

Left Atrial Enlargement as a Predictor of Atrial Fibrillation in Rheumatic Mitral Valve Disease: An Echocardiography-based Retrospective Cross-sectional Study

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ABSTRACT

Background: Rheumatic heart disease is a major cause of cardiovascular morbidity and mortality in developing nations and is a leading cause of hospital admission due to cardiac problems in our country. This study will evaluate the association between left atrial size and the occurrence of atrial fibrillation and describe the clinical characteristics along with complications related to Rheumatic Mitral valve disease.

Methods: A retrospective cross-sectional study was conducted at a tertiary care center from January 2018 to December 2019. Reports of 207 patients admitted to medical and/or surgical wards with echocardiographic diagnosis of rheumatic mitral valve disease with or without atrial fibrillation were reviewed. Data were collected, entered, and analyzed using the Statistical Package for the Social Science version 25.0.

Results: Among 207 patients, atrial fibrillation was present in 90 (43.5%) patients. Atrial fibrillation was higher in patients with mixed mitral valvular lesions compared to isolated mitral stenosis or mitral regurgitation. Univariate and multivariate analysis revealed left atrial size [aOR=1.067, 95% CI: 1.023 – 1.113, P= 0.002] and age [aOR = 1.073, 95% CI: 1.042 – 1.105, P<0.001] as an independent predictor of atrial fibrillation.

Conclusions: Larger left atrium was an independent predictor of atrial fibrillation. Besides this, atrial fibrillation was associated with increasing age, mixed mitral valvular lesion, and moderately reduced left ventricular ejection fraction, but not associated with gender and mitral stenosis severity. Left atrial clot was significantly higher in patients with atrial fibrillation than in sinus rhythm.

Keywords: Atrial fibrillation; left atrium; mitral valve; rheumatic heart diseases.

INTRODUCTION

Rheumatic heart disease (RHD) is a chronic sequel resulting from acute rheumatic fever, causing damage to heart's valve tissue. Global statistics indicate that approximately 33.4 million people are living with RHD, with low- and middle-income countries contributing 79% of cases.^{1, 2} The spectrum of RHD is varied but predominantly involves isolated mitral valve (RMVD) accounting for 46.80% followed by isolated aortic valve (9.36%).³

In endemic areas, RHD is often complicated by heart failure (33%), atrial fibrillation (22%), pulmonary

hypertension (29%), and cardioembolic stroke (7%).⁴ Atrial fibrillation (AF) is caused by structural or electrophysiological alteration in atria.⁵ AF occurrence has direct relation with a left atrial (LA) dimension exceeding 40 mm.⁶

Unfortunately, limited data exist regarding LA size and its correlation with AF in our population affected by rheumatic heart disease. This study was designed to: determine the association between LA size and AF in RMVD, describe the demographic characteristic of patients with RMVD, describe RMVD-related complication, and identify predictors of AF.

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METHODS

This was a hospital-based retrospective cross-sectional study done in Manmohan Cardiothoracic Vascular and Transplant Centre (MCVTC), Kathmandu, Nepal, from January 2018 to December 2019. Patients admitted to the medical and/or surgical ward of MCVTC with echocardiographic diagnosis of RMVD with or without AF were enrolled. Informed written consent was taken from the patients and prior ethical approval was taken from the institutional review board of the Institute of Medicine, Tribhuvan University [Ref: 325 (6-11) E² 077/078].

There were 217 patients diagnosed with RMVD over the course of two years, however 10 were eliminated from our study due to incomplete medical information. A predefined criterion by World Heart Federation was used to diagnose RMVD.⁷ Patients with mitral valvular disease due to other than RHD, heart disease (coronary artery disease, hypertensive heart disease, and so forth) accompanying RHD, and those who had previously undergone any type of mitral valvular surgery were excluded. The demographic data along with clinical profile, electrocardiogram (ECG), and echocardiographic findings of the study population were studied. Antero-posterior diameter of LA was measured in parasternal long axis view in 2D mode. The LA dimension of 40 mm was considered dilated. Planimetry was used to measure the mitral valve area, and the degree of mitral stenosis (MS) was graded as mild: 1.5 cm², moderate: 1-1.5 cm², and severe: 1 cm².⁸ Similarly left ventricular ejection fraction (LVEF) was categorized according to American College of Cardiology as, normal: 50-70%, mild: 40-49%, moderate: 39-49% and severe: <30%.

