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Does isolated mitral annular calcification in the absence of mitral valve disease affect clinical outcomes after transcatheter aortic valve replacement?

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ABBREVIATION AND ACRONYMS

CT = computed tomography

MAC = Mitral annular calcification

MIP = maximal intensity projection

MR = mitral regurgitation

MRI = magnetic resonance imaging

MS = mitral stenosis

MVA = mitral valve area

MVD = mitral valve disease

STS = Society of Thoracic Surgeons

TAVR = transcatheter aortic valve replacement

VARC = Valve Academic Research Consortium

Introduction

Severe mitral annular calcification (MAC) has a prevalence of 9 to 18% in patients undergoing transcatheter aortic valve replacement (TAVR) and has been independently associated with increased mortality (1, 2). MAC often coexists with, or results in mitral regurgitation (MR) or mitral stenosis (MS) (1, 3-8). However, MAC has largely been studied in isolation from functional parameters of mitral valve disease (MVD), which themselves confer an increased risk of death (9-13). MAC has been demonstrated in a majority of TAVR patients with moderate or severe mitral stenosis (12).

We therefore aimed to assess the impact of MAC with and without significant MVD on clinical outcomes in patients undergoing TAVR, integrating both functional and anatomical assessments of the mitral valve apparatus using an integrated analysis of echocardiography and computed tomography (CT).

Methods

Study population

All patients undergoing TAVR at Bern University Hospital, Bern, Switzerland, are consecutively enrolled into a prospective institutional registry that is a part of the Swiss TAVI registry (NCT01368250). Patients were excluded if a non-CE marked device was used or if no transcatheter heart valve was implanted. The registry was approved by the local ethics committee, and patients provided written informed consent to participate. For the purpose of the present study, only patients without prior mitral valve surgery were considered. Furthermore, patients without pre-procedural echocardiographic and CT raw data adequate for a reliable assessment of the mitral valve apparatus were excluded from the present analysis.

Assessment of mitral annular calcification

MAC was assessed by CT, which is a validated modality to predict the extent and location of MAC and assess its severity (14). The ECG-gated multi-slice CT was performed on either a Siemens Somatom Sensation Cardiac 64 scanner with a slice collimation of 64 x 0.75mm or a Siemens Somatom Definition Flash Dual-Source scanner with a slice collimation of 128 x 0.6 mm, tube voltage of 100 or 120 kV, and tube current according to patient size (Siemens Medical Solutions, Inc., Forchheim, Germany). Each patient received an intravenous injection of 80-120 mL of contrast medium at a flow rate of 5 mL/s and image acquisition was performed during an inspiratory breath-hold in a cranio-caudal direction. Acquired CT images were transferred to a dedicated workstation (3mensio Structural Heart, 3mensio Medical Imaging BV, Bilthoven, The Netherlands) in the Corelab and re-evaluated by independent investigators blinded to clinical outcomes. Several views including axial and double oblique views at the mitral annular level as well as a maximal intensity projection (MIP)

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reconstruction were used to assess the presence of MAC and its severity. MAC was defined as calcification located at the junction between the left atrium and left ventricle. MAC severity was qualitatively determined by the circumferential involvement of the mitral ring: mild was defined as involvement in less than 1/3 of the annulus; moderate between 1/3 and 1/2; and severe if the calcification was present in more than half of the mitral annulus circumference (**Figure 1**) (1, 15).

Assessment of mitral valve disease

The assessment of MVD was performed by echocardiography as previously described (11, 12). Briefly, transthoracic and/or transesophageal echocardiography were performed by a board-certified cardiologist with a Philips iE33 machine (Philips Healthcare, Andover, MA, USA). Acquired images were transferred to a dedicated workstation (Syngo Dynamics Workplace, version 9.5, Siemens Medical Solustions, Inc, PA, USA) in the Corelab and re-evaluated by independent investigators blinded to clinical outcome. The degree of MR and MS was assessed at baseline using structural, spectral, and color-Doppler images and were graded as mild, moderate, and severe using multi-parametric assessments according to the European Association of Echocardiography/American Society of Echocardiography recommendations (16, 17). In the present study, significant MVD was considered in the presence of at least moderate mitral regurgitation or mild or greater mitral stenosis. The rationale for this categorization was that these respective grades have been associated with an

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increased risk of mortality in patients undergoing TAVR (9-13).

Transcatheter aortic valve replacement

The optimal therapeutic strategy in each patient was based on a heart team decision. Presence or absence of MVD regularly affected decision-making on the optimal treatment strategy. In contrast, isolated MAC was rarely taken into consideration during the heart team discussion. MAC was however taken into account in combination with MVD for the assessment of anatomical and technical suitability of mitral valve surgery or transcatheter intervention. TAVR was performed via transfemoral access by default. A trans-apical or trans-subclavian approach was used in patients with inadequate peripheral access. Post-procedural care included rhythm monitoring for at least 48h after the intervention, laboratory testing, and daily 12-lead electrocardiograms until discharge.

Data collection and clinical follow-up

Baseline clinical data, procedural characteristics, and follow-up data were entered into a dedicated database, held and maintained by the Clinical Trials Unit of the University of Bern. Clinical follow-up data at 30 days and 1 year were obtained by standardized interviews, documentation from referring physicians, and hospital discharge summaries. All adverse events were systematically collected and adjudicated by a dedicated clinical event committee according to the Valve Academic Research Consortium (VARC-2) criteria (18). The pre-specified primary endpoint of the present study was all-

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cause death at 1 year after TAVR. Secondary endpoints included cardiovascular death and disabling stroke at 1 year, all-cause death, cardiovascular death, myocardial infarction, disabling stroke, major or life-threatening bleeding, major vascular complication, kidney injury (stage 3), and permanent pacemaker implantation at 30 days after TAVR. Composite outcome of all-cause death and disabling stroke at 30 days and 1 year after TAVR are also described.

