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The Natural History of Severe Calcific Mitral Stenosis

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ABSTRACT

BACKGROUND Prevalence of calcific mitral stenosis (MS) increases with age; however, its natural history and relation to cardiac symptoms or comorbidities are not well defined.

OBJECTIVES This study assessed the prevalence of symptoms, comorbidities, and determinants of all-cause mortality in patients with severe calcific MS.

METHODS The authors retrospectively investigated adults with isolated severe calcific MS and mitral valve area ≤1.5 cm^2 from July 2003 to December 2017. Inactivity was defined as requirement for assistance with activities of daily living.

RESULTS Of 491 patients with isolated severe MS, calcific MS was present in 200 (41%; age 78 ± 11 years, 18% men, 32% with atrial fibrillation). Charlson Comorbidity Index was 5.1 ± 1.7 and 14 (7%) were inactive. Mitral valve area and transmitral gradient (TMG) were 1.26 ± 0.19 cm^2 and 8.1 ± 3.8 mm Hg, respectively. Symptoms were present at baseline in 120 (60%); 20 (10%) developed symptoms during follow-up of 2.8 ± 3.0 years. Kaplan-Meier survival at 1 year was 72% without intervention. Inactivity (hazard ratio [HR]: 6.59; 95% confidence interval [CI]: 3.54 to 12.3; $p < 0.01$), Charlson Comorbidity Index >5 (HR: 1.53; 95% CI: 1.04 to 2.26; $p < 0.01$), TMG ≥8 mm Hg (HR: 1.68; 95% CI: 1.12 to 2.51; $p = 0.012$), and right ventricular systolic pressure ≥50 mm Hg (HR: 2.27; 95% CI: 1.50 to 3.43; $p < 0.01$) were independently associated with mortality. Symptoms were not associated with mortality.

CONCLUSION Patients with isolated severe calcific MS had a high burden of comorbidities, resulting in high mortality without intervention. Symptoms were reported in 60%, but not associated with mortality. TMG ≥8 mm Hg and right ventricular systolic pressure ≥50 mm Hg were independently associated with mortality.
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The prevalence of rheumatic mitral stenosis (MS) has declined among developed countries, while calcific MS, which is thought to result from mitral annulus calcification (MAC), has become increasingly prevalent with increasing life expectancy (1,2). MAC is usually the incidental finding of a chronic degenerative process of the fibrous support structure of the mitral valve, typically involving the posterior annulus, and often without hemodynamic significance (3,4). However, the calcification process sometimes extends to the mitral leaflets, reducing mitral leaflet mobility and restricting mitral annulus expansion in diastole, resulting in inflow restriction and consequent calcific MS (5–7). Patients with MAC are typically elderly, debilitated, and have multiple comorbidities (1); MAC is a marker of increased risk of cardiovascular events and is associated with higher all-cause mortality (8,9). The clinical characteristics,

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symptom prevalence, and natural history of patients with severe calcific MS are not well known.

Further, the presence of severe MAC represents a challenge for standard surgical mitral valve replacement (SMVR) due to heightened risk of atrioventricular groove disruption during annular debridement to allow proper prosthesis implantation (10). Therefore, interventions for severe calcific MS are often delayed until symptoms are severely limiting and cannot be adequately managed with diuresis and heart rate control (1). Unlike the case of rheumatic MS, indications and timing of mitral valve interventions for severe calcific MS are less well defined within the current guidelines (1). Identification of determinants of all-cause mortality in calcific MS is important because symptoms and the presence of significant comorbidities would affect treatment considerations. Thus, this study aimed to: 1) assess the clinical characteristics and the prevalence of symptoms in patients with severe calcific MS; and 2) identify the predictors for all-cause mortality in patients with severe calcific MS.

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METHODS

The Mayo Clinic Institutional Review Board approved the study, and research authorization was obtained from all patients. We retrospectively investigated adults in whom severe calcific MS was observed during transthoracic echocardiography (TTE) performed between July 2003 and December 2017 at Mayo Clinic, Rochester, Minnesota. In patients with severe MS defined as mitral valve area (MVA) ≤1.5 cm^2 by the continuity equation (1), calcific MS was identified as obstruction of left ventricular inflow due to degenerative calcification of the mitral annulus (2). In all identified cases, the etiology of MS was determined based on clinical history and echocardiographic and operative findings, including histopathological examination of the explanted mitral valve whenever available, by an experienced level 3 trained echocardiographer and investigators (N.K., R.P., P.A.P.). The deposition of calcification and the mobility of mitral leaflets were also observed and the findings were confirmed to be consistent with severe MS. Less than severe calcific MS (MVA >1.5 to 4.0 cm^2) were identified in patients with MAC according to TTE performed during the same study period to compare the clinical outcomes. Excluded were patients with concomitant moderate or greater aortic stenosis, aortic regurgitation, and/or mitral regurgitation; those with previous intervention for any valve (including balloon valvuloplasty, valve repair, or replacement); and those with congenital heart disease. The first TTE during the study period that described severe MS was defined as the index TTE.

All cardiovascular symptoms attributable to MS were recorded based on review of medical records; these included fatigue, effort dyspnea, atrial fibrillation, heart failure, chest pain, and syncope/pre-syncope. Inactivity was defined as requirement for assistance with activities of daily living and self-care (11). Charlson Comorbidity Index (CCI) was used to quantify the prognostic impact of multiple comorbidities (12). The decision to perform mitral valve interventions was at the discretion of the patients' treating cardiologists and cardiovascular surgeons. Baseline demographic and outcome data were extracted from the electronic medical record.

