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ORIGINAL PAPER

Degenerative mitral stenosis by echocardiography: presentation and outcome

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Aims Degenerative mitral stenosis (DMS) is due to degenerative mitral annular calcification (MAC) and valvular calcification. However, DMS impacts on the outcome, and therefore, potential treatment needs are poorly known. We aimed at evaluating survival after DMS diagnosis by Doppler echocardiography in routine practice.

Methods and results A cohort of 2937 (75 ± 12 years, 67% women) consecutive patients were diagnosed between 2003 and 2014 with DMS (diastolic mean gradient ≥ 5 mmHg), with analysis of short- and long-term survival. All patients had overt mitral annular/valvular degenerative calcification without rheumatic involvement. Mean gradient was 6.5 ± 2.4 mmHg, and DMS was considered mild in 50%, moderate in 44%, and severe in 6%. DMS was associated with left atrial enlargement (52 ± 23 mL/m^2) and elevated pulmonary pressure (49 ± 16 mmHg) despite generally normal ejection fraction (61 ± 13%). DMS was associated with frequent comorbid conditions (74% hypertension, 58% coronary disease, and 52% heart failure) and humoural alterations (haemoglobin 11.3 ± 1.8 g/dL and creatinine 1.5 ± 1.4 mg/dL). One-year mortality was 22%, most strongly related to older age, higher comorbidity, and abnormal haemoglobin/creatinine but only weakly to DMS severity (with anaemia 42% irrespective of DMS severity, $P = 0.99$; without anaemia 18, 23, and 28% with mild, moderate, and severe DMS, respectively, $P < 0.0004$). Long-term mortality was high (56% at 5 years) also mostly linked to aging and weakly to DMS severity [with anaemia $P = 0.90$; without anaemia: adjusted-hazard ratio: 1.30 (1.19–1.42), $P < 0.0001$, for moderate vs. mild DMS and 1.63 (1.34–1.98), $P < 0.0001$, for severe vs. mild DMS].

Conclusion DMS is a condition of the elderly potentially resulting in severe mitral obstruction and haemodynamic alterations. However, DMS is frequently associated with severe comorbidities imparting considerable mortality following diagnosis, whereas DMS severity is a weak (albeit independent) determinant of mortality. Hence, patients with DMS should be carefully evaluated and interventional/surgical treatment prudently considered in those with limited comorbidity burden, particularly without anaemia. Keywords: Degenerative Mitral Stenosis; Outcome; Natural history; Ecocardiography; Mitral Stenosis.

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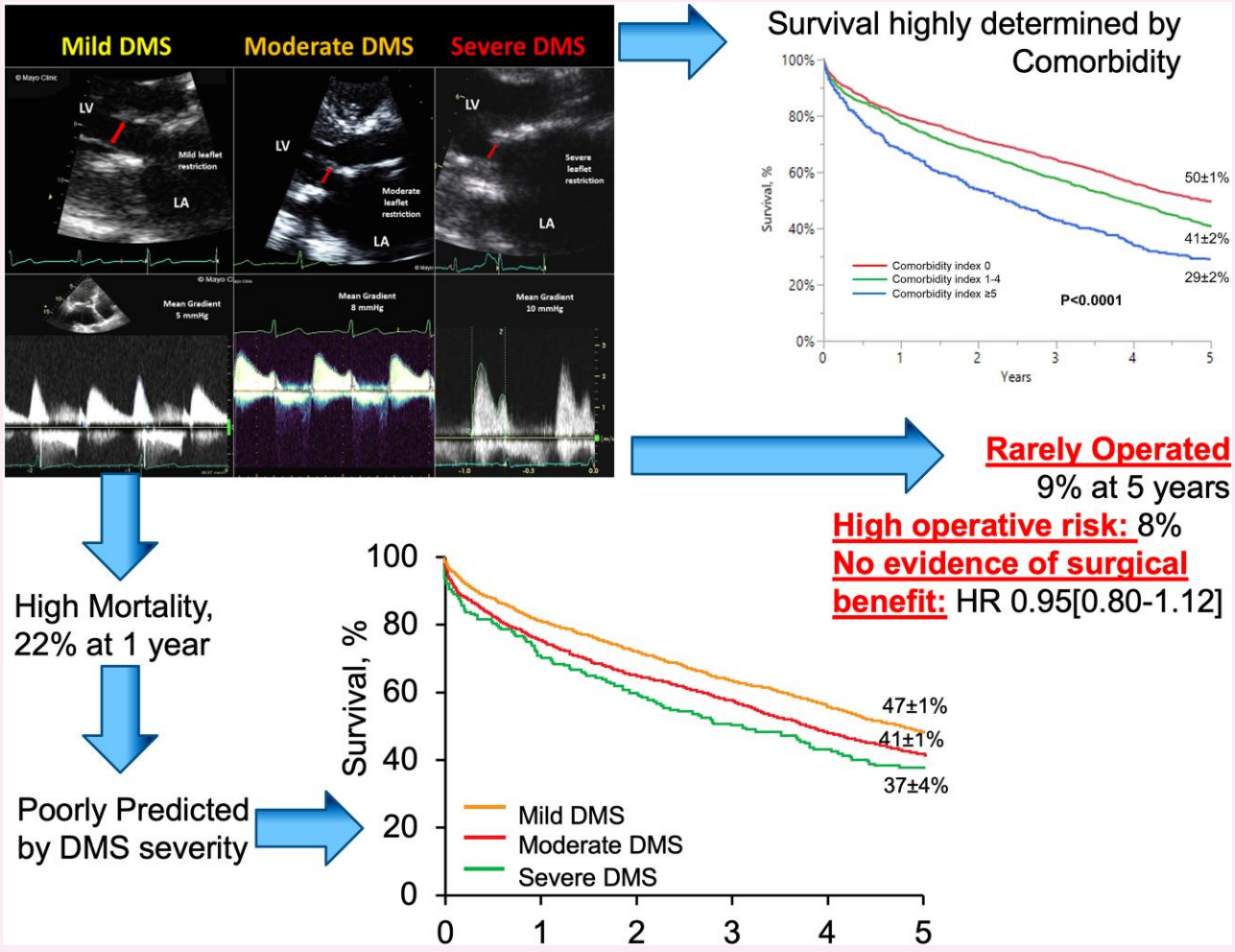
Graphical Abstract