Statistical analysis

Categorical data are represented as frequencies and percentages and the differences between groups are evaluated with the Chi-square test or Fisher's exact test. Continuous variables are expressed as mean values ± standard deviation (SD) and compared between groups using F test. Event-free survival curves were constructed using the Kaplan-Meier method. Univariate unadjusted Cox proportional hazards model was used to calculate crude hazard ratios (HR) and 95% confidence intervals (95% CI) for the clinical outcomes. Multivariable Cox regression was performed to identify independent predictors of all-cause death. All the variables were stepwise tested for entry into the multivariate model, with p-value of <0.10. The adjusted Cox proportional hazards model estimates were based on 20 multiple imputed datasets, combining estimates using Rubin's rule, adjusting for body mass index, NYHA class Ⅲ or Ⅳ, diabetes, prior stroke or transient ischemic attack, peripheral artery disease. Throughout the present study, a p-value of <0.05 was considered significant. Statistical analyses were performed using Stata 15.1 (StataCorp, College Station, TX, USA).

Results

Among 1811 consecutive patients undergoing TAVR between August 2007 and June 2017, a total of 967 individuals met the inclusion criteria and were considered for the purpose of the present analysis. At one year, outcomes were known from 960 patients (99.3%), 6 patients refused follow-up and 1 patient was not traceable. MAC was found in 609 patients (63.0%) and considered mild or moderate in 437 (45.2%) and severe in 172 (17.8%) (**Figure 2**). A total of 87 patients (50.6%) with severe MAC had relevant MVD compared to 228 patients (28.7%) with non-severe MAC (p<0.001) (**Figure 3**).

Baseline and procedural characteristics

The baseline characteristics of the study population are summarized in **Table 1,2**. Patients with severe MAC were more frequently female. Patients with MVD or severe MAC had a higher estimated risk as assessed by the Society of Thoracic Surgeons (STS) risk score.

Overall, transfemoral access was used in 90.6% of the cases and 22.3% of the cases were performed under general anesthesia. The rate of periprocedural complications were comparable across groups and are shown in **Table 3**.

Clinical outcomes

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Survival curves according to severity of MAC are shown in **Figure 4**. Neither patients with severe MAC nor patients with mild or moderate MAC had an increased risk of all-cause [HR: 0.92, 95% CI: 0.56-1.53; HR: 0.87, 95% CI: 0.59-1.28; respectively] or cardiovascular death [HR: 1.22, 95% CI: 0.69-2.15; HR: 0.78, 95% CI: 0.47-1.28; respectively] as compared to patients without MAC.

Clinical outcomes at 30 days and 1 year stratified by presence or absence of severe MAC and relevant MVD are summarized in **Table 4,5**. Compared to patients without severe MAC and MVD, patients with isolated MVD had increased risks of all-cause [6.6% vs. 2.1%, HR: 3.16, 95% CI: 1.48-6.75] and cardiovascular death [6.2% vs. 1.8%, HR: 3.54, 95% CI: 1.57-7.96] at 30 days. Patients with severe MAC in combination with MVD had numerically higher risks of all-cause death [5.7% vs. 2.1%, HR: 2.73, 95% CI: 0.96-7.76] and cardiovascular death [4.6% vs. 1.8%, HR: 2.63, 95% CI: 0.82-8.37] at 30 days. Both patients with isolated MVD and patients with severe MAC in combination with MVD had an increased risk of bleeding compared to patients without severe MAC and MVD [30.4% vs 23.7%, HR: 1.31, 95% CI: 0.98-1.75; 39.3% vs. 23.7%, HR: 1.72, 95% CI: 1.18-2.50; respectively]. Patients with severe MAC in combination with MVD had a numerically higher risk of atrioventricular conductance disturbances and need for permanent pacemaker implantation as compared to patients without severe MAC and MVD [27.9% vs. 20.1%, HR: 1.48, 95% CI: 0.95-2.29].

At 1 year, both patients with isolated MVD and patients with severe MAC in combination with MVD

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had increased risks of all-cause death [23.4% vs. 8.8%, HR: 2.89, 95% CI: 1.96-4.26; 19.5% vs. 8.8%, HR: 2.40, 95% CI: 1.38-4.17; respectively] and cardiovascular death [15.8% vs. 5.1%, HR: 3.32, 95% CI: 2.02-5.45; 17.5% vs. 5.1%, HR: 3.69, 95% CI: 1.97-6.90; respectively], while patients with isolated severe MAC did not have an increased risk of all-cause death [6.0% vs. 8.8%, HR: 0.67, 95% CI: 0.27-1.67] or cardiovascular death [4.8% vs. 5.1%, HR: 0.93, 95% CI: 0.33-2.66] as compared to patients without severe MAC and MVD (**Figure 5**).

The incremental risk of concomitant MVD on mortality in patients undergoing TAVR is summarized in **Figure 6**.

In a multivariate analysis, both isolated MVD and severe MAC concomitant with MVD emerged as independent predictors of all-cause death at 1 year [HR_{adj}: 2.33, 95% CI: 1.56-3.47; HR_{adj}: 1.97, 95% CI: 1.12-3.44; respectively] (**Table 6**). Multivariate Cox regression analysis was also performed to evaluate the independent effects of severe MAC, significant MS, and MR on 1-year mortality. As shown in **Table 7**, significant MS and MR were both independent predictors of all-cause death [HR_{adj}: 2.37, 95% CI: 1.53-3.66; HR_{adj}: 1.88, 95% CI: 1.20-2.94; respectively], whereas severe MAC was not [HR_{adj}: 1.16, 95% CI: 0.69-1.96].

Association between the severity of MAC and the prevalence of MVD

Prevalence and severity of MS and MR according to severity of MAC are summarized in **Figure 7**. The prevalence of mild or greater MS gradually increased with incremental severity of MAC with significant correlation (Spearman's rho=0.185, p<0.001). Although the prevalence of moderate or severe MR was the highest in patients with severe MAC, there was no significant correlation (Spearman's rho = 0.034, p=0.295).

Discussion

The main findings of the present study can be summarized as follows. 1) Patients with severe MAC had comparable survival throughout one year of follow-up compared to patients with non-severe MAC. 2) More than half of all patients with severe MAC had relevant MVD, which was significantly higher than patients with non-severe MAC. 3) Patients with severe MAC and coexisting MVD had an increased risk of all-cause and cardiovascular death at 30 days and 1 year, whereas patients with isolated severe MAC without MVD had comparable survival to patients without severe MAC and MVD.

