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Wijngaarden, A.L. van; Mantegazza, V.; Hiemstra, Y.L.; Volpato, V.; Bijl, P. van der; Pepi, M.; ... ; Bax, J.J.

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ORIGINAL RESEARCH

Prognostic Impact of Extra–Mitral Valve Cardiac Involvement in Patients With Primary Mitral Regurgitation

Aniek L. van Wijngaarden, MD,[a] Valentina Mantegazza, MD,[b] Yasmine L. Hiemstra, MD,[a] Valentina Volpato, MD,[b] Pieter van der Bijl, MD,[a] Mauro Pepi, MD,[b] Meindert Palmen, MD, PhD,[c] Victoria Delgado, MD, PhD,[a] Nina Ajmone Marsan, MD, PhD,[a] Gloria Tamborini, MD,[b] Jeroen J. Bax, MD, PhD[a]

ABSTRACT

BACKGROUND In patients with severe primary mitral regurgitation (MR), the indication for surgery is currently based on the presence of symptoms, left ventricular dilatation and dysfunction, atrial fibrillation, and pulmonary hypertension.

OBJECTIVES The aim of this study was to evaluate the prognostic impact of the presence of extra-mitral valve cardiac involvement (including known risk factors but also severe left atrial [LA] dilatation and right ventricular [RV] dysfunction) in a large multicenter study of patients with primary MR.

METHODS Patients with severe primary MR undergoing surgery were included and categorized according to the extent (highest) of cardiac involvement: group 0, no cardiac involvement; group 1, left ventricular involvement; group 2, LA involvement; group 3, pulmonary vasculature or tricuspid valve involvement; or group 4, RV involvement. The outcome was all-cause mortality.

RESULTS A total of 1,106 patients were included (mean age 63 ± 12 years, 68% male). In total, 377 patients (34%) were classified in group 0, 239 (22%) in group 1, 213 (19%) in group 2, 180 (16%) in group 3, and 97 (9%) in group 4. Kaplan-Meier curve analysis revealed significantly worse survival (log-rank chi-square = 43.4; $P < 0.001$) with higher group. On multivariable analysis, age, male sex, chronic obstructive pulmonary disease, kidney function, and group of cardiac involvement were independently associated with all-cause mortality. For each increase in group, a 17% higher risk for all-cause mortality was observed (95% CI: 1.051-1.313; $P = 0.005$) during a median follow-up time of 88 months.

CONCLUSIONS In patients with severe primary MR, a novel classification system based on extra-mitral valve cardiac involvement may help refine risk stratification and timing of surgery, particularly including severe LA dilatation and RV dysfunction in the assessment. (J Am Coll Cardiol Img 2022;15:961-970) © 2022 by the American College of Cardiology Foundation.

Primary mitral regurgitation (MR) is mostly caused by mitral valve (MV) prolapse and represents one of the most common valvular heart diseases, associated with increased morbidity and mortality.[1,2] As therapeutic solutions are currently limited to surgical or percutaneous repair or replacement, correct timing to refer these patients for surgical treatment is of crucial clinical

From the [a]Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands; [b]Department of Cardiovascular Imaging, Centro Cardiologico Monzino IRCCS, Milan, Italy; and the [c]Department of Cardiothoracic Surgery, Leiden University Medical Center, Leiden, the Netherlands.
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ABBREVIATIONS AND ACRONYMS