ABBREVIATIONS AND ACRONYMS

CCI = Charlson Comorbidity Index

HR = hazard ratio

LVEF = left ventricle ejection fraction

MAC = mitral annulus calcification

MS = mitral stenosis

MVA = mitral valve area

RVSP = right ventricular systolic pressure

SMVR = surgical mitral valve replacement

TMG = transmitral gradient

TMVR = transcatheter mitral valve replacement

TTE = transthoracic echocardiography

ECHOCARDIOGRAPHY. Comprehensive TTE was performed using commercially available ultrasound systems. Assessment of valvular stenosis and regurgitation were performed according to current guidelines (13–15). Specifically, transmitral gradient (TMG) was derived from continuous wave Doppler and MVA was calculated using the continuity equation. Right ventricular systolic pressure (RVSP) was estimated from peak tricuspid valve regurgitant jet velocity, using the simplified Bernoulli equation (16). Right ventricular (RV) basal, mid cavity, and longitudinal diameters were measured at end diastole using RV-focused views. RV dilatation was defined as RV basal dimensions >42 mm, mid cavity diameter >35 mm, or longitudinal diameter >89 mm (16). RV systolic dysfunction was defined as RV fractional area change <35%, s' <9.5 cm/s or tricuspid annular plane systolic excursion <17 mm (13).

MVA measurements in 25 randomly selected patients were performed by an investigator (N.K.) and compared with the original interpretation for assessment of interobserver variability, whereas measurements for intraobserver variability were performed more than 2 weeks apart.

FOLLOW-UP AND CLINICAL OUTCOME. Primary endpoints were all-cause mortality and cardiovascular events during follow-up. Events included all-cause death, mitral valve interventions, or admission for heart failure; and the first event during follow-up was used for event-free survival. The timing and frequency of clinical follow-up and repeat echocardiography varied according to the treating physicians' decision.

TABLE 1 Patient Characteristics (N = 200)

Clinical variables	
Age, yrs	78 ± 11
Male	36 (18)
Body mass index, kg/m^2	28 ± 7
Atrial fibrillation	64 (32)
Hypertension	133 (67)
Diabetes mellitus	82 (41)
Dyslipidemia	112 (56)
Creatinine ≥2.0 mg/dl	27 (14)
Dialysis	10 (5)
Cerebrovascular diseases	48 (24)
Chronic lung disease	29 (15)
Chest irradiation	9 (5)
Inactivity	14 (7)
Charlson Comorbidity Index	5.1 ± 1.7
Previous myocardial infarction	31 (16)
Prior coronary artery bypass graft	16 (8)
β-blocker therapy	115 (58)
Calcium antagonist therapy	71 (36)
Diuretic therapy	104 (52)
Echocardiographic variables	
Heart rate, beats/min	72 ± 15
Left ventricle	
Ejection fraction, %	63 ± 10
Ejection fraction ≤50%	13 (7)
End-diastolic diameter, mm	44 ± 6
End-systolic diameter, mm	28 ± 6
Mass index, g/m^2	94 ± 30
Left atrial volume index, ml/m^2*	51 ± 12
Stroke volume, ml	74 ± 19
Stroke volume index, ml/m^2	42 ± 10
Transmitral gradient, mm Hg	8.0 ± 3.8
Mitral valve area, cm^2	1.26 ± 0.19
Mitral valve area index, cm^2/m^2	0.73 ± 0.15
Right ventricle	
Basal diameter, mm	40 ± 6
Mid cavity diameter, mm	35 ± 7
Longitudinal diameter, mm	68 ± 10
Dilatation	95 (48)
Area at end diastole, cm^2	20 ± 7
Fractional area change, %	39 ± 10
S', cm/s*	11 ± 3
Right ventricular systolic dysfunction	73 (37)
Right ventricular systolic pressure, mm Hg	50 ± 18
Moderate or greater tricuspid regurgitation	49 (25)

Values are mean ± SD or n (%). *Left atrial volume index was available in 90 (45%) patients. S' was available in 138 (69%).

STATISTICAL ANALYSES. Continuous data are expressed as mean ± SD or median (interquartile range) and categorical data as frequency or percentage. A multivariable logistic regression analysis was performed to assess independent determinants for presence of symptoms at index TTE or interventions; variables with $p < 0.10$ in univariate analysis were included as candidate variables for the multivariable model. The final multivariable model was then created using backward elimination until only variables with $p < 0.05$ remained. Cutpoints used for continuous variables were determined using the mean or the values noted in the current guidelines. Survival analysis was performed by the Kaplan-Meier method. All-cause mortality was compared with population rates matched by age and sex using the 1-sample log-rank test. Cox proportional hazard modeling was used to identify independent determinants for all-cause mortality and to compare severe calcific MS (MVA ≤1.5 cm^2) with less than severe calcific MS (MVA >1.5 to 4.0 cm^2); variables were included in the same way as for the logistic regression analysis. The proportional hazards assumption was evaluated both visually by plotting residuals versus time and formally by testing for a correlation between residual and time. No violations of the proportional hazards assumption were observed. Mixed linear regression models were used to assess the progression of MS as the change in MVA after index TTE while controlling for correlation of repeated measurements within the same subject. The date of index TTE was defined as time zero. The annualized change and 95% confidence interval (CI) was estimated from this model. Estimates of intra- and interobserver variability were calculated using intraclass correlation coefficients with corresponding 95% confidence limits. Two-sided $p < 0.05$ was considered statistically significant. Statistical analysis was performed using JMP pro 14 and SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

PATIENT CHARACTERISTICS. Of 491 identified patients with isolated severe MS, calcific MS was present in 200 (41%), rheumatic/post-inflammatory MS

TABLE 2 Cardiovascular Symptoms

Cardiovascular symptoms	146 (73.0)
MS-related symptoms	120 (60.0)
Dyspnea	97 (49.0)
Syncope, pre-syncope, or hypotension	18 (9.0)
Bradycardia requiring pacemaker	12 (6.0)
Shock	3 (1.5)
Chest pain	14 (7.0)
Coronary artery diseases requiring interventions	10 (5.0)
Takotsubo cardiomyopathy	1 (0.5)
Chest discomfort related to atrial fibrillation	9 (4.5)
Lower extremity edema	3 (1.5)
Thrombosis	3 (1.5)
Fatigue	2 (1.0)

Values are n (%).
MS = mitral stenosis.

in 286 (58%), parachute mitral valve in 1 (0.2%), tumor in 1 (0.2%), and unknown mechanisms due to poor images in 3 (0.6%). Clinical and echocardiographic characteristics of the 200 patients with severe calcific MS are shown in Table 1. Age was 78 ± 11 years, 36 (18%) were male, and 64 (32%) had paroxysmal or permanent atrial fibrillation. The mean duration of follow-up was 2.8 ± 3.0 (maximum 12) years. Intra- (0.92; 95% CI: 0.84 to 0.97) and interobserver agreements (0.94; 95% CI: 0.85 to 0.97) for MVA measurement were excellent.

