Novel imaging insights into cardiac remodeling, myocardial function and risk stratification in cardiovascular disease

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Factors influencing post-surgical survival in degenerative mitral regurgitation

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ABSTRACT

Aims

Indications for surgery in patients with degenerative mitral regurgitation (DMR) are increasingly liberal in all clinical guidelines but the role of secondary outcome determinants (left atrial volume index [LAVI] ≥60ml/m^2, atrial fibrillation [AF], pulmonary artery systolic pressure [PASP] ≥50mmHg and moderate to severe tricuspid regurgitation [TR]) and their impact on postoperative outcome remain disputed. Whether these secondary outcome markers are just reflective of the DMR severity or intrinsically affect survival after DMR surgery is uncertain and may have critical importance in the management of patients with DMR. To address these gaps of knowledge the present study gathered a large cohort of patients with quantified DMR, accounted for the number of secondary outcome markers and examined their independent impact on survival after surgical correction of the DMR.

Methods and Results

The Mitral Regurgitation International DAtabase-Quantitative (MIDA-Q) registry includes patients with isolated DMR from centres across North America, Europe, and the Middle East. Patient enrolment extended from January 2003 to January 2020. All patients undergoing mitral valve surgery within 1 year of registry enrolment were selected. A total of 2276 patients (65 [55-73] years, 32% male) across 5 centres met study eligibility criteria. Over a median follow-up of 5.6 (3.6 to 8.7) years, 278 patients (12.2%) died. In a comprehensive multivariable Cox regression model adjusted for age, EuroSCORE II, symptoms, LVEF, LV ESD and DMR severity, the number of secondary outcome determinants was independently associated with post-operative all-cause mortality, with adjusted HRs of 1.56 (95% CI 1.11 to 2.20, P=0.011), 1.78 (95% CI 1.23 to 2.58, P=0.002) and 2.58 (95% CI 1.73 to 3.83, P<0.0001) for patients with one, two and three or four secondary outcome determinants, respectively. A model incorporating the number of secondary outcome determinants demonstrated a higher C-index and was significantly more concordant with post-operative mortality than models incorporating traditional Class I indications alone (the presence of symptoms [P=0.0003], or LVEF ≤60% [P=0.006], or LV ESD ≥40mm [P=0.014]), while there was no significant difference in concordance observed compared to a model that incorporated the number of Class I indications for surgery combined (P=0.71).

Conclusion

In this large cohort of patients treated surgically for DMR the presence and number of secondary outcome determinants was independently associated with post-surgical survival and demonstrated better outcome discrimination than traditional Class I indi-

cations for surgery. Randomised controlled trials are needed to determine if patients with severe DMR who demonstrate a cardiac phenotype with an increasing number of secondary outcome determinants would benefit from earlier surgery.

INTRODUCTION

Degenerative mitral regurgitation (DMR) characterised by mitral valve prolapse (MVP), the most common type of organic mitral valve disease[1,2], is associated with increased morbidity and mortality compared to the general population[3], and is highly amenable to surgical intervention[4,5]. However, despite guideline recommendations, severe undertreatment of the condition is observed with tremendous excess-mortality[6], suggesting the need for additional data to guide DMR surgical correction[4,7].

Although the importance of Class I indications (based on symptoms and left ventricular [LV] function) for surgery are well-acknowledged (culminating as strong recommendations in contemporary guidelines)[5], recent studies have also demonstrated the prognostic importance of secondary outcome determinants, such as pulmonary artery systolic pressure (PASP), atrial fibrillation, tricuspid regurgitation (TR) and left atrial volume index (LAVI)[3,4,8-10]. These secondary outcome determinants, although widely acknowledged and supported by observational data, do not at present represent strong recommendations or Class I indications for surgery in current guidelines[3-5,8-10]. In addition, evaluation of the cumulative importance of the number of secondary outcome determinants, reflecting increased atrial, pulmonary and right ventricular consequences of DMR and a high-risk phenotype, has not been studied in a contemporary population undergoing mitral valve surgery for DMR due to a variety of aetiologies. Whether such phenotype even in the absence of overt LV systolic dysfunction (LV ejection fraction [LVEF] ≤60% and LV end-systolic diameter [LV ESD] ≥40mm)[5] or symptoms, reflects DMR severity or a DMR-linked physiologic response with substantial increase in left atrial pressure, pulmonary venous and possibly arterial pressure[11] is uncertain. This could result in considerable adverse remodelling of the left atrium, pulmonary vasculature, and tricuspid valve, leading to poor outcome. We hypothesised that patients with increased atrial, pulmonary and right ventricular consequences of isolated DMR are a particularly high-risk cohort, even after surgical DMR correction, which could be of critical importance in the consideration of the indication for DMR surgical intervention. We further hypothesised that accounting for the number of secondary outcome markers could provide similar prognostic utility to established class I indications for surgery.

Therefore, the aim of this study was three-fold: (1) To evaluate and validate the prognostic value of LAVI, atrial fibrillation, PASP and moderate to severe TR in a large, international cohort of DMR patients undergoing surgery, (2) To evaluate the prognostic implications of an increasing number of these secondary outcome determinants in DMR, and (3) to evaluate the relative prognostic importance of the number of secondary outcome determinants in comparison with established class I indications for surgery.

METHODS

Study Design

The Mitral Regurgitation International DAtabase-Quantitative (MIDA-Q) registry was created by systematically merging a series of prospectively assembled electronic institutional databases of patients with quantified isolated DMR from countries in North America (Mayo Clinic, Rochester, MN, USA), Europe (Leiden University Medical Center, Leiden, the Netherlands; University of Amiens, Amiens, France; University of Nantes, Nantes, France) and the Middle East (Tel Aviv Medical Center, Tel Aviv, Israel). Patient enrolment extended from January 2003 to January 2020, according to each centre's database. Eligibility criteria included the following: 1) inclusion of consecutive patients with a diagnosis of DMR (due to mitral valve prolapse or flail leaflet) by transthoracic echocardiography; 2) availability of comprehensive clinical evaluation recorded prospectively at the time of index echocardiography; 3) exclusion of functional MR of any aetiology, significant concomitant aortic valve disease, mitral stenosis, congenital heart disease, rheumatic heart disease, active endocarditis, and prior valve surgery. All patients undergoing mitral valve surgery within 1 year of registry enrolment were selected. The study was approved by the Institutional Review Board of each centre, conducted in accordance with institutional guidelines, national legal requirements, and the *Declaration of Helsinki*.

Echocardiography

Echocardiographic studies were performed with commercially available ultrasound systems and analysed by experienced investigators from each centre. Left ventricular ejection fraction (LVEF) was calculated using the biplane Simpson method. LV ESD and LV end-diastolic diameter (LV EDD) were measured using the 2D linear method, as per guideline recommendations[12]. LAVI was calculated from apical 2- and 4-chamber views using the biplane method, indexed for body surface area. PASP was estimated by applying the modified Bernoulli equation to the TR jet peak velocity and adding estimated right atrial pressure. Estimated right atrial pressure was calculated from the inferior vena cava diameter and its collapsibility. TR grade was evaluated using a multiparametric approach according to guideline recommendations, integrating qualitative, semiquantitative and quantitative parameters[13]. MR severity was quantitatively assessed according to current recommendations using a multiparametric approach, including quantification of the effective regurgitant orifice area (EROA) and MR regurgitant volume[4,13].

Follow-up and Study Endpoint

Follow-up began from the date of mitral valve surgery. The primary endpoint of the study was post-surgical all-cause mortality. Follow-up data were complete for all patients and were included up to the last date of follow-up.