MAC prevalence increases with both age, co-existent renal impairment and cardiovascular risk suggesting an association to the pathogenesis of atherosclerosis. It has similarities with the development of calcific aortic stenosis in that foci of endothelial injury at sites of mechanical stress result in an inflammatory response with macrophage and T-cell infiltrates, encouraging the expression of bone morphogenetic proteins from myofibroblasts and preosteoblasts adjacent to these

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lymphocytic infiltrates contributing to calcification (19).

There is limited evidence that MAC is associated with an increased prevalence of MR and MS (3-6). In the study by Abramowitz et al., baseline MR distribution was similar between patients with and without MAC, however, in severe MAC alone, severe MR was frequently observed. Although baseline MS distribution was not described in detail, baseline mitral valve mean gradients were significantly higher in patients with severe MAC (1). In our current analysis, the prevalence and severity of MS were significantly correlated with the CT-assessed MAC severity. Moreover, the prevalence was apparently higher in patients with severe MAC even in comparison with mild or moderate MAC. Although the correlation between MAC severity and MR was not statistically significant, the prevalence of moderate or severe MR was also the highest in patients with severe MAC. Consequently, increased prevalence of MVD was observed in patients with severe MAC but not in patients with mild or moderate MAC. This finding suggests that severe MAC might have a greater impact on mitral valve function.

Previously, MAC has been identified as a risk factor for increased mortality in patients undergoing TAVR as well as in other populations (1, 2, 20-22). However, the association of MAC with mortality has typically been studied in isolation from concomitant MVD (2, 20, 21). Although Abramowitz et al. reported similar prevalence of MR and increased mitral valve mean gradients in patients with severe

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MAC, the multivariate analysis included neither MR nor mitral valve mean gradient (1). Ramaraj et al. identified MAC as an independent predictor of all-cause death in a retrospective analysis of 3169 clinical echocardiograms. Although the multivariate analysis included significant valvular abnormalities, independent prevalence and additional effects on mortality of MR and MS were not analyzed (22). To the best of our knowledge, this study is the first to investigate the prognostic impact of MAC on TAVR in relation to systematically assessed MVD.

In contrast to previous reports (1, 2), we did not document an association of severe MAC with increased mortality. The present study demonstrated that severe MAC was not an independent predictor of mortality in patients undergoing TAVR, whereas concomitant MR and MS were both independent predictors. MAC represents chronic calcification of fibrous tissue surrounding the mitral valve and in most cases has little impact on mitral valve function. In advanced cases, the excessive calcification may freeze normal annular dynamics or encroach upon the leaflet bodies and mitral chordae, reducing leaflet mobility and ultimately causing MS or MR (14). Therefore, MAC itself does not have a prognostic impact but is associated with mortality after TAVR if it affects mitral valve function significantly. A detailed assessment of concomitant MVD may be an avenue for MVD intervention and improvement of survival in patients with severe MAC.

The comprehensive assessment of MVD can be challenging because hemodynamic effects of the different valves are interrelated, and the presence of MAC may add further complexity. While concomitant AS accentuates MR severity due to increased afterload, MS tends to be underestimated by a low-flow low-gradient state with a prolonged pressure half-time caused by impaired left ventricular relaxation. Therefore, anatomical assessment including planimetry is deemed important in these patients. However, the presence of MAC may complicate planimetric assessment by acoustic shadowing and blooming artifacts of the calcification. Recently, the usefulness of CT and magnetic resonance imaging (MRI) for the assessment of MVD has been recognized (23-26). The Integrated approach of echocardiography and CT or MRI for the comprehensive assessment of the mitral valve apparatus including MAC may be of particular importance in patients with AS, since it may affect the decision on the optimal treatment strategy.

Study Limitations

Our results should be interpreted in light of several limitations. Firstly, only patients with adequate echocardiographic and computed tomographic raw data for a comprehensive assessment of the mitral valve apparatus were considered for the purpose of the present analysis. Therefore, unintended selection bias might exist in the present study. Secondly, potential confounders might exist and statistical techniques might not be sufficient to adjust these factors. Thirdly, there is no validated classification for the assessment of MAC on CT. Therefore, we used the qualitative classification of MAC suggested by Abramowitz et al. (1). Further studies are needed to investigate the optimal method for the assessment of MAC on CT. On the other hand, we have several strengths in the present study as compared to the previous studies. The present study was based on a considerably larger number of patients compared to previous reports. Also the present analysis was performed using a rigorous registry database with standardized follow-up and independent event adjudication. Finally, the echocardiographic and computed tomographic raw data were re-evaluated by independent second readers for the purpose of the study.

Conclusion

Isolated severe MAC is not an independent predictor of mortality after TAVR. Severe MAC is however associated with a significantly higher incidence of MVD, especially of MS. Significant MVD is associated with increased 1 year mortality. Risk evaluation in patients undergoing TAVR and coexisting MAC needs to integrate functional assessment of the mitral valve apparatus.

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Tables

Table 1. Comparison of Baseline Characteristics

	No/Non-severe MAC (n=795)		**Severe MAC (n=172)**		**P=value**
	No-MVD (n=567)	**MVD (n=228)**	**No-MVD (n=85)**	**MVD (n=87)**	
Age (years)	81.8 ± 6.4	82.3 ± 6.3	83.1 ± 4.7	83.4 ± 6.6	0.056
Female (n, %)	266 (46.9%)	118 (51.8%)	57 (67.1%)	70 (80.5%)	<0.001
Body mass index (kg/m^2)	26.7 ± 5.0	25.3 ± 5.1	26.7 ± 5.0	26.0 ± 5.5	0.006
STS score: mortality (%)	5.0 ± 3.2	6.5 ± 4.9	5.8 ± 3.4	5.8 ± 3.0	<0.001
NYHA class Ⅲ/Ⅳ (n, %)	380 (67.0%)	169 (74.4%)	57 (67.1%)	63 (72.4%)	0.186
Concomitant diseases					
Hypertension (n, %)	480 (84.7%)	182 (79.8%)	74 (87.1%)	68 (78.2%)	0.159
Diabetes (n, %)	129 (22.8%)	51 (22.4%)	27 (31.8%)	23 (26.4%)	0.271
Dyslipidemia (n, %)	389 (68.6%)	132 (57.9%)	58 (68.2%)	43 (49.4%)	0.001

