

Clinical and echocardiographic differences between rheumatic and degenerative mitral stenosis

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ABSTRACT

Introduction: Degenerative mitral stenosis (DMS) is frequently cited as increasing in prevalence in the developed world, although comparatively little is known about DMS in comparison to rheumatic mitral stenosis (RMS).

Method: A retrospective observational study was conducted on 745 cases of native-valve mitral stenosis (MS) with median follow-up time of 7.25 years. Clinical and echocardiographic parameters were compared. Univariate and multivariate Cox regression analyses were performed for a composite of all-cause mortality and heart failure hospitalisation.

Results: Patients with DMS compared to RMS were older (age, mean $\pm$ standard deviation: 69.6 ± 12.3 versus [vs] 51.6 ± 14.3 years, respectively; $P < 0.001$) and a greater proportion had medical comorbidities such as diabetes mellitus (78 [41.9%] vs 112 [20.0%], $P < 0.001$). The proportion of cases of degenerative aetiology increased from 1.1% in 1991–1995 to 41.0% in 2016–2017. In multivariate analysis for the composite outcome, age (hazard ratio [HR] 95% confidence interval [CI] of 1.032 [1.020–1.044]; $P < 0.001$), diabetes mellitus (HR 1.443, 95% CI 1.068–1.948; $P = 0.017$), chronic kidney disease (HR 2.043, 95% CI 1.470–2.841; $P < 0.001$) and pulmonary artery systolic pressure (HR 1.019, 95% CI 1.010–1.027; $P < 0.001$) demonstrated significant independent associations. The aetiology of MS was not independently associated with the composite outcome.

Conclusions: DMS is becoming an increasingly common cause of native-valve MS. Despite numerous clinical differences between RMS and DMS, the aetiology of MS did not independently influence a composite of mortality or heart failure hospitalisation.

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Keywords: calcific mitral stenosis, degenerative mitral stenosis, mitral stenosis, rheumatic heart disease, valvular heart disease

CLINICAL IMPACT

What is New

- This is the first study to our knowledge, to demonstrate a longitudinal change in the epidemiology of mitral stenosis (MS) from rheumatic to degenerative aetiologies in a developed country.
- The aetiology of MS was not independently associated with adverse clinical outcomes in this study.

Clinical Implications

- There is an increasing need to develop effective treatment options for the growing group of patients with degenerative MS, which is not well understood at present.

INTRODUCTION

Mitral stenosis (MS) commonly arises from either rheumatic heart disease or a degenerative calcification of the mitral valve (MV) apparatus.¹ Rheumatic heart disease is overall the leading cause of valvular heart disease in the developing world, and rheumatic MS (RMS), with its association with rheumatic fever, remains prevalent in developing countries.^{1–3} In contrast, incidence of rheumatic heart disease is declining in developed countries.^{4,5} However, degenerative causes of MS have become increasingly prevalent in developed countries, in concert with increased life expectancy and related comorbidities.⁵

The pathophysiology as well as echocardiographic features and clinical sequelae of RMS are well known, in which valve thickening and commissural fusion together with involvement of

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the subvalvular apparatus develop as a sequel to rheumatic fever.⁶ In contrast, degenerative MS (DMS) arises from a different disease process involving extensive mitral annular calcification (MAC), which is a non-inflammatory, chronic and degenerative process involving the fibrous base of the MV.⁷ MAC gives rise to MS when it causes progressive restriction in valve mobility and limitation of physiological mitral annular diastolic dilatation.^{5,8} MAC is known to be associated with cardiovascular comorbidities, coronary calcification as well as chronic kidney disease, and has been identified as a risk factor for mortality.⁹⁻¹³ On the whole, patients with DMS are therefore typically elderly with a high burden of comorbidities.¹⁴ Contemporary guidelines recognise the significant pathophysiological and clinical differences between RMS and DMS, and recommend a predominantly medical strategy over intervention for patients with DMS due to high procedural and surgical risks.¹⁵ Overall, the natural history, comparative differences and treatment strategies for DMS versus RMS remain an area of active investigation. We sought to investigate the differences in clinical and echocardiographic parameters for DMS and RMS, clarify changing patterns in the incidence of DMS and RMS, and identify risk factors for clinically relevant outcomes in patients with MS.