Statistical Analysis

Categorical variables are expressed as numbers and percentages, while continuous variables are presented as median and interquartile range (IQR). To evaluate the prognostic importance of LAVI, atrial fibrillation, PASP, TR and an increasing number of secondary outcome determinants (LAVI ≥60ml/m^2, atrial fibrillation, PASP ≥50mmHg and the presence of moderate to severe TR) indicative of atrial, pulmonary and right ventricular consequences of isolated DMR, the population was divided into four groups: Group I – No secondary outcome determinants; Group II – One secondary outcome determinant, Group III – Two secondary outcome determinants, Group IV – Three or four secondary outcome determinants. The decision to add the number of secondary outcome determinants together to identify high-risk phenotypes was pre-specified. Pearson's correlation was utilized to evaluate for multicollinearity between secondary outcome determinants (Table S1). Cumulative survival according to group was calculated using the Kaplan–Meier method and compared using the log-rank test. Univariable Cox proportional hazards regression analysis was used to evaluate the association of each secondary outcome determinant and for an increasing number of parameters and all-cause mortality. Multivariable Cox proportional hazards regression analyses were performed using two levels of adjustment: first, adjusted for baseline clinical characteristics: age, sex, EuroSCORE II, symptoms (core model); second, adjusting additionally for prognostically important echocardiographic factors: LVEF, LV ESD and MR grade (comprehensive model). Hazard ratio (HR) and 95% confidence intervals (CIs) were reported for each model. The proportional hazards assumption was verified through the evaluation of scaled Schoenfeld residuals. To compare the prognostic value of the number of secondary outcome determinants with Class I surgical indications (the presence of symptoms, LVEF ≤60% and LV ESD ≥40mm)[5] and an increasing number of Class I indications, the discriminative value of each model was assessed with the C-index. The rank correlation U-statistic for paired censored data was used to compare the concordance of each model with the model including the number of secondary outcome determinants[14]. All tests were two-sided and P-values <0.05 were considered statistically significant. Statistical analysis was performed using R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics

A total of 2276 patients meeting study eligibility criteria from 5 international centres were included. The baseline characteristics of the population according to number of secondary outcome determinants are presented in Table 1. A total of 874 patients (38.4%) had no secondary outcome determinants, 795 (34.9%) had one secondary outcome determinant, 391 (17.2%) had two secondary outcome determinants and 216 (9.5%) had three or four secondary outcome determinants. Patients with an increasing number of secondary outcome determinants were older, more symptomatic, more likely to be male and had a higher EuroSCORE II. In addition, patients with one or more secondary outcome determinants had larger EROAs and MR regurgitant volumes than those with no secondary outcome determinants, indicating an association with increasing MR severity. The proportion of patients using various medications is provided in Table S2.

Prognostic value of LAVI, atrial fibrillation, PASP and TR for post-surgical survival in DMR

Over a median follow-up of 5.6 (3.6 to 8.7) years, 278 patients (12.2%) died. A total of 2083 (92%) patients underwent mitral valve repair and 183 (8%) underwent mitral valve replacement. Post-operative mortality at 30 days was 0.83%. Concomitant tricuspid valve repair was performed in 445 (19.5%) of patients. All secondary outcome determinants (LAVI ≥60ml/m^2, atrial fibrillation, PASP ≥50mmHg and the presence of moderate to severe TR) were significantly associated with all-cause mortality on univariable Cox regression analyses (P<0.0001 for all). In addition, in multivariable Cox regression proportional hazard core models adjusted for age, sex, EuroSCORE II and symptoms, LAVI ≥60ml/m^2, atrial fibrillation, PASP ≥50mmHg and the presence of moderate to severe TR were all significantly associated with post-operative mortality (Table 2). In multivariable Cox regression models further adjusted for LVEF, LV ESD and MR grade, an independent association between post-operative all-cause mortality and LAVI ≥60ml/m^2 (HR 1.38, 95% CI 1.07 to 1.78, P=0.014), atrial fibrillation (HR 1.46, 95% CI 1.14 to 1.89, P=0.003), PASP ≥50mmHg (HR 1.50, 95% CI 1.15 to 1.97, P=0.003) and the presence of moderate to severe TR (HR 1.46, 95% CI 1.09 to 1.96, P=0.010) was retained. In a sensitivity analysis, following further adjustment for specific comorbidities (hypertension, diabetes mellitus and COPD), results were consistent with the main analysis for each model (Table S3).

Table 1: Patient and Echocardiographic Characteristics Divided According to Number of Secondary Outcome Determinants

Variable	Overall N = 2,276	No Secondary Outcome Determinants* N = 874	One Secondary Outcome Determinant* N = 795	Two Secondary Outcome Determinants* N = 391	Three or Four Secondary Outcome Determinants* N = 216	P-value
Age, years	65 (55 to 73)	60 (51 to 69)	64 (55 to 72)	69 (60 to 75)	76 (69 to 81)	<0.001
Male Sex	726 (32%)	251 (29%)	241 (30%)	139 (36%)	95 (44%)	<0.001
Current Smoker	534 (40%)	233 (40%)	181 (41%)	83 (37%)	37 (41%)	0.74
COPD	96 (4.3%)	30 (3.4%)	31 (4.0%)	20 (5.2%)	15 (7.2%)	0.079
Diabetes mellitus	120 (5.3%)	42 (4.8%)	35 (4.5%)	17 (4.4%)	26 (12%)	<0.001
Hypertension	626 (35%)	261 (34%)	199 (34%)	105 (36%)	61 (45%)	0.082
Systolic Blood Pressure, mmHg	120 (110 to 130)	122 (110 to 130)	120 (110 to 13)	120 (110 to 130)	121 (110 to 137)	0.36
Symptoms	1,379 (61%)	474 (54%)	459 (58%)	285 (73%)	161 (75%)	<0.001
EuroSCORE II	0.82 (0.64 to 1.21)	0.69 (0.59 to 0.91)	0.82 (0.62 to 1.14)	1.09 (0.80 to 1.49)	1.47 (1.12 to 2.03)	<0.001
LV ejection fraction, %	65 (61 to 70)	66 (62 to 70)	66 (62 to 70)	65 (60 to 70)	64 (58 to 69)	<0.001
LV end-systolic diameter, mm	35 (31 to 39)	34 (30 to 38)	36 (32 to 40)	36 (32 to 41)	36 (32 to 41)	<0.001
EROA, mm^2	45 (35 to 58)	42 (32 to 53)	46 (37 to 59)	48 (38 to 64)	47 (34 to 61)	<0.001
MR regurgitant volume, ml	69 (54 to 86)	65 (50 to 82)	73 (58 to 92)	70 (55 to 88)	70 (55 to 85)	<0.001
LA volume indexed, ml/m^2	58 (44 to 76)	45 (37 to 51)	66 (53 to 80)	75 (62 to 94)	81 (68 to 99)	<0.001
PA systolic pressure, mmHg	36 (30 to 48)	30 (27 to 36)	36 (30 to 45)	50 (37 to 60)	59 (52 to 67)	<0.001
Moderate or severe TR	321 (14%)	0 (0%)	61 (7.7%)	90 (23%)	170 (79%)	<0.001
Data presented as median (25% to 75%); n (%)						
*Secondary Outcome Determinants include atrial fibrillation, LAVI ≥60ml/m^2, PASP ≥50mmHg and/or the presence of moderate to severe TR						

COPD = chronic obstructive pulmonary disease, EROA = effective regurgitation orifice area, LA = left atrial, LV = left ventricular, MR = mitral regurgitation, PA = pulmonary artery, TR = tricuspid regurgitation

Table 2: Univariable and multivariable hazard ratio (HR) for mortality for LAVI, PASP, atrial fibrillation and TR severity

	Secondary Outcome Determinant Subgroups	Hazard Ratio (95% CI)	P-value
Univariable	LAVI ≥60 ml/m^2	1.64 (1.30 to 2.08)	<0.0001
	PASP ≥50 mmHg	2.67 (2.10 to 3.41)	<0.0001
	Atrial fibrillation	2.53 (1.99 to 3.22)	<0.0001
	Moderate or severe TR	2.57 (1.96 to 3.37)	<0.0001
Adjusted for age, sex, EuroSCORE II, symptoms (core model)	LAVI ≥60 ml/m^2	1.31 (1.03 to 1.67)	0.027
	PASP ≥50 mmHg	1.45 (1.12 to 1.87)	0.005
	Atrial fibrillation	1.52 (1.19 to 1.94)	0.0008
	Moderate or severe TR	1.45 (1.09 to 1.92)	0.011
Further adjustment for LVEF, LV ESD and MR grade (comprehensive model)	LAVI ≥60 ml/m^2	1.38 (1.07 to 1.78)	0.014
	PASP ≥50 mmHg	1.50 (1.15 to 1.97)	0.003
	Atrial fibrillation	1.46 (1.14 to 1.89)	0.003
	Moderate or severe TR	1.46 (1.09 to 1.96)	0.010

ESD = end-systolic diameter, LAVI = left atrial volume index, LV = left ventricular, LVEF = left ventricular ejection fraction, MR = mitral regurgitation, PASP = pulmonary artery systolic pressure, TR = tricuspid regurgitation