CKD (eGFR<60) (n, %)	367 (64.7%)	166 (72.8%)	61 (71.8%)	63 (72.4%)	0.088
COPD (n, %)	76 (13.4%)	30 (13.2%)	8 (9.4%)	8 (9.2%)	0.550
Previous history					
Coronary artery disease (n, %)	353 (62.3%)	145 (63.6%)	56 (65.9%)	44 (50.6%)	0.132
Prior stroke or TIA (n, %)	59 (10.4%)	33 (14.5%)	11 (12.9%)	17 (19.5%)	0.069
Peripheral artery disease (n, %)	66 (11.6%)	35 (15.4%)	20 (23.5%)	8 (9.2%)	0.011
Atrial fibrillation (n, %)	135 (23.8%)	76 (33.3%)	24 (28.2%)	22 (25.3%)	0.051
Permanent pacemaker (n, %)	46 (8.1%)	27 (11.8%)	4 (4.7%)	9 (10.3%)	0.176
Laboratory data					
Hemoglobin (g/L)	123.8 ± 17.0	120.6 ± 16.8	121.3 ± 16.7	119.5 ± 13.8	0.020
BNP (pg/mL)	488.6 ± 681.8	769.7 ± 950.2	581.8 ± 699.5	776.8 ± 1050.8	<0.001
Medications					
Aspirin (n, %)	488 (87.3%)	178 (80.9%)	71 (83.5%)	73 (85.9%)	0.144
Clopidogrel (n, %)	410 (73.3%)	157 (71.4%)	65 (76.5%)	62 (72.9%)	0.838

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Oral anticoagulation (n, %)	168 (30.1%)	82 (37.3%)	26 (30.6%)	24 (28.2%)	0.223

MAC = mitral annular calcification; MVD = mitral valve diseases including mitral stenosis (≥mild) and mitral regurgitation (≥moderate) ; STS = Society of Thoracic Surgeons; NYHA = New York Heart Association; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; TIA = transient ischemic attack.

Table 2. Comparison of Echocardiographic and Computed tomographic Data

	No/Non-severe MAC (n=795)		Severe MAC (n=172)		P=value
	No-MVD (n=567)	MVD (n=228)	No-MVD (n=85)	MVD (n=87)	
Echocardiographic data					
Aortic valve area (cm^2)	0.68 ± 0.24	0.65 ± 0.27	0.62 ± 0.21	0.58 ± 0.23	0.003
LV ejection fraction (%)	56.0 ± 13.5	49.1 ± 16.3	59.2 ± 12.4	56.8 ± 12.8	<0.001
AR ≥ moderate (n, %)	10 (1.8%)	5 (2.2%)	0 (0.0%)	0 (0.0%)	0.322
MR ≥ moderate (n, %)	0 (0.0%)	131 (57.5%)	0 (0.0%)	36 (41.4%)	<0.001
TR ≥ moderate (n, %)	41 (7.3%)	62 (27.3%)	3 (3.6%)	19 (21.8%)	<0.001
Severity of MS (n, %)					<0.001
Mild	0 (0.0%)	98 (43.0%)	0 (0.0%)	49 (56.3%)	
Moderate	0 (0.0%)	11 (4.8%)	0 (0.0%)	8 (17.3%)	
Severe	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (1.1%)	

Mitral valve mean gradient (mmHg)	1.42 ± 0.88	2.26 ± 1.92	2.85 ± 1.64	3.99 ± 2.37	<0.001
Computed tomography data					
Annulus area (mm^2)	460.9 ± 89.2	450.1 ± 77.8	435.2 ± 82.2	419.2 ± 72.0	<0.001
AVC calcium (mm^2)	325.7 ± 384.5	382.7 ± 416.1	356.1 ± 320.2	383.3 ± 346.6	0.218
LVOT calcium (mm^2)	12.9 ± 42.1	22.2 ± 71.6	24.7 ± 53.5	36.4 ± 75.1	0.001

MAC = mitral annular calcification; MVD = mitral valve diseases including mitral stenosis (≥mild) and mitral regurgitation (≥moderate) ; LV = left ventricular; LA = left atrium; AR = aortic regurgitation; MR = mitral regurgitation; MS = mitral stenosis; AVC = aortic valve complex; LVOT = left ventricular outflow tract.

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Table 3. Procedural characteristics and complications

	No/Non-severe MAC (n=795)		Severe MAC (n=172)		P=value
	No-MVD (n=567)	MVD (n=228)	No-MVD (n=85)	With MVD (n=87)	
Fluoroscopy time (min)	19.8 ± 15.2	20.1 ± 8.7	18.7 ± 9.6	20.1 ± 10.9	0.955
General Anesthesia (n, %)	110 (19.4%)	69 (30.3%)	19 (22.4%)	18 (20.7%)	0.011
Trans-femoral access (n, %)	523 (92.2%)	197 (86.4%)	75 (88.2%)	81 (93.1%)	0.053
Type of valve (n, %)					
Balloon-expandable	262 (46.5%)	102 (44.7%)	34 (40.0%)	39 (44.8%)	0.728
Self-expandable	252 (44.7%)	115 (50.4%)	38 (44.7%)	41 (47.1%)	0.517
Mechanically expandable	50 (8.9%)	11 (4.8%)	13 (15.3%)	7 (8.0%)	0.027
Implanted valve size					0.162
≤27mm	367 (65.1%)	149 (65.4%)	61 (71.8%)	66 (75.9%)	
>27mm	197 (34.9%)	79 (34.6%)	24 (28.2%)	21 (24.1%)	

Pre-dilatation (n, %)	402 (70.9%)	168 (73.7%)	66 (77.6%)	74 (85.1%)	0.034
Post-dilatation (n, %)	154 (27.2%)	69 (30.3%)	26 (30.6%)	20 (23.0%)	0.545
Procedural Complications					
Valve in series (n, %)	9 (1.6%)	3 (1.3%)	2 (2.4%)	1 (1.1%)	0.911
Valve dislocation/embolization (n, %)	15 (3.0%)	2 (1.2%)	1 (1.4%)	3 (4.2%)	0.433
Annulus rupture/aortic dissection (n, %)	3 (0.6%)	4 (2.4%)	0 (0.0%)	1 (1.4%)	0.173
Coronary artery occlusion (n, %)	7 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.221

MAC = mitral annular calcification; MVD = mitral valve diseases including mitral stenosis (≥mild) and mitral regurgitation (≥moderate).

