Comparison of Clinical Characteristics, Natural History and Predictors of Disease Progression in Patients With Degenerative Mitral Stenosis Versus Rheumatic Mitral Stenosis

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Mitral annular calcification (MAC) is a common echocardiographic finding and an increasingly recognized cause of degenerative mitral stenosis (DMS). However, little is known about the clinical characteristics and disease progression in DMS, particularly in comparison with rheumatic mitral stenosis (RMS). We retrospectively reviewed 203 consecutive patients with mitral stenosis (113 with DMS and 90 with RMS) who underwent echocardiography at our institution between January 2014 and December 2017. We compared the clinical characteristics and disease progression between the 2 groups. In addition, we analyzed the predictors of disease progression (defined as annual progression rate of a mean gradient >0 mm Hg/year) among patients with DMS. Patients with DMS were significantly older and had higher prevalence of atherosclerotic comorbidities than those with RMS. During the median follow-up period of 2.2 years, the annual progression rates were comparable (0.8 ± 0.8 mm Hg/year in DMS vs 1.0 ± 1.2 mm Hg/year in RMS; p = 0.32) and were highly variable (0.0 to 3.5 mm Hg/year in DMS and 0.0 to 5.5 mm Hg/year in RMS) within both groups among disease progression. In DMS patients, atherosclerotic comorbidities and lower initial mean gradient were significantly associated with disease progression even after adjustment by age and sex. There was no significant difference in the disease progression according to the circumferential MAC severity determined by echocardiography among DMS. In conclusion, DMS disease progression was slow but highly variable, similar to that of RMS. In patients with DMS, the baseline MAC severity did not correlate with disease progression, suggesting the importance of follow-up echocardiography regardless of the MAC severity. **(Am J Cardiol 2021;143:118−124)**

Mitral annular calcification (MAC) is a common echocardiographic finding, particularly in elderly patients.[1−4] MAC is typically confined to the mitral annulus and basal leaflets; however, calcification sometimes extends further into the leaflet, resulting in restricted leaflet mobility and reduction of normal mitral annular dilatation. Indeed, some patients with MAC have significant mitral stenosis (MS), known as "degenerative MS (DMS)."[5−7] DMS prevalence is increasing and accounts for 13% of MS cases among patients in European countries.[8] A slow and variable disease progression of rheumatic MS (RMS) has been reported in previous studies,[9−12] but little is known regarding the natural history and predictors of disease progression among patients with DMS.[13,14] To date, there is no available data comparing the clinical course between patients with DMS and those with RMS in real-world practice. Accordingly, the aims of this study were to compare the clinical characteristics and disease progression between patients with DMS and those with RMS and to investigate the determinants of disease progression among patients with DMS.

Methods

We retrospectively reviewed the records of 203 consecutive patients with MS who underwent transthoracic echocardiography at our institution between January 2014 and December 2017. Patients who had an initial and follow-up echocardiography with a ≥6-month interval and had no prior or interim mitral valve intervention (such as mitral valve replacement, mitral valvuloplasty, percutaneous transvenous mitral commissurotomy, open mitral

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See page 124 for disclosure information.

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commissurotomy, and transcatheter edge-to-edge mitral valve repair) were included.[9] MS was defined as presence of a turbulent antegrade flow with a trans-mitral mean gradient of ≥2 mm Hg assessed by continuous wave Doppler echocardiography, according to previous reports.[15–17] Our study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and has been approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center (R-19078).

We obtained data on the patients' backgrounds, comorbid conditions, laboratory data, and oral prescriptions at the time of initial echocardiography. All echocardiographic findings were reviewed by at least 2 trained investigators and were obtained at rest, in stable conditions. MAC was defined as a bright echo-dense and band-like structure located at the junction between the left atrium and left ventricle.[1] DMS was diagnosed if the increased trans-mitral gradient was associated with MAC with normal or minimally reduced leaflet motion without tips restriction. RMS was defined as MS with tips restriction and thickening and restriction of leaflet mainly.[9,15,17] We defined circumferential MAC severity as mild (focal), moderate (marked density >1/3 but <1/2 of the mitral annulus), and severe (marked density involving >1/2 of the mitral annulus), based on a previous report.[15] The mitral valve area in the DMS group was assessed by either the direct planimetry or the continuity equation method whenever possible, whereas that in the RMS group was assessed by the pressure half time method in addition to these methods.[18] The degree of mitral, aortic, and tricuspid regurgitation was graded semiquantitatively as follows: 0 = none, 1+ = mild, 2+ = moderate, 3+ = moderately severe, and 4+ = severe. The left ventricular ejection fraction was assessed either visually or by the biplane disk summation method. The left atrial volume was also measured using the biplane disk summation method and was also normalized to the body surface area.[19]