Prognostic implications of the number of secondary outcome determinants

Overall post-operative survival at 5-years was markedly different according to the number of secondary outcome determinants: 96.3% for patients with no secondary outcome determinants, versus 93.6%, 88.8% and 72.1% for patients with one, two and three or four secondary outcome determinants, respectively (P<0.0001, Figure 1). In the multivariable Cox regression proportional hazard core model adjusted for age, sex, EuroSCORE II and symptoms, the number of secondary outcome determinants remained associated with all-cause mortality (Table 3). In addition, in a comprehensive model with further adjustment for LVEF, LV ESD and MR grade, the number of secondary outcome determinants was independently associated with all-cause mortality, with adjusted HRs of 1.56 (95% CI 1.11 to 2.20, P=0.011), 1.78 (95% CI 1.23 to 2.58, P=0.002) and 2.58 (95% CI 1.73 to 3.83, P<0.0001) for patients with one, two and three or four secondary outcome determinants, respectively, compared to those with no secondary outcome determinants (Table 3, Figure 2). When added to the comprehensive multivariable Cox regression model, the year of surgery was significantly associated with reduced all-cause mortality (HR 0.96 per year, 95% CI 0.93 to 1.00, P=0.031), while the number of secondary outcome determinants remained significantly associated with the primary endpoint, with adjusted HRs of 1.58 (95% CI 1.12 to 2.23, P=0.009), 1.80 (95% CI 1.24 to 2.61, P=0.002) and 2.60 (95% CI 1.75 to 3.87, P<0.0001) for patients with one, two and three or four secondary outcome determinants, respectively. There was no significant interaction between the year of surgery and the number of secondary outcome determinants ($P_{interaction}$=0.98). In a sensitivity analysis, following additional adjustment for spe-

cific comorbidities (hypertension, diabetes mellitus and COPD), results were consistent with the main analysis (Table S4). The net reclassification improvement according to ≥1, 2 and 3 secondary outcome determinants is demonstrated in Table S5.

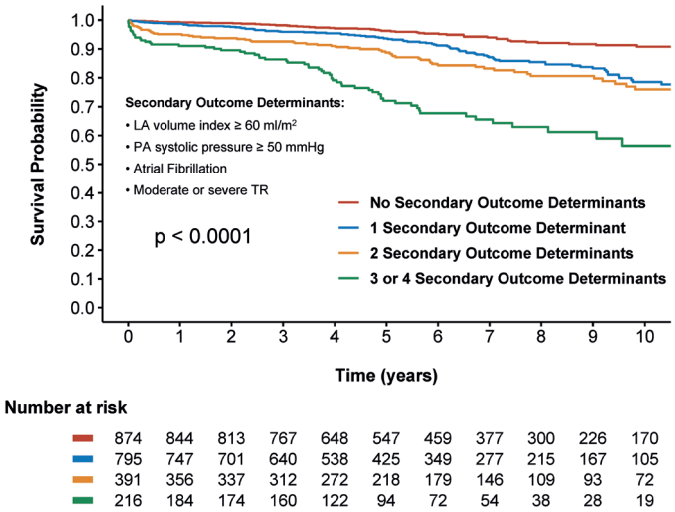

Figure 1: Kaplan Meier survival curves demonstrating the association between the number of secondary outcome determinants and all-cause mortality in DMR. Increasing number of secondary outcome determinants was associated with worse post-operative survival in patients with DMR.
LA = left atrial, DMR = degenerative mitral regurgitation, PA = pulmonary artery, TR = tricuspid regurgitation

Prognostic implications of the number of secondary outcome determinants according to patient subgroup

Further sensitivity analyses were performed to evaluate the prognostic implications of the number of secondary outcome determinants according to patient subgroup (Figure 3, Figures S1-S7). Analyses demonstrated the consistent prognostic value of the number of secondary outcome determinants in patient subgroups divided according to age (Figure S1), LVEF (Figure S2), LV ESD (Figure S3), the presence of symptoms (Figure S4) and the presence of any Class I surgical indication (Figure S7) (P for interaction >0.05 for all, Figure 3). However, while the presence of one or two secondary outcome determinants was associated with all-cause mortality in patients of lower surgical risk (EuroSCORE II <1%), it was not significantly associated with mortality for the patient subgroup of higher (EuroSCORE II ≥1%) surgical risk (HR 1.10, 95% CI 0.77 to 1.58, P=0.60; $P_{interaction}$=0.017, Figure 3). No significant interaction between EuroSCORE II group and the presence of three or four secondary outcome determinants was observed ($P_{interaction}$=0.50), suggesting that this phenotype has a similar association with mortality regardless of surgical risk (Figure S5). There was no significant interaction between mitral valve replacement versus repair group and the number of secondary outcome determinants ($P_{interaction}$=0.13).

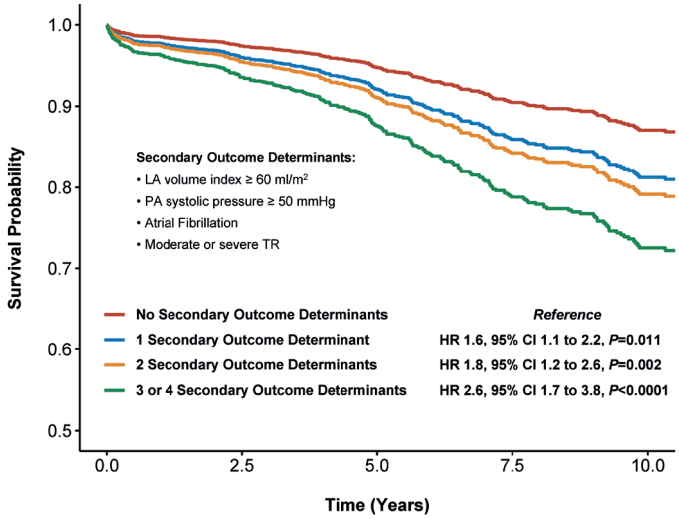

Figure 2: Adjusted survival curves demonstrating the association between the number of secondary outcome determinants and all-cause mortality in DMR. Increasing number of secondary outcome determinants was associated with worse post-operative survival in patients with DMR following adjustment for age, EuroSCORE II, symptoms, LV ejection fraction, LV end-systolic diameter and DMR severity.
LA = left atrial, LV = left ventricular, DMR = degenerative mitral regurgitation, PA = pulmonary artery, TR = tricuspid regurgitation

Superior Prognostic Value of the Number of Secondary Outcome Determinants

To compare the prognostic value of the number of secondary outcome determinants with Class I guideline recommendations for surgery, model discrimination was evaluated. A basal model (comprised of age and EuroSCORE II) incorporating the number of secondary outcome determinants demonstrated a higher C-index value (C-index 0.782, 95% CI 0.752 to 0.811) than models incorporating the presence of symptoms (C-index 0.772, 95% CI 0.743 to 0.802), LVEF ≤60% (C-index 0.773, 95% CI 0.743 to 0.803), LV ESD ≥40mm (C-index 0.771, 95% CI 0.741 to 0.801), or the number of Class I indications combined (C-index 0.776, 95% CI 0.746 to 0.806). The model incorporating the number of secondary outcome determinants was significantly more concordant with all-cause post-operative mortality than models including traditional Class I indications alone (the presence of symptoms (P=0.0003), or LVEF ≤60% (P=0.006), or LVESD ≥40mm (P=0.014)), with no significant difference in concordance compared to the model accounting for an increasing number of Class I indications (P=0.71).