Diagnosis and grading of DMS based on Doppler echocardiography (upper left corner) allows to link DMS to high mortality at 1 year and long-term but with a muted effect of DMS severity on the high mortality (lower left and centre). Comorbidity is more strongly related to survival after diagnosis (right upper corner). Surgery is rarely performed, with high risk and little demonstrable benefit (right lower).

Keywords degenerative mitral stenosis • outcome • natural history • ecocardiography • mitral stenosis

Introduction

Degenerative mitral stenosis (DMS) is caused by mitral annular calcification (MAC) potentially associated with valvular degenerative calcification.[1–4] This form of stenosis is different from rheumatic mitral stenosis in that flow obstruction is not caused by commissural fusion[5] but by impairment of valvular movement[6] due to calcification,[3,7] similarly to aortic stenosis.[8,9] Therefore, DMS is not treatable by balloon valvuloplasty[10] and represents a high-complexity[11,12] and high-risk[9,13] situation for cardiac surgery or interventions.[14,15]

Based on extraordinary success of transcatheter valve replacement in calcified aortic stenosis, the concept that similarly calcified mitral diseases may be treated by similar percutaneous treatment arose.[16] Recent attempts at implantation of transcatheter mitral prostheses raised hopes, although with high risk and many questions remaining outstanding.[17–21] One critical issue is that MAC rarely causes important haemodynamic disturbances,[9] and when it does, little is known about DMS clinical outcome.[22–24] Conversely, MAC presence is associated with atherosclerosis,[25] arrhythmias,[26] strokes,[27] and impaired outcome,[28,29] leaving great doubts on independent determinants of outcome. Recent pilot studies noted high comorbidity and high mortality with DMS[22–24] but could not ascertain whether DMS severity was independently determinant of poor outcomes or whether associated conditions were the main culprit. This uncertain link of DMS severity to mortality rates[22–24] yields considerable doubts on whether it directly causes impaired clinical outcome and warrants intensive interventional therapy[30] or not. Thus, it remains uncertain whether high mortality in these limited DMS cohorts[22–24] resulted from advanced age, comorbidity, frailty, and associated cardiac conditions or whether DMS was intrinsically linked to poor outcomes and what is the balance of those factors.

In view of relative DMS rarity,[31] and of the paucity and contradictory evidence,[22–24] DMS management is barely mentioned in clinical guidelines.[10,32] Despite increasing attempts at interventional treatment,[16,19]

new management recommendations would require a large DMS cohort, robustly characterizing both haemodynamics and concomitant multimorbidity burden with in-depth analysis of their respective impact on mortality. To address this critical gap of knowledge, we gathered a large cohort of patients with DMS and comprehensively characterized and examined the impact of DMS severity on mortality after diagnosis, independently of age, comorbidity, frailty, and associated cardiac conditions.

Methods

Eligibility criteria included all consecutive patients: (i) older than 18; (ii) first diagnosed with DMS caused by MAC and valvular calcification with mean mitral diastolic gradient ≥ 5 mmHg using transthoracic echocardiography; (iii) from 2003 to 2014 at Mayo Clinic, Rochester, MN; (iv) with comprehensive clinical evaluation (within electronic medical record) within 3 months of diagnosis; and (v) comprehensive Doppler echocardiography at diagnosis. Exclusion criteria were as follows: (i) clinical history of rheumatic fever; (ii) rheumatic lesions by echocardiography; (iii) congenital heart diseases (congenital mitral stenosis, atrioventricular canal defect in particular but not patent foramen ovale); (iv) previous mitral valve surgery; and (v) patients who denied research authorization (according to MN Law). Requirement for written informed consent was waived by the Institutional Review Board that approved the study.