The primary endpoint in this study was the annual disease progression rate among patients with DMS and RMS. We calculated the disease progression rate from the annual increase rate of the trans-mitral mean gradient. In order to estimate the impact of MS disease progression on the patients' prognosis, several specific clinical endpoints were also evaluated.[16] Hospitalization due to heart failure was identified as MS-related morbidity. For patients who died, deaths were classified as cardiovascular or non-cardiovascular based on information obtained from the family or medical records. Cardiovascular cause of death included stroke, myocardial infarction, heart failure, and cardiac arrhythmia (including sudden or unwitnessed death).

Continuous variables are expressed as mean ± standard deviation when normally distributed and as median and interquartile range when non-normally distributed. Comparison of differences between groups was performed using unpaired Student's t-test, Mann-Whitney's U test, or 1-way analysis of variance for continuous variables, and the chi-squared test or Fisher's exact test for dichotomous variables, as appropriate. First, we divided the entire cohort of patients with MS into 2 groups according to the etiology (DMS and RMS group) and we compared the clinical backgrounds, echocardiographic parameters, and the disease progression rate between the groups. We further investigated the disease progression rate among patients with disease progression defined as below between the 2 groups. In addition, propensity score matching using the nearest-neighbor matching method was constructed by logistic regression modeling, adjusting for age, sex and initial mean trans-mitral pressure gradient between the groups. Matching was performed in a 1:1 ratio without replacement with caliper of 0.25 × standard deviation. As a sensitivity analysis, we analyzed the patients with an initial mean pressure gradient ≥ 5 mm Hg. Second, we investigated the predictors of disease progression (defined as an annual progression rate of more than 0 mm Hg/year) using logistic regression analysis among patients with DMS. A multivariable logistic regression analysis was performed for the independent determinants of disease progression using the following 2 models: model 1—adjusted by age and sex for independent variables on univariable analysis, and model 2—adjusted by variables with a threshold p value of 0.05 in the univariable analysis. In addition, we further investigated the association between the baseline MAC severity and the annual disease progression rate. Finally, Kaplan-Meier survival plots were constructed by dividing the patients according to the presence or absence of disease progression. All tests were 2-tailed and a value of $p < 0.05$ was considered statistically significant. All analyses were performed with JMP version 14 (SAS Institute, Cary, North Carolina) and Stata MP64 version 15 (StataCorp, College Station, Texas).

Results

A total of 203 patients with MS were included; 113 with DMS and 90 with RMS. The patients' baseline characteristics and echocardiographic parameters are shown in Table 1. Patients in the DMS group were significantly older (DMS; mean age: 80 ± 8, range: 54 to 99 years vs RMS; mean age: 71 ± 9, range: 45 to 91 years). The DMS group had a higher prevalence of hypertension, coronary artery disease and aortic stenosis, and a higher plasma B-type natriuretic peptide level and a lower estimated glomerular filtration rate than those in the RMS group (all $p < 0.01$). The initial trans-mitral mean pressure gradient was slightly albeit significantly lower in patients in the DMS group.

The propensity score-matched cohort adjusted for age, sex, and initial mean gradient is shown in Table 2. Even after adjustment for these variables, patients with DMS had a higher prevalence of hypertension, higher plasma B-type natriuretic peptide level, lower prevalence of atrial fibrillation, and lower hemoglobin level than those with RMS. Regarding the echocardiographic parameters, patients with DMS had a greater wall thickness, higher left ventricular ejection fraction, and lower left atrial volume index than those with RMS.