METHOD

A retrospective observational study was conducted on a cohort of 745 unique cases of native-valve MS from a multi-ethnic Asian population. The cases were identified from a database of patients who underwent transthoracic echocardiography at the National University Heart Centre, Singapore between a time period of 1991 to 2017. The research protocol was approved by the National Healthcare Group Domain Specific Review Board (2021/00603). The study conforms to the ethical principles laid out in the 1975 Declaration of Helsinki.

The aetiology of MS was determined by the reporting echocardiographer at the time of study. In ambiguous cases, a blinded investigator (CHS) adjudicated the aetiology; rheumatic aetiology was determined based on the presence of changes, such as restricted leaflet mobility, doming of the MV leaflets and commissural fusion. A degenerative aetiology was determined by the absence of the above changes with the presence of MAC and evidence of MV stenosis. The first echocardiogram within the study period, which disclosed the presence of MS, was labelled as the index echocardiogram. Baseline clinical data as well as echocardiographic parameters were collected

from the electronic medical record. Outcome data pertaining to all-cause mortality and heart failure hospitalisation were recorded from follow-up encounters and hospitalisations where relevant, and a composite of the 2 outcomes was constructed. The last identified follow-up encounter was determined as the endpoint to calculate the duration of follow-up. During collection of clinical and outcomes data, investigators were blinded as to the aetiology of MS. Data collection was performed up to 31 October 2020.

To identify associations with the composite outcomes, univariate Cox regression analyses were systematically performed using clinical and echocardiographic variables for the groups with RMS and DMS separately. Thereafter, we constructed multivariate Cox regression models incorporating all parameters found to be statistically significant in univariate analysis together with age and sex as biologically important variables.

Continuous variables are presented as mean $\pm$ standard deviation (SD), and categorical variables as frequency and percentages. Continuous variables were analysed with the independent-samples t-test and categorical variables by the chi-square test. Univariate and multivariate survival analyses was performed using multivariate Cox models for the composite outcome. *P* value less than 0.05 were interpreted as statistically significant; 95% confidence intervals (CIs) are presented where relevant. Statistical analysis was performed with IBM SPSS Statistics version 23 (IBM Corp, Armonk, NY, US).

RESULTS

Our study presents data for 745 unique patients with native-valve MS, of whom 559 patients (75.0%) had RMS and 186 patients (25.0%) had DMS. The median time of follow-up duration was 7.25 years (interquartile range: 3.84–14.1 years).

Patients with DMS, compared to those with RMS, were older (mean $\pm$ SD: 69.6 $\pm$ 12.3) versus [vs] 51.6 $\pm$ 14.3 years, respectively; *P*<0.001), with higher body mass index (24.9 $\pm$ 4.9 vs 24.0 $\pm$ 4.9 kg/m², respectively; *P*=0.023) and systolic blood pressure (142.8 $\pm$ 26.0 vs 126.8 $\pm$ 22.3 mmHg, respectively; *P*<0.001). There were no significant differences in proportion of sexes between the 2 groups of patients (*P*=0.190).

In our study, patients with DMS were more likely to have comorbidities including hypertension (147 [79.0%] vs 194 [34.7%]; *P*<0.001), hyperlipidaemia (122 [65.6%] vs 170 [30.4%]; *P*<0.001), diabetes mellitus (78 [41.9%] vs 112 [20.0%]; *P*<0.001). A greater proportion of those with

Table 1. Baseline demographic and clinical parameters for patients with rheumatic mitral stenosis compared to degenerative mitral stenosis.

