is needed to find out the pharmacodynamics of different anticoagulants among those who are on an anticoagulant. One of the major concerns of cardio-embolic stroke is long-term mortality. We analyzed those patients who died in our study duration through a binary logistic regression model to find out predictors of mortality. We have found hypotension, acute myocardial infarction, low ejection fraction; large infarct, severe stroke, and aspiration pneumonia were significantly associated with mortality, similar to Byun JI et al., Henninger N et al., MacDougall NJJ et al [16,20, 23]. So, cardio-embolic stroke patients need specialized units run by a multidisciplinary team including intervention facilities and close monitoring to reduce mortality. Our study has several strengths, like study design was the prospective cohort, patients having an ischemic stroke for the first time were included and conducted in a center equipped with adequate investigation facilities, and a dedicated team who kept all the patients under regular follow-up even in Covid pandemic.

# Limitations

However, we do have some limitations. It is a single-center study; the sample size was small, and did not evaluate adequately who suffered a recurrent ischemic stroke within 90 days of hospital discharge although prescribed medications were appropriate. Moreover, we showed some factors that were associated with poor outcomes (mortality) through a multivariate logistic regression model but further large-scale study is needed to find out a causal relationship between those factors with mortality.

#### **Conclusion**

To the best of our knowledge, our study is the first-ever work done in Bangladesh to determine the frequency of cardio-embolic stroke in a specialized center, narrated clinical outcomes, determined predictors of mortality, and frequency of anticoagulant induced intracerebral hemorrhage among those stroke patients that most clinician fears off. As mortality in cardio-embolic stroke is high so early identification, timely referral to a specialized hospital, and managing those risk factors related to mortality by a multidisciplinary team should be considered as a cornerstone in cardio-embolic stroke management. We believe that it is going to modify not only standard protocol in the different centers but also health policy related to cardio-embolic stroke.

# Acknowledgment

We are grateful to all of our patients and their spouses for their spontaneous participation. Special thanks to the radiology and cardiology department for their support. Moreover, special thanks to Professor Quazi Deen Mohammad Sir and Professor Badrul Alam Sir for their continuous support of our research work.

## **Conflict of Interest**

Authors declared no conflict of interest related to this research work.

## References

- 1. Krishnamurthi RV, Feigin VL, Forouzanfar MH, et al. Global Burden of Diseases IRFS and Group GBDSE. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. Lancet Glob Health 1 (2013): e259-e281.
- 2. Islam MN, Moniruzzaman M, Khalil MI, et al. Burden of stroke in Bangladesh. Int J Stroke 8 (2013): 211-213.
- Chowdhury MZI, Haque MA, Farhana Z, et al. Prevalence of cardiovascular disease among Bangladeshi adult population: a systematic review and meta-analysis of the studies. Vasc Health Risk Manag 14 (2018): 165-181.



- 4. Díaz Guzmán J. Ictus cardioembólico: epidemiología [Cardioembolic stroke: epidemiology]. Neurologia 27 Suppl 1 (2012): 4-9.
- Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 24 (1993): 35-41.
- Hier DB. Stroke Data Banks and Stroke Registries. In: Caplan L.R. (eds) Brain Ischemia. Springer, London (1995).
- 7. Kamel H, Healey JS. Cardioembolic Stroke. Circ Res 120 (2017): 514-526.
- Maier IL, Schregel K, Karch A, et al. Association between Embolic Stroke Patterns, ESUS Etiology, and New Diagnosis of Atrial Fibrillation: A Secondary Data Analysis of the Find-AF Trial. Stroke Res Treat (2017): 1-6.
- 9. Bogiatzi C, Hackam DG, McLeod AI, et al. Secular trends in ischemic stroke subtypes and stroke risk factors. Stroke 45 (2014): 3208-3213.
- 10. Yiin GS, Howard DP, Paul NL, et al. Oxford Vascular Study. Age-specific incidence, outcome, cost, and projected future burden of atrial fibrillation-related embolic vascular events: a population- based study. Circulation 130 (2014): 1236-1244.
- 11. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation 129 (2014): 837-847.
- 12. Islam AK, Majumder AA. Rheumatic fever and rheumatic heart disease in Bangladesh: A review. Indian Heart J 68 (2016): 88-98.
- 13. Lovett JK, Coull AK, Rothwell PM. Early risk of recurrence by subtype of ischemic stroke in population-based incidence studies. Neurology 62 (2004): 569-573.
- 14. Stead LG, Gilmore RM, Bellolio MF, et al. Cardioembolic but not other stroke subtypes predict mortality independent of stroke severity at presentation. Stroke Res Treat 2011 (2011): 281496.
- 15. Bhowmik NB, Abbas A, Saifuddin M, et al. Ischemic Strokes: Observations from a Hospital Based Stroke Registry in Bangladesh. Stroke Res Treat 2016 (2016): 5610797.
- 16. Byun JI, Jung KH, Kim YD, et al. Cardiac Function and Outcome in Patients with Cardio-Embolic Stroke. PLOS ONE 9 (2014): e95277.

- 17. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society [published correction appears in J Am Coll Cardiol. 2014 Dec 2;64(21):2305-7]. J Am Coll Cardiol 64 (2014): e1-e76.
- 18. Manorenj S, Barla S, & Jawalker S. Prevalence, risk factors and clinical profile of patients with cardioembolic stroke in South India: a five-year prospective study. International Journal Of Community Medicine And Public Health 7 (2020): 2708-2714.
- 19. Khoo CW, Lip GYH. Clinical outcomes of acute stroke patients with atrial fibrillation. Expert Rev Neurother 7 (2009): 371-374.
- 20. Henninger N, Goddeau RP Jr, Karmarkar A, et al. Atrial Fibrillation Is Associated With a Worse 90-Day Outcome Than Other Cardioembolic Stroke Subtypes. Stroke 47 (2016): 1486-1492.
- 21. Rahman M, Zaman MM, Islam JY, et al. Prevalence, treatment patterns, and risk factors of hypertension and pre-hypertension among Bangladeshi adults. J Hum Hypertens 32 (2018): 334-348.
- Ogunsua AA, Shaikh AY, Ahmed M, et al. Atrial Fibrillation and Hypertension: Mechanistic, Epidemiologic, and Treatment Parallels. Methodist Debakey Cardiovasc J 11 (2015): 228-234.
- 23. MacDougall NJJ, Amarasinghe S, Muir KW. Secondary prevention of stroke. Expert Rev Neurother 7 (2009): 1103-1115.
- 24. Hart RG. Cardiogenic embolism to the brain. Lancet339 (199 2): 589-594.
- Arboix A, Alió J. Cardioembolic stroke: clinical features, specific cardiac disorders and prognosis. Curr Cardiol Rev 6 (2010): 150-161.
- 26. Ferro JM. Brain embolism. Answers to practical questions. J Neurol 250 (2003): 139-147.
- 27. Hart RG. What causes intracerebral hemorrhage during warfarin therapy? Neurology 55 (2000): 907-908.
- 28. Seiffge DJ, De Marchis GM, Koga M, et al. Ischemic Stroke despite Oral Anticoagulant Therapy in Patients with Atrial Fibrillation [published online ahead of print, 2020 Feb 12]. Ann Neurol 87 (2020): 677-687.