PRESENCE OF SYMPTOMS. At time of index TTE, 146 patients (73%) had cardiovascular symptoms as listed in Table 2. Of them, 120 patients (60%) were considered to have symptoms related to their MS. The remaining 26 patients were considered to have symptoms unrelated to their MS, which included symptomatic bradycardia requiring pacemaker in 12 (6%), coronary artery diseases requiring interventions in 10 (5%), septic shock in 3 (1.5%), and Takotsubo cardiomyopathy in 1 patient (0.5%). As listed in Table 3, paroxysmal or chronic atrial fibrillation (odds ratio [OR]: 2.28; 95% CI: 1.12 to 4.61; p = 0.022), chronic lung diseases (OR: 3.13; 95% CI: 1.17 to 8.37; p = 0.023), stroke volume index <35 ml/m^2 (OR: 2.53; 95% CI: 1.17 to 5.50; p = 0.019), and TMG (OR: 3.86; 95% CI: 1.28 to 11.6; p = 0.016 for TMG ≥10 mm Hg vs. TMG <5 mm Hg and OR: 2.88; 95% CI: 1.18 to 7.00; p = 0.020 for TMG 5 to 9 mm Hg vs. TMG <5 mm Hg) were independently associated with presence of symptomatic MS.

TABLE 3 Determinants of Presence of Symptoms

	Odds Ratio	95% Confidence Interval	p Value
Univariate analysis			
Age, yrs	0.97	0.95–0.99	0.039
Male	1.22	0.58–2.58	0.60
Body mass index, kg/m^2	1.04	1.00–1.08	0.061
Atrial fibrillation	2.14	1.13–4.06	0.020
Diabetes mellitus	1.17	0.66–2.08	0.60
Creatinine ≥2 mg/dl	0.97	0.42–2.20	0.93
Chronic lung disease	2.92	1.13–7.55	0.027
Inactivity	0.65	0.22–1.92	0.43
β-blocker or calcium antagonist therapy	1.20	0.64–2.23	0.57
Left ventricular ejection fraction <50%	1.58	0.47–5.33	0.46
Left atrial volume index, ml/m^2	1.03	0.99–1.06	0.17
Stroke volume index <35 ml/m^2	2.53	1.12–5.22	<0.01
Heart rate, beats/min	1.02	1.00–1.04	0.040
Transmitral gradient ≥10 mm Hg vs. <5 mm Hg	2.59	1.15–5.83	0.022
Transmitral gradient 5 to 9 mm Hg vs. <5 mm Hg	2.13	1.07–4.23	0.031
Mitral valve area ≤1.00 cm^2	0.80	0.31–2.02	0.63
Mitral valve area index ≤0.75 cm^2/m^2*	1.88	1.06–3.35	0.031
RV systolic dysfunction	1.71	0.86–3.39	0.13
RV dilatation	1.87	1.05–3.34	0.033
RV systolic pressure ≥50 mm Hg*	2.02	1.13–3.63	0.018
Moderate or greater tricuspid regurgitation	2.53	1.22–5.22	0.012
Multivariable analysis			
Atrial fibrillation	2.28	1.12–4.61	0.022
Chronic lung diseases	3.13	1.17–8.37	0.023
Stroke volume index <35 ml/m^2	2.53	1.17–5.50	0.019
Transmitral gradient ≥10 mm Hg vs. <5 mm Hg	3.86	1.28–11.6	0.016
Transmitral gradient 5 to 9 mm Hg vs. <5 mm Hg	2.88	1.18–7.00	0.020

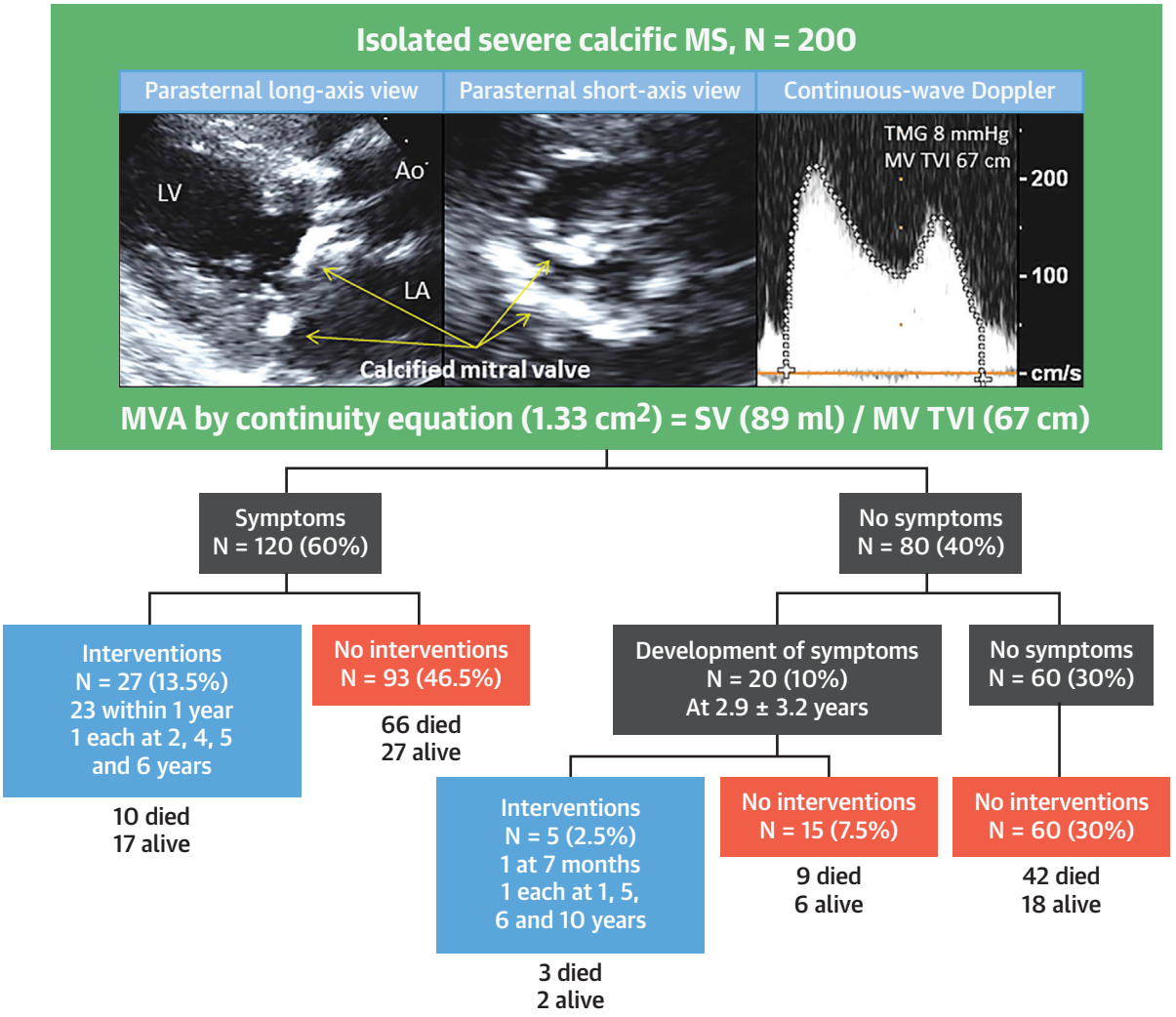
Per 1-U increment for continuous variables. *Mitral valve area index 0.75 cm^2/m^2 and RV systolic pressure 50 mm Hg were determined using the mean values.
RV = right ventricular.