The median period between the initial and last follow-up echocardiography was 2.2 years (interquartile range 1.2 to 3.0 years). Disease progression during the follow-up period was seen in 56 (50%) patients in the DMS group and 49 (54%) in the RMS group ($p = 0.49$). The annual progression rate among the entire cohort was comparable between the groups (0.0 ± 1.5 vs 0.3 ± 1.2 mm Hg/year; $p = 0.12$). The annual progression rate of MS among patients with disease

Table 1
Baseline characteristics in patients with DMS and RMS

Variable	DMS (n = 113)	RMS (n = 90)	p value
Age (years)	80 ± 8	71 ± 9	<0.01
Women	85 (75%)	55 (61%)	0.03
Body mass index (kg/m^2)	22.7 ± 3.6	22.1 ± 3.1	0.24
Hypertension	92 (81%)	42 (48%)	<0.01
Diabetes mellitus	42 (37%)	24 (28%)	0.15
Dyslipidemia	65 (58%)	39 (45%)	0.07
Chronic kidney disease	73 (70%)	51 (63%)	0.30
Coronary artery disease	42 (37%)	11 (13%)	<0.01
Atrial fibrillation	40 (35%)	57 (65%)	<0.01
B-type natriuretic peptide (pg/mL)	254 (129, 427)	121 (85, 211)	<0.01
Estimated GFR (mL/min/1.73 m^2)	48 (35, 63)	57 (45, 71)	<0.01
Hemoglobin (g/dL)	11.6 ± 1.7	12.9 ± 1.6	<0.01
LDL-Cholesterol (mg/dL)	100 ± 29	110 ± 30	0.02
HbA1c (%)	6.0 ± 0.9	6.1 ± 0.8	0.72
Calcium (mg/dL)	9.3 ± 0.5	9.3 ± 0.5	0.45
Phosphorus (mg/dL)	3.8 ± 0.6	3.5 ± 0.6	0.03
<Echocardiographic parameters>			
Heart rate (beats/min)	67 ± 11	68 ± 11	0.83
Mean PG of mitral valve (mm Hg)	3.9 ± 1.9	4.5 ± 1.7	0.02
MVA by PHT (cm^2)*		1.8 ± 0.6	
MVA by planimetry (cm^2)†	1.6 ± 0.8	1.6 ± 0.5	0.90
MVA by continuity equation (cm^2)‡	1.6 ± 0.5	1.4 ± 0.3	0.37
Septal wall thickness (mm)	10 ± 2	9 ± 2	<0.01
Posterior wall thickness (mm)	10 ± 2	9 ± 2	<0.01
LV end-diastolic dimension (mm)	45 ± 6	49 ± 6	<0.01
LV ejection fraction (%)	61 ± 9	58 ± 7	<0.01
Left atrial volume index (ml/m^2)	68 ± 24	85 ± 35	<0.01
Trans-aortic peak velocity (m/s)§	3.5 ± 1.2	2.8 ± 1.0	≤0.01
≥4.0 m/s (%)	26 (37%)	4 (10%)	≤0.01
Mitral regurgitation 3+/4+	2 (2%)	11 (12%)	<0.01
PG of tricuspid regurgitation (mm Hg)	31 ± 10	28 ± 11	0.04
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ACEI/ARB	55 (49%)	28 (32%)	0.02
Beta-blocker	49 (44%)	25 (29%)	0.03
Warfarin	23 (21%)	54 (61%)	<0.01
NOAC	9 (8%)	3 (3%)	0.16
Statin	57 (51%)	24 (28%)	<0.01
Antidiabetic agents	31 (28%)	15 (17%)	0.08

ACEI = angiotensin converting enzyme inhibitors; ARB = angiotensin II receptor blockers; DMS = degenerative mitral stenosis; GFR = glomerular filtration rate; LDL = low density lipoprotein; LV = left ventricular; MVA = mitral valve area; NOAC = novel oral anticoagulants; PG = pressure gradient; PHT = pressure half time; RMS = rheumatic mitral stenosis.

Continuous variables are presented as mean ± SD if normally distributed, and median (interquartile range) if not normally distributed. Categorical variables are presented as number of patients (%).

* data available 89 in RMS.

† data available 7 in DMS and 40 in RMS.

‡ data available 14 in DMS and 13 in RMS.