Table 3: Univariable and multivariable hazard ratio (HR) for mortality for the number of secondary outcome determinants

	Secondary Outcome Determinant Subgroups	Hazard Ratio (95% CI)	P-value
Univariable	None of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	*Reference*	
	1 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	1.90 (1.36 to 2.65)	0.0001
	2 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	2.74 (1.93 to 3.89)	<0.0001
	3 or 4 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	6.40 (4.50 to 9.11)	<0.0001
Adjusted for age, sex, EuroSCORE II, symptoms (core model)	None of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	*Reference*	
	1 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	1.45 (1.04 to 2.03)	0.027
	2 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	1.69 (1.18 to 2.42)	0.004
	3 or 4 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	2.43 (1.67 to 3.54)	<0.0001
Further adjustment for LVEF, LV ESD and MR grade (comprehensive model)	None of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	*Reference*	
	1 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	1.56 (1.11 to 2.20)	0.011
	2 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	1.78 (1.23 to 2.58)	0.002
	3 or 4 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	2.58 (1.73 to 3.83)	<0.0001

AF = atrial fibrillation, ESD = end-systolic diameter, LAVI = left atrial volume index, LV = left ventricular, LVEF = left ventricular ejection fraction, MR = mitral regurgitation, PASP = pulmonary artery systolic pressure, TR = tricuspid regurgitation

DISCUSSION

In this large, international, multicenter study including 2276 patients with isolated DMR undergoing surgery, we observed that: (i) LAVI ≥60ml/m^2, atrial fibrillation, PASP ≥50mmHg and the presence of moderate to severe TR were independently associated with poor outcome even in a selected patient cohort undergoing surgery for severe DMR, (ii) an increasing number of secondary outcome determinants was independently associated with all-cause post-operative mortality, following adjustment for Class I surgical indications including symptoms, EuroSCORE II, age and quantified DMR severity, and (iii) accounting for the number of secondary outcome determinants demonstrated significantly better discrimination for post-surgical survival than traditional Class I indications for surgery.

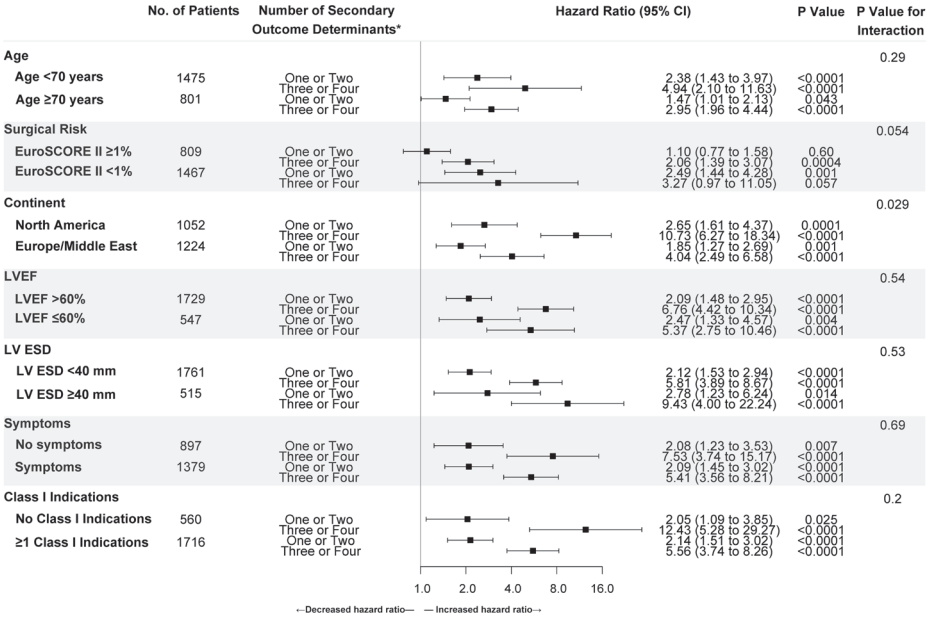

Figure 3: Association of the Number of Secondary Outcome Determinants with Mortality in Selected Sub-groups of Patients with DMR.

The number of secondary outcome determinants were related to outcome across subgroups according to age, surgical risk, geographical location, LVEF, LV ESD, symptoms, and Class I surgical indications.

*Secondary Outcome Determinants include atrial fibrillation, LAVI ≥60ml/m^2, PASP ≥50mmHg and/or the presence of moderate to severe TR. Hazard ratios are in reference to patients with no secondary outcome determinants.

CI=confidence interval, DMR = degenerative mitral regurgitation, ESD = end-systolic diameter, LAVI = left atrial volume index, LV=left ventricular, LVEF=left ventricular ejection fraction, PASP = pulmonary artery systolic pressure, TR = tricuspid regurgitation.

Prognostic validation of left atrial, pulmonary arterial and tricuspid valve remodelling in DMR

The present study demonstrates the independent association of LAVI, atrial fibrillation, PASP and the presence of moderate to severe TR with post-surgical clinical outcome in a large, unique, contemporary, multicenter registry of patients with DMR due to mitral valve prolapse and/or flail leaflet, providing additional supporting data for guideline recommendations regarding surgical timing[4]. Indeed, previous evidence for the association of LA enlargement with post-operative mortality was limited to either smaller studies or to a larger, real-world cohort from a single center[9,15,16]. Conversely, the present study, derived from an expansive international cohort, confirms that LAVI ≥60ml/m^2 retains independent prognostic value, supporting the wider generalisability of the findings from prior studies. Likewise, the prognostic importance of atrial fibrillation in DMR has remained somewhat contentious, with several studies showing no significant association with outcome[17,18], although other larger cohorts have shown an important relationship with mortality[10,19]. In the present study, atrial fibrillation was

independently related to post-operative mortality, strengthening the evidence-base for inclusion in guideline recommendations. In addition, our study confirms the findings of previous studies[20,21] demonstrating that increased PASP is associated with reduced post-surgical survival in patients with DMR. The present study also suggests that moderate or severe tricuspid regurgitation is related to post-operative mortality in patients with severe DMR, in accordance with recently published data[8]. Current guidelines suggest concomitant tricuspid valve repair of mild or moderate TR in the presence of tricuspid annular dilation of ≥40mm[5]. However, in a recent multicenter trial, 401 patients with moderate TR or annular dilatation undergoing mitral-valve surgery were randomised to tricuspid valve repair and mitral valve surgery, or mitral valve surgery alone[22]. This study demonstrated a significant reduction in progression to severe TR, although at the cost of a significant increase in the requirement for permanent pacemaker implantation. Longer term follow-up of the participants in this trial and additional research is required to determine how the presence of moderate or severe TR in severe DMR should influence clinical management, including intervention with tricuspid valve surgery/tricuspid transcatheter repair and for the timing of mitral valve surgery.

Prognostic Implications of the Number of Secondary Outcome Determinants

The present study shows that an increasing number of secondary outcome determinants is independently associated with increased long-term post-surgical mortality. It is probable that an increasing number of secondary outcome determinants identifies patients with more profound atrial, pulmonary and right ventricular consequences of isolated DMR, either due to more hemodynamically severe DMR or a reduced capacity to adapt to the associated volume overload. In severe DMR, the regurgitant jet causes substantial left atrial volume overload and may directly result in progressive left atrial dilatation, reduced compliance, fibrillation and eventually, elevation of left atrial pressures. Backward transmission of elevated left atrial pressure can result in increased pulmonary venous and arterial pressures. Initially, this is a passive process characterised by high left atrial and pulmonary capillary wedge pressures and low pulmonary vascular resistance[23]. However, chronic and/or recurrent increases in left atrial pressure may induce irreversible remodelling of the alveolar capillary membrane and pathological changes in the pulmonary veins and arteries, leading to an elevation of transpulmonary gradient, pulmonary vascular resistance and combined pre-capillary and post-capillary pulmonary hypertension[11]. Progressive right ventricular dilation and hypertrophy secondary to pulmonary hypertension is frequently associated with progressive tricuspid annular dilatation and papillary muscle tethering, and an increase in secondary tricuspid regurgitation severity[11]. Importantly, in patients with DMR, these pathophysiological changes can be observed even in the absence of overt left ventricular systolic or

diastolic dysfunction[23]. Therefore, in accordance with the findings of the present study, it is logical that even when adjusting for LV function, a phenotype of increased left atrial, pulmonary, and right ventricular damage would be associated with disease progression and reduced long-term survival. Furthermore, this association was also observed in patient subgroups with preserved and reduced LV function, suggesting that this phenotype should be considered as a potentially important marker of disease progression, regardless of the presence of LV dysfunction. Moreover, only the presence of three or four secondary outcome determinants was associated with outcome in patients with higher surgical risk (EuroSCORE ≥1%), suggesting that identification of this high-risk phenotype may be particularly important for the risk stratification of this patient group.

