Iranian Heart Journal; 2022; 23 (2)

Original Article

Rheumatic Mitral Stenosis: Correlation Between Mitral Valve Area and Hemodynamic and Echocardiographic Parameters

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ABSTRACT

Background: The relationship between mitral valve area (MVA) and different hemodynamic and echocardiographic parameters is not well defined. This study aimed to assess whether hemodynamic and echocardiographic parameters correlated with MVA in patients with rheumatic mitral stenosis.

Methods: This cross-sectional study assessed 600 patients with rheumatic heart disease who underwent transthoracic echocardiography in a tertiary care center between August 2018 and March 2020. Among them, 265 cases of predominant mitral stenosis were enrolled. Demographic data, as well as hemodynamic and echocardiographic variables, were recorded.

Results: Out of the 265 patients, 29.1% were males, and 71.9% were females at a mean age of 44.80±13.54 years. MVA ranged between 0.5 cm^2 and 2.0 cm^2, with a mean mitral valve gradient of 10.02±3.43 mm Hg. Atrial fibrillation was present in 44.2%. There were positive correlations between MVA and body mass index (r=0.19, P=0.002), systolic blood pressure (r=0.14, P=0.011), diastolic blood pressure (r=0.16, P=0.006), and mean blood pressure (r=0.18, P=0.003). Negative correlations were found between MVA and heart rate (r= −0.20, P=0.001), left atrial size (r= −0.16, P=0.007), mean mitral valve gradient (r= −0.67, P<0.001), and pulmonary artery systolic pressure (r= −0.17, P=0.004).

Conclusions: MVA correlated significantly with body mass index, blood pressure, heart rate, left atrial size, mean mitral valve gradient, and pulmonary artery systolic pressure. This study helps to understand the influence of different clinical parameters and transthoracic echocardiographic findings to accurately assess rheumatic mitral stenosis severity. ***(Iranian Heart Journal 2022; 23(2): 6-15)***

KEYWORDS: Correlation study, Echocardiography, Hemodynamics, Mitral valve stenosis

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Received: December 28, 2020 **Accepted:** February 20, 2021

Mitral stenosis (MS) secondary to rheumatic heart disease is still a major cardiac problem with increased morbidity and mortality in developing countries like Nepal because of the high prevalence of rheumatic fever. The diagnosis of MS is made based on clinical history, examination of hemodynamic parameters, and echocardiographic findings.
Assessment of the mitral valve area (MVA) needs several measurements with more than 1 method to estimate the hemodynamics of the mitral valve (MV). Current guidelines recommend that the severity of MS not be defined by a single value but be assessed by valve area, mean Doppler gradient, and pulmonary pressure.[1] Therefore, clinical measures of hemodynamic parameters and other echocardiographic findings may help to accurately assess the severity of MS.
Despite the high prevalence of MS in our country, the relationships between MVA measured by echocardiography and different hemodynamic parameters and other echocardiographic findings are not well defined. This study aimed to assess whether noninvasive hemodynamic and echocardiographic parameters correlated with MVA in patients with rheumatic MS.

METHODS

Study Population

This observational cross-sectional study initially assessed 600 patients with rheumatic heart disease as screened by transthoracic echocardiography in the outpatient department of the cardiology unit via the convenient sampling method from August 2018 through March 2020. Among them, 265 patients with predominant mild-to-severe cases of MS were enrolled. Diagnosis of rheumatic MS was made according to the 2014 American College of Cardiology (ACC)/American Heart Association (AHA) Valvular Heart Disease and the World Health Organization (WHO) guidelines.[2,3] This study included only patients with predominant rheumatic MS and without significant mitral regurgitation and aortic valve disease. Patients with more-than-mild mitral regurgitation and/or aortic valve disease and a history of previous percutaneous transmitral commissurotomy or valve surgery were excluded.
The demographic data of the patients consisted of age, sex, comorbid illnesses, body weight, height, body mass index, waist-hip ratio, heart rate, and blood pressure. Laboratory parameters included complete blood counts and estimated glomerular filtration rates. Patients were classified as in atrial fibrillation or sinus rhythm based on baseline 12-lead electrocardiography.