§ data available 71 in DMS and 39 in RMS.

progression is shown in Figure 1. The annual progression rate was also comparable between the DMS and RMS groups and varied among individuals. In a subgroup of patients with a trans-mitral mean gradient ≥ 5 mm Hg, the disease progression was also comparable between the DMS and RMS groups (0.7 ± 0.7 vs 0.6 ± 0.6 mm Hg/year; p = 0.51). The annual progression rate adjusted by age, sex, and initial mean gradient among patients with disease progression is shown in Figure 2. The annual progression rate was still comparable between the groups (0.7 ± 0.7 vs 1.2 ± 1.3 mm Hg/year; p = 0.08).

The predictors of disease progression among patients with DMS are shown in Table 3. After adjustment by age and sex (model 1), dyslipidemia, coronary artery disease, HbA1c level, and initial mean gradient were associated with disease progression. In model 2, initial trans-mitral mean gradient was an independent predictor for disease progression. There was no significant difference in the annual progression rate regardless of the MAC severity graded by the circumferential extent among patients with disease progression (mild: 0.8 ± 0.7, moderate: 0.7 ± 0.8, and severe: 0.8 ± 0.8 mm Hg/year; p = 0.90) (Figure 3).

Table 2
Comparison of patients with DMS and RMS adjusted for age, sex, and initial mean trans-mitral gradient

Variable	DMS (n = 47)	RMS (n = 47)	p value
Age (years)	74 ± 7	75 ± 8	0.40
Women	28 (60%)	28 (60%)	1.00
Body mass index (kg/m^2)	23.5 ± 3.9	21.8 ± 3.2	0.02
Hypertension	39 (83%)	28 (61%)	0.02
Diabetes mellitus	19 (40%)	19 (41%)	0.93
Dyslipidemia	23 (49%)	22 (48%)	0.91
Chronic kidney disease	33 (73%)	33 (72%)	0.86
Coronary artery disease	17 (36%)	9 (20%)	0.07
Atrial fibrillation	18 (38%)	31 (67%)	<0.01
B-type natriuretic peptide (pg/mL)	250 (126, 433)	139 (99, 272)	0.04
Estimated GFR (mL/min/1.73 m^2)	45 (9, 62)	51 (39, 63)	0.06
Hemoglobin (g/dL)	11.9 ± 1.7	12.7 ± 1.7	0.02
LDL-Cholesterol (mg/dL)	103 ± 34	110 ± 31	0.36
HbA1c (%)	6.0 ± 1.0	6.2 ± 0.7	0.34
<Echocardiographic parameters>			
Heart rate (beats/min)	67 ± 9	67 ± 12	0.80
Mean PG of mitral valve (mm Hg)	4.2 ± 2.0	4.2 ± 1.5	0.93
Septal wall thickness (mm)	10 ± 2	9 ± 2	0.02
Posterior wall thickness (mm)	11 ± 2	9 ± 2	<0.01
LV end-diastolic dimension (mm)	48 ± 6	48 ± 6	0.57
LV ejection fraction (%)	61 ± 9	57 ± 8	0.03
Left atrial volume index (ml/m^2)	69 ± 24	81 ± 33	0.04
Mitral regurgitation 3+/4+ (%)	1 (2%)	5 (11%)	0.20
PG of tricuspid regurgitation (mm Hg)	31 ± 11	27 ± 8	0.06
<Oral prescription>			
ACEI/ARB	22 (47%)	16 (35%)	0.24
Beta-blocker	20 (43%)	15 (33%)	0.32
Warfarin	11 (23%)	29 (62%)	<0.01
NOAC	3 (6%)	1 (2%)	0.30
Statin	23 (49%)	15 (33%)	0.11
Antidiabetic agents	13 (28%)	12 (26%)	0.86

ACEI = angiotensin converting enzyme inhibitors; ARB = angiotensin II receptor blockers; DMS = degenerative mitral stenosis; GFR = glomerular filtration rate; LDL = low density lipoprotein; LV = left ventricular; MS = mitral stenosis; NOAC = novel oral anticoagulants; PG = pressure gradient; RMS = rheumatic mitral stenosis.

Continuous variables are presented as mean ± SD if normally distributed, and median (interquartile range) if not normally distributed. Categorical variables are presented as number of patients (%).