Clinical Implications

The present study provides additional evidence supporting current guideline recommendations[4] for surgical intervention for patients with severe DMR and either LAVI ≥60ml/m^2, atrial fibrillation or PASP ≥50mmHg. In addition, this study has demonstrated that the identification of a progressively higher risk cardiac phenotype with increased left atrial, pulmonary, and right ventricular consequences of DMR may better stratify risk again, providing better discrimination than well-established Class I surgical indications (the presence of symptoms, LVEF ≤60% and LV ESD ≥40mm) that are strongly recommended to be used, even in isolation, as triggers for surgery due to their association with poor outcome[4,5]. Furthermore, when compared to the number of Class I indications combined, accounting for the number of secondary outcome determinants provided similar and numerically higher indices of discrimination. Indeed, the presence of three or more secondary outcome determinants likely suggests that important haemodynamic consequences of progressive DMR have occurred, and earlier intervention, even in the absence of symptoms or LV dysfunction, may be crucial. However, surgery is probably warranted prior to the development of a cardiac phenotype with three or more secondary outcome determinants, as the prognosis of this subgroup is exceptionally poor, with an estimated mortality of 28% at 5 years, despite surgical intervention. In addition, this study demonstrates that the number of secondary outcome determinants has prognostic value in patients with and without Class I indications for surgery. In clinical practice it is not uncommon to have borderline Class I indications for intervention (i.e., very mild symptoms, LVEF of 59 to 61%, LV ESD 39 to 41 mm) or valvular properties which suggests a lower probability of successful valve repair. In these circumstances, identification of patients with an increasing number of secondary outcome determinants could strengthen any decision to intervene. This study also demonstrates that a paradigm shift in guideline recommendations could be useful: In addition to the well-established thresholds of individual imaging parameters for intervention (LAVI ≥60ml/m^2, atrial fibrillation, PASP ≥50mmHg, LVEF ≤60% and LV ESD ≥40mm), accounting for

the overall cardiac phenotype represented by the presence of multiple prognostically important parameters, may improve patient selection for earlier surgery. Indeed, those with multiple prognostically important parameters probably warrant a stronger recommendation for intervention than any single parameter in isolation.

Limitations

The study is subject to all of the inherent limitations of an observational, non-randomised design, although representing the largest international cohort of patients with isolated DMR undergoing surgery with long-term post-operative follow-up. Definitive recommendations regarding surgical timing would ideally be made following randomised clinical trials enrolling selected patient subgroups (i.e., patients with LAVI ≥60ml/m^2 or with 3 or more secondary outcome determinants). Nonetheless, contemporary guideline recommendations regarding the timing of surgical intervention in DMR are currently only based on strong observational data, and it remains unlikely that such trials will ever be conducted[4,5]. While study cohort identification was retrospective, all measurements were performed prospectively by numerous operators and recorded electronically, reflecting prospective DMR evaluation and quantitation in routine practice with transthoracic echocardiography. This may allow for increased generalizability of the results into clinical practice compared with core laboratory evaluation, which while offering improved uniformity of evaluation, has more limited generalizability. In addition, data pertaining to the cause of death and incident heart failure were not available, precluding these analyses. However, any excess in incident heart failure or cardiovascular death would likely translate into an increase in all-cause mortality. Data regarding post-operative stroke, residual MR, frequency of concomitant AF ablation and mitral valve reintervention were not available, precluding additional analyses. In addition, this study was likely inadequately powered to detect between group differences for mitral valve repair versus replacement. Further studies investigating the prognostic value of Class I indications and secondary outcome determinants are required for patients undergoing mitral valve replacement and in patients with multiple and/or mixed valvular disease. In addition, more research is required to determine if healthcare systems can provide for the increasing number of patients with severe DMR who may benefit from earlier surgery.

CONCLUSION

An increasing number of secondary outcome determinants was independently associated with post-surgical survival in patients with DMR and demonstrated significantly better discrimination than traditional Class I indications for surgery. Randomised con-

trolled trials are needed to determine if patients with severe DMR who demonstrate a cardiac phenotype with an increasing number of secondary outcome determinants would benefit from earlier surgery.

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SUPPLEMENTARY MATERIAL

Table S1: Correlation between Secondary Outcome Determinants

Parameters	Pearson *R* (95% confidence interval)
Atrial fibrillation and moderate or severe TR	0.19 (0.15 to 0.23)
Atrial fibrillation and LAVI ≥60 ml/m^2	0.16 (0.12 to 0.20)
Atrial fibrillation and PASP ≥50 mmHg	0.12 (0.08 to 0.16)
Moderate or severe TR and LAVI ≥60 ml/m^2	0.12 (0.08 to 0.16)
Moderate or severe TR and PASP ≥50 mmHg	0.30 (0.26 to 0.34)
LAVI ≥60 ml/m^2 and PASP ≥50 mmHg	0.16 (0.12 to 0.20)

LAVI = left atrial volume index; PASP = pulmonary artery systolic pressure; TR = tricuspid regurgitation

Table S2: Proportion of Patients on Specific Medications

Medication	Percentage of Population
Vasodilating antihypertensives	38.4%
Diuretics	29.0%
Digoxin	8.1%

Table S3: Univariable and multivariable hazard ratio (HR) for mortality for LAVI, PASP, atrial fibrillation and TR severity

	Secondary Outcome Determinant Subgroups	Hazard Ratio (95% CI)	P-value
Univariable	LAVI ≥60 ml/m^2	1.64 (1.30 to 2.08)	<0.0001
	PASP ≥50 mmHg	2.67 (2.10 to 3.41)	<0.0001
	Atrial fibrillation	2.53 (1.99 to 3.22)	<0.0001
	Moderate or severe TR	2.57 (1.96 to 3.37)	<0.0001
Adjusted for age, sex, EuroSCORE II, symptoms (core model)	LAVI ≥60 ml/m^2	1.31 (1.03 to 1.67)	0.027
	PASP ≥50 mmHg	1.45 (1.12 to 1.87)	0.005
	Atrial fibrillation	1.52 (1.19 to 1.94)	0.0008
	Moderate or severe TR	1.45 (1.09 to 1.92)	0.011
Further adjustment for LVEF, LV ESD and MR grade (comprehensive model)	LAVI ≥60 ml/m^2	1.38 (1.07 to 1.78)	0.014
	PASP ≥50 mmHg	1.50 (1.15 to 1.97)	0.003
	Atrial fibrillation	1.46 (1.14 to 1.89)	0.003
	Moderate or severe TR	1.46 (1.09 to 1.96)	0.010
Further adjustment for COPD, hypertension and diabetes mellitus (extended comorbidity adjusted model)	LAVI ≥60 ml/m^2	1.52 (1.16 to 2.00)	0.002
	PASP ≥50 mmHg	1.46 (1.08 to 1.98)	0.013
	Atrial fibrillation	1.53 (1.16 to 2.01)	0.002
	Moderate or severe TR	1.66 (1.20 to 2.31)	0.002

COPD = chronic obstructive pulmonary disease, ESD = end-systolic diameter, LAVI = left atrial volume index, LV = left ventricular, LVEF = left ventricular ejection fraction, MR = mitral regurgitation, PASP = pulmonary artery systolic pressure, TR = tricuspid regurgitation

Table S4: Univariable and multivariable hazard ratio (HR) for mortality for the number of secondary outcome determinants

	Secondary Outcome Determinant Subgroups	Hazard Ratio (95% CI)	P-value
Univariable	None of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	*Reference*	
	1 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	1.90 (1.36 to 2.65)	0.0001
	2 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	2.74 (1.93 to 3.89)	<0.0001
	3 or 4 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	6.40 (4.50 to 9.11)	<0.0001
Adjusted for age, sex, EuroSCORE II, symptoms (core model)	None of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	*Reference*	
	1 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	1.45 (1.04 to 2.03)	0.027
	2 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	1.69 (1.18 to 2.42)	0.004
	3 or 4 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	2.43 (1.67 to 3.54)	<0.0001
Further adjustment for LVEF, LV ESD and MR grade (comprehensive model)	None of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	*Reference*	
	1 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	1.56 (1.11 to 2.20)	0.011
	2 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	1.78 (1.23 to 2.58)	0.002
	3 or 4 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	2.58 (1.73 to 3.83)	<0.0001
Further adjustment for COPD, hypertension and diabetes mellitus (extended comorbidity adjusted model)	None of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	*Reference*	
	1 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	1.65 (1.15 to 2.37)	0.006
	2 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	1.78 (1.20 to 2.65)	0.005
	3 or 4 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	3.02 (1.96 to 4.66)	<0.0001

AF = atrial fibrillation, COPD = chronic obstructive pulmonary disease, ESD = end-systolic diameter, LAVI = left atrial volume index, LV = left ventricular, LVEF = left ventricular ejection fraction, MR = mitral regurgitation, PASP = pulmonary artery systolic pressure, TR = tricuspid regurgitation