Echocardiographic Examination

Echocardiographic examinations were performed in the left lateral decubitus position by 2 independent trained cardiologists using the GE Vivid 7 Echocardiography system with an S6 Doppler probe (GE Medical System, Norway). All the echocardiographic measurements, including MVA (calculated via 2D planimetry and pressure half time methods), mean mitral valve gradient (MVG), left atrial diameter, left atrial clot, left ventricular ejection fraction, and tricuspid valve maximal velocity, were assessed based on the guidelines from the recent American Society of Echocardiography (ASE).[4]

Statistical Analysis

The collected data were entered in Microsoft Office Excel 2007 and converted into IBM Corp, Released in 2011(IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). Continuous variables were expressed as the mean and the standard deviation, and categorical variables were expressed as frequencies and percentages. The correlations between MVA and hemodynamic and echocardiographic variables were analyzed using the Pearson

correlation coefficient (*r*) for normal data and the Spearman correlation coefficient for skewed data. For all the statistical data, a *P* value of less than 0.05 was indicated as a significant correlation between the mean values of 2 variables.

RESULTS

A total of 600 patients with rheumatic heart disease were screened for MS. Among them, 265 patients (44.16%) with predominant MS were enrolled: 77 men (29.1%) and 188 women (71.9%) at a mean age of 44.80±13.54 years. The age distribution of the patients is shown in Figure 1. Twenty-three patients (15.5%) were current smokers, and 11 (7.4%) were significant alcohol consumers. Mean body mass index was 21.13±4.08 kg/m^2. One hundred seventeen patients (44.20%) had atrial fibrillation, and only 13 (4.90%) had thrombi in the left atrium/left atrial appendage as examined by transthoracic echocardiography. All the patients had predominant mild-to-severe MS based on MVA measurements made by both planimetry and pressure half time, ranging between 0.5 cm^2 and 2.0 cm^2, with a mean MVG of 10.02±3.43 (range=4–25 mm Hg). The baseline characteristics of all the patients, along with sex differences, are depicted in Table 1. Similarly, differences in the characteristics of the patients with or without atrial fibrillation are shown in Table 2

The Pearson correlation test showed positive correlations between MVA and body mass index (*r*=0.19, *P*=0.002), systolic blood pressure (*r*=0.14, *P*=0.011), diastolic blood pressure (*r*=0.16, *P*=0.006), and mean blood pressure (*r*=0.18, *P*=0.003) and negative correlations between MVA and heart rate (*r*= −0.20, *P*=0.001), left atrial size (*r*= −0.16, *P*=0.007), mean MVG (*r*= −0.67, *P*<0.001), and pulmonary artery systolic pressure (*r*= −0.17, *P*=0.004) (Table 3). Multivariate analysis showed positive correlations between MVA and heart rate (β=0.120, *P*=0.020) and serum hemoglobin levels (β=0.099, *P*=0.028) and a negative correlation between MVA and mean MVG (β= −0.711, *P*≤0.001).

Gender-wise analysis of data suggested a positive correlation between MVA and weight (*r*=0.24, *P*=0.031) and a negative correlation between MVA and height (*r*= −0.23, *P*=0.032) only in the male patients. However, there were positive correlations between MVA and systolic blood pressure (*r*=0.17, *P*=0.011), diastolic blood pressure (*r*=0.18, *P*=0.011), and mean blood pressure (*r*=0.14, *P*=0.010) and negative correlations between MVA and heart rate (*r* =−0.20, *P*=0.001), left atrial size (*r*= −0.20, *P*=0.005), mean MVG (*r*= −0.66, *P*<0.001), and pulmonary artery systolic pressure (*r*= −0.18, *P*=0.012) in the female patients (Table 4). Multivariate analysis demonstrated positive correlations between MVA and body mass index (β=1.036, *P*=0.044), heart rate (β=0.131, *P*=0.038), mean blood pressure (β=0.245, *P*=0.023), and serum hemoglobin (β=0.119, *P*=0.034), as well as a negative correlation between MVA and weight (β= −1.170, *P*=0.039) only in the female patients and a negative correlation between MVA and mean MVG (β= −0.692, *P*≤0.001) in both sexes.