Data were entered and analyzed in SPSS 25. The results were expressed in either mean \pm SD or median (range) for the quantitative (continuous) data and analyzed using a t-test. The categorical data were expressed in numbers (percentage) and analyzed using Fischer exact test. Univariate and multivariate logistic regression analysis was used to determine the independent association of clinical variables and echocardiographic variables with AF. Crosstab analysis was used whenever required. P value<0.05 was considered significant.

RESULTS

Among 207 patients, 49 (23.7%) were males and 158 (76.3%) were females, which clearly showed the female preponderance with the sex ratio of 1:3.2. The median age was 40 years ranging from 11-75 years. The majority of RMVD patients belonged to the age group of 30-39

years (21.7%) and 20-29 years (21.7%) followed by the age group of 40-49 years (21.3%) (Table 1).

Table 1. Demographic and clinical characteristics of patients with RMVD.

Parameters	Number (%)
Male	49 (23.7%)
Female	158 (76.3%)
Median Age	40 (range,11-75years)
Age category (years)	
10-19	16 (7.7%)
20-29	45 (21.7%)
30-39	45 (21.7%)
40-49	44 (21.3%)
50-59	34 (16.4%)
60-69	19 (9.2%)
70-79	4 (1.9%)
Presenting symptoms	
Shortness of breath	155(74.9%)
Chest pain	63(30.4%)
Palpitation	55(26.6%)
Orthopnoea/PND	47(22.7%)
Leg swelling	40(19.3%)
No symptoms	39(18.8%)
Presentation in pregnancy	14 (6.8%)
Antenatal	5 (2.4%)
Postnatal	9 (4.3%)
Treatment received after admission	85 (41.06%)
Medical	112 (54.1%)
Surgical (PTMC/MVR)	10 4.8%)
No treatment received	

Mixed mitral valvular lesions (MR and MS) was the most prevalent, present in 132 (63.8%) individuals, followed by isolated mitral stenosis in 46 (22.2%) patients and isolated mitral regurgitation in only 29 (14%) patients (Table 2).

Out of 207 patients, AF was present in 90 (43.5%) patients. Regarding the distribution of AF, it was present in 68 (51.5%) out of 123 patients having mixed mitral valvular lesions, making it the most frequent valvular lesion. Similarly, AF was present in 14(30.4%) of 46 patients with isolated mitral stenosis and 8(27.6%) of 29 patients with isolated mitral regurgitation. In addition, the association between AF and mixed mitral valvular lesions is statistically significant, compared to isolated MS or MR [51.5 % vs. 30.4 % and 27.6 % respectively, P = 0.008].

Table 2. Echocardiographic findings of patients with RMVD.

Findings	Number (%) (n=207)
Isolated mitral stenosis	46 (22.2%)
Isolated mitral regurgitation	29 (14%)
Mixed mitral stenosis and regurgitation	132 (63.8%)
Total mitral stenosis (isolated + mixed lesion)	178 (85.99%)
Mild	28 (15.7%)
Moderate	100 (56.2)
Severe	50 (28.1%)
Total mitral regurgitation (isolated + mixed lesion)	161
Mild	52 (34.2%)
Moderate	55 (34.2%)
Severe	54 (33.5%)
LVEF	
Normal	160 (77.3%)
Mild	32 (15.5%)
Moderate	11 (5.3%)
Severe	4 (1.9%)
LA clot	19 (9.2%)

Univariate analysis of various variables was done to assess association with AF. One important finding was that patients with greater LA sizes had a significantly higher incidence of AF. Further, the LA size in patients with AF was larger than those in normal sinus rhythm; the median value in AF being 54mm (range, 38 - 96mm) as compared to normal sinus rhythm 46mm (range, 28 - 75mm). Together with LA size, increasing age and moderate reduction in LVEF were also significantly associated with the occurrence of AF (Table 3). In addition to univariate analysis, multivariate analysis was performed which showed, age [aOR = 1.073, 95% CI: 1.042 - 1.105, P<0.001] and LA size [aOR=1.067, 95% CI: 1.023 - 1.113, P= 0.002] were only significant predictors of AF occurrence. Whereas, AF occurrence was not associated with gender, type of valvular lesion, MS valve area, and LVEF.