CLINICAL COURSE. The patient flow chart is shown in the Central Illustration. Of 120 (60%) who had symptomatic MS at index TTE, mitral valve interventions were performed in 27: within 1 year after index TTE in 23 and at 2, 4, 5, and 6 years in 1 each. Of 80 patients without symptoms at index TTE, 20 developed symptoms at mean 2.9 ± 3.2 years and mitral valve interventions were performed in 5. Of 200 patients with severe calcific MS, probabilities of event-free survival were 53% at 1 year and 34% at 3 years, as shown in Figure 1A. Events occurred in 151 (76%), including death in 108 (54%), mitral valve intervention in 31 (16%), and admission for heart failure in 12 (6%).

Of 32 receiving mitral valve interventions, SMVR was performed in 27, mitral valve bypass surgery in 4, and transcatheter mitral valve replacement (TMVR) in 1. Age (OR: 0.96; 95% CI: 0.93 to 0.99; p = 0.011), MS-related symptoms at index TTE (OR: 3.43; 95% CI: 1.22 to 9.65; p = 0.019), TMG ≥8 mm Hg (OR: 3.36; 95% CI: 1.42 to 7.92; p = 0.019), and MVA index ≤0.75 cm^2/m^2 (OR: 5.19; 95% CI: 1.70 to 15.9; p < 0.01) were independently associated with performing interventions. Of 168 who did not receive mitral valve interventions, 60 (36%) did not develop symptoms during follow-up; 58 (35%) were considered to have moderate MS; 46 (27%) were not offered surgery because of high risk due to advanced age, multiple comorbidities, or heavy calcification; and 2 (1%) declined interventions. The other 2 patients could not receive interventions because of death due to severe MS before planned TMVR in 1 (0.5%) and no attempt of cardiotomy due to lung injury at the time of planned SMVR in 1 (0.5%) with a history of chest irradiation, who is still alive. The other patients with a history of chest irradiation did not receive mitral valve interventions. Chest radiation was not associated with more severe MS.

DETERMINANTS OF ALL-CAUSE MORTALITY WITHOUT INTERVENTION. In patients with severe

CENTRAL ILLUSTRATION Patient Flow Chart



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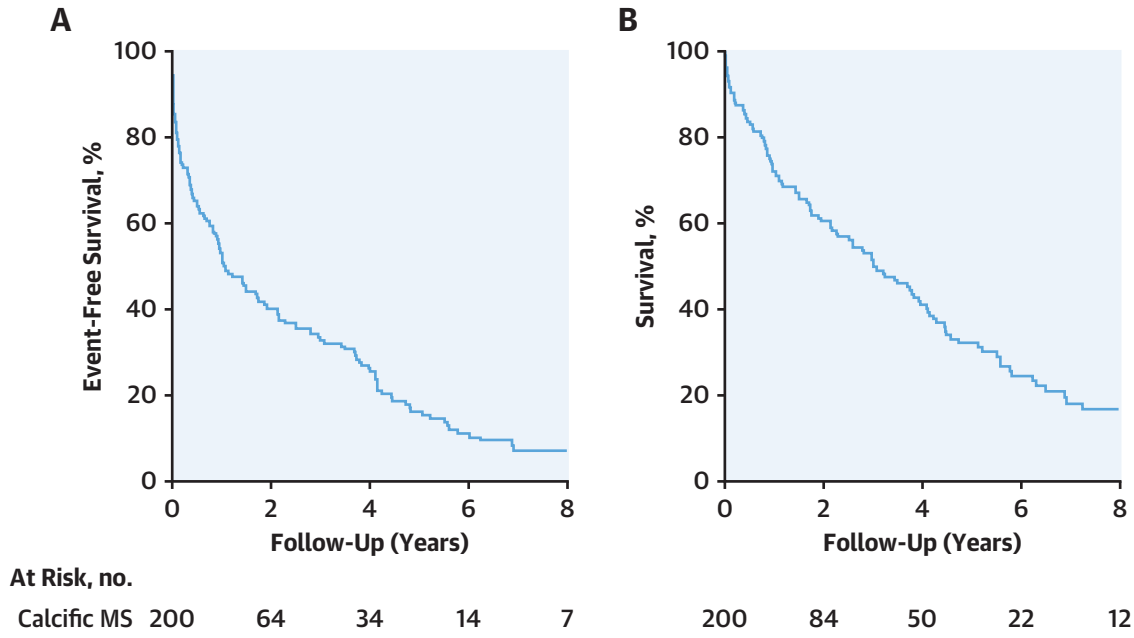
The calcification extended to the mitral leaflets, reducing mitral leaflet mobility and restricting mitral annulus expansion in diastole at parasternal long axis **(left)**. Mitral leaflets were often hidden by heavy calcification at parasternal short axis view **(center)**. Continuity equation method was used in MVA assessment and planimetry method was challenging. Ao = aorta; LA = left atrium; LV = left ventricle; m = months; MS = mitral stenosis; MVA = mitral valve area; MV TVI = mitral valve time-velocity integral; SV = stroke volume; TMG = transmitral gradient.