Clinical evaluation

The patient's personal physician recorded the medical history, clinical characteristics, symptoms, physical examination, and clinical decision in the clinical notes of the electronic medical record, and details are included in Supplementary data online, *Appendix S1*.

Echocardiographic evaluation

Echocardiographic examinations were performed in routine practice by multiple trained sonographers under the supervision of consultant cardiologists experienced in echocardiographic imaging. All measurements were guided by American Society of Echocardiography recommendations.[7] MAC was present in all cases, and DMS severity was classified as mild, moderate, and severe using final impressions of responsible physicians based on integrative grading (which combine all the information gathered from M-mode/2D and Doppler measurements) of calcific mitral diastolic inflow restriction (*Graphical Abstract*; Supplementary data online, *Figure S1*). Continuous wave Doppler was used to measure mitral diastolic mean gradient as main measure of mitral obstruction with also recording of instantaneous peak velocities. Mitral valve area by planimetry was rarely measurable but was often measurable by continuity equation method in the absence of valve regurgitation. Left atrial volume index (LAVI), left ventricular diameters, wall thickness, mass, and ejection fraction were measured as recommended by the American Society of Echocardiography. Tricuspid regurgitation presence, severity, and velocity were also assessed allowing calculation of estimated systolic pulmonary artery pressure (SPAP). Left ventricular stroke volume and cardiac output were measured as recommended in the absence of significant aortic regurgitation. All echocardiographic data (qualitative and quantitative) and diagnoses of valve diseases were extracted from the digital repository as they were originally stated in the final report without any modification; this approach was specifically chosen to provide a picture of the routine practice evaluation of DMS performed prospectively by physicians unaware of the patients' clinical outcome.

Follow-up data

The outcome measure was overall mortality after diagnosis measured throughout follow-up. Death occurrence and date were obtained using Accurint®, a proprietary electronic resource gathering numerous national sources, including social security death index, interrogated in June 2019. Patients considered alive based on Accurint® data were censored on 31 December 2018, to ensure accurate mortality counts. Mortality was analysed short term within 1 year of diagnosis and long term throughout follow-up.

Statistical analysis

Results were expressed as mean ± SD or as percentages as appropriate. Group comparisons were performed using analysis of variance or χ^2. Univariable and multivariable models of survival were analysed with the main independent variable of interest defined by DMS severity grades (mild, moderate, or severe). Alternatively, quantitative measures of DMS severity, mean gradient, and mitral valve area by continuity equation were used in survival analysis with plotting of spline curves associating those to mortality risk ratios within the cohort. Cox proportional hazards regression models were used to analyse DMS severity association with long-term mortality and logistic regression for the association to 1-year mortality. We created three models: unadjusted; core model adjusted for age, gender, and comorbidity index; and comprehensive model adjusted additionally for left ventricle ejection fraction, dyspnoea, haemoglobin, and creatinine. Nested models were used to analyse incremental value of DMS severity grading over quantitative measures of DMS severity. Hazard ratios and odds ratios are presented with 95% confidence intervals. Survival rates were displayed using Kaplan–Meier method and compared using log-rank test. No imputation for missing data was adopted. $P < 0.05$ was considered significant. Statistical analysis used JMP Pro 14 (SAS Institute Inc.) and R software.

Results

Baseline characteristics

The cohort enrolled 2937 patients diagnosed at Mayo Clinic, Rochester, between 2003 and 2014 with DMS ≥mild and baseline clinical characteristics in *Table 1* (left column).

Stratification by DMS severity grading showed severe DMS in 6%, moderate in 44%, and mild in 50%. Comparison of these DMS subsets (*Table 1*, right columns) showed that female predominance was universal with slightly younger age in severe DMS. Comparatively, DMS grades presented with similar integrated comorbidity index or frailty index. Severe DMS presented with slightly lower haemoglobin, but albumin and creatinine were similar. Echocardiographically, with increasing DMS severity, there was a marked and gradual increase in mitral mean gradient, LAVI, and pulmonary pressure, all $P < 0.0001$ (*Table 1*). With higher calcified DMS severity, there was a trend for more frequent calcified aortic valve disease.