Splitting of data in terms of sinus rhythm and atrial fibrillation revealed positive correlations between MVA and body mass index (*r*=0.27, *P*=0.003), waist-hip ratio (*r*=0.22, *P*=0.011), systolic blood pressure (*r*=0.19, *P*=0.030), diastolic blood pressure (*r*=0.24, *P* =0.008), and mean blood pressure (*r*=0.25, *P*=0.005) and negative correlations between MVA and height (*r*= −0.19, *P*=0.031), left atrial size (*r*= −0.23, *P*=0.009), mean MVG (*r*= −0.70, *P*<0.001), and pulmonary artery systolic pressure (*r*= −0.19, *P*=0.009) in patients with atrial fibrillation (Table 5).

There was also a consistent and strong correlation between MVA and mean MVG in all subsets of patients.

Table 1: Baseline characteristics of the patients with mitral stenosis (n=265)

Variables	Total (N=265)	Male (n=77)	Female (n=188)	*P* value
Age, y ± SD	44.80 ± 13.54	43.64 ± 12.07	45.27±14.10	0.370
Weight, kg	49.95 ± 11.06	56.27 ± 11.85	47.36 ± 9.76	<0.001
Height, m	1.53 ± 0.09	1.62 ± 0.09	1.49 ± 0.05	<0.001
Body mass index, kg/m^2	21.13 ± 4.08	21.26 ± 4.10	21.08 ± 4.08	0.750
Waist/hip ratio	0.86 ± 0.08	0.85 ± 0.08	0.86 ± 0.08	0.700
Mean BP, mm Hg	86.26 ± 9.74	86.85± 8.89	86.02±10.08	0.529
Mean systolic BP, mm Hg	111.69 ± 13.73	112.91±14.12	111.19 ± 13.57	0.356
Mean diastolic BP, mm Hg	73.55 ± 9.94	73.83 ± 9.08	73.44 ± 17.82	0.773
Mean heart rate, BPM	89.84 ± 17.86	88.56 ± 18.03	90.36 ± 18.60	0.457
Hemoglobin, g/dL	12.53 ± 1.67	12.78 ± 1.63	12.42 ±1.67	0.119
Total leucocyte count/dL	7722.54 ± 2625	7863.95 ± 2822	7664.62±2545	0.576
Total platelet count/dL	237.49 × 10^3 ± 55.10	225 .74× 10^3 ± 46.70	242.31×10^3±57.62	0.026
eGFR, mL/min	74.81 ± 24.95	79.93 ± 25.37	72.71 ± 24.54	0.032
LA size, mm	49.17 ± 7.04	49.43 ± 6.37	49.06 ± 7.32	0.700
Mean LVEF, %	55.12 ± 7.77	55.51 ± 7.72	54.96±7.80	0.603
PA pressure, mm Hg	36.09 ± 13.26	37.53 ± 13.50	35.50 ±13.15	0.252
Mitral valve area, cm^2	1.18 ± 0.39	1.14 ± 0.37	1.12 ± 0.40	0.334
Mean MVG, mm Hg	10.02 ± 3.43	9.68 ± 3.35	10.16 ± 3.53	0.310
Atrial fibrillation (n, %)	117 (44.20%)	37 (48.10%)	80 (42.60%)	0.410
LA clot	13 (4.9%)	4 (5.2%)	9 (4.8%)	1.000
Smoking	42 (15.8%)	17 (22%)	25 (13.3%)	0.052
Alcohol use	23 (8.7%)	6 (7.8%)	17 (9%)	0.810
Hypertension	11 (4.2%)	6 (7.8%)	5 (2.7%)	0.085
Diabetes mellitus	5 (1.9%)	2 (2.6%)	3 (1.6%)	0.630
Stroke	15 (5.7%)	2 (2.6%)	13 (6.9%)	0.244

