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Research Article

Impact of Left Atrial Volume on Clinical Outcome in severe rheumatic Mitral Regurgitation

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Abstract

Introduction: left atrial volume is now considered superior to left atrial diameter and larger left atrial volume associated with increased incidence of cardiac events including. **Aim of the work :** to determine the predictive value of left atrial volume index measured at diagnosis on outcome in patients with asymptomatic severe rheumatic mitral regurgitation. **Methods** : our study included 200 patients with asymptomatic severe rheumatic mitral regurgitation for them assessment of left atrial volume, left ventricular volumes and mitral regurgitation severity using vena contracta width and proximal isovelocity surface area. **Results:** it was found that patients with left atrial volume index > 60 ml/ m^2 had higher incidence for developing cardiac events during follow up 28.5% (10 patients developed atrial fibrillation, 7 patients reported hospitalization for congestive heart failure, and 3 cases died) versus patients with left atrial volume index 40 : 59 ml/m^2 (8 patients 12%) (6patients developed atrial fibrillation, 2 patients reported hospitalization for congestive heart failure) Versus patients with left atrial volume index < 40 ml/m^2 (2 patients 3%, (1 patient developed atrial fibrillation, 1 patient reported hospitalization for congestive heart failure) with p value 0.001). **Conclusion and recommendations:** left atrial volume index should be assessed in routine clinical practice for decision-making in patients with asymptomatic severe rheumatic mitral regurgitation since it is an early predictor for development of cardiac events in those individuals.

Key words: severe rheumatic mitral regurgitation, left atrial volume, and rheumatic heart disease.

Introduction

Rheumatic heart disease (RHD) continue to be a major health issue in many developing countries and studies have reported mitral regurgitation (MR) as a common valvular lesion [(1)]. In fact , European and American guidelines recommend referring patients with severe rheumatic MR to surgical treatment in presence of either symptoms or overt left ventricular (LV) dilation and dysfunction , high pulmonary pressure , left atrial (LA) dilation , and / or atrial fibrillation (AF), in order to spare risk of cardiac surgery[(2&3)] . Patients with severe rheumatic (mitral regurgitation) MR remain asymptomatic long period due to adaptive remodeling of the left ventricle (LV) & left atrium (LA)[(4).] The optimization of the timing for MR open or percutaneous surgical treatment has become a main concern which highly raised scientific interest[(5).] Early structural alterations due to high filling pressures are not recognized since LV & LA are still capable to face hemodynamic overload[(5).]

Left atrial (LA) enlargement is a pathophysiologic response to volume overload in rheumatic MR[(6&7).]

Left atrial volume measurement is now considered superior to LA diameter and in the general population, larger LA volume has been associated with atrial fibrillation, stroke, congestive heart failure, and mortality [(8)].

In patients with rheumatic MR, LA size is a marker for subsequent AF[9]. However, actual impact of LA volume on outcome, particularly survival after diagnosis, and its usefulness in managing patients with rheumatic MR, are poorly defined [10&11]. To examine the hypothesis that LA volume index measured at diagnosis predicts outcome during follow up for patients with asymptomatic severe rheumatic MR we prospectively enrolled patients with chronic asymptomatic severe rheumatic MR in sinus rhythm and prospectively performed triple quantitation of LA volume, MR severity, and left ventricular (LV) characteristics to evaluate the predictive value of left atrial volume index(LAVI) measured at diagnosis on outcome [12,13].

Aim of The Work: as to assess the link between left atrial volume index measured at diagnosis and outcome of patients with asymptomatic severe rheumatic mitral regurgitation (MR) during follow up.

Patients and Methods

200 patients with chronic, asymptomatic severe rheumatic mitral regurgitation were included in our study. They were chosen from the cardiology department's outpatient clinics between October 2021 and October 2022.

Patients with the following criteria were excluded : Co-existence moderate or severe other valvular disease, Coronary artery disease by history of angina or ECG changes suggestive of coronary artery disease (CAD) or regional wall motion abnormalities (RWMA) detected by echocardiography, Atrial fibrillation (AF) at time of examination, Hypertrophic cardiomyopathy (HCM), Congenital heart disease with MR, Prior open heart surgery, Poor 2D Echo windows, Hypertension.