Table S5: Net Reclassification Improvement over comprehensive multivariable model according to secondary outcome determinants

	NRI for 2.5% threshold (95% CI)	NRI for 5.0% threshold (95% CI)	NRI for 7.5% threshold (95% CI)
≥1 secondary outcome determinant	0.16 (-0.05 to 0.36)	0.00 (-0.03 to 0.08)	-0.01 (-0.04 to 0.02)
≥2 secondary outcome determinants	0.33 (0.10 to 0.39)	0.16 (-0.03 to 0.37)	0.00 (-0.03 to 0.25)
≥3 secondary outcome determinants	0.07 (0.00 to 0.18)	0.16 (0.07 to 0.23)	0.17 (0.00 to 0.23)

NRI = Net Reclassification Improvement

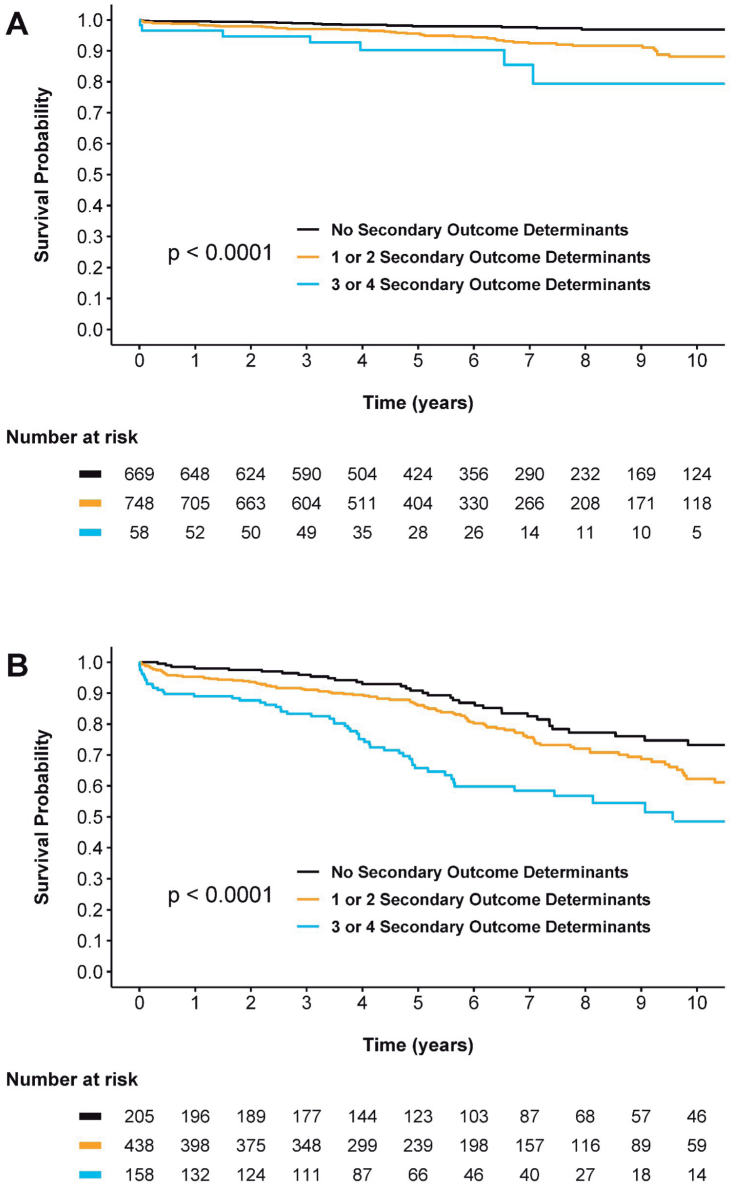

Figure S1: Kaplan Meier survival curves demonstrating the association between the number of secondary outcome determinants and all-cause mortality in DMR according to age. Increasing number of secondary outcome determinants was associated with worse post-operative survival in patients with DMR in subgroups <70 years (A) and ≥70 years (B). Secondary Outcome Determinants include atrial fibrillation, LAVI ≥60ml/m^2, PASP ≥50mmHg and/or the presence of moderate to severe TR.

DMR = degenerative mitral regurgitation, LA = left atrial volume index, PASP = pulmonary artery systolic pressure, TR = tricuspid regurgitation

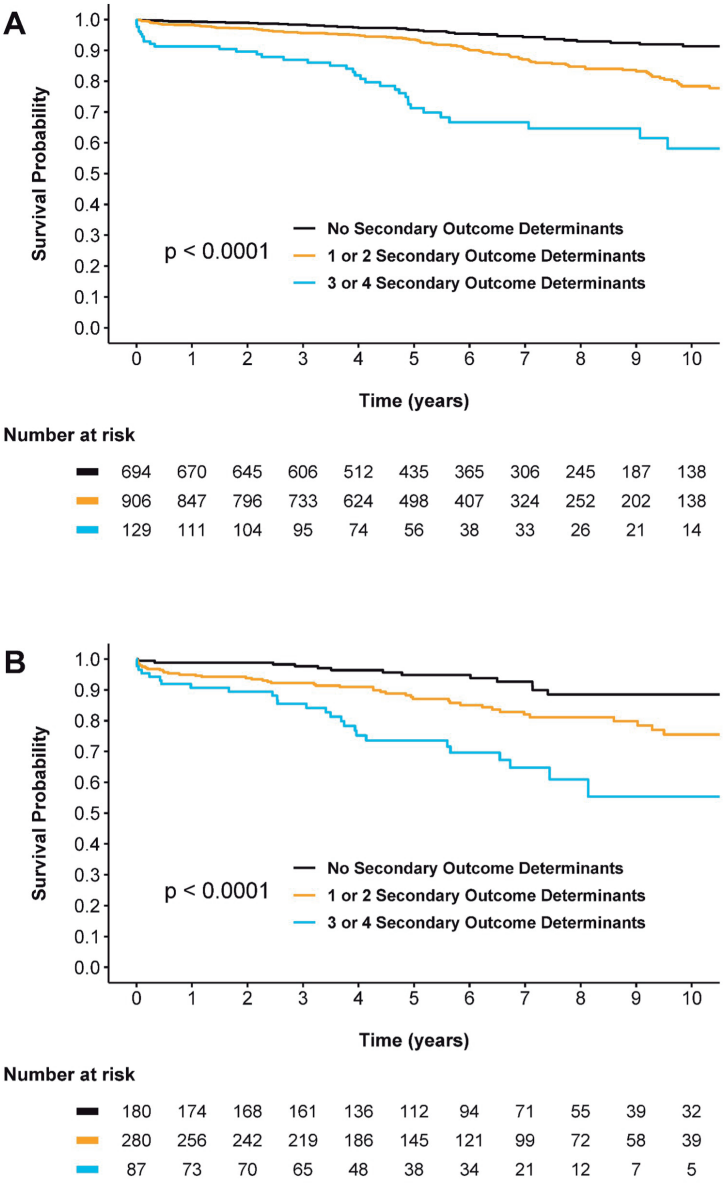

Figure S2: Kaplan Meier survival curves demonstrating the association between the number of secondary outcome determinants and all-cause mortality in DMR according to LVEF. Increasing number of secondary outcome determinants was associated with worse post-operative survival in patients with DMR in subgroups with a LVEF >60% (A) and ≤60% (B).

Secondary Outcome Determinants include atrial fibrillation, LAVI ≥60ml/m^2, PASP ≥50mmHg and/or the presence of moderate to severe TR.

