Extramitral Valvular Cardiac Involvement in Patients With Significant Secondary Mitral Regurgitation

Gurpreet K. Singh, MD[a], Farnaz Namazi, MD[a], Kensuke Hirasawa, MD, PhD[a], Pieter van der Bijl, MD, PhD[a], Aniek L. van Wijngaarden, MD[a], N. Mai Vo, MD[a], Gregg W. Stone, MD[b,c], Nina Ajmone Marsan, MD, PhD[a], Victoria Delgado, MD, PhD[a], and Jeroen J. Bax, MD, PhD[a,d,*]

Patients with secondary mitral regurgitation (SMR) often have extramitral valve cardiac involvement, which can influence the prognosis. SMR can be defined according to groups of extramitral valve cardiac involvement. The prognostic implications of such groups in patients with moderate and severe SMR (significant SMR) are unknown. A total of 325 patients with significant SMR were classified according to the extent of cardiac involvement on echocardiography: left ventricular involvement (group 1), left atrial involvement (group 2), tricuspid valve and pulmonary artery vasculature involvement (group 3), or right ventricular involvement (group 4). The primary end point was all-cause mortality. The prevalence of each cardiac involvement group was 17% in group 1, 12% in group 2, 23% in group 3%, and 48% in group 4. Group 3 and group 4 were independently associated with all-cause mortality (hazard ratio 1.794, 95% confidence interval 1.067 to 3.015, p = 0.027 and hazard ratio 1.857, 95% confidence interval 1.145 to 3.012, p = 0.012, respectively). In conclusion, progressive extramitral valve cardiac involvement (group 3 and group 4) was independently associated with all-cause mortality in patients with significant SMR. **(Am J Cardiol 2021;00:1−7)**

Guideline-directed medical therapy for heart failure (including cardiac resynchronization therapy [CRT]) has been demonstrated to reverse left ventricular (LV) remodeling and reduce secondary mitral regurgitation (SMR) in selected patients.[1,2] However, patients who remain with moderate-to-severe or severe SMR despite guideline-directed medical therapy exhibit high morbidity and mortality.[3] The high operative risk and relatively high SMR recurrence rate may explain the low referral rate for mitral valve intervention.[4−6] More recently, transcatheter mitral valve repair with MitraClip (Abbott, Abbott Park, Illinois) was demonstrated to improve the prognosis of selected patients with heart failure and SMR with symptoms refractory to medical therapy.[7] The echocardiographic criteria that indicate the need for mitral valve intervention comprise measures of SMR severity, LV ejection fraction (LVEF), and LV volumes.[7−9] However, the spectrum of cardiac abnormalities that accompany SMR and that influence patient outcomes is broader. Cardiac classification algorithms have been applied to severe aortic stenosis and have shown that extra-aortic valve, cardiac involvement provides incremental prognostic value over measures of aortic stenosis severity.[10] Accordingly, the present study proposes an algorithm to divide patients with SMR into groups based on their extramitral valve, cardiac involvement and evaluated its prognostic implications.

Methods

Patients with moderate and severe SMR (significant SMR) and reduced LVEF <50% were identified between 1999 and 2018 from ongoing registries of patients with SMR at the Leiden University Medical Center (The Netherlands) and are included in this analysis. Patients were classified into 4 groups of cardiac involvement, based on the presence of extramitral valvular cardiac involvement derived from the first echocardiogram performed with patients in a hemodynamic stable condition showing significant SMR (Figure 1): group 1: LV involvement (LV end-diastolic diameter ≥57 mm and/or LVEF <50%); group 2: left atrial (LA) involvement (LA volume index >34 ml/m^2 and/or history of atrial fibrillation); group 3: tricuspid valve or pulmonary artery vasculature involvement (systolic pulmonary artery pressure [SPAP] ≥40 mm Hg and/or significant tricuspid regurgitation [TR]); group 4: right ventricular (RV) involvement (tricuspid annular plane systolic excursion [TAPSE] ≤17 mm). Importantly, patients were classified according to the highest cardiac involvement group; thus, for example, if patients had LVEF <50% and TAPSE ≤17 mm, they were included in group 4.

Patients with previous mitral valve intervention (surgical mitral valve repair, mitral valve replacement, or transcatheter edge-to-edge mitral valve repair) or incomplete echocardiographic data to determine the extramitral valvular cardiac involvement were excluded. Clinical and demographic data were collected using the departmental patient

[a]Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands; [b]The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York; [c]The Cardiovascular Research Foundation, New York, New York; and [d]Turku Heart Center, University of Turku and Turku University Hospital, Turku, Finland. Manuscript received May 27, 2021; revised manuscript received and accepted September 17, 2021.

See page 6 for disclosure information.