SD, Standard deviation; BP, Blood pressure; BPM, Beat per minute; LA, Left atrium; LVEF, Left ventricular ejection fraction; eGFR, Estimated glomerular filtration rate

Table 2: Baseline characteristics of the patients who had mitral stenosis with or without atrial fibrillation

Variables	Sinus rhythm (n=148)	Atrial fibrillation (n=117)	*P* value
Age, y ± SD	43.82 ± 13.29	51.09 ± 11.05	<0.001
Weight, kg	51.58 ± 10.72	47.89 ± 11.18	0.007
Height, m	1.54 ± 0.08	1.52 ± 0.09	0.322
Body mass index, kg/m^2	21.69 ± 3.94	20.43 ± 4.16	0.013
Waist/hip ratio	0.86 ± 0.09	0.85 ± 0.07	0.105
Mean blood pressure, mm Hg	85.39 ± 9.94	86.26 ± 9.74	0.102
Mean systolic BP, mm Hg	111.95 ± 14.00	111.37 ± 13.43	0.734
Mean diastolic BP, mm Hg	72.12 ± 10.07	75.37 ± 9.50	0.008
Mean heart rate, BPM	86.62 ± 15.55	93.91 ± 19.74	0.001
Hemoglobin, g/dL	12.32 ± 1.64	12.79 ± 1.67	0.022
Total leucocyte count/dL	7355.22 ± 2656.14	8187.18 ± 2520.38	0.010
Total platelet count/dL	238.61 × 10^3 ± 56.85	236.08× 10^3 ± 53.02	0.710
eGFR, ml/min	85.06 ± 24.93	63.10 ± 19.54	<0.001
LA size, mm	48.77 ± 6.90	49.68 ± 7.22	0.300
Mean LVEF,%	56.60 ± 6.67	53.22 ± 8.63	<0.001
PA pressure, mm Hg	33.01 ± 12.07	39.99 ± 13.72	<0.001
Mitral valve area, cm^2	1.19 ± 0.36	1.17 ± 0.42	0.623
Mean MVG	9.53 ± 3.13	10.63 ± 3.80	0.010
LA clot	1 (0.7%)	12 (10.3%)	<0.001
Smoking	23 (15.5%)	19 (16.2%)	0.871
Alcohol use	11 (7.4%)	12 (10.3%)	0.412
Hypertension	3 (2%)	8 (6.8%)	0.052
Diabetes mellitus	2 (1.4%)	3 (2.6%)	0.470
Stroke	5 (3.4%)	10 (8.5%)	0.071

SD, Standard deviation; BP, Blood pressure; BPM, Beat per minute; LA, Left atrium; LVEF, Left ventricular ejection fraction; eGFR, Estimated glomerular filtration rate; MVG, Mitral valve gradient

Table 3: Correlations between mitral valve area and different variables

Variables	Bivariate, *r* (*P* value)	Multiple Linear Regression, B (*P* value)
Age	-0.047 (0.447)	-0.027 (0.672)
Weight	0.090 (0.143)	-0.010 (0.979)
Height	-0.136 (0.027)	-0.115 (0.585)
Body mass index	0.191(0.002)	0.044 (0.894)
Waist/hip ratio	0.090 (0.143)	0.049 (0.266)
Heart rate	-0.205 (0.001)	0.120 (0.020)
Systolic blood pressure	0.145 (0.018)	0.048 (0.362)
Diastolic blood pressure	0.167 (0.006)	0.071 (0.186)
Mean blood pressure	0.182 (0.003)	0.081 (0.273)
Estimated glomerular filtration rate	0.078 (0.208)	-0.076 (0.365)
Serum hemoglobin	0.082 (0.184)	0.099 (0.028)
Total leucocyte count	-0.055 (0.374)	-0.035 (0.442)
Serum platelet count	-0.029 (0.633)	-0.043 (0.345)
Left atrium size	-0.167 (0.007)	-0.052 (0.278)
Mean mitral valve gradient	-0.671 (<0.001)	-0.711 (<0.001)
Left ventricular ejection fraction	0.005(0.937)	-0.059 (0.218)
Pulmonary artery systolic pressure	-0.176 (0.004)	-0.067 (0.160)