The hospital ethical committee approved this study and a written consent was obtained from each subject (Approval number:73:9/2021

Date of approval: 13 September 2021

Methods: ECG, trans-thoracic echocardiography, and clinical evaluation (i.e., medical history and physical examination)

1-Clinical assessment and follow-up after 6 month: age, sex, previous history of CAD , and hypertension are all part of a person's medical history.

ECG, general examination, cardiac examination, and measurement of arterial blood pressure were performed.

Clinical outcome was evaluated during follow-up in order to identify any cardiac events, such as AF, heart failure or death.

2- 2D transthoracic echocardiography evaluation: Transthoracic Echocardiography was performed using SIEMENS ACUSON SC 2000 ultrasound (Germany, Siemens) with its dedicated probe (4V1 probe) to all participants. All Echocardiographic measurements were performed according to the recommendations of American Society of Echocardiography/European Association of Cardiovascular Imaging (ASE/EACVI) guidelines [14].

1- LVEF: was calculated by estimating LV end-diastolic volume (EDV, mL) and end-systolic volume (ESV, mL) using the Teichholz formula

LVEF(%)= ((LVEDV – LVESV)/ (LVEDV)) x 100% [14].

2- Chambers dimensions: Left ventricular volumes (LVEDV & LVESV) and left atrium volume (LAV) were calculated at left ventricular end systole in apical four-chamber view (area-length method), Left atrium dimensions and left ventricular dimensions were calculated by M-mode in long para-sternal axis view [15].

3- RWMAs, valvular lesions and other structural heart diseases also have been assessed.

4- MR severity: MR was assessed using a multiparametric integrated approach as recommended, including vena contracta width and, when feasible, effective regurgitant orifice area and regurgitant volume and also proximal isovelocity surface area were calculated. Severe MR was defined by vena contracta width ≥7 mm, effective regurgitant orifice area (PISA) ≥40 mm2 and regurgitant volume ≥60 ml \beat [15].

5- Pulmonary artery systolic pressure (PASP) was evaluated using the gradient of the tricuspid regurgitation velocity in accordance with the 2015 ESC |ERS recommendations [16].

Statistical analysis: Data analysis and entry was done using SPSS version 21 quantitative data presented as mean and SD while

qualitative data as frequency distributions, Comparing between the 3 groups done by independent sample t test for quantitative data and chi square test for qualitative data, comparison between the three groups done by one way ANOVA test, Event rates, estimated using Kaplan-Meier method, and were compared using log-rank test, Univariate and multivariate Cox proportional hazards analyzed LA index prediction of mortality and cardiac events with calculation of hazard ratios (HRs) A value of $p < 0.05$ was considered statistically significant.

Results

This study included 200 patients with asymptomatic severe rheumatic mitral regurgitation who were divided into 3 groups according to their LAVI, there were no significant differences between the three groups as regarding demographic and anthropometric measures table (1)

Table (1): demographic and anthropometric measures of the studied patients

Data		G I NO = 70	G II NO = 60	G III NO = 70	P value
Age	**Range**	21-50	20-49	22-51	0.7
Sex	**Male** **Female**	40(57.1%) 30(42.9%)	27(45%) 23(55%)	32(45.7%) 38(54.3%)	0.4
Height	**Range** **Mean±SD**	162-185 178.9±5.9	160-189 179.8±5.4	161-188 177.8±5.4	0.2
Weight	**Range** **Mean±SD**	67-100 85.8±10.01	67-98 87.7±7.4	68-96 86.7±7.4	0.1
BMI	**Range** **Mean±SD**	18-25 23±2.5	18-25 22.4±2.7	18-25 22.4±2.7	0.5

Numerical data displayed as mean, standard deviation and range, analysed by independent sample t-test, Categorical data displayed as number and percent, analysed by chi-squared and fisher exact test.
BMI= body mass index, SD = standard deviation

There were no significant difference between the three groups as regard vital data Table (2)

Table (2): vital data of the studied patients:

Data		G I NO = 70	G II NO = 60	G III NO = 70	P value
SBP (mmHg)	**Range** **Mean±SD**	100-120 116.5±3.9	112-120 114.5±4.4	110-120 115.5±4.4	0.09
DBP (mmHg)	**Range** **Mean±SD**	76-85 76.8±4.1	70-84 74.6±4.3	70-80 75.6±4.3	0.4
pulse(bpm)	**Range** **Mean±SD**	68-100 81.8±8.7	66-100 82.3±10.1	62-100 81.3±10.1	0.6
RR(cycle/minute)	**Range** **Mean±SD**	11-18 14.9±2.7	12-18 14.7±3.06	11-16 14.6±3.06	0.6

Numerical data displayed as mean, standard deviation and range, analysed by independent sample t-test, Categorical data displayed as number and percent, analysed by chi-squared and fisher exact test
P-value considered significant at <0.05
SBP= systolic blood pressure, DBP= diastolic blood pressure, RR = respiratory rate .

3-<u>Transthorasic 2D echocardiography evaluation</u>:
Patients were divided according to LAVI into three groups:
Group I: Patients with LAVI < 40 ml/m2 : number = 70 patients
this group of patients had lower LVESVI , LVEDVI, PASP than other two groups of patients with P value 0.0001* but no significant difference as regard LVEF.
Group II: Patients with LAVI 40 : 59 ml/m2: number 60 patients

this group of patients had larger LVESVI, LVEDVI, PASP than first group of patients but lower than 3rd group of patients with P value 0.0001*
But no significant difference as regard LVEF.
Group III: Patients with LAVI > 60 ml/m2: number 70 patients this group of patients had larger LVESVI, LVEDVI, PASP than other two groups of patients with P value 0.0001* But no significant difference as regard LVEF

Table (3): Comparison between three groups according to 2D echocardiographic parameters LVESVI, LVEDVI, PASP and LVEF:

Characters	(Cases) No=200			P
	Group I LAVI < 40 NO= 70	Group II LAVI 40 : 59 NO= 60	Group II LAVI ≥ 60 No = 70	
LV ESVI, ml/m2	28 ± 10	32 ± 39	39 ± 15	P1=0.0001* P2=0.0001* P3=0.0001*
LV EDVI, ml/m2	88 ± 19	107 ± 23	130 ±25	P1=0.0001* P2=0.0001* P3=0.0001*
PASP mmHg	34 ± 6	35 ± 8	45 ± 16	P1=0.0001* P2=0.0001* P3=0.0001*
LVEF %	68 ± 8	71 ± 8	70 ± 8	P1=0.1 P2=0.1 P3=0.1

P1= GI vs GII, P2= GI vs GIII, P3= GII vs GIII, Comparing the 3 groups done by one way ANOVA test. LVESVI = left ventricular end systolic volume index, LV EDVI = left ventricular end diastolic volume index , PASP= pulmonary artery systolic pressure, LVEF = left ventricular ejection fraction

Incidence of cardiac events among our patients During 6 month follow-up:
there were significant statistically difference between the three groups as regarding incidence of cardiac events (Atrial fibrillation, congestive heart or death) during 6 month follow up with P value 0.001.
GIII NO 70 Patients with LA index > 60 ml/m 2 had frequent cardiac events (AF, hospitalization with CHF, death) 20 patients 28.5% (10 patients developed AF, 7 patients reported hospital admission with CHF , 3 patients died during follow up versus GII NO 60 patients with LAVI 40 to 59 ml/m 2 (8 patients 12%) (6 patients developed AF, 2 patients reported hospital admission with CHF) Versus GI NO 70 patients with LAVI < 40 ml/m 2 (2 patients 3%, (1 patient developed AF, 1 patients reported hospital admission with CHF) with p value 0.001) table (4) and table (5)

Table (4): Comparison between three groups as regarding Incidence of cardiac events During 6 month follow-up