*Corresponding author: Tel: +3175262020; fax: +31715266809.
E-mail address: j.j.bax@lumc.nl (J.J. Bax).

0002-9149/

https://doi.org/10.1016/j.amjcard.2021.09.022

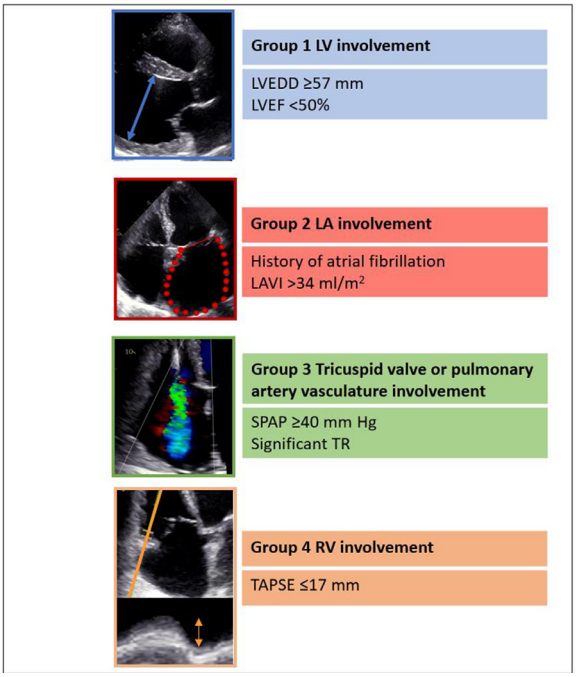

Figure 1. Groups of cardiac involvement in patients with significant secondary mitral regurgitation. LA= left atrial; LAVI = left atrial volume index; LV = left ventricular; LVEDD = left ventricular end diastolic diameter; LVEF = left ventricular ejection fraction; RV= right ventricular; SPAP = systolic pulmonary arterial pressure; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

information system. For retrospective analysis of clinically acquired data which were anonymously handled, the institutional review board waived the need for patient written informed consent.

Transthoracic echocardiography was performed with the patients at rest, lying in the left lateral decubitus position, using commercially available ultrasound systems (GE Vingmed Ultrasound, General Electric, Milwaukee, Wisconsin) equipped with 3.5 MHz or M5S transducers. Two-dimensional and Doppler data were acquired from parasternal, apical, and subcostal views. LV end-diastolic diameter was measured on the parasternal long-axis view.[11] The apical 2- and 4-chamber views were used to measure the LV end-diastolic and end-systolic volumes, and LVEF was calculated according to Simpson's biplane method.[11] LA volumes were measured at the end of ventricular systole on the 2- and 4-chamber apical views, using the biplane method of disks, and indexed for body surface area (LA volume index).[11] Stroke volume was calculated with the following equation: Stroke volume = LV outflow tract velocity time integral × cross-sectional area of the LV outflow tract.[12] The severity of mitral regurgitation was assessed according to current recommendations, using qualitative, semiquantitative, and quantitative data. If measurable, quantitative measurements were conducted according to the proximal isovelocity surface area method, for which the effective regurgitant orifice area was measured and regurgitant volume was calculated by multiplying effective regurgitant orifice area by the mitral valve velocity time integral.[12,13] The severity of TR was semiquantitatively assessed using vena contracta width: mild <0.3 cm, moderate 0.3 to 0.69 cm, and severe ≥0.7 cm.[12,13] Significant TR was defined as moderate or severe TR. RV systolic function was assessed using the TAPSE measured on the focused 4-chamber apical view and M-mode.[11,14] To estimate the SPAP the RV pressure was calculated from the peak velocity of the TR jet, according to the simplified Bernoulli's equation, to which the right atrial pressure was identified by the inspiratory collapse and diameter of the inferior vena cava were added.[11,14]

Patients were followed up for the occurrence of mitral valve intervention (i.e., surgical mitral valve repair, mitral valve replacement, and percutaneous edge-to-edge mitral valve repair) and all-cause mortality. The primary outcome was all-cause mortality. Mortality data were collected from the departmental patient information system, which is linked to the governmental death registry database. In addition, to evaluate the heart failure treatment in this population, the occurrence of CRT was investigated.

Continuous data are presented as mean ± SD when normally distributed or as median and interquartile range when non-normally distributed. Categorical data are presented as frequencies and percentages. Comparison of continuous data, when normally distributed, was performed using the one-way analysis of variance analysis with Bonferroni's post hoc analysis or, when non-normally distributed, with the Kruskal-Wallis test. Categorical data were compared using the chi-square test. Kaplan-Meier analysis was used to estimate the event-free survival rates of patients in the various groups during follow-up. The event-free survival rates were compared using the log-rank test. Univariable Cox proportional hazards analysis was performed to evaluate the association between the extramitral valvular cardiac involvement groups and other clinical and echocardiographic variables with all-cause mortality. Mitral valve intervention was also included as a time-dependent variable in this analysis. The hazard ratio and 95% confidence interval were reported. In the univariable analysis, clinically relevant variables were selected and included in the multivariable Cox proportional hazards model. A two-sided $p < 0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0. (Armonk, New York: IBM Corp.)