LA = left atrial

LV = left ventricular

MIDA = mitral regurgitation international database

MR = mitral regurgitation

MV = mitral valve

RV = right ventricular

TAPSE = tricuspid annular plane systolic excursion

TR = tricuspid regurgitation

importance. Currently, the indication for surgery is based on the severity of MR and the presence of symptoms, left ventricular (LV) dilatation and dysfunction, atrial fibrillation, and pulmonary hypertension.[3,4] However, the prognosis (also postsurgery) of patients with severe primary MR is influenced by numerous other risk factors, such as left atrial (LA) size, MV anatomy suitability to repair, presence of tricuspid regurgitation (TR), and right ventricular (RV) dysfunction,[5-7] which are all to be considered when risk-stratifying these patients. In an attempt to develop a more comprehensive assessment, the MIDA (Mitral Regurgitation International Database) registry proposed a risk score based on some of the aforementioned factors.[5] Recently, a novel classification system based on the presence of cardiac involvement was also proposed, specifically for patients with symptomatic or asymptomatic severe aortic stenosis. This classification system included LV involvement, LA or MV involvement, pulmonary vasculature or tricuspid involvement, and RV involvement and was shown to be independently associated with prognosis.[8,9] A similar approach has not been tested in severe primary MR, although it might significantly help clinicians systematically identify the anatomical and functional extent of extra-MV cardiac involvement in these patients. Therefore, the aim of this study was to propose a classification system customized for primary MR and to evaluate its prognostic value in a large population of patients with moderate to severe and severe primary MR referred for surgical intervention.

METHODS

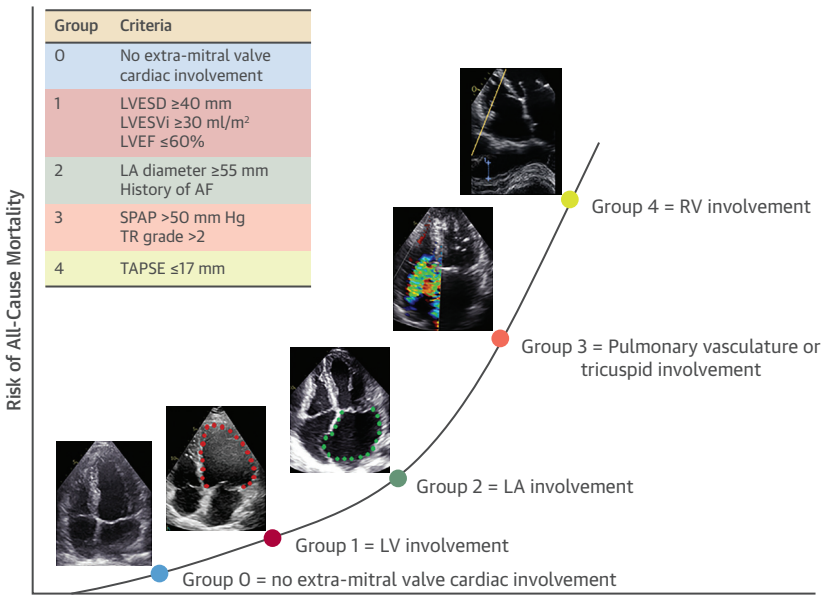
STUDY POPULATION AND CLINICAL CHARACTERISTICS. Patients with moderate to severe and severe primary MR caused by myxomatous degeneration or prolapse who underwent MV surgery at the Leiden University Medical Center (Leiden, the Netherlands) or at Centro Cardiologico Monzino (Milan, Italy) between 2000 and 2017 were included in this analysis on the basis of available echocardiographic images before surgery (considered as the baseline echocardiogram). Patients with infective endocarditis, rheumatic heart disease, and previous valvular intervention were excluded. Demographic characteristics, New York Heart Association functional class, cardiovascular risk factors, concomitant cardiovascular disease, comorbidities, medication use, kidney function, and clinical follow-up data were collected using hospital records and the information systems used in the cardiology departments and retrospectively analyzed. The primary outcome was all-cause mortality, as verified by reviewing hospital records, which are connected to the governmental death registry database. The study complied with the Declaration of Helsinki and was approved by the Institutional Review Board and medical ethics committee, which waived the need to obtain written informed consent.

STANDARD ECHOCARDIOGRAPHY. Standard transthoracic 2-dimensional echocardiographic images were obtained for all patients before surgery in the left lateral decubitus position at rest using commercially available ultrasound equipment (Vivid 5, Vivid 7, System 5, and E9 [GE Healthcare]; iE33 and Epic [Philips Medical Systems]). Conventional 2-dimensional, M-mode, continuous, pulsed-wave, and color Doppler images were acquired in parasternal and apical views,[10] digitally stored, and analyzed off-line using EchoPAC versions 112, 202, and 203 (GE Medical Systems) and ComPACS version 10.10.3 (MediMatic).