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Table 4. 30-days Clinical Outcomes

	No/No-severe MAC (n=795)		Severe MAC (n=172)		No/No-severe MAC with MVD*		Severe MAC with No-MVD*		Severe MAC with MVD*	
	No-MVD (n=567)	MVD (n=228)	No-MVD (n=85)	MVD (n=87)	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Composite outcome (death/disabling stroke)	16 (2.8)	20 (8.8)	2 (2.4)	6 (6.9)	3.17 (1.64-6.11)	0.001	0.82 (0.19-3.59)	0.797	2.47 (0.97-6.31)	0.059
All-cause death	12 (2.1)	15 (6.6)	1 (1.2)	5 (5.7)	3.16 (1.48-6.75)	0.003	0.55 (0.07-4.23)	0.566	2.73 (0.96-7.76)	0.059
Cardiovascular death	10 (1.8)	14 (6.2)	1 (1.2)	4 (4.6)	3.54 (1.57-7.96)	0.002	0.66 (0.08-5.16)	0.693	2.63 (0.82-8.37)	0.103
Myocardial infarction	7 (1.2)	3 (1.4)	1 (1.2)	0 (0.0)	1.07 (0.28-4.13)	0.924	0.95 (0.12-7.72)	0.962		
Disabling stroke	9 (1.6)	7 (3.1)	1 (1.2)	4 (4.7)	1.96	0.181	0.73	0.769	2.92	0.075

					(0.73-5.27)		(0.09-5.79)		(0.90-9.47)	
Bleeding (Any)	134 (23.7)	69 (30.4)	26 (30.6)	34 (39.3)	1.31 (0.98-1.75)	0.071	1.33 (0.87-2.02)	0.183	1.72 (1.18-2.50)	0.005
Life-threatening	34 (6.0)	25 (11.0)	5 (5.9)	6 (6.9)	1.85 (1.10-3.10)	0.020	0.98 (0.38-2.51)	0.968	1.16 (0.49-2.76)	0.742
Major	62 (11.0)	32 (14.1)	14 (16.5)	19 (22.0)	1.30 (0.85-2.00)	0.225	1.52 (0.85-2.72)	0.155	2.04 (1.22-3.41)	0.007
Vascular complication (Major)	56 (9.9)	21 (9.3)	9 (10.6)	13 (15.0)	0.93 (0.56-1.54)	0.783	1.07 (0.53-2.17)	0.848	1.52 (0.83-2.78)	0.173
Kidney injury stage 3	10 (1.8)	6 (2.7)	3 (3.5)	0 (0.0)	1.50 (0.55-4.13)	0.433	1.99 (0.55-7.22)	0.297		
Pacemaker implantation	113 (20.1)	45 (20.2)	14 (16.5)	24 (27.9)	1.02 (0.72-1.44)	0.915	0.81 (0.47-1.41)	0.461	1.48 (0.95-2.29)	0.083

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*Tested versus the reference group, which is no/non-severe MAC with no-MVD.

HR = hazard ratio; CI = confidence interval; MAC = mitral annular calcification; MVD = mitral valve diseases including mitral stenosis (≥mild) and mitral regurgitation (≥moderate).

Table 5. 1-year Clinical Outcomes

	No/No-severe MAC (n=795)		Severe MAC (n=172)		No/No-severe MAC with MVD*		Severe MAC with No-MVD*		Severe MAC with MVD*	
	No-MVD (n=567)	MVD (n=228)	No-MVD (n=85)	MVD (n=87)	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Composite outcome (death/disabling stroke)	59 (10.5)	58 (25.6)	9 (10.7)	18 (20.7)	2.64 (1.84-3.79)	<0.001	1.01 (0.50-2.03)	0.987	2.11 (1.24-3.57)	0.006
All-cause death	49 (8.8)	53 (23.4)	5 (6.0)	17 (19.5)	2.89 (1.96-4.26)	<0.001	0.67 (0.27-1.67)	0.386	2.40 (1.38-4.17)	0.002
Cardiovascular death	28 (5.1)	35 (15.8)	4 (4.8)	15 (17.5)	3.32 (2.02-5.45)	<0.001	0.93 (0.33-2.66)	0.898	3.69 (1.97-6.90)	<0.001
Disabling stroke	16 (2.9)	8 (3.6)	4 (4.9)	4 (4.7)	1.30 (0.56-3.03)	0.547	1.65 (0.55-4.93)	0.372	1.68 (0.56-5.02)	0.354

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*Tested versus the reference group, which is no/non-severe MAC with no-MVD.

HR = hazard ratio; CI = confidence interval; MAC = mitral annular calcification; MVD = mitral valve diseases including mitral stenosis (≥mild) and mitral regurgitation (≥moderate).

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Table 6. Predictive factors for all-cause death at 1 year

Variables	Univariate analysis		Variables	Multivariate analysis	
	HR (95% CI)	p value		HR (95% CI)	p value
No/Non-severe MAC + Non-MVD	[Reference]		No/Non-severe MAC + non-MVD	[Reference]	
No/Non-severe MAC + MVD	2.89 (1.96-4.26)	<0.001	No/Non-severe MAC + MVD	2.33 (1.56-3.47)	<0.001
Severe MAC + Non-MVD	0.67 (0.27-1.67)	0.386	Severe MAC + non-MVD	0.52 (0.21-1.33)	0.173
Severe MAC + MVD	2.40 (1.38-4.17)	0.002	Severe MAC + MVD	1.97 (1.12-3.44)	0.018
Age	1.01 (0.98-1.04)	0.439	Body mass index	0.94 (0.90-0.98)	0.004
Female	0.77 (0.54-1.10)	0.149	NYHA class Ⅲ/Ⅳ	1.98 (1.23-3.19)	0.005
Body mass index	0.94 (0.91-0.98)	0.004	Hypertension	0.60 (0.39-0.93)	0.022
STS score: mortality	1.08 (1.05-1.12)	<0.001	Diabetes	2.37 (1.61-3.49)	<0.001
NYHA class Ⅲ/Ⅳ	2.27 (1.42-3.63)	0.001	Prior stroke or TIA	1.44 (0.92-2.27)	0.114
Hypertension	0.64 (0.42-0.97)	0.035	Peripheral artery disease	1.73 (1.11-2.71)	0.016
Diabetes	2.03 (1.41-2.91)	<0.001			