Results

A total of 325 patients (mean age 69 ± 10 years, 66% male) with severely reduced LVEF (mean 29 ± 9%) were included. The distribution of patients across the different groups of cardiac involvement is presented in Figure 2. The

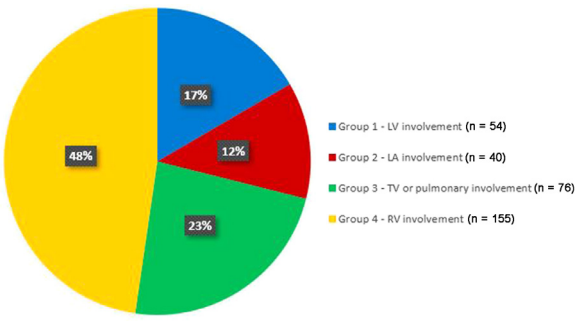

Figure 2. Distribution of the total population according to different groups of cardiac involvement. LA = left atrial; LV = left ventricular; RV = right ventricular; TV = tricuspid valve.

Table 1
Clinical characteristics according to cardiac involvement

Variable	Total population (n=325)	Group 1 LV involvement (n=54)	Group 2 LA involvement (n=40)	Group 3 TV or pulmonary artery vasculature involvement (n=76)	Group 4 RV involvement (n=155)	p-value
Male	213 (66%)	32 (59%)	25 (63%)	48 (63%)	108 (70%)	0.480
Age (years)	69 ± 10	62 ± 12	67 ± 12	66 ± 10	68 ± 9*	0.001
Body surface area (m^2)	1.9 ± 0.21	1.9 ± 0.21	1.9 ± 0.23	1.9 ± 0.21	1.9 ± 0.20	0.987
Creatinine (μmol/L)	101 (81-136)	90 (75-117)	103 (75-132)	98 (87-133)	109 (85-153)*	0.009
NYHA ≥ II	306 (94%)	51 (94%)	38 (95%)	71 (93%)	146 (94%)	0.987
Atrial fibrillation	172 (53%)	0 (0%)	23 (58%)	40 (53%)	109 (70%)	<0.001
CRT	33 (10%)	3 (6%)	5 (13%)	5 (7%)	20 (13%)	0.279
Diabetes mellitus	69 (21%)	9 (17%)	7 (18%)	15 (20%)	38 (25%)	0.550
Hypertension	132 (41%)	22 (41%)	18 (45%)	28 (37%)	64 (41%)	0.850
COPD	38 (12%)	4 (7%)	3 (8%)	10 (13%)	21 (14%)	0.509
Beta-blocker	236 (73%)	41 (76%)	28 (70%)	54 (71%)	113 (73%)	0.911
ACE or ARB	263 (81%)	46 (85%)	34 (85%)	64 (84%)	119 (77%)	0.344
Diuretics	278 (86%)	42 (78%)	29 (73%)	66 (87%)	141 (91%)	0.008

Values are mean ± SD, median [IQR], or n (%).

* p<0.05 versus stage 1.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; LA = left atrial; LV = left ventricular; NYHA = New York Heart Association; RV = right ventricular; TV = tricuspid valve.

clinical and echocardiographic characteristics of the overall population and for each cardiac involvement group are listed in Tables 1 and 2, respectively. Patients in group 4 (RV involvement) were older and had worse kidney function compared with group 1 (LV involvement). During a median follow-up of 67 months (interquartile range: 27 to 121 months), 192 patients died (59%), 148 patients (46%) underwent mitral valve intervention and 258 patients (79%) received CRT (Table 3). The Kaplan-Meier analysis for all-cause mortality in the total population is shown in Figure 3. Patients in group 1 had better survival as compared with the patients in groups 3 and 4. The 1- and 8-year mortality rates for patients in group 1 were 6% and 33% respectively, which is lower than the mortality rates of patients in groups