Variables	Overall (n=745)	RMS (n=559)	DMS (n=186)	P value
Age, mean $\pm$ SD, years	56.1 $\pm$ 15.9	51.6 $\pm$ 14.3	69.6 $\pm$ 12.3	<0.001
Female sex, no. (%)	512 (68.7)	377 (67.4)	135 (72.6)	0.190
Ethnicity, no. (%)				0.007
Chinese	459 (61.6)	341 (61.0)	118 (63.4)	
Malay	158 (21.2)	120 (21.5)	38 (20.4)	
Indian	65 (8.7)	41 (7.3)	24 (12.9)	
Caucasian	3 (0.4)	2 (0.4)	1 (0.5)	
Non-local ethnicity	60 (8.1)	55 (9.8)	5 (2.7)	
Height, mean $\pm$ SD, cm	157 $\pm$ 9	158 $\pm$ 9	154 $\pm$ 9	<0.001
Body mass index, mean $\pm$ SD, kg/m ²	24.2 $\pm$ 4.9	24.0 $\pm$ 4.9	24.9 $\pm$ 4.9	0.023
Body surface area, mean $\pm$ SD, m ²	1.61 $\pm$ 0.20	1.62 $\pm$ 0.20	1.59 $\pm$ 0.20	0.119
Systolic blood pressure, mean $\pm$ SD, mmHg	131.5 $\pm$ 24.6	126.8 $\pm$ 22.3	142.8 $\pm$ 26.0	<0.001
Hypertension, no. (%)	341 (45.8)	194 (34.7)	147 (79.0)	<0.001
Hyperlipidaemia, no. (%)	292 (39.2)	170 (30.4)	122 (65.6)	<0.001
Diabetes mellitus, no. (%)	190 (25.5)	112 (20.0)	78 (41.9)	<0.001
Ischaemic heart disease, no. (%)	159 (21.3)	81 (14.5)	78 (41.9)	<0.001
Stroke or transient ischaemic attack, no. (%)	106 (14.2)	71 (12.7)	35 (18.8)	0.039
Heart failure, no. (%)	162 (21.7)	122 (21.8)	40 (21.5)	0.927
Atrial fibrillation, no. (%)	337 (45.2)	293 (52.4)	44 (23.7)	<0.001
Chronic kidney disease, no. (%)	110 (14.8)	45 (8.1)	65 (34.9)	<0.001
Peripheral vascular disease, no. (%)	28 (3.8)	11 (2.0)	17 (9.1)	<0.001
Asthma or COPD, no. (%)	66 (8.9)	43 (7.7)	23 (12.4)	0.52
Antiplatelet usage, no. (%)	228 (30.6)	123 (22.0)	105 (56.5)	<0.001
Anticoagulation usage, no. (%)	298 (40.0)	266 (47.6)	32 (17.2)	<0.001
Beta-blocker usage, no. (%)	321 (43.1)	228 (40.8)	93 (50.0)	0.028
ACEI or ARB usage, no. (%)	213 (28.6)	128 (22.9)	85 (45.7)	<0.001
Calcium channel blocker usage, no. (%)	132 (17.7)	57 (10.2)	75 (40.3)	<0.001
Diuretic usage, no. (%)	231 (31.0)	175 (31.3)	56 (30.1)	0.760
Statin usage, no. (%)	294 (39.5)	175 (31.3)	119 (64.0)	<0.001
MRA usage, no. (%)	24 (3.2)	16 (2.9)	8 (4.3)	0.336
Digoxin usage, no. (%)	211 (28.3)	199 (35.6)	12 (6.5)	<0.001
Antiarrhythmic usage, no. (%)	22 (3.0)	17 (3.0)	5 (2.7)	0.805

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor; COPD: chronic obstructive pulmonary disease; DMS: degenerative mitral stenosis; MRA: mineralocorticoid receptor antagonist; RMS: rheumatic mitral stenosis; SD: standard deviation
P values in bold are statistically significant.