DMR = degenerative mitral regurgitation, LA = left atrial volume index, LVEF = left ventricular ejection fraction, PASP = pulmonary artery systolic pressure, TR = tricuspid regurgitation

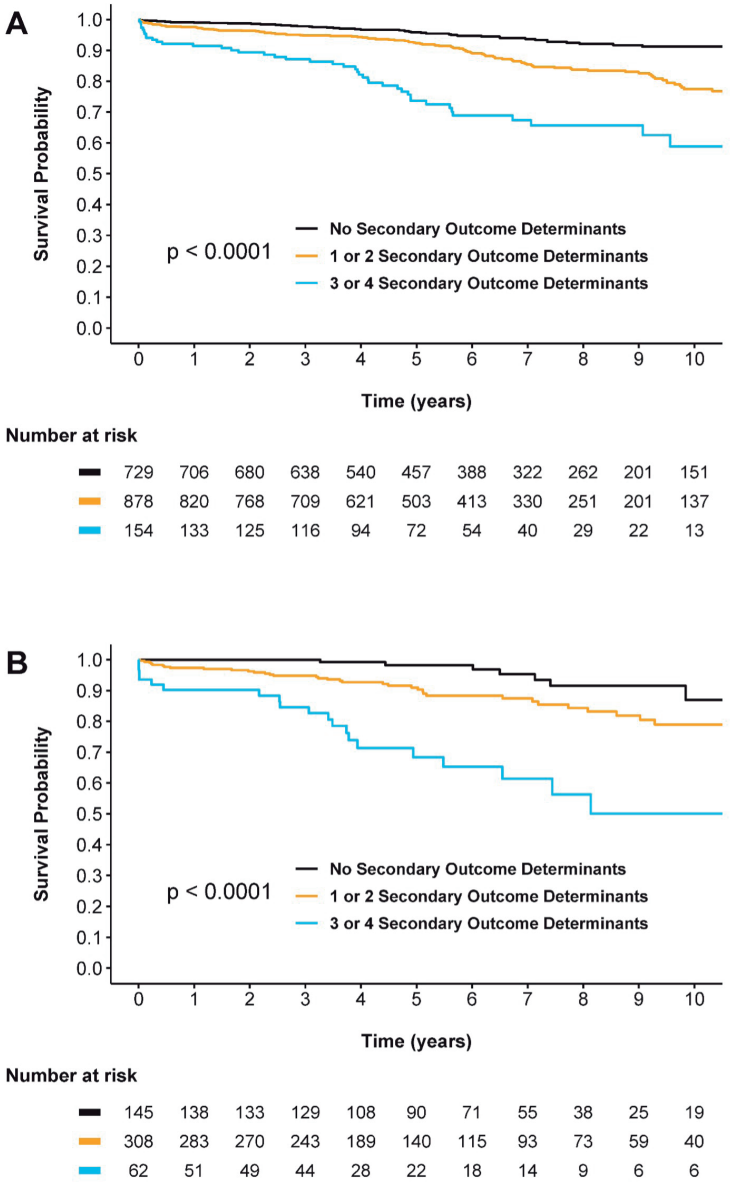

Figure S3: Kaplan Meier survival curves demonstrating the association between the number of secondary outcome determinants and all-cause mortality in DMR according to LV ESD. Increasing number of secondary outcome determinants was associated with worse post-operative survival in patients with DMR in subgroups with a LVESD <40 mm (A) and ≥40 mm (B).

Secondary Outcome Determinants include atrial fibrillation, LAVI ≥60ml/m^2, PASP ≥50mmHg and/or the presence of moderate to severe TR.

DMR = degenerative mitral regurgitation, LA = left atrial volume index, LV ESD = left ventricular end-systolic diameter, PASP = pulmonary artery systolic pressure, TR = tricuspid regurgitation

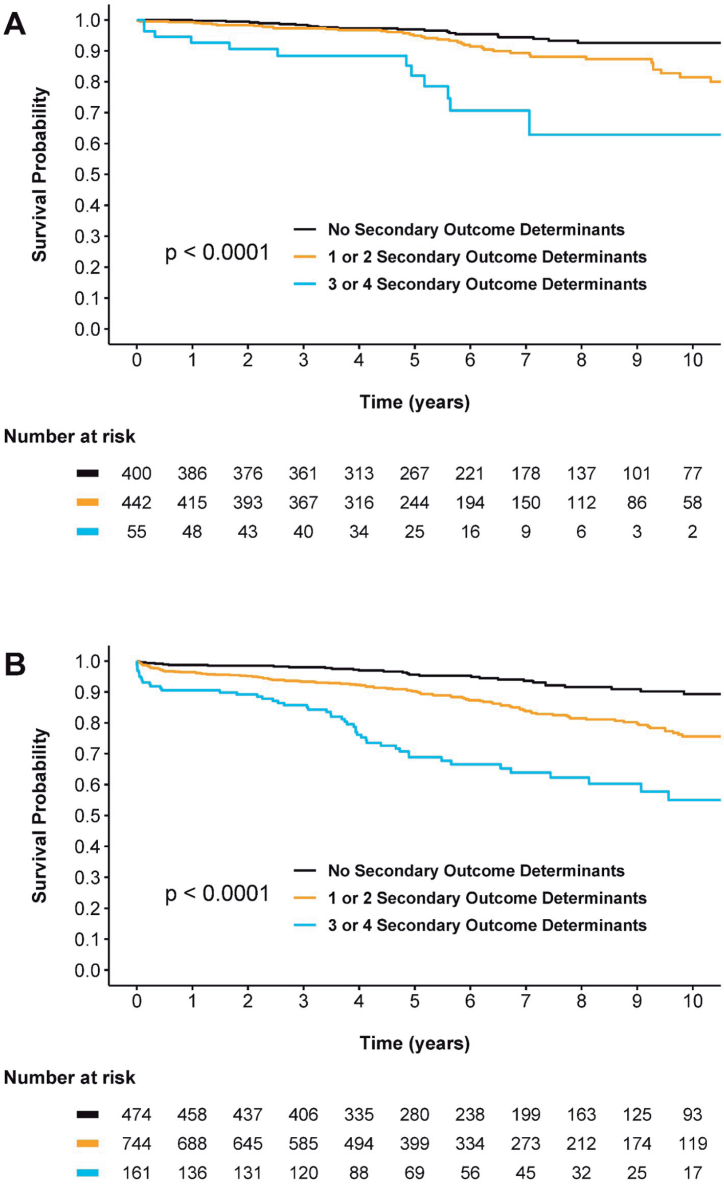

Figure S4: Kaplan Meier survival curves demonstrating the association between the number of secondary outcome determinants and all-cause mortality in DMR according to symptoms. Increasing number of secondary outcome determinants was associated with worse post-operative survival in patients with DMR in subgroups without symptoms (A) and with symptoms (B).

Secondary Outcome Determinants include atrial fibrillation, LAVI ≥60ml/m^2, PASP ≥50mmHg and/or the presence of moderate to severe TR.

DMR = degenerative mitral regurgitation, LA = left atrial volume index, PASP = pulmonary artery systolic pressure, TR = tricuspid regurgitation

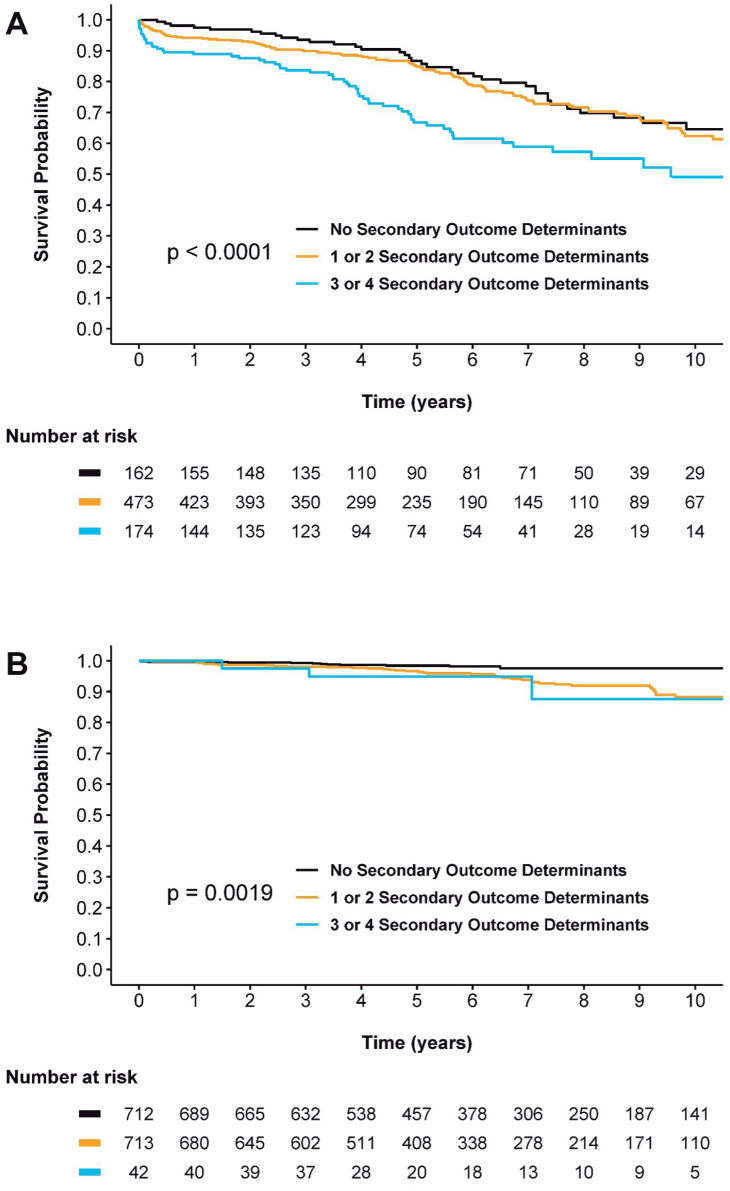

Figure S5: Kaplan Meier survival curves demonstrating the association between the number of secondary outcome determinants and all-cause mortality in DMR according to EuroSCORE II. Increasing number of secondary outcome determinants was associated with worse post-operative survival in patients with DMR in subgroups with a EuroSCORE II ≥1% (A) and <1% (B).