Table 2
Echocardiographic characteristics according to cardiac involvement

Variable	Total population (n=325)	Group 1 LV involvement (n=54)	Group 2 LA involvement (n=40)	Group 3 TV or pulmonary artery vasculature involvement (n=76)	Group 4 RV involvement (n=155)	p-value
LV end-diastolic diameter (mm)	67 ± 10	67 ± 9	70 ± 11	67 ± 11	65 ± 9	0.073
LV end-diastolic volume (ml)	196 (144-250)	209 (172-255)	200 (129-268)	193 (144-248)	185 (139-240)	0.304
LV end-systolic volume (ml)	142 (97-184)	155 (110-188)	135 (88-186)	138 (97-181)	136 (93-186)	0.468
Stroke volume (ml)	43 ± 13	46 ± 12	47 ± 12	43 ± 11	40 ± 14*,†	0.005
LV ejection fraction (%)	29 ± 9	28 ± 9	30 ± 9	30 ± 9	28 ± 9	0.452
Left atrial volume index (ml/m^2)	38 (29-49)	25 (19-30)	40 (34-52)*	38 (35-49)*	44 (36-56)*	<0.001
SPAP (mmHg)	43 ± 13	28 ± 7	32 ± 6	49 ± 12*,†	49 ± 12*,†	<0.001
TAPSE (mm)	18 (13-20)	20 (19-22)	19 (18-21)	20 (18-23)	13 (11-15)*,†,‡	<0.001
EROA (mm2)	20 (14-29)	16 (12-20)	19 (11-24)	20 (15-30)*	20 (15-30)*	0.006
Regurgitant volume (ml)	31 ± 15	28 ± 15	31 ± 13	33 ± 16	31 ± 15	0.405
Mitral regurgitation						0.002
Moderate	52 (16%)	15 (28%)	6 (15%)	9 (12%)	22 (14%)	
Moderate-severe	129 (40%)	28 (52%)	20 (50%)	27 (36%)	54 (35%)	
Severe	144 (44%)	11 (20%)	14 (35%)	40 (53%)	79 (51%)	
Tricuspid regurgitation						<0.001
Moderate	74 (23%)	0 (0%)	0 (0%)	18 (25%)	56 (37%)	
Severe	23 (7%)	0 (0%)	0 (0%)	6 (8%)	17 (11%)	

Values are mean ± SD, median [IQR], or n (%). Missing: EROA 91/325; left atrial volume index 2/325; regurgitant volume 92/325; SPAP 5/325; stroke volume 34/325; tricuspid regurgitation 4/325.

* p<0.05 versus stage 1.

† p<0.05 versus stage 2.

‡ p<0.05 versus stage 3.

EROA = effective regurgitant orifice area; LA = left atrial; LV = left ventricular; RV = right ventricular; SMR = secondary mitral regurgitation; SPAP = systolic pulmonary artery pressure; TAPSE = tricuspid annular plane systolic excursion; TV = tricuspid valve.

Table 3
Clinical outcomes during follow-up

Variable	Total population (n=325)	Group 1 LV involvement (n=54)	Group 2 LA involvement (n=40)	Group 3 TV or pulmonary artery vasculature involvement (n=76)	Group 4 RV involvement (n=155)	p-value
CRT at baseline + follow-up	258 (79%)	47 (87%)	29 (73%)	60 (79%)	122 (79%)	0.370
MV intervention at follow-up						0.168
Transcatheter edge-to-edge repair	51 (16%)	3 (6%)	7 (18%)	9 (12%)	32 (21%)	
MV repair	95 (29%)	13 (24%)	13 (33%)	27 (36%)	42 (27%)	
MV replacement	2 (1%)	-	-	1 (1%)	1 (1%)	
Concomitant TVP	71 (22%)	8 (15%)	7 (18%)	19 (25%)	37 (24%)	0.420
Concomitant AVR	2 (1%)	1 (2%)	-	1 (1%)	-	0.367
Concomitant CABG	29 (9%)	5 (9%)	2 (5%)	10 (13%)	12 (8%)	0.439

Values are n (%). CRT at baseline is included in this follow-up table.

AVR = aortic valve replacement; CABG = coronary artery bypass graft; CRT = cardiac resynchronization therapy; LA = left atrial; LV = left ventricular; MV = mitral valve; RV = right ventricular; TV = tricuspid; TVP = tricuspid valvuloplasty.

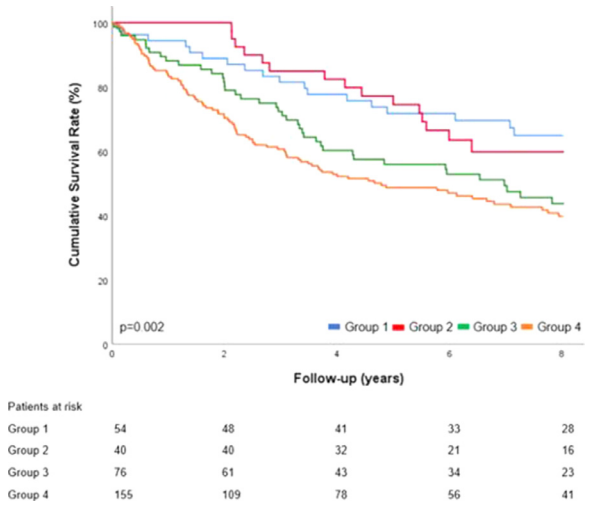

Figure 3. Kaplan-Meier curve analysis for all-cause mortality for the overall population according to the groups of cardiac involvement. Group 1 = Left ventricular involvement; Group 2 = Left atrial involvement; Group 3 = Tricuspid valve or pulmonary artery vasculature involvement; Group 4 = Right ventricular involvement.

