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Prevalence and Determinants of Thromboembolic Events among Adult Rheumatic Heart Disease Patients with Atrial Fibrillation at Tikur Anbessa Hospital Addis Ababa Ethiopia

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ABSTRACT

Background: Rheumatic heart disease (RHD) combined with atrial fibrillation (AF) significantly contributes to thromboembolic complications, including ischemic stroke. The coexistence of these conditions increases the risk of cardiovascular issues, underscoring the need for targeted management strategies.

Objective: This study aims to assess the prevalence and determinants of thromboembolic events among patients with RHD and AF at the Tikur Anbessa Specialized Hospital adult cardiac outpatient clinic in Addis Ababa, Ethiopia.

Methods: An institution-based retrospective chart review of adult patients with RHD and AF was conducted. Data were gathered from electronic medical records using structured data extraction check list. Descriptive analysis using frequency with percentage and mean with standard deviation was conducted. Binary logistic regression was employed to analyze the relationship between predictor variables and thromboembolic events.

Results: A total of 182 participants were included in this study. The mean age of participants was 40.37 (SD± 13.01) and majority of participants were female participants (70.9%). The overall rate of cardioembolic events was 19.78% (95% CI: 14.3-6.3), with stroke occurring in 18.1% (33) of the participants. Disease duration (AOR: 1.07, 95% CI: 1.03–1.13), left atrial size (AOR: 1.14, 95% CI: 1.07–1.24), presence of left atrial thrombus (AOR: 9.83, 95% CI: 1.53–63.21), mitral stenosis (AOR: 1.88, 95% CI: 1.21–17.14), and Subtheraputic INR levels (<2) (AOR: 4.27, 95% CI: 1.15–15.94) were significantly associated with cardioembolic events.

Conclusion and recommendation: This study highlights the high prevalence of cardioembolic events in patients with RHD and AF, identifying both modifiable and non-modifiable factors that contribute to increased risk. Monitoring left atrial size and INR levels could help reduce the risk of thromboembolic complications. Further research is needed to develop preventive strategies and optimize management to improve patient outcomes.

KEYWORDS: AF, RHD, Cardioembolic Complications, stroke, Ethiopia

INTRODUCTION

Rheumatic heart disease (RHD) is a life-threatening heart condition that results from damage to heart valves caused by one or several episodes of rheumatic fever, an autoimmune inflammatory reaction to infection with streptococcal bacteria (streptococcal pharyngitis or strep throat). [1, 2] RHD is the most common form of cardiac disease that affects people of low socioeconomic status,

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with a worldwide prevalence of 40.5 million individuals [3]. Thromboembolic (ischemic stroke and systemic peripheral embolism) events are one of the complications of rheumatic heart disease patients with AF, with significant morbidity and mortality burden [4]. AF is the most common arrhythmia that is associated with a high risk of stroke [5].

Globally, the burden of RHD has declined in high-income countries due to improved prevention and healthcare access, but it continues to exert a disproportionate impact in Africa and Asia, where young adults are commonly affected [1]. It is estimated that 3–7.5% of all strokes in less developed countries are related to RHD, representing 144,000–360,000 strokes and 108,000–269,000 stroke-related deaths each year [6]. A hospital-based studies have shown as much as 45% of patients admitted with Cardioembolic stroke are due to RHD [7, 8]. Furthermore, studies have shown that the presence of atrial fibrillation (AF) along with RHD resulted in additional significantly increased burden of stroke compared to those with AF alone [9, 10].

A study done in a tertiary setting in Addis Ababa has reported prevalence of cardioembolic events among RHD patients to be 9.2% and identified the presence of AF as a risk factor for cardioembolic events [11]. Moreover, one study done in a large referral hospital in Ethiopia has found RHD as the commonest risk factors present in stroke in the young [12]. Despite the clinical and public health relevance of thromboembolic events in RHD, data regarding the prevalence of thromboembolic complications among RHD patients with AF in Ethiopia is largely lacking and not comprehensive. Identifying the prevalence and determinants of thromboembolic events in RHD patients with AF is critical for understanding the magnitude, guiding appropriate prophylaxis, and improving clinical outcomes. Thus, this study aims to assess the prevalence and determinants of thromboembolic events among RHD patients with AF at Tikur Anbessa Specialized Hospital adult.