DMS had ischaemic heart disease (78 [41.9%] vs 81 [14.5%]; $P<0.001$), stroke or transient ischaemic attack (35 [18.8%] vs 71 [12.7%]; $P=0.039$), chronic kidney disease (65 [34.9%] vs 45 [8.1%]; $P<0.001$). Conversely, patients with RMS were more likely to have co-existing atrial fibrillation compared to those with DMS (293 [52.4%] vs 44 [23.7%]; $P<0.001$). The baseline demographic and clinical parameters for the 2 groups of patients are presented in Table 1.

Table 2 presents echocardiographic data for the 2 groups. Patients with DMS had a higher left ventricular ejection fraction (mean $\pm$ SD: 60.9 ± 12.1 vs 56.9 ± 11.1 ; $P<0.001$), with a smaller left atrial volume index (46.6 ± 21.2 vs 65.4 ± 33.2 mL/m²; $P<0.001$) and lower pulmonary artery systolic pressure (PASP) (42.2 ± 13.5 vs 46.5 ± 16.7 mmHg; $P=0.002$). The MV area by planimetry was also larger (1.69 ± 0.44 vs 1.44 ± 0.49 cm²; $P<0.001$) with a lower MV mean pressure gradient (4.87 ± 2.06 vs 7.41 ± 3.89 ; $P<0.001$). While the left-ventricular outflow tract time-velocity integral was greater in patients with DMS compared to RMS (22.9 ± 6.3 vs 18.9 ± 6.0 cm; $P<0.001$), ultimately there were no significant differences in stroke volume (60.5 ± 20.6 vs 64.3 ± 22.9 mL; $P<0.001$).

Regarding concomitant valve disease, patients with DMS were more likely to have moderate-or-greater aortic stenosis (42 [22.6%] vs 72 [12.9%]; $P=0.001$). Conversely more patients with RMS compared to DMS had moderate-or-greater mitral regurgitation (129 [23.1%] vs 19 [10.2%]; $P<0.001$) and aortic regurgitation (67 [12.0%] vs 6 [3.2%]; $P<0.001$). Between the 2 aetiologies, the prevalence of tricuspid regurgitation was not significantly different (RMS: 23.1% vs DMS: 17.2%; $P=0.092$).

Fig. 1 pictorially represents the longitudinal changes in the relative incidence of RMS and DMS, expressed in intervals of 5 years each (except for 2016 to 2017). From 1991 to 2000, nearly all cases of native-valve MS were rheumatic in aetiology. Thereafter, degenerative cases of MS steadily increased as a proportion of the total number of newly diagnosed cases of MS within each subsequent time period, with 41.0% of all cases of MS from 2016 to 2017 being degenerative in aetiology.

In total, 366 (49.1%) events for the composite outcome were recorded during follow-up. Of these, 288 (38.7%) were deaths while 151 (20.3%) represented heart failure hospitalisation. The results of univariate and multivariate Cox regression analysis are presented in Table 3. While the aetiology of MS was significant on univariate analysis for the composite outcome, it was not independently associated with outcomes ($P=0.100$). Instead, the factors that were independently

associated with outcomes in multivariate analysis were age ($P<0.001$; hazard ratio [HR] 1.032, 95% CI 1.020–1.044), diabetes mellitus ($P=0.017$; HR 1.443, 95% CI 1.068–1.948), chronic kidney disease ($P<0.001$; HR 2.043, 95% CI 1.470–2.841), and PASP ($P<0.001$; HR 1.019, 95% CI 1.010–1.027).

DISCUSSION

In summary, our results show that patients with DMS tended to be older with a higher burden of medical comorbidities compared to those with RMS. In the period from 1991 to 2017, the proportion of newly diagnosed cases of MS due to degenerative aetiologies increased while those of RMS decreased, and the aetiology of MS was not independently associated with our composite outcome of all-cause mortality or hospitalisation for heart failure.