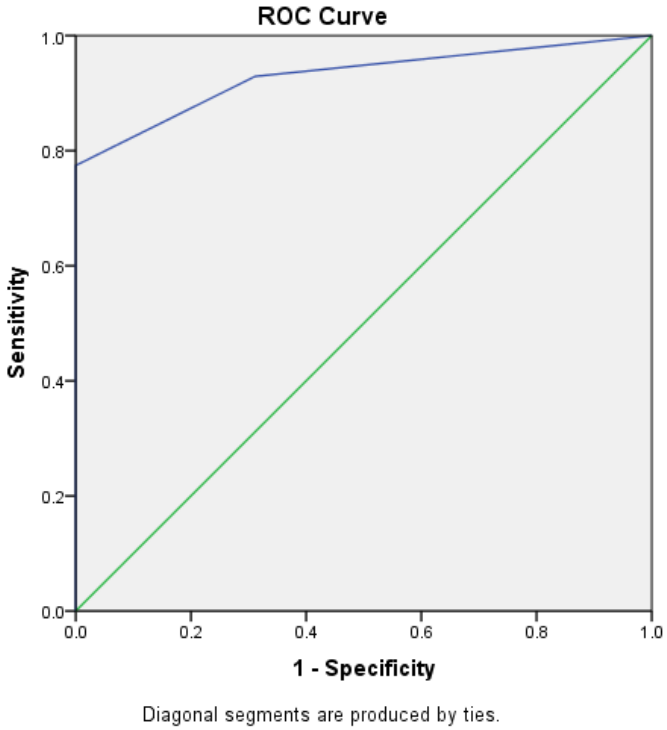
	Group I LAVI < 40	Group II LAVI 40 : 59	Group III LAVI ≥ 60	P value
AF	1	6	10	P1=0.001* P2=0.001* P3=0.001*
Hospitalization with (CHF)		2	7	P1=0.001* P2=0.001* P3=0.001*
Death	0	0	3	P1=0.001* P2=0.001* P3=0.001*
Total number	70	60	70	

P1= GI vs GII , P2= GI vs GIII , P3= GII vs GIII , Event rates, estimated using Kaplan-Meier method, and were compared using log-rank test.
CHF = congestive heart failure , AF = atrial fibrillation

Table (5): Hazard ratio for development of cardiac events between the three groups :

	HR (95% CI)	P value
LAVI < 40 ml/m2	1.3 (1.1–1.5)	< 0.001
LAVI 40 : 59 ml/m2	2.8 (1.5–5.5)	<0.001
LAVI ≥ 60 ml/m2	5.2 (2.6–10.9)	< 0.001

Cardiac events were defined as (death, hospitalization with CHF, and development of AF . hazard ratio adjusted for sex, age, symptoms, Regurgitation volume and LVEF, Univariate and multivariate Cox proportional hazards analyzed LA index prediction of mortality and cardiac events with calculation of hazard ratios (HRs) A value of $p < 0.05$ was considered statistically significant.



ROC curve of mean LAVI for prediction of development of symptoms during 6 month follow up

Prediction of developing symptoms in patients by mean LAVI

	Cut off value	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy
Mean LAVI	58 ml/m2	0.92	91.9%	67.9%	90.1%	72.8%	86.5%

Cut off point of developing symptoms for mean of LAVI is (58 ml/m2)

Discussion

Effect of MR on left atrial dilatation and Left atrial remodeling is common in chronic severe rheumatic MR , progressive left atrial dilation due to severe rheumatic MR is a mechanism which delay development of symptoms and heart failure [17].

So our study was done to evaluate the predictive value of LAVI at diagnosis on outcome for patients with asymptomatic severe rheumatic mitral regurgitation (MR).
In our study we focused on the LA enlargement as a predictor for prognosis in patients with severe rheumatic MR. we found that LAVI at diagnosis predicts cardiac events in patients with severe rheumatic MR, Patients with LA VI $\geq$ 60 ml/m 2 had higher incidence of cardiac events (AF, hospitalization with CHF, death) (6 month follow up: 20 patients 28.5%) versus patients with LAVI 40 to 59 ml/m 2 (8 patients 12%) and patients with LAVI 40 ml/m 2(2 patients 3%, p value 0.001), so that assessment of left atrium dilation by LAVI should be routinely performed in patients with severe rheumatic MR and used for decision making as regarding intervention.

Our study included 200 patients with severe rheumatic MR in whom triple assessment of LV volume, LA volumes, and MR severity and follow up for 6 month done for detection development of cardiac events including (AF, hospitalization with CHF, death).