calcific MS, probabilities of survival were 72% at 1 year and 52% at 3 years without intervention, as shown in Figure 1B. Severe calcific MS was associated with higher all-cause mortality than the general population (hazard ratio [HR]: 2.6; 95% CI: 2.1 to 3.1; $p < 0.01$) as shown in Figure 2. Compared with 3054 patients with less than severe calcific MS (MVA >1.5 to 4.0 cm^2, age 76 ± 10 years, 33% male), mortality was higher in patients with severe calcific MS adjusted for age and sex (adjusted HR: 1.3; 95% CI: 1.1 to 1.6; $p < 0.01$).

In patients with severe calcific MS, factors associated with increased risk of all-cause death are outlined in Table 4 and Figure 3. Inactivity (HR: 6.59; 95% CI: 3.54 to 12.3; $p < 0.01$), left ventricular ejection fraction (LVEF) <50% (HR: 5.48; 95% CI: 2.68 to 11.2; $p < 0.01$), TMG ≥8 mm Hg (HR: 1.68; 95% CI: 1.12 to 2.51; $p = 0.012$), and RVSP ≥50 mm Hg (HR: 2.27; 95% CI: 1.50 to 3.43; $p < 0.01$) were independently associated with higher all-cause mortality. In the model 2 where inactivity, a strong determinant of all-cause mortality, was excluded, CCI >5 (HR: 1.53;

FIGURE 1 Clinical Outcomes in Severe Calcific MS



Event-free survival **(A)** and survival without intervention **(B)**. MS = mitral stenosis.

95% CI: 1.04 to 2.26; p = 0.031) and paroxysmal or permanent atrial fibrillation (HR: 1.84; 95% CI: 1.21 to 2.80; p < 0.01) were also independently associated with all-cause mortality. MS-related symptoms at index TTE were not associated with mortality.

PROGRESSION OF MS. Progression of MS was assessed in 65 patients who had a total of 176 TTEs after the detection of severe calcific MS. MVA decreased by 0.05 (95% CI: 0.03 to 0.07) cm^2 per year. LVEF remained ≥50% in 60 (92%), decreased to <50% in 2 (3%) who developed obstructive coronary artery diseases or Takotsubo cardiomyopathy, and remained <50% in 3 (5%). RVSP remained <50 mm Hg in 22 (33%), increased to ≥50 mm Hg in 14 (22%), and remained ≥50 mm Hg in 29 (45%).

Of 135 excluded from this analysis, follow-up TTE was not performed in 117 because of death within 1 year after the index TTE in 37, mitral valve interventions in 18, and unknown reasons in 62. Follow-up TTE could not be included in 18 because of the progression of aortic or mitral valvular heart diseases in 8 and insufficient MVA assessment in 9 who underwent TTE for other reasons.

DISCUSSION

This is the first study to assess the prevalence of symptoms and the natural history of patients with severe calcific MS. Our major findings were as follows: 1) these patients are frequently symptomatic (60% at baseline) and have a high burden of comorbidities; and 2) mortality was high without intervention (probability of death 28% at 1 year). TMG ≥8 mm Hg, LVEF <50%, RVSP ≥50 mm Hg, and atrial fibrillation, as well as CCI >5 and inactivity, but not symptomatic status, were independently associated with all-cause mortality. RV dilatation was frequently observed and RVSP was elevated, suggesting patients were at an advanced stage at the time that severe calcific MS was detected.

In this study, in patients with degenerative calcification of the mitral annulus and severe valve stenosis by Doppler, MVA was measured using the continuity method. MVA assessment is challenging in patients with calcific MS. Unlike rheumatic MS, the pressure half-time method is unreliable due to concomitant left ventricular (LV) diastolic dysfunction, a common comorbidity among patients with

TABLE 4 Univariate Analyses for Determinants of All-cause Death Without Intervention

	Hazard Ratio	95% Confidence Interval	p Value
Age, yrs	1.02	0.99–1.04	0.12
Male	0.84	0.52–1.36	0.47
Body mass index, kg/m^2	1.00	0.97–1.02	0.75
Symptoms at baseline	1.57	1.08–2.27	0.018
Atrial fibrillation	1.90	1.30–2.79	<0.01
Hypertension	1.01	0.67–1.52	0.97
Diabetes mellitus	0.68	0.47–0.99	0.040
Creatinine ≥2.0 mg/dl	1.63	0.98–2.71	0.060
Dialysis	1.48	0.65–3.39	0.35
Cerebrovascular diseases	0.93	0.62–1.39	0.71
Chronic lung diseases	1.57	0.98–2.53	0.060
Chest irradiation	0.66	0.21–2.08	0.48
Previous myocardial infarction	1.10	0.68–1.76	0.70
Prior coronary artery bypass graft	1.28	0.69–2.39	0.44
Inactivity	5.04	2.82–9.00	<0.01
Charlson Comorbidity Index >5*	1.71	1.18–2.48	<0.01
Left ventricular ejection fraction <50%	3.00	1.53–5.91	<0.01
Left ventricular mass index, g/m^2	1.00	0.99–1.01	0.74
Transmitral gradient, mm Hg	1.04	0.99–1.10	0.10
Transmitral gradient ≥8 mm Hg*	1.86	1.27–2.71	<0.01
Mitral valve area ≤1.00 cm^2	1.40	0.73–2.68	0.32
Mitral valve area index ≤0.75 cm^2/m^2*	1.32	0.91–1.90	0.23
RV systolic dysfunction	1.33	0.92–1.95	0.13
RV dilatation	1.37	0.94–1.98	0.10
RV systolic pressure ≥50 mm Hg*	2.19	1.50–3.19	<0.01
Moderate or greater tricuspid regurgitation	1.88	1.24–2.86	<0.01

Per 1-U increment for continuous variables. *Charlson Comorbidity Index 5, transmitral gradient 8 mm Hg, mitral valve area index 0.75 cm^2/m^2 and RV systolic pressure 50 mm Hg were determined using the mean values.
RV = right ventricular.