The associations of DMS with metabolic conditions and atherosclerotic cardiovascular disease are similar to those previously reported in the literature.^{9–12} Our findings are most directly comparable to 2 relevant studies: a 2009 single-centre cohort study of 70 patients in the UK by Akram et al. and a 2020 cohort study by Pressman et al. comparing 115 American DMS patients with 510 Korean RMS patients.^{16,17} Akram et al. found that DMS patients were more likely to have hypertension and hyperlipidaemia but found no significant differences in age, diabetes mellitus or renal function; other clinical information was not presented.¹⁶ Pressman et al. found a similar association between DMS and older age, presence of hypertension, diabetes mellitus as well as chronic kidney disease.¹⁷ Our finding that RMS is associated with atrial fibrillation was also observed in the study by Pressman et al.¹⁷ Data comparing the prescription or use of medications for DMS and RMS patients were not previously available in the literature to our knowledge.

Pressman et al. also demonstrated a smaller MV area, greater MV mean pressure gradient and larger left atrial volume index in patients with RMS, though conversely it found a lower PASP in such patients despite these relationships.¹⁷ In our cohort, patients with RMS tended to have more severe MS with smaller MV area by planimetry and pressure half-time. An important caveat is that MV area measurements in patients with DMS should be interpreted with caution as traditional echocardiographic measurements for MV area are extrapolated from RMS and not validated in the DMS population.¹⁸ It is often challenging to planimeter the narrowest flow limiting orifice in DMS, which typically occurs at the base of the

Table 2. Comparison of echocardiographic parameters for patients with rheumatic mitral stenosis versus degenerative mitral stenosis.

Variable	Overall (n=745)	RMS (n=559)	DMS (n=186)	P value
Left atrial volume index, mean $\pm$ SD, mL/m ²	59.1 $\pm$ 31.1	65.4 $\pm$ 33.2	46.6 $\pm$ 21.2	<0.001
LV end-diastolic diameter, mean $\pm$ SD, mm	46.9 $\pm$ 7.1	47.3 $\pm$ 7.2	45.5 $\pm$ 6.8	0.002
LV end-systolic diameter, mean $\pm$ SD, mm	31.2 $\pm$ 7.1	31.8 $\pm$ 6.7	29.5 $\pm$ 7.7	<0.001
LV end diastolic volume, mean $\pm$ SD, mL	105.1 $\pm$ 38.3	107.5 $\pm$ 39.3	98.0 $\pm$ 34.3	0.004
LV end systolic volume, mean $\pm$ SD, mL	41.8 $\pm$ 25.0	43.3 $\pm$ 24.8	37.4 $\pm$ 25.2	0.006
LV ejection fraction, %	58.1 $\pm$ 11.3	56.9 $\pm$ 10.7	60.9 $\pm$ 12.1	<0.001
LV mass index, mean $\pm$ SD, g/m ²	102.2 $\pm$ 37.5	96.4 $\pm$ 35.8	115.0 $\pm$ 38.0	<0.001
LVOT diameter, mean $\pm$ SD, mm	19.9 $\pm$ 1.9	20.0 $\pm$ 2.0	19.7 $\pm$ 1.75	0.51
LVOT time-velocity integral, mean $\pm$ SD, cm	20.1 $\pm$ 6.4	18.9 $\pm$ 6.0	22.9 $\pm$ 6.3	<0.001
LVOT stroke volume, mean $\pm$ SD, mL	62.6 $\pm$ 21.8	60.0 $\pm$ 22.6	68.7 $\pm$ 18.4	<0.001
Cardiac output, mean $\pm$ SD, L/min	4.55 $\pm$ 1.40	4.43 $\pm$ 1.41	4.85 $\pm$ 1.32	<0.001
Cardiac index, mean $\pm$ SD, L/min/m ²	2.85 $\pm$ 0.90	2.75 $\pm$ 0.88	3.09 $\pm$ 0.91	<0.001
MVA by planimetry, mean $\pm$ SD, cm ²	1.48 $\pm$ 0.49	1.44 $\pm$ 0.49	1.69 $\pm$ 0.44	<0.001
MVA by PHT, mean $\pm$ SD, cm ²	1.68 $\pm$ 0.68	1.55 $\pm$ 0.58	2.00 $\pm$ 0.81	<0.001
PHT, mean $\pm$ SD, ms	155.3 $\pm$ 96.3	163.6 $\pm$ 92.7	136.1 $\pm$ 102.0	0.003
Transmitral mean pressure gradient, mean $\pm$ SD, mmHg	6.65 $\pm$ 3.6	7.41 $\pm$ 3.89	4.87 $\pm$ 2.06	<0.001
Pulmonary artery systolic pressure, mean $\pm$ SD, mmHg	45.2 $\pm$ 16.0	46.5 $\pm$ 16.7	42.2 $\pm$ 13.5	0.002