LV dimensions (LV end-diastolic and end-systolic diameter) were assessed in the parasternal long-axis view. From the apical 2- and 4-chamber views, LV end-diastolic and end-systolic volumes were measured using the Simpson biplane method and indexed to body surface area; LV ejection fraction was then calculated.[10] The maximum LA diameter was assessed in the parasternal long-axis plane at end-systole. LA volumes were measured at end-systole in the apical 2- and 4-chamber views using the Simpson biplane method and indexed to body surface area (LA volume index).[10] In addition, peak early (E) diastolic velocity was measured using pulsed-wave Doppler images of transmitral flow.[11] MV prolapse was diagnosed as leaflet displacement >2 mm beyond the mitral annulus in the long-axis plane.[7,12] MR and TR severity were graded according to current guidelines using a multiparametric approach.[12] RV pressure was determined using the peak velocity of the TR jet according to the Bernoulli equation and right atrial pressure on the basis of the diameter and inspiratory collapse of the inferior vena cava to evaluate the systolic arterial pulmonary pressure.[13,14] To assess RV systolic function, anatomical M-mode imaging was used on the (focused) apical 4-chamber view of the right ventricle to determine the tricuspid annular plane systolic excursion (TAPSE).[10]

DEFINITION OF EXTRA-MV CARDIAC INVOLVEMENT. On the basis of the presence of extra-MV cardiac involvement on baseline transthoracic echocardiography, patients were categorized into 5 groups: group 0, no signs of extra-MV cardiac involvement; group 1,

FIGURE 1 **Extra-Mitral Valve Cardiac Involvement in Moderate to Severe and Severe Primary MR**



Proposed classification system based on the extent of echocardiographic findings of extra-mitral valve cardiac involvement associated with increased risk for mortality. AF = atrial fibrillation; LA = left atrial; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESVi = left ventricular end-systolic volume index; MR = mitral regurgitation; SPAP = systolic pulmonary artery pressure; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

LV involvement (LV end-systolic diameter ≥40 mm, LV end-systolic volume index ≥30 mL/m^2, or LV ejection fraction ≤60%); group 2, LA involvement (LA maximum diameter ≥55 mm or history of atrial fibrillation); group 3, pulmonary artery vasculature or tricuspid valve involvement (systolic pulmonary artery pressure >50 mm Hg or TR grade >2); or group 4, RV involvement (TAPSE ≤17 mm) (Figure 1). These criteria with corresponding cutoff values were selected on the basis of current recommendations for the management of valvular heart disease (indication for surgery) and evidence from previous studies.[3-5,8,15] Patients were allocated on the basis of the criteria of the highest group present.

STATISTICAL ANALYSIS. Categorical variables are expressed as absolute numbers and percentages. Continuous variables are presented as mean ± SD when normally distributed and as median (IQR) when not normally distributed. Patients were categorized on the basis of the extent of extra-MV cardiac involvement. Differences in continuous variables between the groups were tested using 1-way analysis of variance (normally distributed variables) or the Kruskal-Wallis test (non-normally distributed variables). Differences in categorical variables were tested using the chi-square test. To calculate the survival and event rates for the separate groups of cardiac involvement, the Kaplan-Meier method was used. The log-rank test was used for the comparison of cumulative event rates among the different groups. Univariable Cox proportional hazards analyses were performed to evaluate the association of the group classification and other clinical and echocardiographic parameters with the primary endpoint. From this univariable analysis, statistically significant or clinically relevant variables were selected and introduced as covariates in multivariable Cox proportional hazards models. For both univariable and multivariable analyses, HRs with 95% CIs are reported. Statistical analysis was performed using SPSS version 25.0 (IBM). For all tests, a 2-sided P value <0.05 was considered to indicate statistical significance.