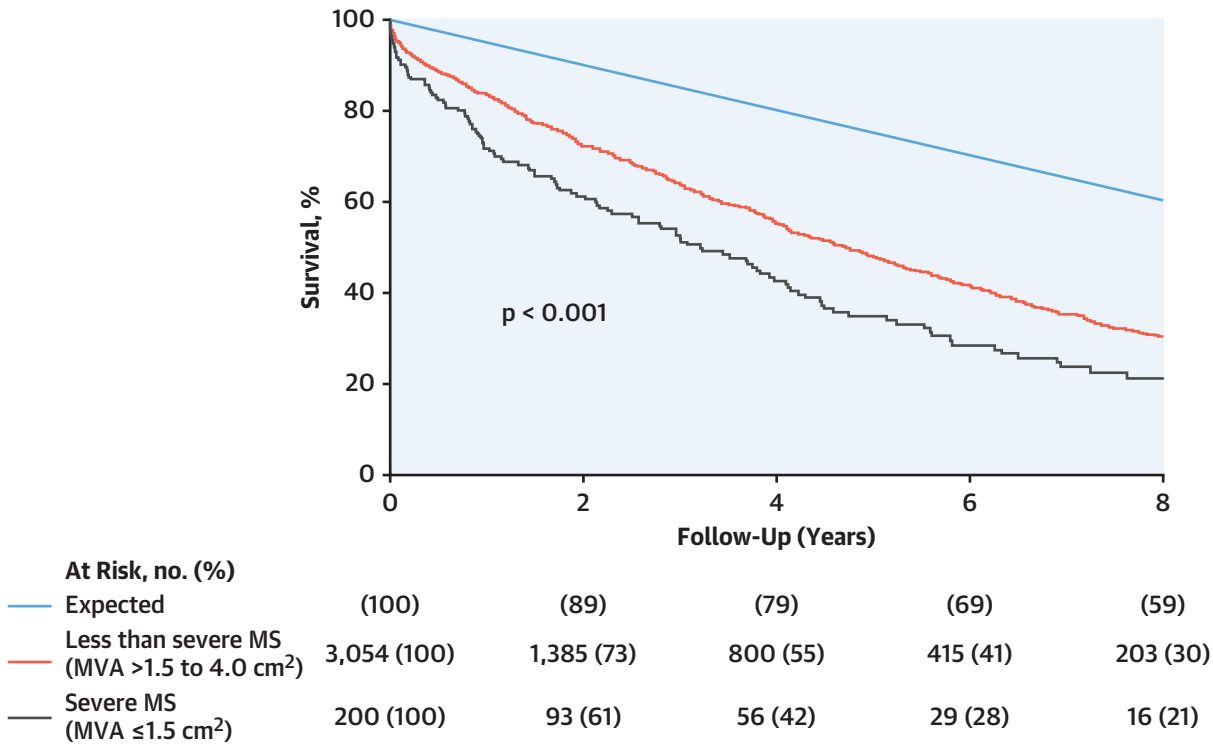
increasing age, and the planimetry method is challenging due to the difficulty in identifying the limiting orifice, which may not be at the leaflet tips and is frequently hindered by heavy MAC, as shown in the **Central Illustration**. The continuity equation method is preferred for evaluation of effective MVA, although the diagnoses should be confirmed with an integrated approach.

In patients with severe calcific MS, CCI was high and inactivity was present in 7%. As a high burden of comorbidities, defined as CCI score >4, was previously associated with a 3-fold increase in relative risk of mortality in patients with heart failure (17), it is not surprising that survival rates were low in our population. Moreover, inactivity and high comorbid burden were associated with mortality in patients with severe calcific MS. However, isolated severe calcific MS was identified in only 200 patients during the study period of 14 years; severe rheumatic MS was more prevalent. MVA has previously been reported to narrow by 0.1 to 0.3 cm^2 per year in patients with rheumatic MS (18), whereas it decreased by 0.05 cm^2 per year in our patients with isolated calcific MS. Without conditions that increase mitral valve stress, such as aortic stenosis and hypertrophic cardiomyopathy, progression of calcific MS might be slow (8). Interestingly, 82% of the patients in our study (age 78 ± 11 years) were women, which may suggest a relation between severe MAC and postmenopausal osteoporosis (19).

At the diagnosis of isolated severe calcific MS, 60% had symptoms. Surprisingly, symptoms were not associated with all-cause mortality. Elevated TMG and low stroke volume due to LV inflow obstruction typically increase left atrial pressure, causing dyspnea and pulmonary edema, concordant with our results (20). However, symptoms are generally multifactorial in the elderly, with multiple comorbidities, including chronic obstructive pulmonary diseases, pulmonary hypertension, or heart failure with preserved ejection fraction (18). Notably, we could not assess LV diastolic dysfunction, which frequently coexists with calcific MS and is reported to increase left atrial pressure (21). The assessment of diastolic function using TTE is challenging in patients with calcific MS because inflow obstruction increases diastolic transmitral velocities and lateral or posterior e' decreases due to restriction of the posterior mitral leaflet excursion (22). Moreover, some patients might be unaware of symptoms due to their limited activity caused by advanced age or comorbidities (23). Additional assessment including exercise stress echocardiography or cardiac catheterization might improve the diagnosis of symptoms related to MS or the other diseases.