DMS: degenerative mitral stenosis; LV: left ventricle; LVOT: left ventricular outflow tract; MS: mitral stenosis; MVA: mitral valve area; PHT: pressure half-time; RMS: rheumatic mitral stenosis
P values in bold are statistically significant.

Fig. 1. Incident cases of rheumatic and degenerative mitral stenosis, expressed as a percentage of total numbers of newly diagnosed cases per 5-year timeframe.

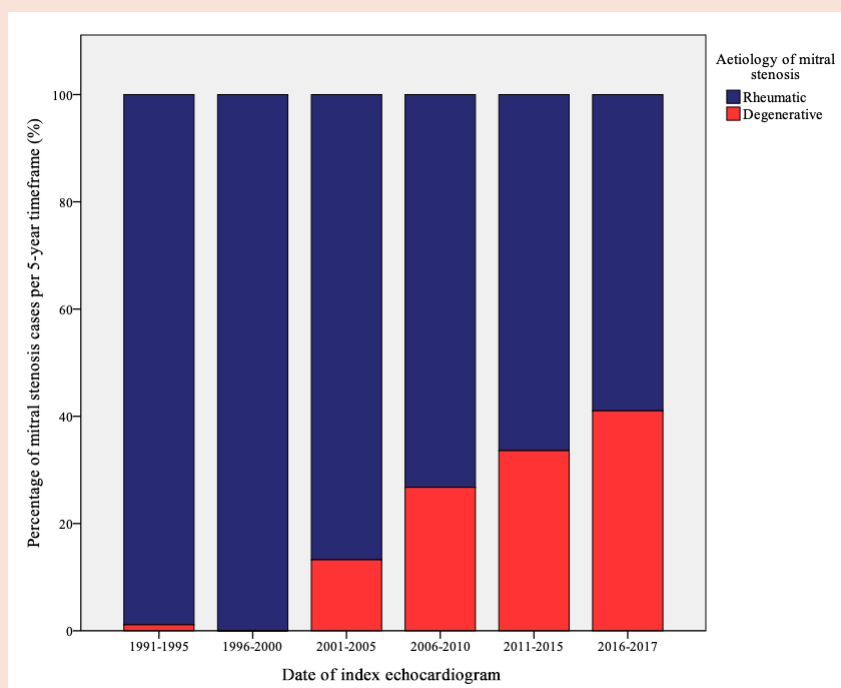


Table 3. Cox regression analysis for the combined outcome of all-cause mortality and hospitalisation for heart failure.