Table 4: Gender-wise correlations between mitral valve area and different variables

Variables	Male, (n=77)		Female, (n=188)	
	Bivariate R (*P* value)	Multiple Linear Regression B (*P* value)	Bivariate R (*P* value)	Multiple Linear Regression B (*P* value)
Age	0.033 (0.773)	0.219 (0.375)	-0.077 (0.29)	-0.070 (0.302)
Weight	0.246 (0.031)	-0.049 (0.952)	0.066 (0.368)	-1.170 (0.039)
Height	-0.239 (0.036)	-0.111 (0.812)	-0.07 (0.330)	0.384 (0.084)
Body mass index	0.394 (<0.001)	0.204 (0.801)	0.11 (0.113)	1.036 (0.044)
Waist/hip ratio	0.189 (0.100)	0.033 (0.677)	0.052 (0.480)	0.031 (0.559)
Heart rate	-0.223 (0.051)	0.140 (0.177)	-0.203 (0.005)	0.131 (0.038)
Systolic blood pressure	0.073 (0.526)	-0.109 (0.208)	0.179 (0.014)	0.108 (0.105)
Diastolic blood pressure	0.135 (0.243)	0.012 (0.891)	0.180 (0.014)	0.065 (0.360)
Mean blood pressure	0.130 (0.258)	0.451 (0.324)	0.203 (0.005)	0.245 (0.023)
Estimated glomerular filtration rate	0.114 (0.323)	0.069 (0.717)	0.076 (0.302)	-0.046 (0.662)
Serum hemoglobin	-0.014 (0.905)	0.031 (0.750)	0.126 (0.086)	0.119 (0.034)
Total leucocyte count	-0.080 (0.487)	-0.132 (0.119)	-0.042 (0.571)	-0.011 (0.844)
Serum platelet count	-0.095 (0.409)	-0.180 (0.034)	-0.021 (0.779)	0.011 (0.844)
Left atrium size	-0.054 (0.640)	0.028 (0.744)	-0.202 (0.005)	-0.070 (0.230)
Mean Mitral valve gradient	-0.732 (0.000)	-0.776 (<0.001)	-0.665 (<0.001)	-0.692 (<0.001)
Left ventricular ejection fraction	-0.050 (0.664)	-0.159 (0.098)	0.028 (0.708)	-0.088 (0.147)
Pulmonary artery systolic pressure	-0.145 (0.209)	0.037 (0.685)	-0.183 (0.010)	-0.102 (0.081)

Table 5: Correlations between mitral valve area in the patients with sinus rhythm and atrial fibrillation

Variables	Sinus rhythm (n=148) *r* (*P* value)	Atrial Fibrillation (n=117) *r* (*P* value)
Age	-0.131 (0.114)	0.084 (0.371)
Weight	0.046 (0.582)	0.130 (0.163)
Height	-0.085(0.304)	-0.194 (0.036)
Body mass index	0.104 (0.208)	0.276 (0.003)
Waist-hip ratio	-0.005 (0.953)	0.224 (0.015)
Heart rate	-0.257 (0.002)	-0.157 (0.090)
Systolic blood pressure	0.102 (0.215)	0.198 (0.035)
Diastolic blood pressure	0.116 (0.161)	0.245 (0.008)
Mean blood pressure	0.126 (0.126)	0.257 (0.005)
Estimated glomerular filtration rate	0.111 (0.179)	0.019 (0.836)
Serum hemoglobin	0.213 (0.009)	-0.049 (0.602)
Total leucocyte count	-0.071 (0.391)	-0.028 (0.767)
Serum platelet count	0.002 (0.985)	-0.068 (0.467)
Left atrium size	-0.095 (0.252)	-0.239 (0.009)
Mean mitral valve gradient	-0.655 (<0.001)	-0.703 (<0.001)
Left ventricular ejection fraction	-0.087 (0.295)	0.070 (0.451)
Pulmonary artery systolic pressure	-0.148 (0.073)	-0.199 (0.031)