Despite a high burden of comorbidities, elevated TMG was independently associated with higher all-cause mortality. Our results might suggest that mitral valve interventions could improve survival of patients with severe calcific MS independent of their symptom status and comorbidities. Although heart rate or cardiac output should be considered in TMG assessment, TMG is also affected with MVA and remarkable decrease in TMG after TMVR was reported in patients with severe MAC (24). Although elevated RVSP may be multifactorial, it developed with progression of MS in 22% and earlier interventions may lead to better clinical outcomes in patients with severe calcific MS. In patients with reduced EF, relief from severe MS would be expected to be beneficial because the combination of reduced LVEF and inadequate left ventricle filling due to severe MS may result in greater reduction in forward cardiac output (25,26). SMVR for calcific MS often needs prolonged cardiopulmonary bypass, which increases the morbidity of the procedure (10). Chest irradiation

FIGURE 2 Comparison of Survival in Calcific MS Versus the General Population



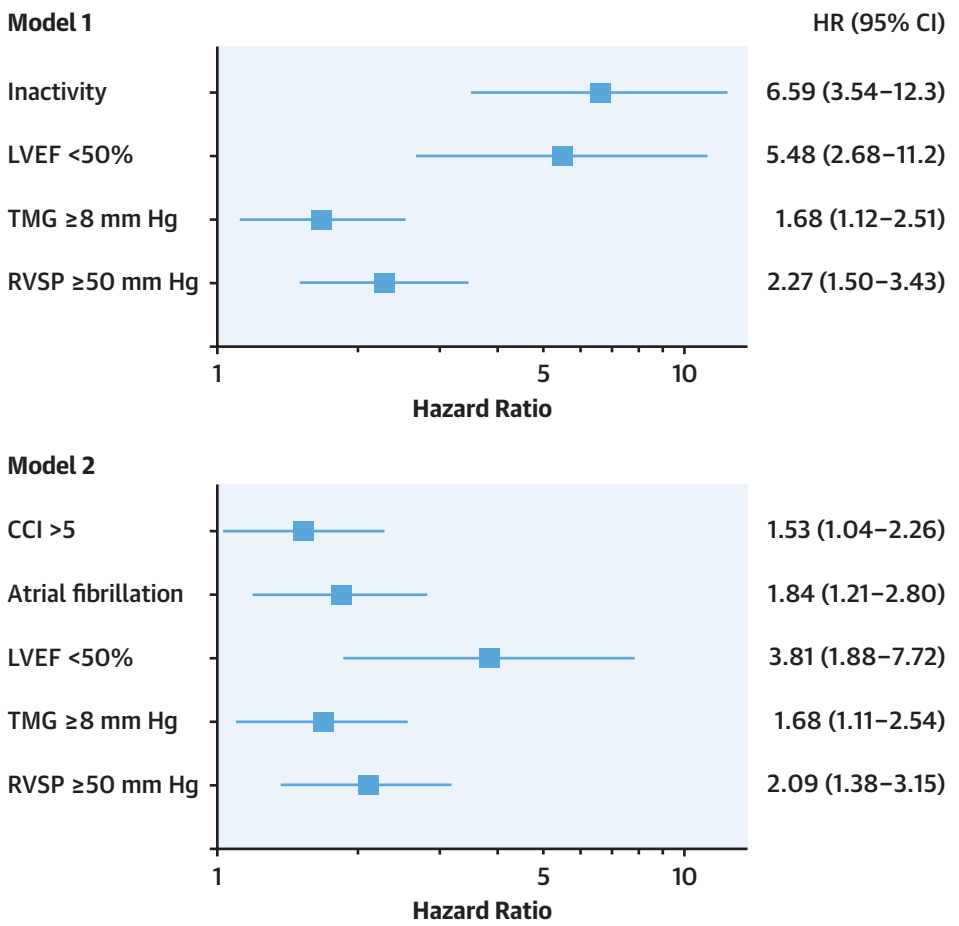
Severe calcific MS was associated with higher all-cause mortality compared with less than severe calcific MS or the population rates matched by age and sex. MS = mitral stenosis; MVA = mitral valve area.

leads to various cardiac effects and varying degree of pulmonary fibrosis (27) and radiation-associated valvular diseases have been associated with higher operative mortality (28). On the other hand, clinical outcomes were favorable in patients with MAC after successful decalcification and reconstruction, as previously reported (29). In patients at high risk for cardiac surgery, TMVR would be expected to be an alternative treatment option for certain patients with suitable anatomy (24,30). Further studies would be needed to improve selection of patients who may receive the best benefit from mitral valve interventions after accounting for the degree of calcification and comorbidity.

CLINICAL IMPLICATIONS. Patients with isolated severe calcific MS had a high burden of comorbidities, resulting in high mortality without intervention. They are frequently symptomatic, but the presence of symptoms was not associated with mortality. TMG ≥8 mm Hg and RVSP ≥50 mm Hg were associated with higher all-cause mortality independent of their comorbidities. Mitral valve interventions could potentially improve survival in selected patients with severe calcific MS.

STUDY LIMITATIONS. Our study was performed in a single institution and the sample size was small. State-of-the-art TTE systems from multiple vendors were used but varied over the 14-year period of the study. As this was a retrospective study, symptoms were determined based on review of medical records. We might not have correctly assessed which symptoms were truly related to MS. Because symptoms were not assessed using an exercise test, patients might have been symptomatic with more vigorous activity. Measurement error in MVA determination might exist due to limitations of the continuity equation method. Because calcific MS severity assessment is challenging and decision making for intervention complicated, MVA 1.0 to 1.5 cm^2 or low TMG were sometime clinically regarded as moderate MS and interventions not recommended in some patients who may have benefited. We could not determine why follow-up TTE was not performed in more patients; multiple comorbidities and reduced

FIGURE 3 Multivariable Analysis for Determinants of All-Cause Death Without Intervention



In model 2, inactivity was excluded. CCI = Charlson Comorbidity Index; CI = confidence interval; HR = hazard ratio; LVEF = left ventricular ejection fraction; RVSP = right ventricular systolic pressure; TMG = transmitral gradient.

mobility may have contributed to not returning for follow-up. Because MVA was assessed using the continuity equation, excluded were patients in whom stroke volume derived from Doppler echocardiography was not recorded. The number of patients who needed admission for heart failure might be underestimated. Only all-cause mortality is reported here because of limitations in accurately assessing cause of death (31).