Univariate Cox regression analysis		Multivariate Cox regression analysis	
Variables	P value HR (95% CI)	Variables	P value HR (95% CI)
Age, years	P<0.001 1.047 (1.039–1.055)	Age (years)	P<0.001 1.032 (1.020–1.044)
Female sex	P=0.599 1.061 (0.850–1.324)	Female sex	P=0.362 0.879 (0.665–1.160)
Degenerative aetiology of MS	P<0.001 2.768 (2.186–3.505)	Degenerative aetiology of MS	P=0.100 1.297 (0.951–1.767)
Hypertension	P<0.001 2.431 (1.957–3.020)	Hypertension	P=0.316 0.844 (0.606–1.176)
Hyperlipidaemia	P<0.001 1.807 (1.463–2.231)	Hyperlipidaemia	P=0.952 1.009 (0.750–1.359)
Diabetes mellitus	P<0.001 2.539 (2.025–3.184)	Diabetes mellitus	P=0.017 1.443 (1.068–1.948)
Ischaemic heart disease	P<0.001 2.110 (1.658–2.685)	Ischaemic heart disease	P=0.963 0.993 (0.727–1.356)
Stroke or transient ischaemic attack	P=0.002 1.546 (1.172–2.038)	Stroke or transient ischaemic attack	P=0.341 1.174 (.844–1.632)
Pre-existing atrial fibrillation	P=0.930 1.009 (0.821–1.240)	NA	
History of heart failure	P=0.007 1.383 (1.094–1.749)	History of heart failure	P=0.685 1.066 (0.782–1.455)
Chronic kidney disease	P<0.001 3.131 (2.424–4.044)	Chronic kidney disease	P<0.001 2.043 (1.470–2.841)
Left atrial volume index, mL/m ²	P=0.641 0.999 (0.995–1.003)	NA	
Left ventricle ejection fraction, %	P=0.062 0.990 (0.979–1.001)	NA	
Left ventricle mass index, g/m ²	P<0.001 1.008 (1.006–1.010)	Left ventricle mass index, g/m ²	P=0.125 1.002 (0.999–1.006)
MVA by planimetry, cm ²	P=0.955 0.991 (0.732–1.343)	NA	
Transmitral MPG, mmHg	P=0.032 0.962 (0.929–0.997)	Transmitral MPG, mmHg	P=0.594 0.988 (0.944–1.034)
PASP, mmHg	P<0.001 1.013 (1.005–1.020)	PASP, mmHg	P<0.001 1.019 (1.010–1.027)

CI: confidence interval; HR: hazard ratio; MPG: mean pressure gradient; MS: mitral stenosis; MVA: mitral valve area; NA: not applicable; PASP: pulmonary artery systolic pressure
P values in bold are statistically significant.

MV leaflets as opposed to leaflet tips in RMS. Furthermore, heavy MAC tends to create acoustic shadowing artifacts, which obscure the MV annular interface and makes planimetry even more technically difficult.^{18,19} Pressure half-time measurements rely on atrioventricular compliance, which can be confounded by reduced ventricular

compliance as found in diastolic dysfunction.²⁰ Diastolic dysfunction commonly coexists in elderly or hypertensive patients and is associated with MAC, therefore suggesting a source of inaccuracy for pressure half-time-derived MV area in DMS. Notwithstanding these limitations for the assessment of MV area in DMS, we also found

that RMS was associated with a higher transmitral mean gradient and higher PASP compared to DMS, which supports the finding that patients with RMS had relatively more severe MS.

To our knowledge, a comparison of co-existing valve lesions in DMS versus RMS patients has not been previously described in the literature. In our study, a greater proportion of patients with RMS compared to DMS had concomitant mitral and aortic regurgitation; the former is notable given that MAC is itself a known cause of mitral regurgitation.^{21,22} A retrospective cohort study by Pasca et al. of patients with DMS alone reported comparable figures for the prevalence of grade 3 or 4+ mitral regurgitation and tricuspid regurgitation of 13% and 8%, respectively, and a lower prevalence of moderate or severe aortic stenosis of 9%.²³ Conversely, the group with DMS had a higher proportion of patients with aortic stenosis, which may support a common pathophysiological process of degenerative calcification giving rise to both valve lesions.