Dyslipidemia	0.84 (0.59-1.20)	0.340
CKD (eGFR<60)	1.59 (1.05-2.41)	0.029
COPD	1.36 (0.84-2.19)	0.212
Coronary artery disease	1.02 (0.71-1.46)	0.921
Prior stroke or TIA	1.79 (1.15-2.79)	0.011
Peripheral artery disease	1.80 (1.17-2.77)	0.008
Permanent pacemaker	1.59 (0.94-2.68)	0.085
Atrial fibrillation	1.89 (1.32-2.70)	0.001
Hemoglobin	0.99 (0.98-0.99)	0.005
BNP	1.00 (1.00-1.00)	<0.001
Aortic valve area	1.15 (0.57-2.31)	0.700
LV ejection fraction	0.98 (0.97-0.99)	0.000
AR ≥ moderate	¶	
TR ≥ moderate	4.00 (1.63-9.78)	0.002

Annulus area	1.00 (1.00-1.00)	0.152
AVC calcium	1.00 (1.00-1.00)	0.076
LVOT calcium	1.00 (1.00-1.01)	0.003
Trans-femoral access	0.63 (0.38-1.06)	0.080

All the variables were stepwise tested for entry into the multivariate model, with p value of entry of 0.10. Estimates were based on 20 multiple imputed datasets, combining estimates using Rubin's rule.

HR = hazard ratio; CI = confidence interval; MAC = mitral annular calcification; MVD = mitral valve diseases including mitral stenosis (≥mild) and mitral regurgitation (≥moderate); STS = Society of Thoracic Surgeons; NYHA = New York Heart Association; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; TIA = transient ischemic attack; LBBB = left bundle branch block; RBBB = right bundle branch block; LV = left ventricular; LA = left atrium; AR = aortic regurgitation; MR = mitral regurgitation; MS = mitral stenosis; AVC = aortic valve complex; LVOT = left ventricular outflow tract.

Table 7. Independent effects of severe MAC, MS, and MR on 1-year mortality

Variables			Unadjusted		Adjusted	
	sample size	Deaths (%)	HR (95% CI)	p-value	HR (95% CI)	p-value
Non-severe MAC + Non-MVD	567	49 (8.8)	[Reference]		[Reference]	
+ severe MAC	172	22 (12.8)	1.51 (0.91-2.49)	0.110	1.16 (0.69-1.96)	0.570
+ MS	168	38 (22.8)	2.81 (1.84-4.30)	<0.001	2.37 (1.53-3.66)	<0.001
+ MR	167	38 (22.8)	2.82 (1.84-4.30)	<0.001	1.88 (1.20-2.94)	0.005
+ severe MAC + MS	58	11 (19.0)	2.33 (1.21-4.48)	0.011	1.67 (0.85-3.30)	0.14
+ severe MAC + MR	36	8 (22.2)	2.77 (1.31-5.85)	0.008	1.62 (0.73-3.56)	0.23
+ MR + MS	20	6 (30.0)	3.87 (1.66-9.05)	0.002	1.90 (0.77-4.67)	0.16
+ severe MAC +MS + MR	7	2 (28.6)	3.87 (0.94-15.92)	0.061	1.06 (0.23-4.93)	0.94

Adjusted for body mass index, NYHA class Ⅲ/Ⅳ, hypertension, diabetes, prior stroke or TIA, peripheral artery disease.

HR = hazard ratio; CI = confidence interval; MAC = mitral annular calcification; MVD = mitral valve diseases including mitral stenosis (≥mild) and mitral regurgitation (≥moderate); MS = mitral stenosis (≥mild); MR = mitral regurgitation (≥moderate).

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FIGURE LEGENDS

Figure 1 Grading of MAC severity by Computed Tomography

MAC severity was qualitatively determined by the circumferential involvement of the mitral ring: mild was defined as involvement in less than 1/3 of the annulus; moderate between 1/3 and 1/2; and severe if the calcification was present in more than half of the mitral annulus circumference (1, 15). MAC = mitral annular calcification.

Figure 2 Study flow chart.

TAVR = transcatheter aortic valve replacement; CT = computed tomography; MAC = mitral annular calcification; MR = mitral regurgitation; MS = mitral stenosis; MVD = mitral valve disease including moderate or severe MR and mild or greater MS.

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Figure 3 Prevalence of MVD according to the presence or absence of severe MAC.

The prevalence of MVD significantly increased in patients with severe MAC (p<0.001). MAC = mitral annular calcification; MS = mitral stenosis (≥mild); MR = mitral regurgitation (≥moderate); MSR = mitral stenosis (≥mild) with regurgitation (≥moderate); MVD = mitral valve disease including MS and MR.

Figure 4 Kaplan-Meier curves of (A) all-cause death and (B) cardiovascular death according to the severity of MAC.

Blue lines indicate no MAC; orange lines indicate mild/moderate MAC; red lines indicate severe MAC. MAC = mitral annular calcification; HR = hazard risk; CI = confidence interval.

Figure 5 Survival curves stratified by the presence or absence of severe MAC and relevant MVD.

The Kaplan-Meier curves show similar increased risks of (A) all-cause and (B) cardiovascular death both in patients with MVD regardless of presence or absence of severe MAC, whereas patients with isolated severe MAC had comparable survival compared to patients without severe MAC and MVD. Light blue lines indicate non-severe MAC without MVD; blue lines indicate isolated MVD; orange lines indicate isolated severe MAC; red lines indicate severe MAC concomitant with MVD. MAC = mitral annular calcification; MS = mitral stenosis (≥mild); MR = mitral regurgitation (≥moderate); MSR = mitral stenosis (≥mild) with regurgitation (≥moderate); MVD = mitral valve disease including MS and MR.

Figure 6 Bar graph illustrating all-cause death at 1 year according to concomitant MAC, MR, and MS.

MAC = mitral annular calcification; MR = mitral regurgitation (≥moderate); MS = mitral stenosis (≥mild); MSR = mitral stenosis

(≥mild) with regurgitation (≥moderate); MVD = mitral valve disease including MS and MR.