In term of DMS symptoms/complications, while DMS of increasing severity presented with more history of heart failure (frequent in all subsets), there was no more dyspnoea at diagnosis. In multivariable modelling, DMS severity was unrelated to dyspnoea at diagnosis ($P > 0.30$ in all models), which was essentially determined by chronic pulmonary disease, frailty score, and comorbidity score (all $P < 0.0001$) with very few other contributors. The analysis of interactions of DMS-associated conditions (see Supplementary data online, *Table S2*) shows no interaction detectable regarding symptom occurrence. Additionally, no link between dyspnoea and ejection fraction or moderate/severe aortic valve disease was detected (both $P > 0.13$) and no interaction with DMS severity grading found.

One-year mortality

During the first year after DMS diagnosis, a considerable proportion of patients ($n = 655$–22%) died. Comparison of patients who incurred 1-year mortality vs. 1-year survivors is presented in Supplementary data online, *Table S3*.

Table 1 Cohort clinical characteristics, overall, and DMS severity

Clinical characteristics	Overall (*n* = 2937)	Mild DMS (*n* = 1486)	Moderate DMS (*n* = 1284)	Severe DMS (*n* = 167)	*P* value
Age, y	75 ± 12	75 ± 11	74 ± 12	71 ± 13	0.0008
Female, *n* (%)	1969 (67)	963 (65)	889 (70)	117 (70)	0.03
BMI, kg/m^2	30 ± 8	30 ± 8	30 ± 8	30 ± 8	0.18
Heart rate, b.p.m.	80 ± 15	78 ± 14	82 ± 15	81 ± 15	<0.0001
SBP, mmHg	130 ± 22	131 ± 22	129 ± 23	127 ± 23	0.02
DBP, mmHg	67 ± 13	67 ± 13	66 ± 13	68 ± 13	0.05
Symptoms					
Dyspnoea, *n* (%)	1062 (36)	570 (38)	441 (34)	51 (31)	0.03
Angina, *n* (%)	231 (8)	117 (8)	109 (8)	5 (3)	0.02
Syncope, *n* (%)	227 (8)	118 (8)	99 (8)	10 (6)	0.7
Clinical history					
HTN, *n* (%)	2188 (74)	1119 (75)	961 (75)	108 (65)	0.01
CAD, *n* (%)	1692 (58)	875 (59)	725 (56)	92 (55)	0.3
Hx HF, *n* (%)	1518 (52)	767 (51)	651 (51)	100 (60)	0.08
Dyslipidaemia, *n* (%)	1432 (49)	765 (51)	611 (48)	55 (33)	<0.0001
DM, *n* (%)	1322 (45)	696 (47)	560 (44)	70 (42)	0.2
AF, *n* (%)	1082 (37)	545 (37)	465 (36)	72 (43)	0.2
CKD, *n* (%)	995 (34)	488 (33)	450 (35)	57 (34)	0.5
Coronary intervention, *n* (%)	544 (19)	307 (21)	212 (17)	25 (15)	0.009
Cancer, *n* (%)	390 (13)	220 (15)	159 (12)	11 (7)	0.003
PVD, *n* (%)	322 (11)	177 (12)	140 (11)	5 (3)	0.0003
COPD, *n* (%)	336 (11)	169 (11)	139 (11)	28 (17)	0.08
Comorbidity index	3.2 ± 3.0	3.2 ± 3.0	3.2 ± 3.0	2.9 ± 2.9	0.4
Frailty index	18 ± 9.3	18 ± 9.6	18 ± 9.2	17 ± 8.6	0.3
Humoural					
Albumin	3.6 ± 0.6	3.6 ± 0.6	3.6 ± 0.6	3.6 ± 0.6	0.3
Haemoglobin	11.3 ± 1.8	11.4 ± 1.8	11.1 ± 1.8	11 ± 2.0	<0.0001
Creatinine	1.5 ± 1.4	1.5 ± 1.4	1.5 ± 1.4	1.7 ± 1.6	0.19
Echocardiographic					
LVEDD, mm	48 ± 7	48 ± 6.9	47 ± 7.1	45 ± 7.5	<0.0001
LVESD, mm	30 ± 7.8	31 ± 7.8	30 ± 7.8	28 ± 7	<0.0001
LVEF, %	61 ± 12.5	60 ± 12.5	62 ± 12.6	64 ± 11.6	0.001
SV, mL	87 ± 22.8	88 ± 23	86 ± 23	83 ± 21	0.005
Mass index, g/m^2	112 ± 38	113 ± 35	112 ± 41	104 ± 35	0.03
MV mean gradient, mmHg	6.5 ± 2.4	5.2 ± 0.9	7 ± 1.4	13 ± 3.8	<0.0001
LAV index, mL/m^2	52 ± 23	50 ± 18	53 ± 27	63 ± 33	<0.0001
e′, m/s	0.06 ± 0.03	0.06 ± 0.03	0.06 ± 0.04	0.05 ± 0.02	0.6
sPAP, mmHg	49 ± 16	47 ± 15	50 ± 15	62 ± 21	<0.0001
MR, moderate/severe, *n* (%)	832 (28)	410 (28)	370 (29)	52 (31)	0.6
AS/AR moderate/severe, *n* (%)	1246 (42)	591 (40)	571 (44)	84 (50)	0.005