In 155 (74.9%) patients, shortness of breath was the predominant complaint at the time of presentation. Similarly, 63 (30.4 percent) patients reported chest pain, 55 (26.6 percent) reported palpitation, and 39 (18.8%) had no complaints since they were diagnosed during screening and visited merely for elective surgery. There was total 14(6.8%) obstetric cases, five (2.4%) females presented during antepartum period and nine (4.3%) females presented during postpartum period.

Table 3. Univariate analysis of clinical and echocardiographic variables.

Variables	Atrial fibrillation		P-value
	Present (n = 90)	Absent (n = 117)	
Age (years)	46 (19 - 75)	32 (11 - 70)	<0.001
Gender (M/F)	25/65	24/93	0.223
Type of valvular lesion			
Isolated MS	14	32	
Isolated MR	8	21	
Mixed MS and MR	68	64	0.008
MS valve area	1.20 (0.50 - 2.70)	1.10 (0.60 - 3.10)	0.057
Left Atrial size	54 (38 - 96)	46 (28 - 75)	<0.001
Category based on LVEF			
Normal	64	96	
Mild	14	18	
Moderate	9	2	
Severe	3	1	0.029

Medical management which includes antiarrhythmic, anticoagulant, antiplatelet, and/or penicillin prophylaxis, was received by 85(41.06%) patients. Surgical treatment was required in 112(54.1%) patients, among them 57 (27.5%) patients underwent PTMC and 55 (26.6%) patients underwent MVR. There were 10(4.8%) patients who received neither medical nor surgical treatment mentioned above.

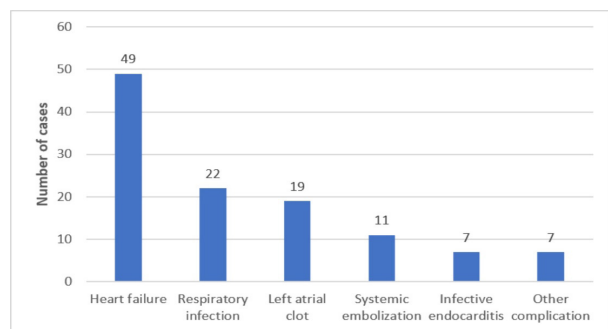


Figure 1. Showing complication in patients with RMVD.

Complications were present in 135 (65.3%) patients and heart failure was the most frequent followed by respiratory infection and left atrial clot (Fig. 1). LA clot was seen in 14 (15.6%) patients with AF and our study revealed a significant association between AF and higher

rates of LA clots (15.6% vs 4.3%, $P = 0.007$), but not with other complications such as infective endocarditis, systemic embolism, and respiratory infections (Table 4).

Table 4. Association of complications with atrial fibrillation.

Complications	With AF (n = 90)	Without AF (n = 117)	P-value
LA clot, n (%)	14 (15.6)	5 (4.3)	0.007
Infective endocarditis, n (%)	2 (2.2)	5 (4.3)	0.70
Systemic embolism (Cardioembolic stroke, acute limb ischemia), n (%)	3 (3.3)	7 (6.0)	0.52
Respiratory infection, n (%)	10 (11.1)	12 (10.3)	1.0

DISCUSSION

The majority of RMVD patients in our study (76.3%) were females in their middle age (20-30 years and 30-40 years), which is consistent with earlier research demonstrating a female preponderance and a peak age of 25-45 years.^{9, 10} Though the reason is unclear, females are more prone to RHD because of greater autoimmune vulnerability and greater exposure to GAS infection during child-rearing.¹¹ Lack of health awareness related to RHD and poor access to health services, especially among females in our country, had also played an additional role.³ RHD is a chronic immune-mediated condition, and mitral stenosis progresses at a very slow rate of 0.09 cm on average, thus many people don't have symptoms until they are in their middle years.^{2, 12, 13}

Mitral stenosis (85.99%) is the commonest valve to be involved followed by mitral regurgitation (78.92%), in our study. This is because the majority of the patients in our study are middle-aged, and mitral stenosis also begins to manifest in the middle decade of life. In contrast, mitral regurgitation is common in the second decade of life, and mixed mitral valvular lesion develops in the third decade.⁴