Secondary Outcome Determinants include atrial fibrillation, LAVI ≥60ml/m^2, PASP ≥50mmHg and/or the presence of moderate to severe TR.

DMR = degenerative mitral regurgitation, LA = left atrial volume index, PASP = pulmonary artery systolic pressure, TR = tricuspid regurgitation

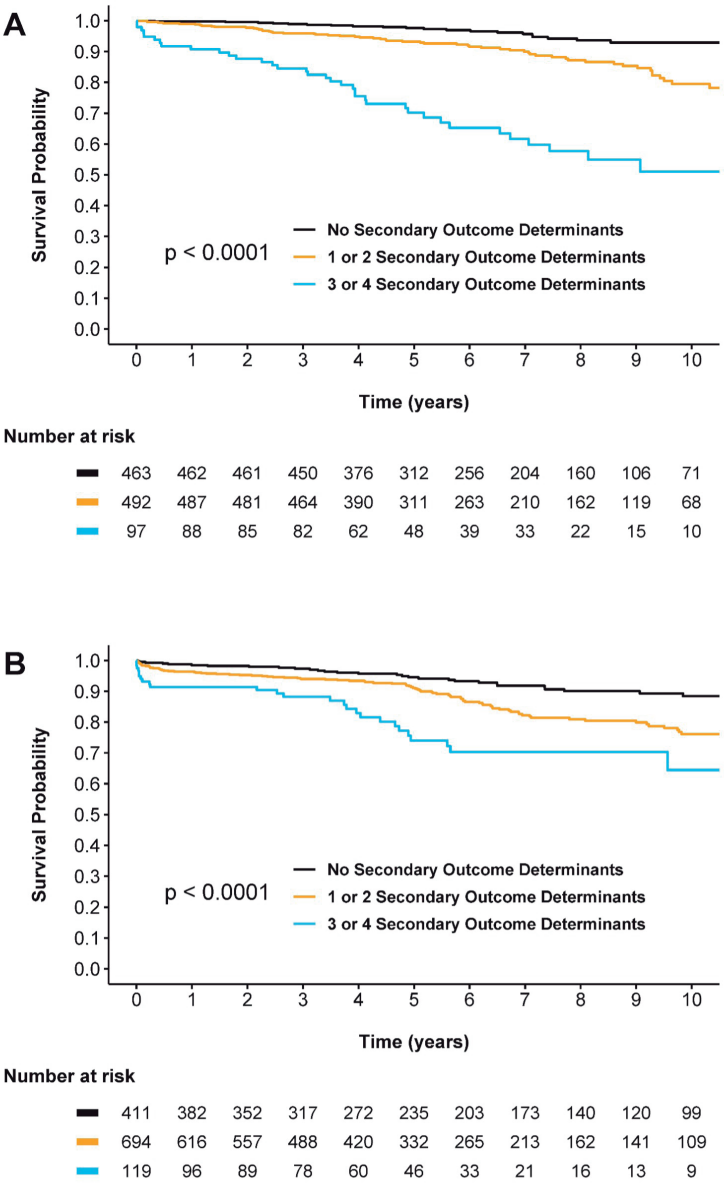

Figure S6: Kaplan Meier survival curves demonstrating the association between the number of secondary outcome determinants and all-cause mortality in DMR according to geographical location. Increasing number of secondary outcome determinants was associated with worse post-operative survival in patients with DMR in subgroups from North America (A) and from Europe/Middle East (B).

Secondary Outcome Determinants include atrial fibrillation, LAVI ≥60ml/m^2, PASP ≥50mmHg and/or the presence of moderate to severe TR.

DMR = degenerative mitral regurgitation, LA = left atrial volume index, PASP = pulmonary artery systolic pressure, TR = tricuspid regurgitation

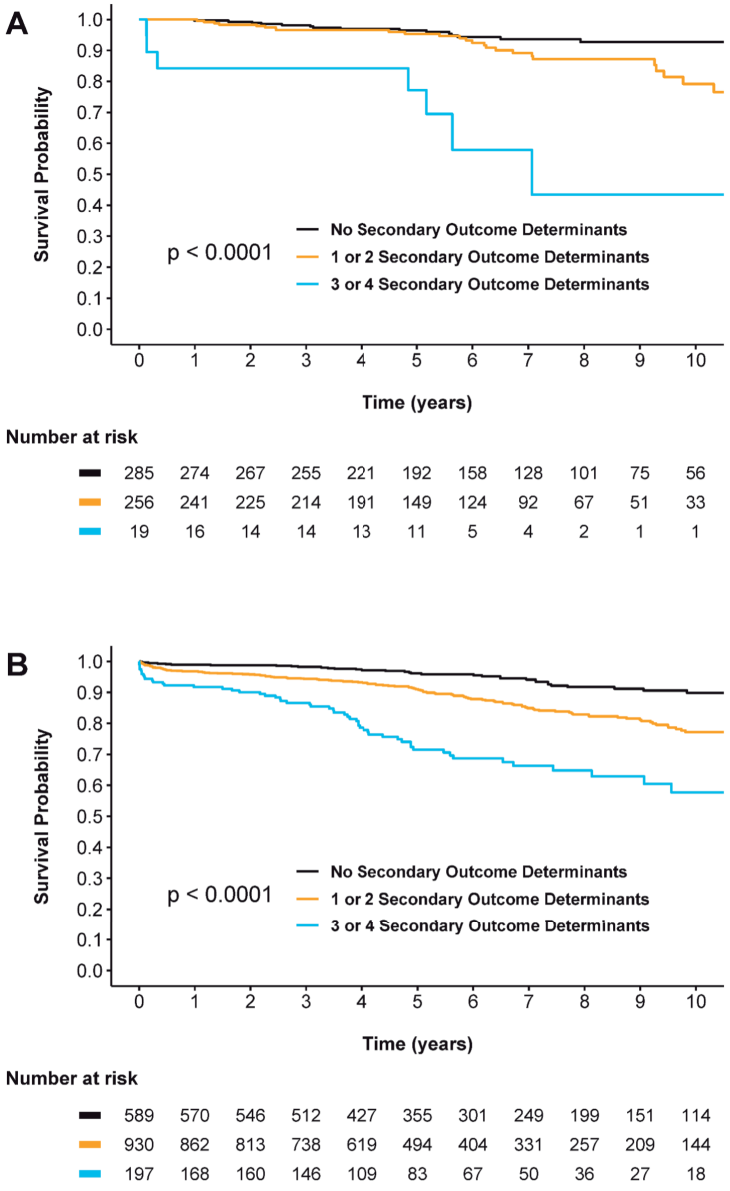

Figure S7: Kaplan Meier survival curves demonstrating the association between the number of secondary outcome determinants and all-cause mortality in DMR according to the presence of a Class I indication for surgery. Increasing number of secondary outcome determinants was associated with worse post-operative survival in patients with DMR in subgroups with no Class I indications (A) and with ≥1 Class I indications (B).

Secondary Outcome Determinants include atrial fibrillation, LAVI ≥60ml/m^2, PASP ≥50mmHg and/or the presence of moderate to severe TR.

DMR = degenerative mitral regurgitation, LA = left atrial volume index, PASP = pulmonary artery systolic pressure, TR = tricuspid regurgitation