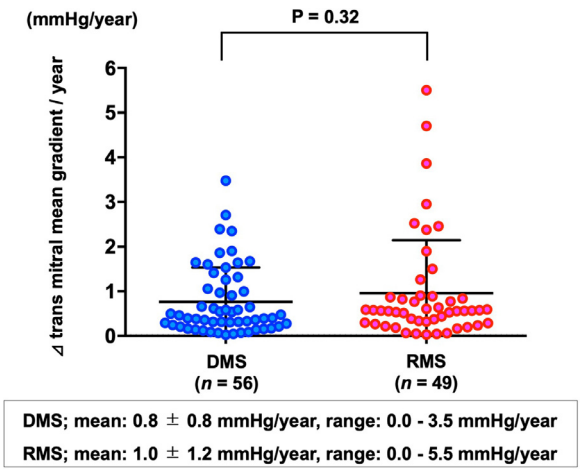

Figure 1. Annual progression rate of trans-mitral mean gradient in DMS and RMS patients. DMS = degenerative mitral stenosis; RMS = rheumatic mitral stenosis.

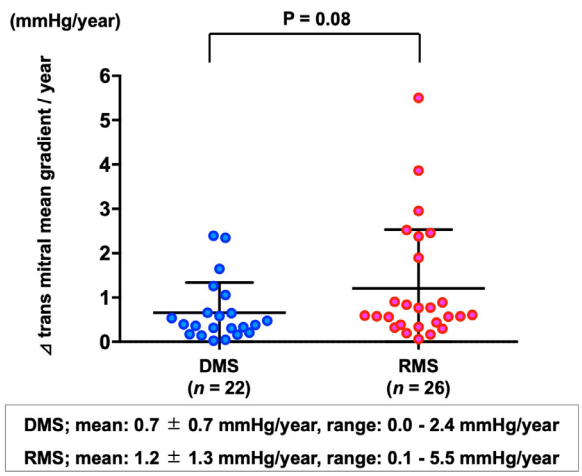

Figure 2. Annual progression rate of trans-mitral mean gradient in DMS and RMS patients adjusted for age, sex and initial mean gradient. DMS = degenerative mitral stenosis; RMS = rheumatic mitral stenosis.

Table 3
Determinants of disease progression among DMS group

Variable	Univariable analysis		Multivariable analysis (model 1)		Multivariable analysis (model 2)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Age (/1 year)	0.97 (0.92-1.01)	0.18				
Female sex	0.81 (0.34-1.90)	0.62				
Hypertension	2.28 (0.86-6.50)	0.10				
Diabetes mellitus	2.22 (1.03-4.92)	0.04	2.06 (0.94-4.64)	0.07	1.07 (0.34-3.39)	0.91
Dyslipidemia	2.35 (1.10-5.11)	0.03	2.47 (1.15-5.47)	0.02	1.67 (0.58-4.88)	0.34
Chronic kidney disease	2.15 (0.91-5.06)	0.08				
Coronary artery disease	2.61 (1.18-5.74)	0.02	2.58 (1.16-5.92)	0.02	1.24 (0.44-3.49)	0.68
B-type natriuretic peptide (/1 pg/ml)	1.00 (0.99-1.00)	0.82				
Estimated GFR (/1 mL/min/1.73 m^2)	0.99 (0.97-1.01)	0.27				
LDL cholesterol (/1 mg/dL)	1.00 (0.99-1.02)	0.64				
HbA1c (/1 %)	2.28 (1.28-4.59)	<0.01	2.25 (1.23-4.64)	<0.01	1.95 (0.87-4.98)	0.11
Calcium (/1 mg/dL)	0.91 (0.45-1.84)	0.78				
Phosphorus (/1 mg/dL)	1.54 (0.76-3.13)	0.22				
Beta-blocker	1.44 (0.68-3.07)	0.34				
Statin	1.43 (0.68-3.03)	0.34				
Mean PG of mitral valve (/1 mm Hg)	0.69 (0.51-0.88)	<0.01	0.69 (0.52-0.90)	<0.01	0.64 (0.45-0.86)	<0.01
Septal wall thickness (/1 mm)	1.16 (0.97-1.40)	0.10				
LV end-diastolic dimension (/1 mm)	1.05 (0.98-1.12)	0.15				
LV ejection fraction (/1 %)	1.01 (0.97-1.06)	0.59				
Trans-aortic peak velocity (/1 m/s)	0.94 (0.64-1.39)	0.77				

CI = confidence interval; DMS = degenerative mitral stenosis; GFR = glomerular filtration rate; LDL = low-density lipoprotein; LV = left ventricular; OR = odds ratio; PG = pressure gradient.