3 and 4, which were 12% and 17% at 1-year and 53%, and 57% at 8 years of follow-up, respectively.

The univariable and multivariable Cox regression analysis evaluating the association between the groups of extramitral valvular cardiac involvement and all-cause mortality in the total population are listed in Table 4. In the univariable analysis, group 3 and group 4 were significantly associated with all-cause mortality. After correcting for age, male gender, kidney function, and chronic obstructive pulmonary disease, groups 3 and 4 remained independently associated with worse survival.

The univariable and multivariable Cox regression analysis evaluating the association between the groups of extramitral valvular cardiac involvement and all-cause mortality in the total population, while adding mitral valve intervention as a time-dependent variable, are listed in Table 5. After correcting in the multivariable analysis, for age, male gender, kidney function, chronic obstructive pulmonary disease, and mitral valve intervention (as a time-dependent variable), groups 3 and 4 remained independently associated with worse survival.

Discussion

This study showed that progressive extramitral valvular cardiac involvement is independently associated with all-cause mortality, a finding mainly driven by group 3 (tricuspid valve or pulmonary artery vasculature involvement) and group 4 (RV involvement).

SMR is characterized by LV remodeling and dysfunction that leads to leaflet malcoaptation with the mitral valve leaflets being structurally normal.[15] If left untreated, progression of LV dysfunction and mitral regurgitation can cause volume and pressure overload which can lead to further LV and LA dilation. Chronically elevated LA pressures can cause sustained pulmonary hypertension that can ultimately result in TR with RV dilation and dysfunction.[16,17] The prevalence of extramitral valvular cardiac involvement in patients with SMR has previously been reported.[7,18–23] Atrial fibrillation has been reported in 34% of patients with severe SMR[22] and 55% in moderate-to-severe and severe SMR.[7] TR has been observed in 30% of the patients who underwent mitral valve repair.[21] The prevalence of pulmonary hypertension in patients with SMR and LV systolic dysfunction is approximately 40%.[20] Another study reported an SPAP of ≥40 mm Hg in 58% of the patients with severe SMR.[19] RV dysfunction is present in 42% to 83% of patients with at least moderate SMR.[18,23] This study provides further insights regarding the prevalence of various aspects of extravalvular cardiac involvement and classified them. Group 4, characterized by RV involvement, was the most prevalent (48%) indicating that our patient population is representative of a cohort with advanced heart disease.

Several studies have shown an association between the various groups of extravalvular cardiac involvement and outcomes in patients with SMR. LV dysfunction[24,25] and LA dilation[26,27] have been independently associated with an increased risk for mortality. In a large cohort of 1,256 patients with heart failure (73% with SMR), LV systolic dysfunction was independently associated with all-cause mortality.[25] Rossi et al[27] reported an independent relation

Table 4
Univariable and multivariable Cox proportional hazard analysis in the total population

	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (years)	1.032 (1.017-1.048)	<0.001	1.025 (1.009-1.041)	0.002
Men	1.622 (1.184-2.224)	0.003	1.220 (0.878-1.694)	0.236
Creatinine (μmol/L)	1.007 (1.005-1.009)	<0.001	1.005 (1.003-1.008)	<0.001
Atrial fibrillation	1.268 (0.952-1.687)	0.104		
COPD	2.005 (1.367-2.939)	<0.001	1.434 (0.968-2.123)	0.072
MV intervention at follow-up	1.166 (0.875-1.555)	0.295		
LV ejection fraction (%)	0.981 (0.965-0.997)	0.018		
LA volume index (ml/m^2)	1.011 (1.004-1.017)	0.002		
SPAP (mmHg)	1.026 (1.015-1.036)	<0.001		
Significant TR	1.412 (1.042-1.913)	0.026		
TAPSE (mm)	0.957 (0.929-0.987)	0.005		
SMR moderate (reference)		<0.001		
SMR moderate-severe	2.951 (1.766-4.933)			
SMR severe	3.516 (2.111-5.857)			
Group 1 (reference)				
Group 2	1.386 (0.751-2.560)	0.296	1.114 (0.600-2.070)	0.732
Group 3	2.165 (1.294-3.622)	0.003	1.794 (1.067-3.015)	0.027
Group 4	2.562 (1.598-4.107)	<0.001	1.857 (1.145-3.012)	0.012

COPD = chronic obstructive pulmonary disease; LA = left atrial; LV = left ventricular; MV = mitral valve; SMR = secondary mitral regurgitation; SPAP = systolic pulmonary artery pressure; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation. Group 1 = LV involvement; Group 2 = LA involvement; Group 3 = Tricuspid valve or pulmonary artery vasculature involvement; Group 4 = Right ventricular involvement.