RESULTS

PATIENT CHARACTERISTICS. A total of 1,106 patients with moderate to severe or severe primary MR who underwent MV surgery were included (mean age 63 ± 12 years, 68% male). In Table 1, baseline characteristics of the total study population are presented. The majority of patients were symptomatic

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TABLE 1 Clinical Characteristics of the Total Patient Population and According to the Presence of Extra-Mitral Valve Cardiac Involvement

	Total Population (N = 1,106)	Group 0: Normal (n = 377)	Group 1: LV Involvement (n = 239)	Group 2: LA Involvement (n = 213)	Group 3: Pulmonary Involvement (n = 180)	Group 4: RV Involvement (n = 97)	*P* Value
Age, y	63 ± 12	61 ± 12	58 ± 13	65 ± 11	68 ± 10	69 ± 10	<0.001
Male	757 (68)	248 (66)	187 (78)	163 (77)	103 (57)	56 (58)	<0.001
Body mass index, kg/m^2	25 ± 4	24 ± 3	25 ± 4	25 ± 4	25 ± 3	25 ± 5	0.331
Hypertension	460 (42)	159 (42)	89 (37)	94 (44)	71 (39)	47 (49)	0.319
Diabetes mellitus	36 (3)	11 (3)	4 (2)	3 (1)	12 (7)	6 (6)	0.009
Coronary artery disease	236 (21)	78 (21)	44 (18)	41 (19)	38 (21)	35 (36)	0.006
History of smoking	333 (30)	100 (27)	86 (36)	61 (29)	54 (30)	32 (33)	0.147
Chronic obstructive pulmonary disease	77 (7)	25 (7)	16 (7)	11 (5)	20 (11)	5 (5)	0.170
History of atrial fibrillation	278 (25)	0 (0)	0 (0)	154 (72)	61 (34)	63 (65)	<0.001
NYHA functional class							<0.001
I	294 (27)	120 (32)	82 (34)	56 (26)	24 (13)	12 (12)	
II	563 (51)	209 (55)	116 (49)	114 (54)	86 (48)	38 (39)	
III	225 (20)	47 (13)	36 (15)	38 (18)	61 (34)	43 (44)	
IV	24 (2)	1 (1)	5 (2)	5 (2)	9 (5)	4 (4)	
NYHA functional class ≥II	812 (73)	257 (68)	157 (66)	157 (74)	156 (87)	85 (88)	<0.001
Estimated glomerular filtration rate, mL/min/1.73 m^2	82 ± 27	85 ± 26	92 ± 28	83 ± 27	71 ± 23	67 ± 27	<0.001
Medication use							
Oral anticoagulant agent	186 (17)	13 (3)	10 (4)	82 (39)	43 (24)	38 (39)	<0.001
Beta-blocker	361 (33)	98 (26)	66 (28)	96 (45)	68 (38)	33 (34)	<0.001
ACE inhibitor/ARB	489 (44)	160 (42)	112 (47)	103 (48)	73 (41)	41 (42)	0.327
Calcium channel blocker	75 (7)	21 (6)	15 (6)	14 (7)	14 (8)	11 (11)	0.102
Diuretic agent	334 (30)	86 (23)	44 (18)	79 (37)	80 (44)	45 (46)	<0.001
Surgical parameters							
MV replacement	31 (3)	10 (3)	9 (4)	6 (3)	2 (1)	4 (4)	0.500
CABG	172 (16)	59 (16)	28 (12)	30 (14)	31 (17)	24 (25)	0.047
TVP	372 (34)	71 (19)	49 (21)	92 (43)	105 (58)	55 (57)	<0.001
Maze	212 (19)	7 (2)	6 (3)	116 (55)	46 (26)	37 (38)	<0.001
Postoperative MR grade ≥2	31 (3)	12 (3)	5 (2)	5 (2)	5 (3)	4 (4)	0.839

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; LA = left atrial; LV = left ventricular; MR = mitral regurgitation; MV = mitral valve; NYHA = New York Heart Association; RV = right ventricular; TVP = tricuspid valvuloplasty.

before surgery: 73% of patients presented in New York Heart Association functional class II or higher. The presence of cardiovascular risk factors was relatively low (hypertension and diabetes mellitus in 42% and 3%, respectively), and only 21% of the patients had coronary artery disease.