CONCLUSIONS

Patients with isolated severe calcific MS were frequently symptomatic (60% at baseline) and have a high burden of comorbidities. Probability of survival was 72% at 1 year without intervention and a high burden of comorbidities was associated with higher mortality. Presence of symptoms was not independently associated with mortality. TMG ≥8 mm Hg, LVEF <50%, RVSP ≥50 mm Hg, and atrial fibrillation were also independent determinants of all-cause mortality. Among patients with isolated severe calcific MS and MVA ≤1.5 cm^2, Doppler echocardiographic parameters may be better than symptomatic status in identifying patients at highest risk.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with isolated severe calcific mitral stenosis are often symptomatic, but comorbidities, rather than symptoms, are associated with mortality. A transmitral gradient ≥8 mm Hg and right ventricular systolic pressure ≥50 mm Hg are more predictive of mortality than symptom status or comorbid conditions.

TRANSLATIONAL OUTLOOK: Further studies are needed to identify factors other than the severity of calcification and comorbidities that characterize patients most likely to benefit from mitral valve interventions.

REFERENCES

1. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:e57–185.

2. Sud K, Agarwal S, Parashar A, et al. Degenerative mitral stenosis: unmet need for percutaneous interventions. Circulation 2016;133:1594–604.

3. Benjamin EJ, Plehn JF, D'Agostino RB, et al. Mitral annular calcification and the risk of stroke in an elderly cohort. N Engl J Med 1992;327:374–9.

4. Nishimura RA, Vahanian A, Eleid MF, Mack MJ. Mitral valve disease—current management and future challenges. Lancet 2016;387:1324–34.

5. Osterberger LE, Goldstein S, Khaja F, Lakier JB. Functional mitral stenosis in patients with massive mitral annular calcification. Circulation 1981;64:472–6.

6. Movva R, Murthy K, Romero-Corral A, Seetha Rammohan HR, Fumo P, Pressman GS. Calcification of the mitral valve and annulus: systematic evaluation of effects on valve anatomy and function. J Am Soc Echocardiogr 2013;26:1135–42.

7. Carpentier AF, Pellerin M, Fuzellier JF, Relland JY. Extensive calcification of the mitral valve anulus: pathology and surgical management. J Thorac Cardiovasc Surg 1996;111:718–29; discussion 729–30.

8. Abramowitz Y, Jilaihawi H, Chakravarty T, Mack MJ, Makkar RR. Mitral annulus calcification. J Am Coll Cardiol 2015;66:1934–41.

9. Fox CS, Vasan RS, Parise H, et al. Mitral annular calcification predicts cardiovascular morbidity and mortality: the Framingham Heart Study. Circulation 2003;107:1492–6.

10. Eleid MF, Foley TA, Said SM, Pislaru SV, Rihal CS. Severe mitral annular calcification: multimodality imaging for therapeutic strategies and interventions. J Am Coll Cardiol Img 2016;9:1318–37.

11. Pellikka PA, Sarano ME, Nishimura RA, et al. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. Circulation 2005;111:3290–5.

12. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.

13. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1–39.e14.

14. Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. J Am Soc Echocardiogr 2009;22:1–23. quiz 101–2.

15. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr 2017;30:303–71.

16. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685–713. quiz 786–8.

17. Rashid M, Kwok CS, Gale CP, et al. Impact of co-morbid burden on mortality in patients with coronary heart disease, heart failure, and cerebrovascular accident: a systematic review and meta-analysis. Eur Heart J Qual Care Clin Outcomes 2017;3:20–36.

18. Chandrashekhar Y, Westaby S, Narula J. Mitral stenosis. Lancet 2009;374:1271–83.

19. Davutoglu V, Yilmaz M, Soydinc S, et al. Mitral annular calcification is associated with osteoporosis in women. Am Heart J 2004;147:1113–6.

20. Rahimtoola SH, Durairaj A, Mehra A, Nuno I. Current evaluation and management of patients with mitral stenosis. Circulation 2002;106:1183–8.

21. Reddy YNV, Murgo JP, Nishimura RA. Complexity of defining severe "stenosis" from mitral annular calcification. Circulation 2019;140:523–5.

22. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29:277–314.

23. Izumi C. Asymptomatic severe aortic stenosis: challenges in diagnosis and management. Heart 2016;102:1168–76.

24. Guerrero M, Urena M, Himbert D, et al. 1-Year outcomes of transcatheter mitral valve replacement in patients with severe mitral annular calcification. J Am Coll Cardiol 2018;71:1841–53.

25. Wisenbaugh T, Essop R, Middlemost S, Skoularigis J, Sareli P. Excessive vasoconstriction in rheumatic mitral stenosis with modestly reduced ejection fraction. J Am Coll Cardiol 1992;20:1339–44.

26. Snyder RW 2nd., Lange RA, Willard JE, et al. Frequency, cause and effect on operative outcome of depressed left ventricular ejection fraction in mitral stenosis. Am J Cardiol 1994;73:65–9.

27. Desai MY, Karunakaravel K, Wu W, et al. Pulmonary fibrosis on multidetector computed tomography and mortality in patients with radiation-associated cardiac disease undergoing cardiac surgery. J Thorac Cardiovasc Surg 2014;148:475–81.e3.

28. Wu W, Masri A, Popovic ZB, et al. Long-term survival of patients with radiation heart disease undergoing cardiac surgery: a cohort study. Circulation 2013;127:1476–85.

29. Uchimuro T, Fukui T, Shimizu A, Takanashi S. Mitral valve surgery in patients with severe mitral annular calcification. Ann Thorac Surg 2016;101:889–95.

30. Eleid MF, Cabalka AK, Williams MR, et al. Percutaneous transvenous transseptal transcatheter valve implantation in failed bioprosthetic mitral valves, ring annuloplasty, and severe mitral annular calcification. J Am Coll Cardiol Intv 2016;9:1161–74.

31. Lauer MS, Blackstone EH, Young JB, Topol EJ. Cause of death in clinical research: time for a reassessment? J Am Coll Cardiol 1999;34:618–20.

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