METHODS AND MATERIALS

Study area and Study design

The study was conducted in Tikur Anbessa Specialized Hospital, in Addis Ababa, the capital city of Ethiopia. An institutional-based retrospective electronic medical record review was done to examine the prevalence and determinants of cardioembolic events among RHD patients with AF.

Source and study population

The source population for this study are all RHD with AF patients who attended Tikur Anbessa Specialized Hospital Adult Cardiac OPD Clinic from June 30, 2016 to October 31, 2024.

Those patients with RHD with AF patients who attended Tikur Anbessa Specialized Hospital Adult Cardiac OPD from June 30, 2016 to October 31, 2024 and who fulfilled the inclusion criteria were taken as the study population.

Inclusion and exclusion criteria

Inclusion criteria

- all patients diagnosed with RHD with AF who have documented echocardiographic and ECG evidence attending Tikur Anbessa Specialized Hospital, adult cardiac OPD clinic from, June 30, 2016, to October 31, 2024, with at least six months of follow-up were included in the study;
- Documented presumed cardioembolic event(CNS or systemic) confirmed by imaging(CT scan, MRI, or Doppler study)

Exclusion criteria

- Patients with a diagnosis of malignancy, anti-phospholipid syndrome, deep venous thrombosis, pulmonary embolism and peripheral arterial disease.

Sample size determination and sampling procedure

Sample size was determined using a single population proportion formula and for the presumed prevalence of 9.2% cardioembolic events in patients with AF and RHD [11], 95% CI, and precision of 5%. After considering 10% for missing charts the final sample size of 182 charts was used. A simple random sampling using a table of random numbers was used to select charts for the study.

Data collection instrument, Data collection procedure, Quality Assurance

A structured checklist was used to collect data from patients' medical record charts. The checklist contained three parts. The first part assessed the socio-demographic characteristics of the patients. The second part assessed independent variables at baseline. The third part assessed the treatment related variables and types of thromboembolic events. The checklist was pretested on 18 charts to

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check for inconsistencies and errors. Charts that were involved in the pretest were excluded from the main data collection. Inconsistencies and errors were corrected accordingly. Two data collectors were employed for the data collection and a formal orientation was given to the data collectors by the primary investigator prior to the commencement of data collection. The primary investigator superintended the process of data collection for accuracy.

Data management and analysis

First, the collected data were checked for completeness and consistency. Data were entered, coded, cleaned using Epidata software. Subsequently, data were exported and analyzed using SPSS version 26. Descriptive statistics was conducted using frequency with percentages and mean with standard deviation and presented in tables. A binary logistic regression model was used to assess the associations between independent variables and thromboembolic events among RHD patients with AF. Univariate analysis was performed to calculate the unadjusted odd ratio (OR) and identify independent variable to be included in the multivariable binary logistic regression model. Odds ratio with p-value and 95% CI was reported. Variables with a P value of less than 0.05 were considered to have a statistically significant association with the outcome variable.

Ethical consideration

Ethical clearance was obtained from the Institutional Review Board (IRB) of Addis Ababa University, College of Health Sciences. A formal letter of permission was submitted to the College of Health Sciences, School of Medicine, and Department of Internal Medicine before starting the study. Written or verbal consent was not required as the study only used secondary data. The collected data was kept confidential and was used for the study purposes only.

RESULTS

Socio-demographic profile and Comorbidities

The study included a total of 182 participants. More than two-third of the participants were Females comprising 70.9% (129/182) of the group. The mean age of the participants was 40.37 years (SD± 13.01). Most participants (62.6%), resided outside of Addis Ababa, while 37.4% (68) lived within the city. In terms of age distribution, 31.3% (57) were in the 30-39 age group, and 24.7% (45) were over 50 years old. Regarding comorbidities, 91.2% (166) of the participants had heart failure, with 34.1% (62) having been hospitalized due to this condition. Among the total of 62 hospital admissions, 45 patients experienced one admission episode, 13 had two admission episodes, and 10 had three or more episodes. Additionally, 19.2% (35) of participants had kidney disease, 6.6% (12) had hypertension, and 2.2% (4) had diabetes. The mean duration of the disease was 9.28 years (SD ± 5.5). The majority of participants, 45.1% (82), had lived with the disease for 6-10 years. (**Table 1**)