BMI, body mass index; SBP, systolic blood pressure; DPB, diastolic blood pressure; HTN, systemic hypertension; CAD, history of coronary artery disease; Hx HF, history of heart failure; DM, diabetes mellitus; AF, atrial fibrillation; CKF, chronic kidney disease; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; LVEDD, left ventricular end-diastolic dimension; ESD, left ventricular end-systolic dimension; LVED, left ventricular ejection fraction; SV, stroke volume; MV, mitral valve; MR, mitral regurgitation; LAV, left atrial volume; e′, peak velocity of early diastolic mitral annular motion; sPAP, systolic pulmonary pressure; AS, aortic stenosis and AR aortic regurgitation.

Logistic (*Table 2*, left column) univariable analysis of 1-year mortality showed increasing risk with DMS severity with odds ratios 1.34 (1.12–1.61) for moderate DMS and 1.71 (1.20–2.45) for severe DMS (vs. mild). *Figure 1* shows that while overall 1-year mortality was 22% and was 29.3% for severe DMS, it remained very high for moderate DMS (24.6%) and for mild DMS (19.5%). Multivariable analysis (*Table 2*) showed with core or comprehensive adjustment that DMS severity impact on 1-year mortality remained significant. Also, severe DMS was

Table 2 Univariable and multivariable analysis of 1-year and long-term mortality

Model	DMS severity	1-year mortality		Long-term mortality	
		OR (95% CI)	*P* value	HR (95% CI)	*P* value
Univariable	Mild	Reference		Reference	
	Moderate	1.34 (1.12–1.61)	0.0012	1.24 (1.14–1.35)	<0.0001
	Severe	1.71 (1.20–2.45)	0.0031	1.27 (1.06–1.52)	0.01
Core model	Mild	Reference		Reference	
	Moderate	1.40 (1.16–1.69)	0.0004	1.29 (1.18–1.40)	<0.0001
	Severe	2.08 (1.43–3.02)	0.0001	1.47 (1.23–1.76)	<0.0001
Comprehensive model	Mild	Reference		Reference	
	Moderate	1.36 (1.12–1.65)	0.0016	1.27 (1.17–1.38)	<0.0001
	Severe	2.09 (1.43–3.05)	0.0001	1.50 (1.25–1.80)	<0.0001

Comprehensive model adjusted for age, gender, Charlson Index, LVEF, dyspnoea, haemoglobin, and creatinine. Core model adjusted for age, gender, and Charlson Index.
LVEF, left ventricle ejection fraction; CI, confidence interval; OR, odds ratio; HR, hazard ratio.

independently linked to higher 1-year mortality with odds ratio 1.53 (1.05–2.24), $P = 0.027$, vs. moderate DMS. While, in this model, χ^2 of DMS grade was close to that of ejection fraction (19 and 20), those paled in comparison with those of age, comorbidity index, reduced haemoglobin, and elevated creatinine (all >35) suggest that the main determinants of 1-year mortality were aging/comorbidity characteristics. Symptoms weak association to 1-year mortality did not reach significance ($P = 0.34$). With additional adjustment for serum albumin, DMS severity remained independently associated with 1-year mortality [odds ratio moderate vs. mild DMS 1.35 (1.06–1.71), $P = 0.013$, and severe vs. mild 2.46 (1.52–3.99), $P < 0.001$] but lower serum albumin added an additional strong determinant of 1-year mortality with high χ^2. Nested models showed that integrative DMS severity grading provided incremental power over mean gradient and valve area (both $P < 0.0001$) despite its modest (albeit independent) association to 1-year mortality.

Stratified analysis by presence of anaemia (Hb < 9) demonstrated (*Figure 1*) that 1-year mortality, although considerable in all subsets, was in the subgroup without anaemia different between DMS subsets, 18% with mild DMS, 23% with moderate DMS, and 27% with severe DMS ($P = 0.0004$). Conversely, with anaemia, 1-year mortality was extraordinarily high and identical (42%) in all DMS severity grades ($P = 0.99$). Multivariable analysis in patients with anaemia showed only age and elevated creatinine independently linked to 1-year mortality with no impact detected for DMS severity ($P = 0.62$), but in the subset with Hb ≥ 9 g/dL, while age, comorbidity, and elevated creatinine levels concentrated prediction of 1-year mortality, ejection fraction and DMS severity remained weakly but independently linked to the 1-year mortality endpoint (both $P < 0.0001$). Similarly, stratifying by markedly elevated creatinine (≥2.5 mg/dL), the subset with lower creatinine displayed high 1-year mortality linked to DMS severity (18, 22, and 26% for mild, moderate, and severe DMS, respectively, $P = 0.005$, *Figure 1*), but patients with creatinine ≥ 2.5 mg/dL had much higher 1-year mortality with link to DMS severity not reaching significance (36, 43, and 52%, respectively, $P = 0.30$). Multivariable analysis confirmed this pattern with creatinine ≥ 2.5 mg/dL ($P = 0.06$). With creatinine < 2.5 mg/dL, age, comorbidity, and anaemia concentrated the prediction of 1-year mortality, but ejection fraction and DMS severity remained weakly but independently linked to this endpoint (both $P < 0.001$).