Table 5
Univariable and multivariable Cox proportional hazard analysis in the total population with mitral valve intervention as a time-dependent variable

	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (years)	1.032 (1.017-1.048)	<0.001	1.025 (1.009-1.042)	0.002
Men	1.622 (1.184-2.224)	0.003	1.307 (0.936-1.824)	0.116
Creatinine (μmol/L)	1.007 (1.005-1.009)	<0.001	1.005 (1.003-1.008)	<0.001
COPD	2.005 (1.367-2.939)	<0.001	1.342 (0.902-1.997)	0.146
MV intervention at follow-up*	1.489 (1.118-1.984)	0.006	1.383 (1.027-1.862)	0.033
Group 1 (reference)				
Group 2	1.386 (0.751-2.560)	0.296	1.074 (0.578-1.997)	0.821
Group 3	2.165 (1.294-3.622)	0.003	1.700 (1.009-2.865)	0.046
Group 4	2.562 (1.598-4.107)	<0.001	1.760 (1.082-2.862)	0.023

* Mitral valve intervention as a time-dependent variable.

COPD = chronic obstructive pulmonary disease; MV = mitral valve. Group 1 = Left ventricular involvement; Group 2 = Left atrial involvement; Group 3 = Tricuspid valve or pulmonary artery vasculature involvement; Group 4 = Right ventricular involvement.

between LA size and mortality in patients with heart failure, while Palmiero et al[26] confirmed that LA function is a powerful predictor of clinical outcomes in patients with heart failure and SMR. However, these studies did not group the patients according to the extent of cardiac involvement. In the present study, LV dysfunction and LA dilation were not associated with all-cause mortality when the extravalvular cardiac involvement groups were taken into consideration. This finding suggests that the more advanced groups have a stronger association with the outcome than LVEF and LA dilation considered individually. Other studies have also shown that pulmonary hypertension,[19,20,28,29] significant TR[30,] and RV dysfunction[18,23] are associated with an increased risk for mortality in patients with SMR. In a cohort of 692 patients with LV systolic dysfunction and SMR, the presence of pulmonary hypertension was independently associated with an increased risk of mortality.[29] Dini et al[18] reported that in patients with chronic heart failure and moderate-to-severe SMR, RV function (assessed by TAPSE) was a major determinant of clinical outcomes. In our study group, 3 (tricuspid valve or pulmonary artery vasculature involvement) and group 4 (RV involvement) were the strongest predictors for all-cause mortality. Interestingly, mitral valve intervention was also independently associated with all-cause mortality when taking into account as a time-dependent variable. This could be explained by the fact that in our study, patients in the advanced groups more often received mitral valve intervention. Future studies are needed to investigate if these advanced groups benefit and show any cardiac improvement (allowing reclassification to a lower group) after mitral valve intervention.

The present study has limitations related to its retrospective design. The majority of the patients were included in group 4, suggesting that our population represents a cohort with advanced heart disease. For the evaluation of RV dysfunction, only TAPSE was used. A combination of other RV function parameters may have provided stronger

prognostic information. Moreover, the specific cause of death was unknown in this study.

In conclusion, extramitral valvular cardiac involvement, beyond LV dysfunction, was present in most patients with significant SMR. Group 3 (tricuspid valve or pulmonary artery vasculature involvement) and group 4 (RV involvement) were the strongest predictors for all-cause mortality.

Disclosures

The Department of Cardiology of the Leiden University Medical Center received research grants from Abbott Vascular, Bayer, Bioventrix, Biotronik, Boston Scientific, Edwards Lifesciences, GE Healthcare, and Medtronic. Victoria Delgado received speaker fees from Abbott Vascular, Edward Lifesciences, GE Healthcare, Merck Sharp & Dohme, and Medtronic. Nina Ajmone Marsan received speakers fees from Abbott Vascular and GE Healthcare. Jeroen J Bax received speaker fees from Abbott Vascular. The remaining authors have no conflicts of interest to declare.