Model 1 was adjusted by age and sex for variables with a p value <0.05 on univariable analysis.

Model 2 was adjusted by variables with a threshold p value of 0.05 on univariate analysis.

During a median follow-up period of 4.0 years (interquartile range 2.7 to 4.8 years), there was no significant difference with regard to hospitalization due to heart failure between the DMS and RMS groups (29 patients [26%] vs 26 patients [29%], log-rank; p = 0.61). However, among patients with DMS, those with disease progression had a higher incidence of hospitalization due to heart failure than those without disease progression (19 patients [34%] vs 10 patients [18%], p = 0.046). The Kaplan-Meier curve analysis demonstrated that the disease progression group tended to have a higher incidence of hospitalization due to heart failure than the non-progression group (log-rank; p = 0.07) (Figure 4). Nonetheless, the disease progression was not associated with all-cause death (log-rank; p = 0.88) and cardiovascular death (log-rank; p = 0.38).

Discussion

In this study, we investigated the clinical characteristics, natural history, and predictors of disease progression in DMS and RMS. Serial echocardiographic analysis revealed

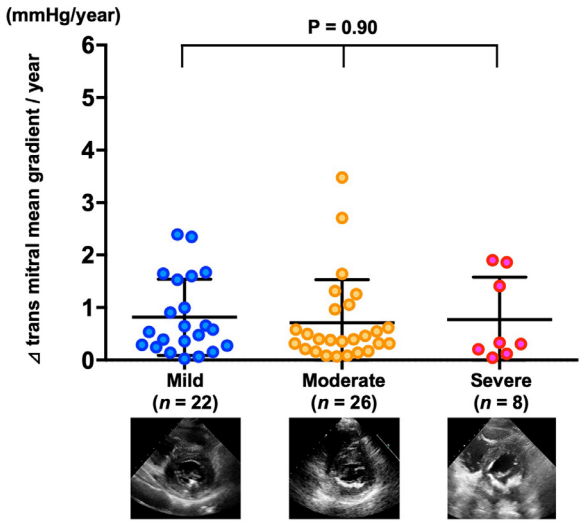

Figure 3. Relationship between severity of mitral annular calcification and disease progression in patients with degenerative mitral stenosis.

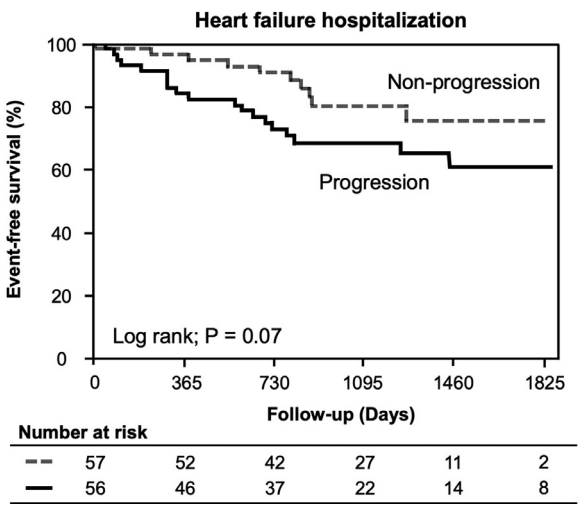

Figure 4. Kaplan-Meier curve analysis for the hospitalization due to heart failure among patients with disease progression and those without.

the following findings. First, the disease progression in DMS was generally slow and similar to that in RMS, but highly variable among individuals. Second, the presence of atherosclerotic factors and lower initial trans-mitral mean gradient, but not the MAC severity, were associated with disease progression in the DMS group.