Our study reported that patients with higher LAVI had higher incidence for cardiac events than patients with lower LAVI.
And these findings support those of Benjamin EJ et al., Participants who were 50 years of age or older were included in their study to assess the association between the size of the left atrium and the risk of stroke and mortality. 1828 female patients and 1371 male patients participated in their study, which had an 8-year follow-up period. According to the findings, 296 (21.6%) male patients and 271 (15.7%) female patients died, while 64 of the 1371 male patients (4.7%) and 73 of the 1828 female patients (4.2%) had strokes. Men had a stroke risk of 2.4 (95% CI: 1.6 to 3.7) and women had a risk of 1.4 (95% CI: 0.9 to 2.1) with every 10 mm increase in LA size, while women had a risk of 1.3 (95% CI: 1.0 to 1.5) and men had a risk of 1.4 (95% CI: 1.1 to 1.7). [18].

According to Andrea Rossi et al., 337 patients with dilated cardiomyopathy (age 60 +/- 13 years; 84% male) participated in their study. LAVI was measured at left ventricular end systole (apical four chamber view using area-length method); (LVEDV and LVESV); LVEF; and mitral regurgitation severity was also assessed. Mitral E-wave (E) and A-wave (A) velocities, as well as the (E/A) ratio, were measured offline. They discovered that as the left atrial volume is associated with diastolic dysfunction, LV remodelling, and the degree of mitral regurgitation [19], it has a prognostic value for patients with dilated cardiomyopathy.

Additionally, 176 patients (mean age, 57 +/- 14 years) who had MVR and were followed up for 3.8 +/- 0.5 years were included in Reed D et al's study. To estimate the likelihood of postoperative cardiac mortality, clinical, laboratory, two-dimensional echocardiography, and cardiac catheterization data were analyzed. 39 deaths from cardiac causes were reported (29 from CHF and 10 from sudden). When the four categories were looked at separately, the most reliable predictors of postoperative death were two clinical, one laboratory, two 2DE, and one catheterization variable. Only three of these six factors—left atrial size, the presence of pulmonary congestion, left atrial volume, and the ratio of left ventricular wall thickness to left

ventricular dimension in end systole—were discovered to be reliable indicators of cardiac-related death [20].

In their study, conducted between 1990 and 1998 on 1495 patients with a mean age of 75 7 years who were referred for transthoracic echocardiography testing, Takemoto Y et al. concluded that Left atrial (LA) volume is a marker of diastolic dysfunction. These individuals were monitored for 4.3 +/- 2.7 years and had sinus rhythm and no history of heart failure. 1,375 individuals, or 92% of the 1,495 patients examined, had LV ejection fractions higher than 50%, making up the research population. Congestive heart failure eventually developed in 138 of them, or 10%. They asserted that an early indication of CHF was a LAVI volume more than 32 ml/m2 at the time of diagnosis (p value 0.001). In 98 of the 138 patients with first CHF, there was an increase in LA volume of 8–10 ml/m2 (p 0.001), and LVEF was assessed in 74 (76%) of these patients within 4 weeks of diagnosis. Age-adjusted congestive heart failure free survival rates were 95%, 91%, and 83%, respectively, for LA volumes of less than 28, between 28 and 37, and greater than 37 ml/m2 (p 0.001). Additionally, they pointed out that LA volume was a primary predictor for CHF in elderly patients with well-preserved LVEF [21].

The Tsang TS et al., study comprised 317 patients with sinus rhythm upon diagnosis, 62 of whom had 90 additional cardiac events over the length of the 3.5 2.3-year follow-up. All three LA size characteristics (all p values 0.0001) predicted the overall results. They asserted that the only study to link LA enlargement to the frequency of cardiovascular events was LAVI. In individuals with AF, there was no association between LA size and cardiovascular events. They asserted that left atrial volume is a more accurate predictor of cardiovascular events in people with sinus rhythm than LA diameter. Whatever the method used to evaluate LA size, it had a poor prognostic value for cardiovascular events in AF [22].

Conclusions: In patients with asymptomatic severe rheumatic MR LAVI at diagnosis is a predictor for outcome and for development of cardiac events (AF , hospitalization with CHF and death) during 6 month follow up .

Recommendations: LAVI should be measured in clinical practice for decision making in patients with asymptomatic severe rheumatic MR , because early intervention for those patients improves outcome.

Limitation:

1- Our study included patients with severe rheumatic MR with sinus rhythm and patients with atrial fibrillation were excluded despite of AF is an important factor of LA remodeling, which we excluded and the role of LA enlargement in patients with severe rheumatic MR and AF will require
future studies.

2- short follow-up duration.

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