When patients were categorized according to the groups of extra-MV cardiac involvement, 34% of patients (n = 377) were classified in group 0 (no extra-MV cardiac involvement), 22% (n = 239) in group 1 (LV involvement), 19% (n = 213) in group 2 (LA involvement), 16% (n = 180) in group 3 (pulmonary vasculature or tricuspid valve involvement), and 9% (n = 97) in group 4 (RV involvement). When comparing the different groups, patients in the higher extra-MV cardiac involvement groups were older, probably also explaining the higher prevalence of comorbidities such as diabetes mellitus, coronary artery disease, and worse renal function. Furthermore, patients in the higher extra-MV involvement groups had more severe symptoms and more frequently used diuretic medications. In addition, these patients more often used oral anticoagulation and beta-blockers, probably because of their more frequent histories of atrial fibrillation (part of the classification criteria).

In Table 2, the baseline echocardiographic parameters for the total population and for each group of cardiac involvement are shown. The mean LV ejection fraction was 64% ± 7% for the total population. The largest LV dimensions and volumes (LV end-systolic diameter 37 ± 7 mm, LV end-systolic volume index 33 ± 8 mL/m^2) were observed in group 1 (LV involvement), and the largest LA dimensions and volumes (LA maximum diameter 51 ± 9 mm, LA volume index 63 ± 27 mL/m^2) were observed in group 2 (LA involvement), while TR was present only in groups 3 and 4. The incidence of the individual criteria for every group of extra-MV cardiac

TABLE 2 Echocardiographic Characteristics of the Total Patient Population and According to the Presence of Extra-Mitral Valve Cardiac Involvement

	Total Population (N = 1,106)	Group 0: Normal (n = 377)	Group 1: LV Involvement (n = 239)	Group 2: LA Involvement (n = 213)	Group 3: Pulmonary Involvement (n = 180)	Group 4: RV Involvement (n = 97)	*P* Value
LV end-diastolic diameter, mm	54 ± 7	53 ± 5	57 ± 6	55 ± 7	55 ± 7	53 ± 7	<0.001
LV end-systolic diameter, mm	33 ± 7	30 ± 4	37 ± 7	35 ± 7	34 ± 7	35 ± 7	<0.001
LV end-diastolic volume, mL	140 ± 42	125 ± 29	160 ± 40	147 ± 47	142 ± 45	126 ± 44	<0.001
LV end-diastolic volume index, mL/m^2	74 ± 20	68 ± 13	84 ± 19	76 ± 22	76 ± 21	67 ± 22	<0.001
LV end-systolic volume, mL	50 ± 20	40 ± 10	63 ± 16	55 ± 23	50 ± 22	51 ± 24	<0.001
LV end-systolic volume index, mL/m^2	27 ± 10	21 ± 5	33 ± 8	29 ± 11	27 ± 10	27 ± 12	<0.001
LV ejection fraction, %	64 ± 7	68 ± 4	61 ± 6	63 ± 8	65 ± 8	60 ± 9	<0.001
LA end-systolic diameter, mm	46 ± 8	42 ± 6	44 ± 5	51 ± 9	48 ± 8	48 ± 9	<0.001
LA volume index, mL/m^2	59 ± 24	46 ± 15	49 ± 15	63 ± 27	59 ± 23	59 ± 27	<0.001
Peak E-wave velocity, cm/s	111 ± 33	102 ± 26	101 ± 29	106 ± 31	132 ± 35	113 ± 34	<0.001
Systolic pulmonary arterial pressure, mm Hg	37 ± 13	31 ± 7	32 ± 8	33 ± 7	58 ± 11	42 ± 15	<0.001
Tricuspid regurgitation							<0.001
Grade 3	57 (5)	0 (0)	0 (0)	0 (0)	45 (25)	12 (12)	
Grade 4	9 (1)	0 (0)	0 (0)	0 (0)	5 (3)	4 (4)	
Tricuspid annular plane systolic excursion, mm	24 ± 5	25 ± 4	25 ± 4	25 ± 4	24 ± 4	15 ± 2	<0.001

Values are mean ± SD or n (%).
Abbreviations as in Table 1.

involvement and of the individual components of the extent of cardiac involvement in the total population is presented in Supplemental Table 1.