Long-term survival

During follow-up [4.13 (1.26–7.09) years], 2320 (80%) patients died with overall survival 78 ± 0.7% at 1 year, 67 ± 0.8% at 2 years, and 44 ± 0.9% at 5 years. Stratified by DMS severity (*Figure 2*), 5-year survival was lower in patients with higher DMS severity, 37 ± 4% for severe DMS and 41 ± 1% for moderate DMS, but although significantly higher ($P < 0.001$), 5-year survival was quite low for mild DMS (47 ± 1%).

With adjustment for baseline characteristics, severe DMS displayed higher hazard ratios vs. mild DMS (*Table 2*) and significant differences vs. moderate DMS [hazard ratio 1.19 (0.995–1.433), $P = 0.056$, for core adjustment and 1.22 (1.02–1.46), $P = 0.034$, for comprehensive adjustment]. Similar to 1-year mortality analysis, long-term mortality determinants, age, comorbidity index (Graphical Abstract; Supplementary data online, *Figure S3*), and elevated creatinine had largest χ^2, considerably higher than cardiac variables (with DMS severity as strongest, $P < 0.0001$). Moderate/severe aortic valve disease, when added to models, affected adversely prognosis [adjusted hazard ratio 1.17 (1.08–1.27), $P < 0.001$] but did not modify general results (largest χ^2 for age, comorbidity, and creatinine level) or link of DMS to mortality [adjusted hazard ratio of severe vs. mild DMS 1.47 (1.23–1.77), $P < 0.0001$]. Replacing comorbidity index by frailty index in the model showed that this variable was highly predictive of long-term survival with high χ^2 (larger than DMS) but did not alter model results or DMS significance ($P < 0.0001$). Adding albumin level to models showed this variable as very strong determinant of long-term survival with χ^2 only second to age but did not change other determinants of long-term survival and did not affect DMS significance ($P < 0.0001$). Replacing DMS grading by mitral mean gradient or valve area (continuity equation) showed those as independent determinants of survival (both $P < 0.001$), but in nested model, addition of DMS severity grading always improved models (both $P < 0.001$) and eliminated significance of mitral gradient or valve area (both $P > 0.50$).

Stratified analysis of long-term survival is presented in Supplementary data online, *Appendix S2*.

Cardiac surgery was performed in 547 patients and included mitral valve surgery in 246 (216 valve replacements and 30 repairs). Mitral surgery was rarely isolated, associated with aortic valve replacement in 124 (50%), tricuspid surgery in 74 (30%), coronary bypass surgery in 56 (23%), and MAZE procedure in 17 (7%). Mitral surgery was performed in younger patients (68 ± 12 vs. 75 ± 11) with lower comorbidity index (2.2 ± 2.6 vs. 3.3 ± 3.0) and less frailty (15.6 ± 7.8 vs. 18.1 ± 9.5, all $P < 0.001$). At 5-year post-diagnosis, surgery rate was 9 ± 1% overall, 39 ± 4% in severe DMS, 10 ± 1% in moderate DMS, and 5 ± 1% in mild DMS ($P < 0.0001$). Thirty-day mortality was 8% and survival after mitral surgery 76 ± 3% at 1 year and 55 ± 3% at 5 years. With this high mortality, after adjusting in comprehensive model, mitral valve surgery as time-dependent variable, the trend for improved survival was

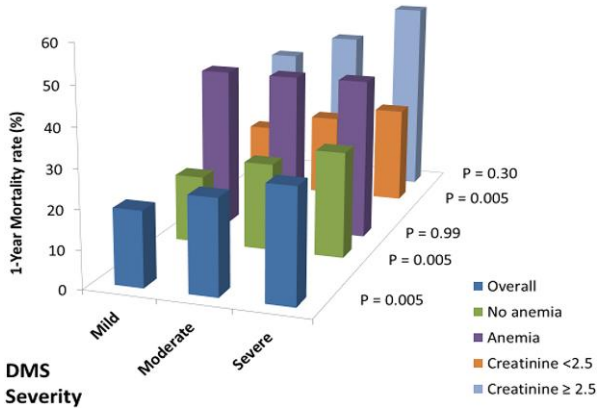


Figure 1 One-year mortality by grades of DMS severity. The graph presents on the *y*-axis 1-year mortality and on the *x*-axis the grades of DMS severity, overall and stratified by presence of anaemia and markedly elevated creatinine. Note the considerable 1-year mortality (average 22%) overall, higher in severe DMS but very high even in mild DMS. Note also that patients with anaemia have considerable 1-year mortality (42%) with anaemia irrespective of DMS severity. Mortality was also quite high with high creatinine with small difference between DMS subsets.