1. Nasser R, Van Assche L, Vorlat A, Vermeulen T, Van Craenenbroeck E, Conraads V, Van der Meiren V, Shivalkar B, Van Herck P, Claeys MJ. Evolution of functional mitral regurgitation and prognosis in medically managed heart failure patients with reduced ejection fraction. *JACC Heart Fail* 2017;5:652–659.
2. St John Sutton MG, Plappert T, Abraham WT, Smith AL, DeLurgio DB, Leon AR, Loh E, Kocovic DZ, Fisher WG, Ellestad M, Messenger J, Kruger K, Hilpisch KE, Hill MR. Multicenter InSync Randomized Clinical Evaluation (MIRACLE) Study Group. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. *Circulation* 2003;107:1985–1990.
3. Agricola E, Ielasi A, Oppizzi M, Faggiano P, Ferri L, Calabrese A, Vizzardi E, Alfieri O, Margonato A. Long-term prognosis of medically treated patients with functional mitral regurgitation and left ventricular dysfunction. *Eur J Heart Fail* 2009;11:581–587.
4. Goldstein D, Moskowitz AJ, Gelijns AC, Ailawadi G, Parides MK, Perrault LP, Hung JW, Voisine P, Dagenais F, Gillinov AM, Thourani V, Argenziano M, Gammie JS, Mack M, Demers P, Atluri P, Rose EA, O'Sullivan K, Williams DL, Bagiella E, Michler RE, Weisel RD, Miller MA, Geller NL, Taddei-Peters WC, Smith PK, Moquete E, Overbey JR, Kron IL, O'Gara PT, Acker MA, CTSN. Two-year outcomes of surgical treatment of severe ischemic mitral regurgitation. *N Engl J Med* 2016;374:344–353.
5. Lorusso R, Gelsomino S, Vizzardi E, D'Aloia A, De Cicco G, Lucà F, Parise O, Gensini GF, Stefàno P, Livi U, Vendramin I, Pacini D, Di Bartolomeo R, Miceli A, Varone E, Glauber M, Parolari A, Giuseppe Arlati F, Alamanni F, Serraino F, Renzulli A, Messina A, Troise G, Mariscalco G, Cottini M, Beghi C, Nicolini F, Gherli T, Borghetti V, Pardini A, Caimmi PP, Micalizzi E, Fino C, Ferrazzi P, Di Mauro M, Calafiore AM, ISTIMIR Investigators. Mitral valve repair or replacement for ischemic mitral regurgitation? The Italian study on the treatment of ischemic mitral regurgitation (ISTIMIR). *J Thorac Cardiovasc Surg* 2013;145:128–138.
6. Petrus AHJ, Dekkers OM, Tops LF, Timmer E, Klautz RJM, Braun J. Impact of recurrent mitral regurgitation after mitral valve repair for functional mitral regurgitation: long-term analysis of competing outcomes. *Eur Heart J* 2019;40:2206–2214.
7. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, Rajagopal V, Sarembock IJ, Brieke A, Marx SO, Cohen DJ, Weissman NJ, Mack MJ, COAPT Investigators. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018;379:2307–2318.
8. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, Rosenhek R, Sjögren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL, ESC Scientific Document Group. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2017;38:2739–2791.
9. Nishimura RA, Otto CM, Bonow RO, Carabello BA, 3rd Erwin JP, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, Rigolin VH, Sundt TM 3rd, Thompson A. 2017 aha/acc focused update of the 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 clinical practice guidelines. *J Am Coll Cardiol* 2017;70:252–289.
10. Généreux P, Pibarot P, Redfors B, Mack MJ, Makkar RR, Jaber WA, Svensson LG, Kapadia S, Tuzcu EM, Thourani VH, Babaliaros V, Herrmann HC, Szeto WY, Cohen DJ, Lindman BR, McAndrew T, Alu MC, Douglas PS, Hahn RT, Kodali SK, Smith CR, Miller DC, Webb JG, Leon MB. Staging classification of aortic stenosis based on the extent of cardiac damage. *Eur Heart J* 2017;38:3351–3358.
11. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;16:233–270.
12. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, Hahn RT, Han Y, Hung J, Lang RM, Little SH, Shah DJ, Shernan S, Thavendiranathan P, Thomas JD, Weissman NJ. 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;30:303–371.
13. Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, Badano L, Zamorano JL, Scientific Document Committee of the European Association of Cardiovascular. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2013;14:611–644.
14. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. 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;23:685–788.
15. Asgar AW, Mack MJ, Stone GW. Secondary mitral regurgitation in heart failure: pathophysiology, prognosis, and therapeutic considerations [published correction appears in *J Am Coll Cardiol* 2015;65:2265]. *J Am Coll Cardiol* 2015;65:1231–1248.
16. Patel H, Desai M, Tuzcu EM, Griffin B, Kapadia S. Pulmonary hypertension in mitral regurgitation. *J Am Heart Assoc* 2014;3:e000748.
17. Sanz J, Sánchez-Quintana D, Bossone E, Bogaard HJ, Naeije R. Anatomy, function, and dysfunction of the right ventricle: JACC state-of-the-art review. *J Am Coll Cardiol* 2019;73:1463–1482.
18. Dini FL, Conti U, Fontanive P, Andreini D, Banti S, Braccini L, De Tommasi SM. Right ventricular dysfunction is a major predictor of outcome in patients with moderate to severe mitral regurgitation and left ventricular dysfunction. *Am Heart J* 2007;154:172–179.
19. Kainuma S, Taniguchi K, Toda K, Funatsu T, Kondoh H, Nishino M, Daimon T, Sawa Y. Pulmonary hypertension predicts adverse cardiac events after restrictive mitral annuloplasty for severe functional mitral regurgitation. *J Thorac Cardiovasc Surg* 2011;142(4):783–792.
20. Magne J, Pibarot P, SenGupta PP, Donal E, Rosenhek R, Lancellotti P. Pulmonary hypertension in valvular disease: a comprehensive review on pathophysiology to therapy from the HAVEC group. *JACC Cardiovasc Imaging* 2015;8:83–99.
21. Matsunaga A, Duran CM. Progression of tricuspid regurgitation after repaired functional ischemic mitral regurgitation. *Circulation* 2005;112(suppl):I453–I457.
22. Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, Lefèvre T, Piot C, Rouleau F, Carrié D, Nejjari M, Ohlmann P, Leclercq F, Saint Etienne C, Teiger E, Leroux L, Karam N, Michel N, Gilard M, Donal E, Trochu JN, Cormier B, Armoiry X, Boutitie F, Maucort-Boulch D, Barnel C, Samson G, Guerin P, Vahanian A, Mewton N, MITRA-FR Investigators. Percutaneous repair or medical