Figure 7 Prevalence of MS and MR according to the severity of MAC.

MAC = mitral annular calcification; MS = mitral stenosis; MR = mitral regurgitation.

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Figures

Figure 1 Grading of MAC severity by Computed Tomography

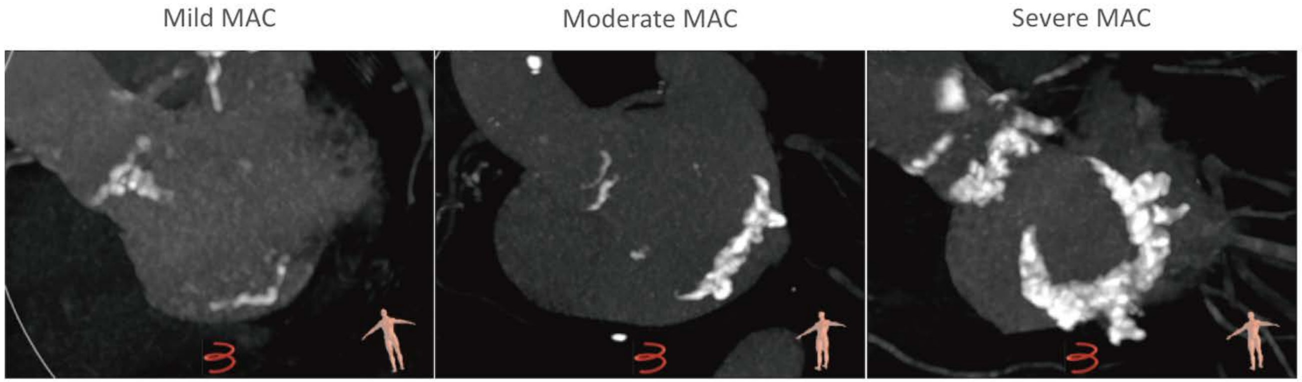

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Figure 2 Study flow chart.

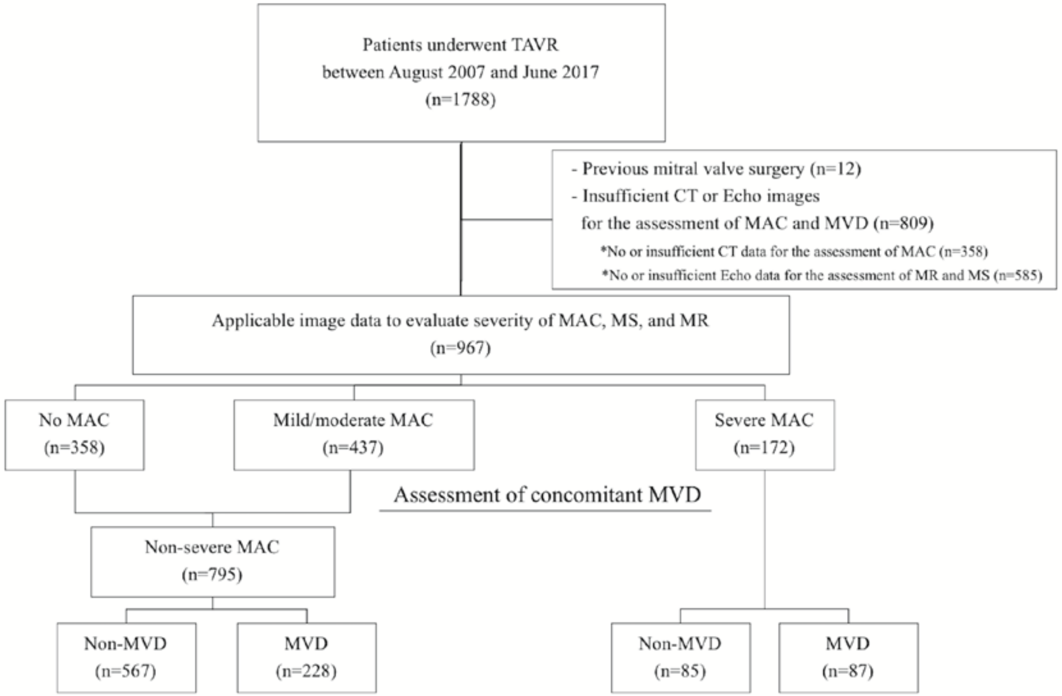

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Figure 3 Prevalence of MVD according to the presence or absence of severe MAC.

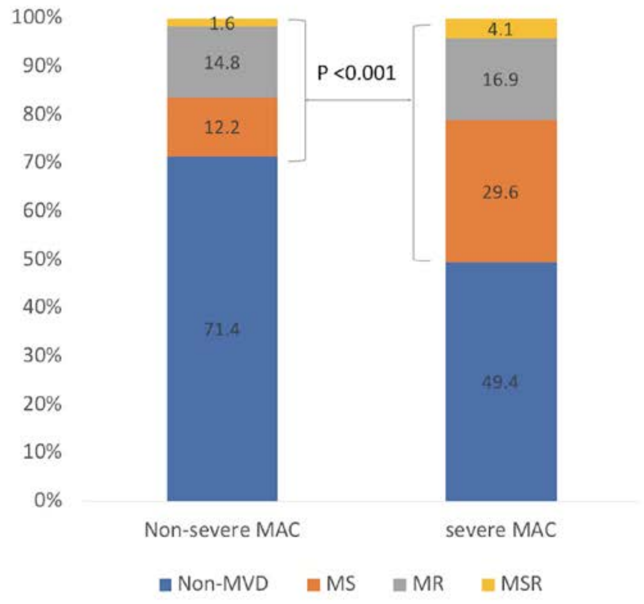

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Figure 4 Kaplan-Meier curves of (A) all-cause death and (B) cardiovascular death according to the severity of MAC.