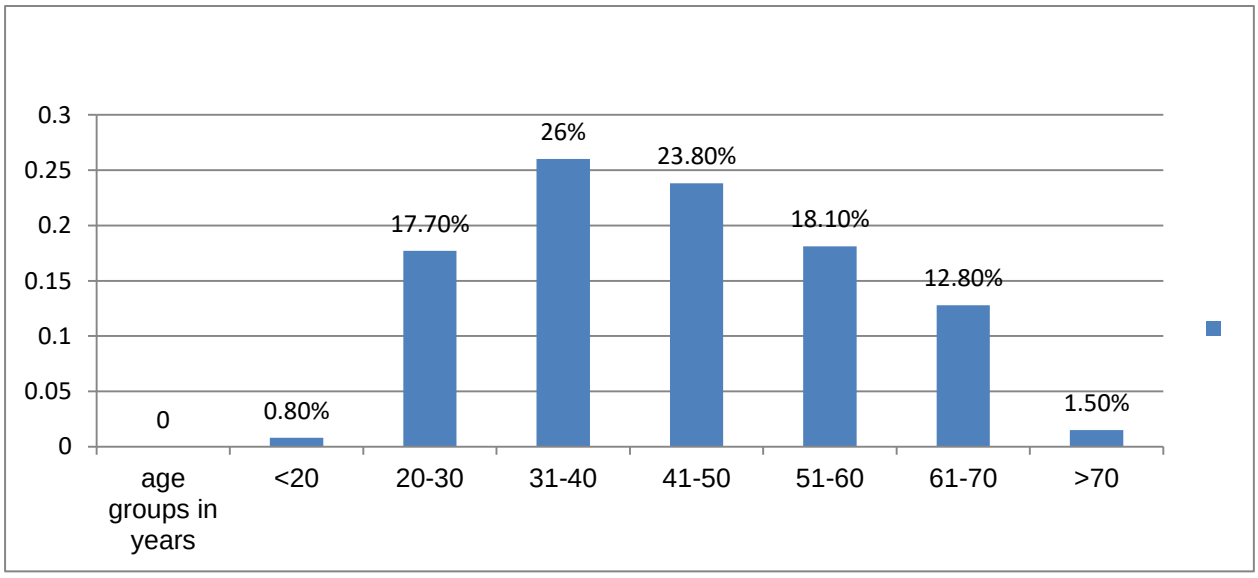

Figure 1: The image depicts age distribution among the studied patients with rheumatic mitral stenosis.