The main aim of our study was to investigate and determine the role of left atrial enlargement along with other clinical parameters in the occurrence of AF. Univariate analysis revealed that larger LA size, increasing age, mixed mitral valvular lesion (MS and MR), and moderate reduction in LVEF were all significant

predictors of AF in our study. One important aspect of our study is that larger LA size was significantly associated with AF, in both univariate (54mm vs 46 mm, $P < 0.001$) and multivariate analysis (aOR=1.067, 95% CI: 1.023 - 1.113, $P = 0.002$). Besides this, increasing age was another independent determinant of AF to be significant in both univariate and multivariate analysis. Previously, Probst et.al (1973) had confirmed that age is an important contributory factor in the genesis of atrial fibrillation.⁹ Later, many retrospective and prospective studies found that age and larger LA diameters were strong predictors of atrial fibrillation.¹⁴⁻¹⁶ The Framingham Heart Study even showed that every 0.5cm increase in LA diameter increases the risk of AF by 39%.¹⁷ This is because, in rheumatic mitral valve disease, there is a chronic stretch in the atrium due to altered hemodynamics which leads to an increase in the size of cardiac myocyte and fibrosis. Besides this, there is direct injury to the myocardium due to inflammatory rheumatic insult. Ultimately, both result in increased anisotropy and formation of re-entry circuit contributing to development and stability of AF.^{18, 19} However, it is still debatable whether left atrial dilatation is a cause or an effect of AF. Both, however, are dependent on one another.

The mixed mitral valvular lesion was significantly associated with the occurrence of AF in our study. Similarly, AF was highest in patients with mixed mitral valvular lesions (51.5%). Based on this, we can conclude that the presence of MS and MR exert a more hemodynamic effect in the atria. However, our study did not find a strong association between the degree of mitral valve stenosis and AF. Zafar N et al. (2005) and Probst et al. (1973) also showed no significant relationship between the severity of mitral stenosis and the occurrence of atrial fibrillation but other studies have shown a significant relationship.^{9, 20, 21} It is our considered view that this relationship needs to be further explored in yet newer studies because many patients receive PTMC for severe symptomatic mitral stenosis and this intervention could be upgraded in the guidelines for the prevention of AF even in asymptomatic severe mitral stenosis.

Endemic areas present with advanced disease and complications such as heart failure (33%), atrial fibrillation (22%), pulmonary hypertension (29%), and cardioembolic events (7%) are well known to be common. In our study complication was present in more than half of the patients and heart failure (23.7%) was the commonest. Furthermore, we analyzed to find out the relation of various complications with AF, and LA clot was significantly higher in patients having AF compared to patients with

sinus rhythm (15.6% vs 4.3%, $p = 0.005$). Many studies to date, have shown that large LA and AF are significantly associated with left atrial thrombus formation.²¹⁻²³ However, the incidence of LA clots in our study is much less compared to studies done by Saidis S et al (2004) and Goswami et al (2000) (15.6% vs 26.1% and 59% respectively). The lower incidence of LA clots is due to the predominance of the mixed mitral valvular lesion (MS and MR) as mitral regurgitation is protective against thrombus formation.^{24, 25}

There are some limitations to this study. Being a retrospective cross-sectional study conducted in a single centre, it has some inherent limitations. Only those cases that were admitted to the medical or surgical ward were included; those that were being treated as outpatients were ignored. Additionally, we determined LA size by measuring the anteroposterior (AP) diameter of the left atrium but previous studies have shown that left atrial volume is a good representation of LA size than AP diameter.²⁶

CONCLUSIONS

The rheumatic mitral valvular disease primarily affects young females. Among RMVD, the most prevalent lesion was mitral stenosis, followed by MR, whereas mixed mitral valve was common in individuals with AF. Besides large LA size, additional variables such as increasing age, mixed mitral valvular lesion, and moderately reduced LVEF were significant predictors of AF. However, MS severity was not associated, so future studies are required to resolve the debate regarding the association between degree of MS and AF. RMVD was often complicated by heart failure and atrial fibrillation however, only the left atrial clot was significantly associated with AF as compared to sinus rhythm.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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