Epidemiologically, the increasing prevalence of DMS and concomitant decline in RMS in developed countries has been frequently referenced, but contemporary longitudinal data directly comparing RMS and DMS are, to our knowledge, not available.^{5,16} Several studies have produced estimates of the prevalence of DMS in varying populations, such as the EuroHeart study in 2003 that reported a prevalence of 12.5% of DMS in patients with native valve disease²⁴ while other studies yielded a prevalence of 6–8% of DMS in patients with pre-existing MAC.^{25,26} To our knowledge this is the first study to demonstrate a clear increase in incident cases of DMS with a concomitant decline in the incident cases of RMS in a developed-country setting. The socioeconomic context of rapid industrialisation, economic growth, improved healthcare and increased lifespan in Singapore over the period of our study provides additional support to the hypothesis that the increase in cases of DMS is linked to these socioeconomic factors, while the decline in RMS is similar to other parts of the developed world.^{4,5}

Our results suggest that the aetiology of MS, whether rheumatic or degenerative, was not independently associated with the studied composite outcome of all-cause mortality or hospitalisation for heart failure. Instead, age, diabetes mellitus, chronic kidney disease and PASP were identified as independently associated with these outcomes in the overall cohort. An elevated PASP is well-established as prognostically significant in the context of MS, and represents an established indication to consider MV intervention in existing guidelines that largely

pertain to RMS; it has also been associated with increased mortality in DMS.^{14,15} The presence of diabetes mellitus has also been shown to be linked to an accelerated rate of progression of DMS.²³ Notably, our results did not demonstrate an association between MV area by planimetry and the composite outcome, despite the central role of MV area in assessing severity of the valve lesion, particularly in RMS.¹⁵ As previously discussed, in DMS, the quantification of MV area is challenging and the validity of methods such as planimetry have yet to be established. In previous work in isolated DMS, Kato et al. suggested that the continuity equation might be better suited for the assessment of MV area in DMS; even so, MV area by continuity was not found to be associated with mortality.¹⁴ In our real-world cohort, the continuity equation was not applicable due to the substantial numbers of patients with concomitant mitral or aortic regurgitation.

Limitations

The chief limitation of the study relates to the retrospective nature of the study design allowing us to infer correlation but not causation from the data. We did not have transesophageal echocardiogram-derived three-dimensional MV that could have permitted accurate assessment of MV area in both groups with RMS and DMS. Our echocardiographic data pertaining to MV area and mitral pressure gradients were not verified against invasive haemodynamic studies, although invasive cardiac catheterisation is now rarely performed for the assessment of MS. In addition, we did not have serial echocardiographic studies that would have allowed us to identify differences in rates of progression between patients with RMS and DMS. We did not study outcomes pertaining to new onset atrial fibrillation or stroke in this cohort; this was related to the high baseline prevalence of atrial fibrillation with nearly half of the cohort having pre-existing atrial fibrillation. With multiple analyses to examine for differences in clinical and echocardiographic characteristics between the study groups, there is a risk of multiplicity and type I error. However, the associations we have identified, such as the increased prevalence of metabolic comorbidities in patients with DMS have been well-identified in similar studies. Lastly, our epidemiological findings pertaining to an increasing incidence of DMS may not be generalisable to other populations outside of Singapore given its unique socioeconomic and healthcare system characteristics. Further studies in other countries across the spectrum of socioeconomic development should be considered to identify temporal trends in the changing nature of aetiologies of MS.

CONCLUSION

Our data demonstrate an increase in the incidence of DMS as a proportion of cases of native-valve mitral stenosis at our centre, which we hypothesise may be related to rapid socioeconomic development and healthcare delivery in our Asian, developed-country patient cohort. The aetiology of MS, whether rheumatic or degenerative was not associated with increased all-cause mortality.

Ethics statement

The research was conducted in accordance with the principles of the Declaration of Helsinki. Ethics approval was granted by the National Healthcare Group Domain-Specific Review Board (2021/00603).

Declaration

The authors declare they have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript. This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Use of Artificial Intelligence (AI)

Generative AI or other forms of AI-assisted technologies were not used in the study or preparation of the manuscript.

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