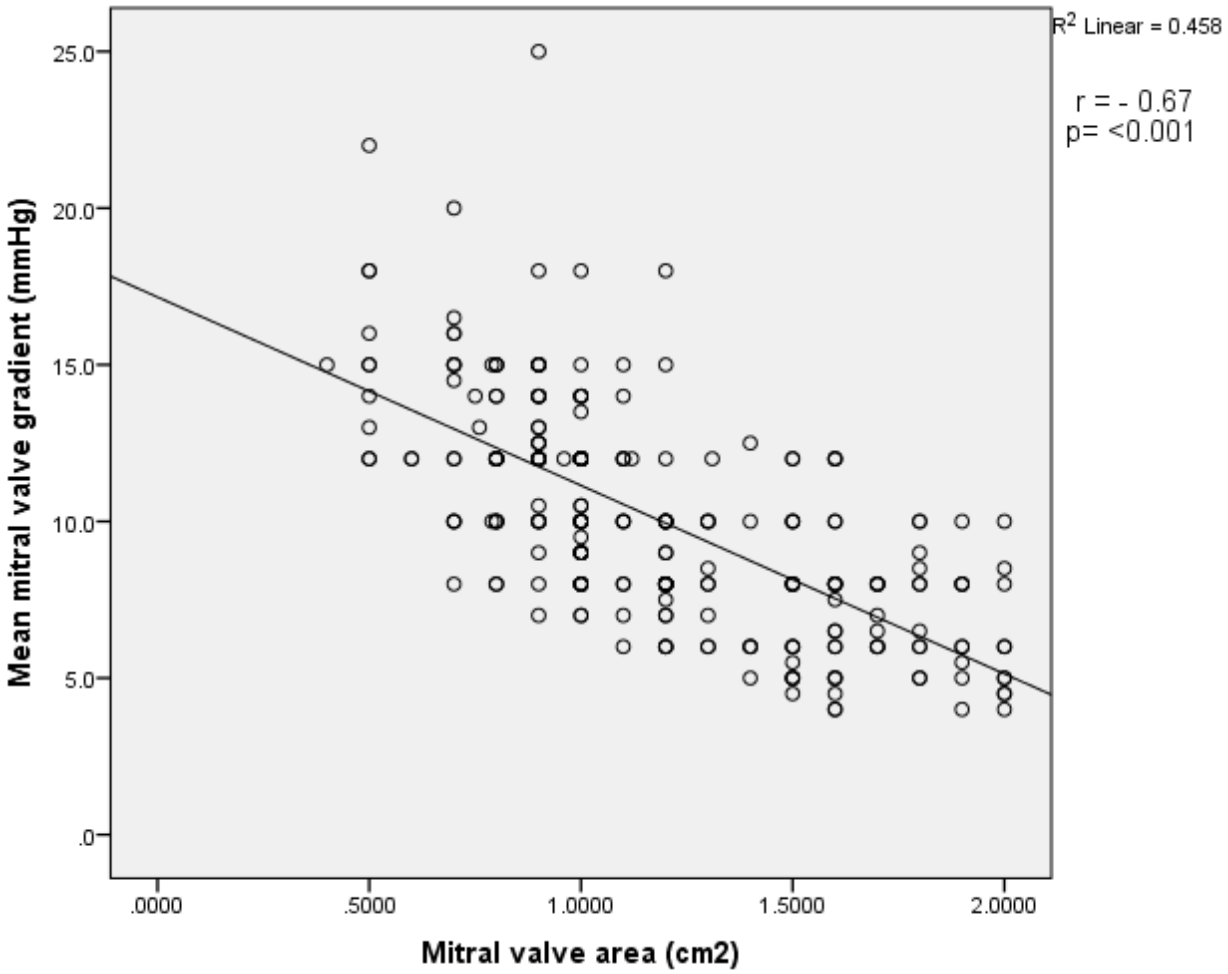

Figure 2: The image illustrates the relationship between mitral valve area and mean mitral valve gradient.

DISCUSSION

This study was conducted to assess the relationship between MVA and various hemodynamic and echocardiographic parameters in patients with rheumatic MS. The results showed significant correlations between MVA and body mass index, blood pressure, heart rate, left atrial size, MVG, and pulmonary artery systolic pressure.

There was a female predominance of MS (female/male ratio=2.4:1) with a higher prevalence in the age group of 20 to 50 years, constituting around two-thirds (67.5%) of the cases. This is in line with a large study done in south India, which showed that nearly two-thirds of patients with MS were female with a higher prevalence at 30–39 years.[5] Although the exact reason is not known, the female predominance could be due to some social factors, genetic factors, or others.

In this study, 44.12% of all the patients screened had predominant MS with severe lesions in 48.67%, which is slightly more than the figure in a previous large study, which showed dominant MS in 37.1% with a severe lesion in 47.2%. [6]

The reported prevalence of atrial fibrillation is 31.7% to 33% in rheumatic MS in different studies.[7,8] Left atrial size and MS severity are independent predictors of atrial fibrillation development as reported in a retrospective analysis of patients with rheumatic MS.[9] In our study, the prevalence

of atrial fibrillation was 44.20% with a mean left atrial size of 49.17±7.04 mm.

Echocardiography is the most useful measure for diagnosis, severity assessment, and planning for appropriate interventions. Estimation of MVA by planimetry has shown the best correlation with anatomical MVA measured on explanted valves,[10] probably due to the direct tracing of MVA on planimetry. However, in some patients, distorted valve pathology and poor echo windows may impede the accurate estimation of MVA.