There is paucity of evidence regarding the comparison of the clinical characteristics and disease progression between patients with DMS and those with RMS. This study showed that patients with DMS had a higher incidence of atherosclerotic comorbidities but a lower rate of atrial fibrillation than those with RMS, and also revealed the echocardiographic characteristics of patients with DMS and RMS. These findings were consistent with the pathophysiological mechanisms, which are that DMS might be induced by a degenerative calcific process due to atherosclerotic risk factors and RMS might be concurrent with atrial and ventricular remodeling.[17,20]

In addition, we demonstrated that the annual progression rate of the trans-mitral mean gradient among patients with DMS was similar to that among patients with RMS even after adjustment for age, sex, and initial mean gradient. RMS was generally characterized with a slow progression, as already shown in previous studies.[9−11] Slow DMS disease progression, comparable to that of RMS, was an interesting finding of our study, suggesting that degenerative mitral valve change might be as gradual as rheumatic valve change. Furthermore, we found a wide variation of disease progression in both patient groups. Although the precise mechanism of the variable disease progression among individuals was unknown, this phenomenon has been also noted in calcific aortic stenosis.[21,22]

In this study, the progression of DMS was inversely associated with the mean trans-mitral gradient at baseline. Regarding disease progression in RMS, the rate of progression was reportedly higher in patients with a larger initial mitral valve area.[10,11] The speculated mechanism was that the severely narrowed mitral valve did not have much leaflet tissues available for further damage. Conversely, those with mild stenosis might have remaining normal valve leaflets that could be further traumatized. These mechanisms would also be applicable to the DMS progression. However, investigations of the association between the disease progression and initial MS severity have conflicting results not only for RMS,[9−11] but also DMS,[16,23] and further studies are strongly warranted. With regard to the atherosclerotic risk factors, these have been recognized as a strong risk for developing MAC,[20,24,25] and could be a predictor of disease progression; however, there are few studies addressing the correlation between the atherosclerotic risk factors and the progression of DMS. The possible association between them, as was shown in our study, implies the importance of controlling these factors for preventing the progression of DMS.

Previous studies addressing the disease progression in DMS focused on the population noted to have severe MAC,[16,23] whereas we analyzed a population with varying severity of MAC and demonstrated that MAC severity did not correlate with the disease progression in DMS. Previous studies suggested that the calcific extension onto the mitral leaflet and the reduction of normal mitral annular dilation during diastole, irrespective of MAC severity, were responsible for producing a significant mitral valve gradient.[7,26] Although a recent study reported that severe MAC was associated with rapid disease progression,[27] considering the underlying pathophysiology and our results, there might be a possibility that the stenosis might progress in some patients with DMS with nonsevere MAC, if the MAC dominantly extends onto the leaflet. Therefore, our results may highlight the importance of follow-up echocardiography for patients with DMS regardless of the baseline MAC severity.

Several limitations should be noted in this study. First, it was a retrospective and observational study with a relatively small sample size. In addition, as all subjects were Japanese, the results might not be applicable to the populations of other countries and ethnicities. Second, the follow-up period in our study was relatively short considering the progression rate among patients with MS, although it was comparable to those in previous studies.[16,23] Third, in some patients, we had difficulty in completely distinguishing the RMS and DMS groups. The mitral valve calcification may be seen in patients with RMS as a result of degenerative changes, particularly in elderly patients, and DMS patients with relatively deformed leaflet might be enrolled in RMS group. Fourth, we evaluated the severity of MS according to the mitral valve gradient, as we could not obtain sufficient data about the mitral valve area.

In conclusion, the progression of DMS was highly variable, but generally slow, similar to that of RMS. The initial mean gradient was inversely associated with disease progression, and the baseline circumferential MAC severity did not correlate with the progression of DMS, suggesting the importance of follow-up echocardiography regardless of the MAC severity and initial mean gradient.

Authors' Contributions

Naoto Kuyama: conceptualization, methodology, formal analysis, investigation, resources, writing - original draft, Yasuhiro Hamatani: conceptualization, methodology, validation, investigation, resources, writing − review & editing, Atsushi Okada: investigation, resources, writing − review & editing, Yuki Irie: investigation, resources, writing − review & editing, Michikazu Nakai: investigation, resources, writing − review & editing, Hiroyuki Takahama: investigation, resources, writing − review & editing, Yoshiki Yanagi: investigation, resources, Yoshito Jo: investigation, resources, Hideaki Kanzaki: investigation, resources, Satoshi Yasuda: investigation, resources, writing − review & editing, supervision, Kenichi Tsujita: review & editing, supervision, Chisato Izumi: investigation, resources, writing − review & editing, supervision.

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Disclosures

The authors have no conflicts of interest to disclose

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