Table 1: Socio-demographic Characteristics and Comorbidities of the Study Population

Variables		Count	Percentage
sex	Female	129	70.9
	Male	53	29.1
Age group	17-29	38	20.9
	30-39	57	31.3
	40-49	42	23.1
	≥50	45	24.7
Residency	Addis Ababa	68	37.4
	Outside Addis Ababa	114	62.6
Comorbidities			
Hypertension	Yes	12	6.6
Diabetes	Yes	4	2.2
Heart Failure	Yes	166	91.2
Kidney disease	Yes	35	19.2
HF hospitalization	Yes	62	34.1
Duration of disease			

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	≤5	44	24.2
	6-10	82	45.1
	≥11	56	30.8

Echocardiographic Findings in Study Participants

The echocardiographic findings revealed that the average left atrial (LA) size was 52.37 ± 13.92 mm. Among the participants, 47.8% (87) had severely enlarged left atria (greater than 50 mm), while 23.6% (43) exhibited moderately enlarged left atria (ranging from 45 to 49 mm). A significant portion of the population had mitral stenosis, with 89.6% (129 out of 144) experiencing severe stenosis. Mitral regurgitation was noted in 75.3% (137) of the participants, with 43.1% (59 out of 137) classified as having severe regurgitation. Aortic regurgitation was observed in 42.9% (78) of participants, predominantly of mild severity. Additionally, 61.5% (112 out of 182) of the participants had tricuspid regurgitation, with 60.7% (68 out of 112) showing severe regurgitation. There were two patients with moderate pulmonic regurgitation, and no cases of pulmonic stenosis were reported. (**Table 2)**

Table 2: Echocardiographic Findings, Including LA Size, Valve Abnormalities, and Severity in Study Participants

Variables	Number	Percentage
Left atrial size		
Normal	18	9.9
Mildly (40-44 mm)	34	18.7
Moderately (45-49 mm)	43	23.6
Severely (>50 mm)	87	47.8
Mitral stenosis	**144**	**79.1**
Mild	9	6.3
Moderate	6	4.2
Sever	129	89.6
Mitral regurgitations	**137**	**75.3**
Mild	37	27.0
Moderate	41	29.9
Sever	59	43.1
Aortic stenosis	**20**	**11.0**
Mild	8	40.0
Moderate	9	45.0
Sever	3	15.0
Aortic registration	**78**	**42.9**
Mild	49	62.8
Moderate	23	29.5
Sever	6	7.7
Tricuspid stenosis	**13**	**7.1**
Mild	1	7.7
Moderate	3	23.1
Sever	9	69.2
Tricuspid regurgitation	**112**	**61.5**
Mild	19	17.0
Moderate	25	22.3
Sever	68	60.7
Presence of LA thrombus	14	7.7

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Stroke Prevalence, Surgical Procedures, and Antithrombotic Management

A total of 19.78% (36; 95%CI 14.3%-6.3 %.) of the study participants experienced cardioembolic events. Stroke occurred in 18.1% (33 out of 182) of participants, including one patient who had two episodes, and limb ischemia was observed in 1.6% (3) of participants. No other sites of ischemia were documented. Prosthetic valve replacement was performed in 7.1% (13 out of 182) of participants, with 12 of these being mechanical valves. Among those who underwent prosthetic valve replacement, 61.5% (8 out of 13) had the procedure performed following a stroke. Similarly, 66.7% (14 out of 21) of patients who received PBMC procedures also did so after experiencing a stroke. The majority of participants, 91.8% (146 out of 159), were treated with warfarin. Over a period of six months, 70.3% (128 out of 182) achieved documented therapeutic targets. Among these, 63.3% (81 out of 128) were within the therapeutic range, while 31.3% (40 out of 128) had sub-therapeutic levels. (**Table 3**)

Table 3: Surgical Procedures, Antithrombotic Management, and Therapeutic Target Achievement in Study Participants