SURVIVAL ANALYSIS. In total, 178 patients (16%) died during follow-up, with a median follow-up time of 88 months (IQR: 50-120 months). Kaplan-Meier curve analysis revealed that patients in higher groups of extra-MV cardiac involvement had significantly worse survival (log-rank chi-square = 43.4; $P < 0.001$) (Figure 2). Interestingly, significantly higher all-cause mortality cumulative event rates were observed for groups 2, 3, and 4 compared with group 0 ($P < 0.001$ for all), while group 1 compared with group 0 did not show significant differences in survival rates ($P = 0.591$).

Table 3 reports the correlates of all-cause mortality on univariable and multivariable Cox regression analysis. On multivariable analysis, age, male sex, chronic obstructive pulmonary disease, renal function, and group of extra-MV cardiac involvement were independently associated with all-cause mortality. For each increasing group, a 17% higher risk for all-cause mortality was observed (95% CI: 1.051-1.313; $P = 0.005$).

DISCUSSION

The present study demonstrates that in a large multicenter cohort of patients with moderate to severe and severe primary MR referred for surgery, extra-MV cardiac involvement such as severe LA dilatation, pulmonary hypertension, and RV dysfunction can frequently occur. Using a novel classification system, extra-MV cardiac involvement was independently associated with all-cause mortality. Of interest, patients with severe LA dilatation showed higher mortality compared with patients with LV dilatation, while RV involvement was associated with the highest rates of mortality (Central Illustration).

MECHANISM AND PREVALENCE OF EXTRA-MV CARDIAC INVOLVEMENT IN PRIMARY MR. Significant primary MR leads initially to LA and LV dilatation as adaptive mechanisms to volume overload.[7] In most cases, during this phase LV systolic function and pulmonary pressures remain within normal limits, and patients are asymptomatic. Chronic severe MR (if left untreated) frequently results in progressive LV dilatation and decreased LV systolic function (using a higher threshold of LV ejection fraction considering the reduced afterload in MR) and may be accompanied by symptoms. In addition, chronic MR results in further LA dilatation and eventually elevated pulmonary pressures. Long-standing elevated pulmonary pressures often induce RV dilatation with secondary TR (by annular dilatation), and ultimately the impaired right ventricle supervenes.[7] However, this pathophysiological cascade does not occur in the same way in all patients, and how each patient hemodynamically adapts to the presence of severe MR in terms of chamber remodeling, and therefore of

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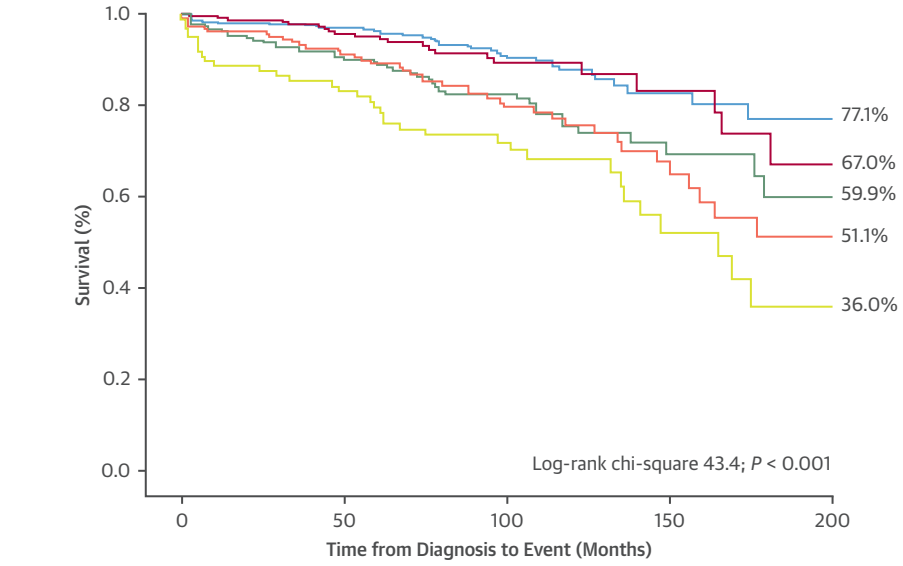
FIGURE 2 Survival Analysis According to the Different Groups of Extra-Mitral Valve Cardiac Involvement