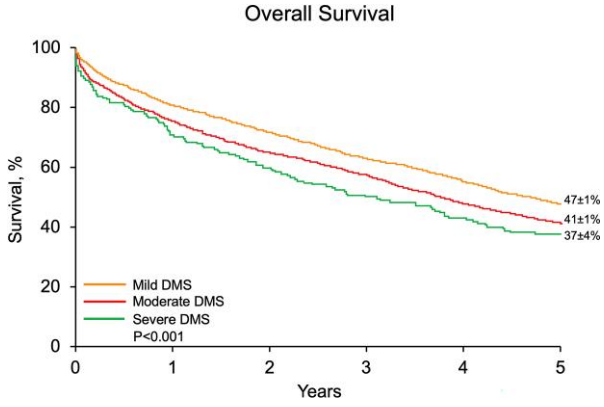


Figure 2 Long-term survival by grads of DMS severity. The Kaplan–Meier curves show the considerable mortality in all grades of DMS, somewhat higher with severe DMS demonstrating a continued excess mortality throughout follow-up.

minimal [adjusted hazard ratio 0.95 (0.80–1.12)] and insignificant ($P = 0.52$). The 301 patients who underwent cardiac surgery without mitral surgery mostly underwent aortic valve replacement ($n = 257$ including 48 transcatheter).

Discussion

The present cohort by gathering the largest and most extensively characterized DMS cohort by far provides insights into this poorly defined valvular heart disease. DMS, while involving similar calcified mechanism and similarly affecting the elderly as degenerative aortic stenosis, is profoundly different in its clinical presentation affecting predominantly women and rarely resulting in severe mitral stenosis. Furthermore, DMS is exceptionally isolated with considerable burden of comorbidity and frailty. DMS of increasing severity is associated with haemodynamic consequences, increasing mitral diastolic gradient, left atrial enlargement, and elevated pulmonary pressure without obvious alteration of left ventricular size and function. However, the main results of our study regard clinical outcome. Short-term (1-year) mortality following the diagnosis of DMS is considerable, >20% overall and >40% in patients with anaemia. While mortality is higher with more severe DMS, it is mostly determined by associated comorbidity/frailty. Long-term mortality is also considerable, also linked independently to DMS severity but also mostly determined by excess comorbidity/frailty, with mortality remaining high even in mild DMS. Mitral surgery is performed in a minority of patients but unfortunately entails high operative and long-term mortality, and its benefit is unclear. Therefore, in contrast to degenerative aortic stenosis for which valve replacement benefit is paramount, DMS has a radically different profile of therapeutic evaluation, requiring careful selection based on comorbid conditions and frailty. Consideration for surgical or transcatheter interventions should be restrictive, requiring carefully designed clinical trials.

The mysterious nature of DMS

Mitral stenosis in its classic form is rheumatic, quite uniform in its mechanism involving commissural fusion, readily identifiable by Doppler

echocardiography, and has been the earliest treatable valvular disease by commissurotomy initially surgical and more recently by balloon valvuloplasty.[1] Rheumatic mitral stenosis affects young to middle-aged patients, and outcome is mainly determined by severity of mitral obstruction under medical treatment[33] and by the residual obstruction/regurgitation after interventional/surgical treatment.[34] While age at intervention has grown progressively older in rheumatic mitral stenosis,[35] and there is a similar trend for predominance in women,[1] differences with DMS are quite outstanding. Inflow obstruction mechanism in DMS is different, involving MAC, valvular calcification, and no commissural fusion, and is assumed to be related to valvular rigidity,[3,6] but much remains to be understood in addition to mechanisms of progression towards severe DMS.[36] The clinical question arising from these data is whether the reluctance to intervene is appropriate or excessive[30] in the context of the observed accumulation of comorbidities and frailty.