Variables	Number	Percentage
Surgical procedures		
Prosthetic valve	13	7.1
PBMC	21	11.5
Anticoagulant and antiplatelet	**159**	**87.4**
Warfarin	146	91.8
Rivaroxaban	11	6.9
Aspirin	2	1.3
Documented therapeutic target(6months)	**128**	**70.3**
Therapeutic (INR= 2-3)	81	63.3
Subtherapeutic (INR <2)	40	31.3
Supratherapeutic(INR>3)	7	5.5

Factors Associated with Cardioembolic Events

After performing the unadjusted analysis, factors with a P-value less than 0.25 were considered for inclusion in the multivariable analysis. Duration of disease, left atrial (LA) size, presence of hypertension, presence of LA thrombus, presence of mitral stenosis, mitral regurgitation, and sub-therapeutic INR levels met the inclusion criteria and were included in the multivariable logistic regression model. The multivariable analysis revealed several factors significantly associated with the risk of cardioembolic events, all with P-values less than 0.05. Duration of disease was found to significantly increase the odds of cardioembolic events with each additional year of disease duration increasing the likelihood of thromboembolic events by 7% (adjusted odds ratio [AOR]: 1.07, 95%CI: 1.03–1.13). LA size also had a significant association, with each millimeter increase in size raising the odds of cardioembolic events by 14% (AOR: 1.14, 95% CI: 1.07–1.24). The presence of a LA thrombus was linked to a dramatic increase in the odds of experiencing a cardioembolic event, presenting an almost 10-fold higher risk (AOR: 9.83, 95% CI: 1.53–63.21, P = 0.01). Additionally, mitral stenosis was associated with an 88% increase in the odds of cardioembolic events (AOR: 1.88, 95% CI: 1.21–17.14). Lastly, patients with sub-therapeutic INR levels (below 2) faced a 4.27-fold increased risk of cardioembolic events (AOR: 4.27, 95% CI: 1.15–15.94). (**Table 4**)

Table 4: Bivariable and Multivariable Analysis of Factors Associated with the Risk of Cardioembolic Events

Variables	COR (95%CI)	P-value	AOR (95%CI)	P-value
Duration of disease (year)	1.14(1.06,1.229)	0.001	1.07(1.03,1.13)	0.002
Left atrium size (millimeter)	1.07(1.04,1.09)	0.01	1.14(1.07,1.24)	0.001
Presences of HTN*	2.13 (0.61,7.60)	0.23	3.01(0.55,16.65)	0.33
Presences LA thrombus*	4.79 (1.56,14.71)	0.006	9.83(1.53,63.21)	0.01
Presences mitral stenosis*	5.16 (1.18,22.56)	0.029	1.88(1.21 17.14)	0.04
Presences Mitral regurgitation*	0.82(0.36,1.87)	0.21	0.77(0.71,2.87	0.19
Subtherapeutic INR (<2)	3.2(0.97, 10.17)	0.06	4.27(1.145,15.94)	0.03

COR: crude odd ration, AOR: Adjusted odd ratio, * the comparative groups in the absence of the indicated variables

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DISCUSSION

Cardioembolic events, including stroke, pose a significant risk for patients with cardiovascular diseases. In this study, we assessed the prevalence and determinants of thromboembolic events among adult patients with rheumatic heart disease (RHD) complicated by atrial fibrillation (AF) at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. Our findings demonstrate a substantial burden in this high-risk group, consistent with evidence from other low- and middle-income countries where RHD remains endemic. In this study, we found that 19.78% of the participants had experienced cardioembolic events, with stroke being the most common manifestation. This is considerably higher than rates observed by two studies conducted in India that reported 3.9 % [13] and 6.72 % [14] prevalence of thromboembolic events among patients with RHD and AF. It is also higher than reported by a multicenter study done across multiple continents (2.8%) [15] and a study conducted in Ethiopia that showed a 9.2% prevalence of presumed cardioembolic events [11]. However, our findings is comparable with reports from a systematic review conducted in Asia that reported prevalence ranging from 3.4% to 23.2% [9]. The differences in cardioembolic event rates may be attributed to variations in patient demographics, disease severity, and comorbidity profiles.