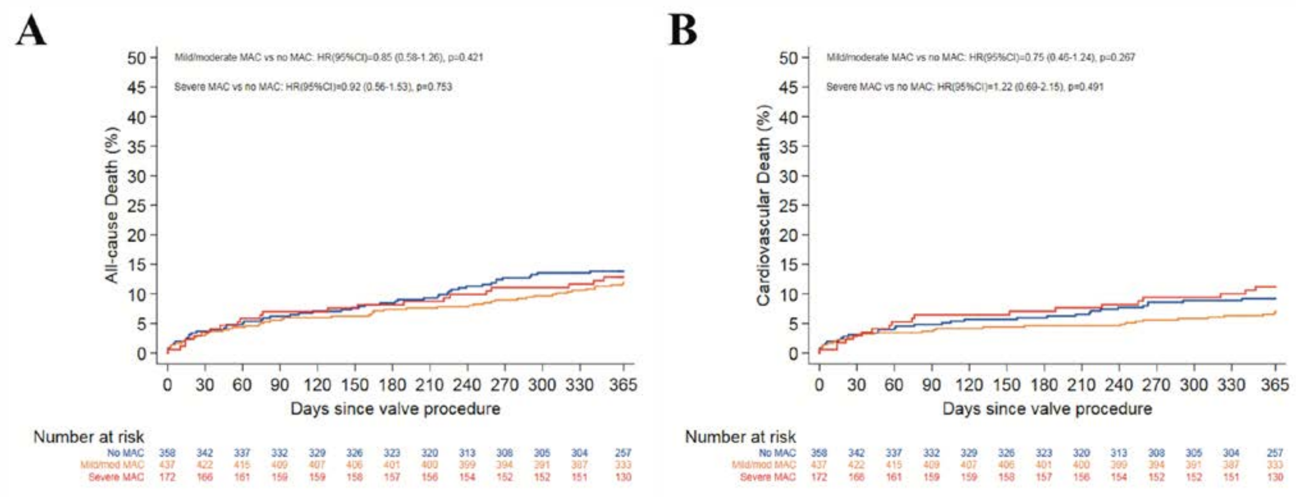

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Figure 5 Survival curves stratified by the presence or absence of severe MAC and relevant MVD.

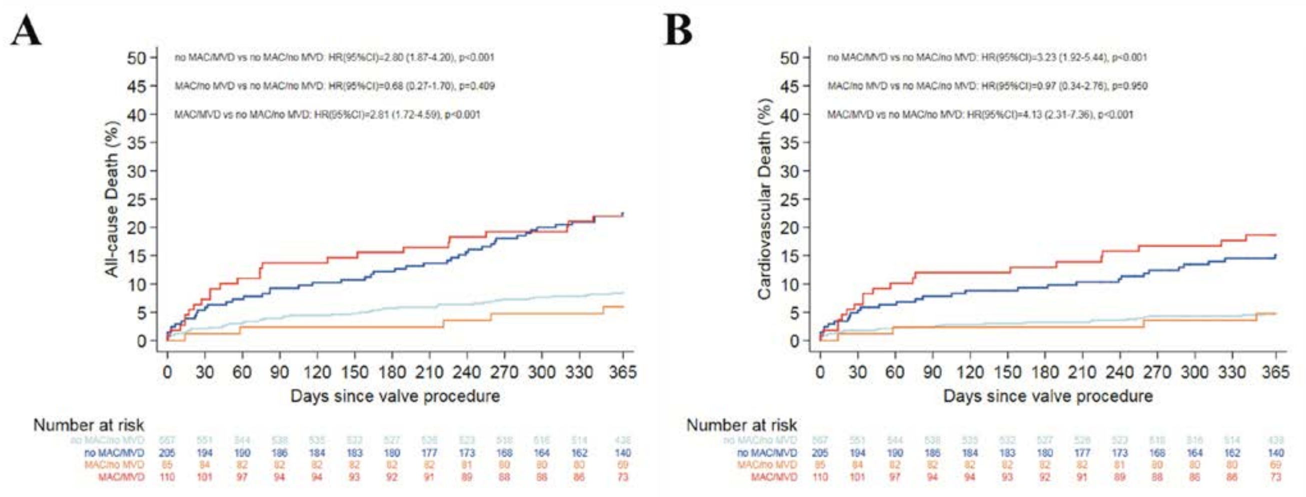

Figure 6 Bar graph illustrating all-cause death at 1 year according to concomitant MAC, MR, and MS.

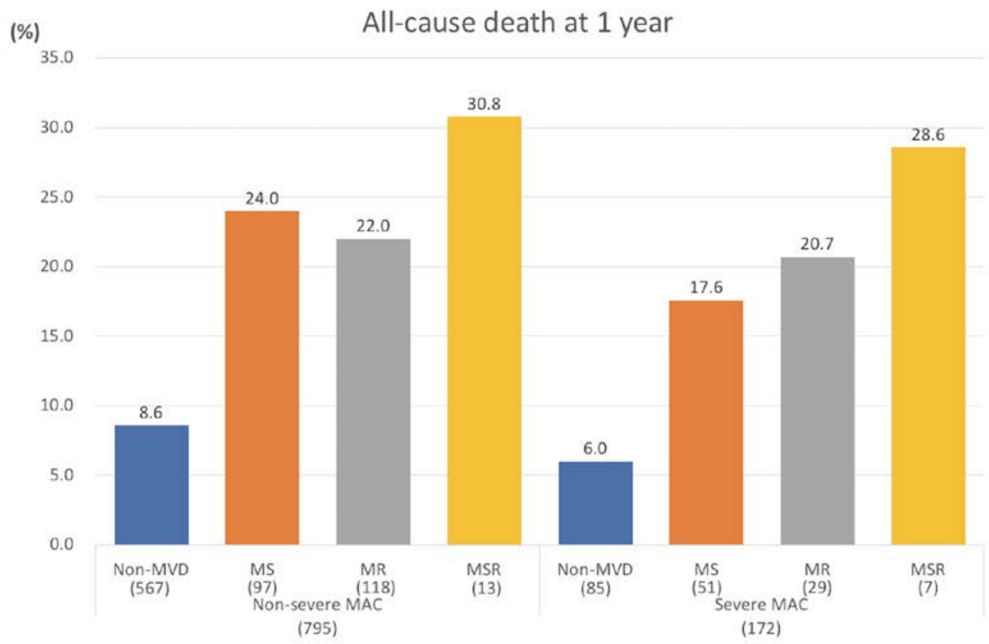

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Figure 7 Prevalence of MS and MR according to the severity of MAC.