Patients at risk					
Group 0	377	296	177	42	11
Group 1	239	167	74	22	2
Group 2	213	158	89	27	7
Group 3	180	137	77	25	4
Group 4	97	74	41	13	4

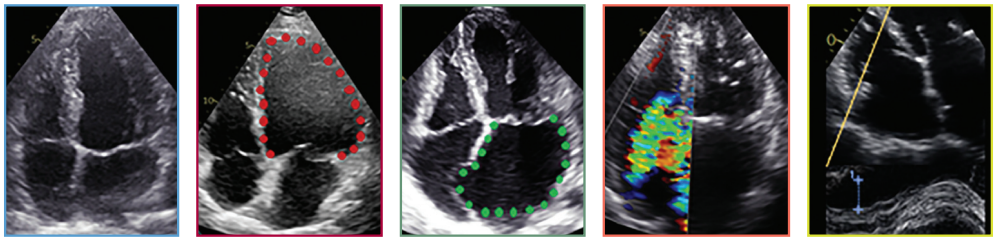
Kaplan-Meier curves estimated for cumulative event rates of all-cause mortality.

extra-MV cardiac involvement, can vary significantly. Patients with more acute onset of MR, for example, may present immediately in group 3 or 4, as the left atrium and left ventricle may not have had the time to adapt to the acute volume overload, thereby transferring the pressure rapidly to the pulmonary circulation.[16] Also, increased LV and LA stiffness may lead, through the pressure-volume relation, to higher pulmonary pressure without severe dilatation of the left atrium and left ventricle. In addition, the presence of atrial fibrillation may significantly affect LA dimension in addition to severe MR.[17] Similarly, chronic obstructive pulmonary disease could further increase the involvement of the pulmonary vasculature or the tricuspid valve.[18] The presence of comorbidities could therefore affect cardiac response to MR (eg, explaining why patients might be in group 3 or 4 without LV or LA dilatation) but also have a direct impact on outcome. On the basis of these considerations, the term "group" was used in this study to identify a phenotype (associated with higher or lower risk for mortality) with which a patient may present during clinical evaluation rather than a defined stage of the disease. The presence of different extra-MV involvement may therefore reflect not only the hemodynamic consequences of severe MR but also overall patient vulnerability and may be taken into account when considering the indication for surgery, which is currently based on symptoms or on the occurrence of LV dilatation and dysfunction, new-onset atrial fibrillation, or pulmonary hypertension.[3,4]

The prevalence of different extra-MV cardiac involvements has been investigated in previous studies. Tribouilloy et al[19] reported 26% LV enlargement on the basis of LV end-systolic diameter ≥40 mm in patients with primary MR caused by flail leaflet. LV dysfunction, defined as LV ejection fraction ≤60%, has been reported in 19% of patients in the most recent cohorts[20,21] and in up to 40% in older cohorts.[22] Atrial fibrillation has been frequently reported in patients with primary MR, with a prevalence of up to 30%[23] and a linearized rate of 5% per year when patients received conservative