Furthermore, we found that the duration of atrial fibrillation (AF) significantly increased the likelihood of occurrence of cardioembolic events (AOR=1.07, 95%CI: 1.03–1.13). This finding is consistent with findings from the Framingham study[16] and a study conducted in Ethiopia[11] that showed patients with a longer duration of AF experiencing a higher incidence of stroke and other embolic events. We also identified an increased left atrial (LA) size as a key predictor of cardioembolic events. This aligns with a prospective cohort study conducted in China, which demonstrated that larger LA sizes were significantly associated with an elevated risk of systemic embolism in patients with rheumatic mitral stenosis (MS), particularly those with AF[17]. Furthermore, a study conducted in Ethiopia [11] similarly identified a LA size greater than 40 mm as a significant predictor of cardioembolic events. This finding underscore the importance of monitoring LA size as part of risk stratification for patients with AF and RHD, since an enlarged atrium increases the likelihood of thrombus formation and subsequent embolization.

In addition, the presence of a LA thrombus was found to be an important risk factor linked to a higher risk of cardioembolic events in our study (AOR= 9.83, 95%CI: 1.53-63.21). This finding is consistent with a study conducted in India, which showed that LA spontaneous echo contrast and thrombus were significantly associated with the occurrence of stroke in patients with RHD and AF[18]. These finding highlight the critical need for early detection of LA thrombus and appropriate anticoagulation therapy to reduce thromboembolic complications. Moreover, mitral stenosis (MS) was found to be a statistically significant factor associated with cardioembolic events in our study (AOR: 1.88, 95% CI: 1.21–17.14). The association between MS and embolic events is well-documented, as the hemodynamic disturbances caused by the narrowed mitral valve promote thrombus formation in the left atrium. Previous studies conducted in northern India [13] and Ethiopia [11] had also shown similar association with cardioembolic events. The hemodynamic consequences of MS, especially when combined with AF, lead to blood stasis, significantly raising the risk of thromboembolism. Therefore, patients with both MS and AF should be closely monitored for potential thromboembolic complications.

Sub-therapeutic international normalized ratio (INR) levels was also found to have statistically significant association with the risk of cardioembolic events in our study (AOR: 4.27, 95% CI: 1.15–15.94). Sub-optimal anticoagulation therapy is a well-established risk factor for thromboembolic events in patients with AF and RHD, as it does not adequately prevent thrombus formation in the left atrium. A study from the RE-LY AF registry, which included patients from 47 countries, indicated that inadequate anticoagulation was a significant risk factor for stroke in patients with RHD [10]. Additionally, an study conducted in Ethiopia have found that patients with INR values below 2.0 were at significantly higher risk of embolic complications [11]. These findings emphasize the critical importance of maintaining therapeutic INR levels in patients with AF and RHD to reduce the risk of stroke and systemic embolism.

STRENGTH AND LIMITATIONS

Our study included a substantial cohort of patients with atrial fibrillation (AF) and rheumatic heart disease (RHD), providing a robust dataset for examining cardioembolic risk factors and allowing a comprehensive analysis of the factors associated with cardioembolic events. However, our study was not without limitations. First, we used a retrospective chart review design and this restricts our ability to establish causality between the identified risk factors and cardioembolic events. Second, since the study was conducted at a referral center, the findings may be subject to referral bias where patients with more severe conditions or

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complications are more likely to be referred and could lead to overestimation of our outcome. Finally, reliance on medical records for socio-demographic, comorbidity, and imaging data have introduced issues with data completeness and accuracy.

CONCLUSION AND RECOMMENDATIONS

Our study found a comparatively higher prevalence of cardioembolic events compared to international and regional studies. We identified modifiable risk factors (sub-therapeutic INR, the presence of LA thrombus, and inadequate anticoagulation) and non-modifiable risk factors (disease duration, LA size, and mitral stenosis). We recommend optimizing anticoagulation therapy to consistently maintain therapeutic INR levels, thereby reducing the risk of thromboembolic events. Regular imaging should be employed to monitor LA size and detect thrombus presence, facilitating timely interventions when necessary. In patients with mitral stenosis, vigilant monitoring and management are critical to prevent complications such as stroke. Additionally, early identification and management of cardiovascular conditions, especially in individuals with longer disease durations, can help mitigate the risk of cardioembolic events. Lastly, a personalized care approach that considers both modifiable and non-modifiable risk factors should be adopted to effectively prevent cardioembolic events in patients with cardiovascular diseases

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