Mean MVG is the recommended method for the estimation of MVA. This has shown a good correlation with the invasive measurement of MVG during catheterization.[11] Nonetheless, it is influenced by cardiac output and concomitant mitral regurgitation, and heart rate and is not the best measure of MS severity. Still, it may have a special benefit if there is a poor echo window for the planimetry of MV. We found a significant negative correlation between MVA and MVG in all subsets of patients irrespective of sex and patients with sinus rhythm or atrial fibrillation. Consequently, such findings further underscore the usefulness of MVG to accurately assess the severity of MS in case of fallacy with planimetry.

Patients with MS tend to have tachycardia due to low cardiac output, heart failure, onset of atrial fibrillation, or associated comorbid illnesses. Heart rate control with the prolongation of the diastole has been effective in reducing MVG and improving exercise capacity.[12] MVA is significantly higher in patients with sinus rhythm than in patients with atrial fibrillation.[13] Our results showed a significant negative correlation between MVA and heart rate in both groups of patients with sinus rhythm and atrial fibrillation, signifying that heart rate could be a useful additional clinical parameter to assess the severity of MS.

Cardiac index is the best hemodynamic parameter to correlate with the severity of MS. A cardiac index below 2.8 L/min/m^2 is almost always predictive of severe MS.[14] The reduced ventricular filling in MS decreases left ventricular stroke volume with a subsequent fall in cardiac output, resulting in a reduction in systolic blood pressure. Our study showed positive correlations between MVA and systolic blood pressure, diastolic blood pressure, and mean blood pressure.

In patients with MS, the magnitude of pulmonary hypertension is expected to be associated with the severity of MV stenosis. A persistent increase in left atrial pressure occurs, and a gradient develops across the MV, which elevates pulmonary capillary pressure with subsequent pulmonary hypertension.[15] Cardiac catheterization studies have shown a significant correlation between pulmonary artery systolic pressure and MVA. Pulmonary artery systolic pressure levels above 50 mm Hg are almost always associated with severe MS.[14] In this study, there was a significant negative correlation between MVA and the echocardiographic estimation of pulmonary artery systolic pressure based on tricuspid regurgitation velocity.

MS is associated with increased left atrial dilation and abnormal contractility secondary to a chronic increase in left atrial pressure. Large population-based studies have shown a strong association between left atrial size and the risk of the development of atrial fibrillation.[16,17] Patients suffering from MS with dilated left atria develop atrial fibrillation at a rate of 6.0% per annum.[9] Our results demonstrated a significant negative correlation between MVA and left atrial size in patients with atrial fibrillation. However, there was no significant difference in baseline left atrial size between patients with sinus rhythm and those with atrial fibrillation, indicating that

the presence of atrial fibrillation may better predict the severity of MS.

Limitations

In the current noninvasive, cross-sectional study, aimed at determining correlations between MVA and hemodynamic and echocardiographic findings, single-visit parameters were noted and correlated. Repeated measures could have yielded more robust results. Larger studies supplemented by invasive measures may confirm the correlations between these noninvasive parameters and MVA.

CONCLUSIONS

This study evaluated correlations between MVA and different echocardiographic and clinical parameters. The results showed positive correlations between MVA and body mass index, systolic blood pressure, diastolic blood pressure, and mean blood pressure, as well as negative correlations between MVA and heart rate, left atrial size, mean MVG, and pulmonary artery systolic pressure. Additionally, mean MVG had a significant correlation with MVA in all groups of patients. Our study results will help physicians, especially in low-income countries where the prevalence of rheumatic MS is high, to understand more about the relationship between different simple clinical and echocardiographic parameters to judge the severity of rheumatic MS.

Conflict of Interest

The authors declare that there is no conflict of interest.

Acknowledgments

We would like to express our sincere thanks to junior residents and nursing staff of the Cardiology Unit of Nobel Medical College Teaching Hospital for their support to collect data regarding the study participants.

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