treatment for secondary mitral regurgitation. *N Engl J Med* 2018;379:2297–2306.
23. Yalonetsky S, Eden H, Lessick J, Kapeliovich M, Dragu R, Mutlak D, Carasso S, Reisner S, Agmon Y, Hammerman H, Aronson D. Impact of functional mitral regurgitation on right ventricular function and outcome in patients with right ventricular infarction. *Am J Cardiol* 2014;114:36–41.
24. Bursi F, Barbieri A, Grigioni F, Reggianini L, Zanasi V, Leuzzi C, Ricci C, Piovaccari G, Branzi A, Modena MG. Prognostic implications of functional mitral regurgitation according to the severity of the underlying chronic heart failure: a long-term outcome study. *Eur J Heart Fail* 2010;12:382–388.
25. Rossi A, Dini FL, Faggiano P, Agricola E, Cicoira M, Frattini S, Simioniuc A, Gullace M, Ghio S, Enriquez-Sarano M, Temporelli PL. Independent prognostic value of functional mitral regurgitation in patients with heart failure. A quantitative analysis of 1256 patients with ischaemic and non-ischaemic dilated cardiomyopathy. *Heart* 2011;97:1675–1680.
26. Palmiero G, Melillo E, Ferro A, Carlomagno G, Sordelli C, Ascione R, Monda V, Severino S, Ascione L, Caso P. Significant functional mitral regurgitation affects left atrial function in heart failure patients: haemodynamic correlations and prognostic implications. *Eur Heart J Cardiovasc Imaging* 2019;20(9):1012–1019.
27. Rossi A, Temporelli PL, Quintana M, Dini FL, Ghio S, Hillis GS, Klein AL, Marsan NA, Prior DL, Yu CM, Poppe KK, Doughty RN, Whalley GA, MeRGE Heart Failure Collaborators. Independent relationship of left atrial size and mortality in patients with heart failure: an individual patient meta-analysis of longitudinal data (merge heart failure). *Eur J Heart Fail* 2009;11:929–936.
28. Ghoreishi M, Evans CF, DeFilippi CR, Hobbs G, Young CA, Griffith BP, Gammie JS. Pulmonary hypertension adversely affects short- and long-term survival after mitral valve operation for mitral regurgitation: implications for timing of surgery. *J Thorac Cardiovasc Surg* 2011;142:1439–1452.
29. Miller WL, Mahoney DW, Enriquez-Sarano M. Quantitative doppler-echocardiographic imaging and clinical outcomes with left ventricular systolic dysfunction: independent effect of pulmonary hypertension. *Circ Cardiovasc Imaging* 2014;7:330–336.
30. Gyoten T, Messroghli D, Schenk S, Rochor K, Grimmig O, Just S, Fritzsche D. Impact of preinterventional tricuspid regurgitation on outcome of MitraClip therapy in patients with severely reduced ejection fraction. *Open Heart* 2020;7:e001203.