DMS clinical context and outcome

A crucial fact demonstrated by all subsets of our cohort is the presence of numerous cardiovascular risk factors and of multiple comorbidities at diagnosis.[9,37] Age at DMS diagnosis is not different from aortic stenosis,[38] in which patients inoperable because of comorbid conditions still greatly benefited from valve replacement.[39] Conversely, the impact of comorbidities vs. severity of the valve disease on DMS outcome has yet remained undefined. In that regard, our large cohort provides information of considerable importance. Indeed, we observe that DMS severity is indeed a determinant of survival short and long term, with a magnitude of effect similar to that of ejection fraction. After comprehensive adjustment, severe DMS vs. mild is associated with an approximate doubling of the risk of 1-year mortality and a 50% increase in long-term mortality. Therefore, our cohort established without a doubt that DMS severity plays an independent role in the poor outcomes observed, a fact that had remained undefined yet.[22–24] This impact is also independent of the frequently associated aortic stenosis and is not a surrogate for the aortic valve disease. However, the separation of survival curves between mild and severe DMS is nowhere near that separating the survival of mild vs. severe aortic stenosis.[38] This modest separation reflects the fact that aging factors, including age, comorbidity, frailty, and humoural alterations, by far outweigh the cardiac factors and impact heavily on the survival of patients with DMS, irrespective of its severity. This fact demonstrated for the first time in our cohort is quite sobering, with absolute 1-year mortality of 22% overall, remaining quite considerable around 20% for mild DMS, while 5-year mortality in the same mild DMS group is 53%. Of particular notice among the comorbid conditions associated with DMS is anaemia. In the context of anaemia presence, DMS is associated with 1-year mortality > 40% and a long-term survival not only dismal but also unrelated to DMS severity. But all comorbidity, frailty and humoural alterations, exert a profound impact on mortality without a single group demonstrating a large separation of survival according to DMS severity.

Clinical implications

DMS is a peculiar valvular heart condition of mystifying mechanisms, characteristics, and outcomes. While DMS is diagnosed in large numbers of patients, it is fortunately rarely severe, but when it is, associated atrial enlargement and pulmonary hypertension reveal its notable haemodynamic consequences, which should be carefully evaluated in clinical practice.

DMS is diagnosed generally in the elderly, with frequently associated cardiac conditions, such as aortic stenosis, and most importantly non-cardiac comorbid conditions and humoural alterations, which play a critical role and warrant careful systematic-assessment.

DMS-associated mortality short and long term is considerable, much higher than that expected,[22,23] and shown to remain quite high even in patients with mild DMS in our study, mostly dependent on non-cardiac comorbid conditions. While DMS severity is an independent determinant of survival, therapeutic interventions are high risk and their benefit is unclear. Under those circumstances, very careful evaluation is warranted to select the few patients that may benefit from interventions based, not only on technical feasibility of these interventions, but mostly on paucity of associated comorbidities, frailty markers, and humoural alterations.

Limitations

The present study has some limitations. First, the cohort was not prospectively enrolled with protocolized care and was identified retrospectively. However, all measurements were performed prospectively at diagnosis and were unaltered for analysis, and patients were treated by their personal physicians based on these values. Therefore, our cohort is fully representative of routine clinical practice. DMS presents with considerable associated conditions, implying that isolating patients exclusively referred for this diagnosis was impossible. However, the very large cohort gathered with comprehensive characterization of clinical, echocardiographic, and humoural allows us to account fully for associated factors/conditions. Causality of the outcome linked to DMS is difficult to establish without clinical trial. However, progressive increase in mortality with increasing disease severity is suggestive of a causal link of DMS to mortality. Our considerable power establishes that DMS severity modestly contributes to total mortality, dominated by aging/comorbidity factors. The diagnosis of DMS severity is complex and has not been codified by scientific societies. Compared with mean gradient or valve area, DMS integrative grading provided incremental power in predicting mortality (both $P < 0.001$). Furthermore, spline curves for gradient (see Supplementary data online, *Figure S6*) or valve area by continuity equation (see Supplementary data online, *Figure S7*) show weak links of these measures to mortality, with large overlap between 95% confidence interval and the line of average cohort mortality. The magnitude of the cohort together with the lack of strictly standard measurements to effectively quantify DMS and MAC did not allow an extensive and reliable post-hoc severity attribution and inter-/intra-observer variability. The final evaluation of the reporting physician, combining both 2D and Doppler information, was used for DMS grading. The current study is not tailored to evaluate specific surgical approaches, and specific information on how MAC was managed during surgical intervention was not available. Ultimately, the present cohort does not establish mechanisms yielding more severe DMS, as it focuses on the urgent matter of outcome and current therapy. However, future studies should delineate the anatomic characteristics associated with more severe/progressive DMS.

Conclusion

The present largest and extensively characterized DMS cohort provides new insights into this poorly defined valvular disease. DMS affects large numbers of elderly patients, predominantly women, but rarely results in severe mitral stenosis and is exceptionally isolated with considerable burden of comorbidity and frailty. In regard to clinical outcome, while mortality is independent of all characteristics, higher with more severe DMS, it is mostly determined by associated aging/comorbidity/frailty. Mitral surgery, performed in few patients, entails high operative and long-term mortality, and its benefit is unclear. Thus, consideration for surgical/transcatheter interventions should be prudent, requiring carefully designed clinical trials.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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Data availability

Data cannot be made available due to institutional policy.

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