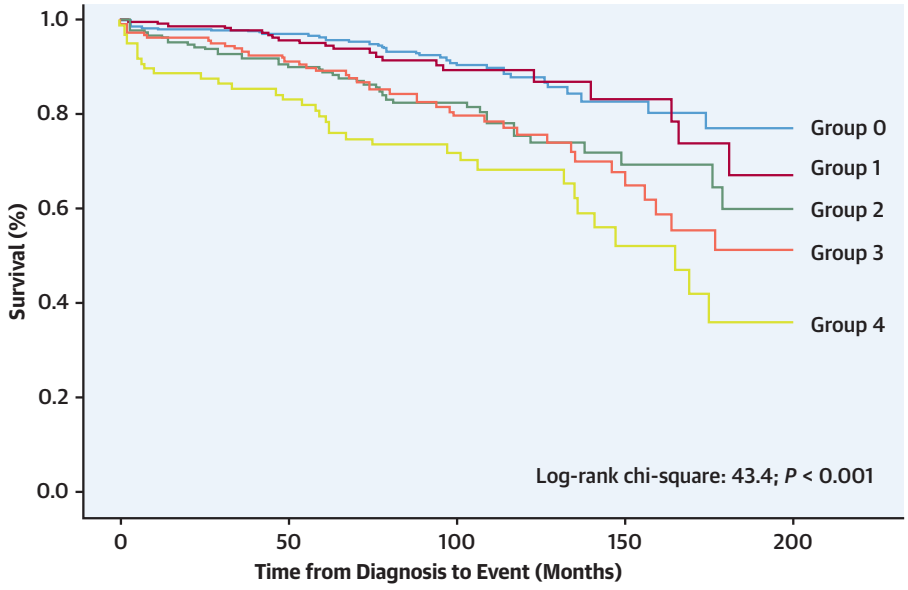
CENTRAL ILLUSTRATION **Clinical Outcome in Relation to the Presence of Extra-Mitral Valve Cardiac Involvement: Results From a Multicenter Severe Primary Mitral Regurgitation Cohort**

Classification of Primary Mitral Regurgitation Based on Extra-Mitral Valve Cardiac Involvement



Group 0	Group 1	Group 2	Group 3	Group 4
No extra-mitral valve cardiac involvement	Left ventricular involvement	Left atrial involvement	Pulmonary vasculature or tricuspid involvement	Right ventricular involvement
N = 377 (34%)	N = 239 (22%)	N = 213 (19%)	N = 180 (16%)	N = 97 (9%)

Survival According to the Extent of Extra-Mitral Valve Cardiac Involvement



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(Top) Proposed novel classification system based on the extent of echocardiographic signs of extra-mitral valve cardiac involvement in patients with severe primary mitral regurgitation. **(Bottom)** For all-cause mortality, patients with increasing extent of extra-mitral valve cardiac involvement (ie, groups 2, 3, and 4) had significantly worse survival.

treatment.[17] Furthermore, severe LA dilatation (LA diameter ≥55 mm) has been reported in 18% of patients with primary MR caused by MV flail.[15] The prevalence of significant TR and severe pulmonary hypertension varies among studies but has been reported to be 50%[24,25] and 24%,[16,23] respectively. Similarly, RV dysfunction rates range from 16% to 51% in published studies.[26,27] In the present study, the

TABLE 3 Univariate and Multivariate Cox Proportional Hazard Analyses in the Total Study Population

	Univariate Analysis		Multivariate Analysis	
All-Cause Mortality	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, per 1-y increase	1.095 (1.076-1.115)	<0.001	1.069 (1.044-1.094)	<0.001
Male gender, yes/no	0.744 (0.549-1.007)	0.055	1.522 (1.079-2.145)	0.017
NYHA functional class ≥II, yes/no	1.890 (1.276-2.800)	0.001	1.010 (0.668-1.527)	0.964
Hypertension, yes/no	1.124 (0.836-1.510)	0.440		
Diabetes mellitus, yes/no	1.167 (0.517-2.636)	0.710		
COPD, yes/no	2.646 (1.753-3.994)	<0.001	1.932 (1.278-2.921)	0.002
Coronary artery disease, yes/no	1.519 (1.104-2.092)	0.010	0.876 (0.629-1.220)	0.434
Concomitant TVP, yes/no	1.114 (0.822-1.511)	0.487		
eGFR per 1 mL/min/1.73 m^2 increase	0.968 (0.961-0.975)	<0.001	0.986 (0.976-0.995)	0.004
Group of cardiac involvement, per 1-group increase	1.389 (1.250-1.543)	<0.001	1.174 (1.051-1.313)	0.005
Groups of cardiac involvement		<0.001		
Group 0 vs group 1	1.122 (0.662-1.903)	0.669		
Group 0 vs group 2	2.088 (1.341-3.249)	0.001		
Group 0 vs group 3	2.324 (1.489-3.626)	<0.001		
Group 0 vs group 4	3.742 (2.363-5.926)	<0.001		

COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; other abbreviations as in Table 1.

observed prevalence of LV and LA involvement is consistent with previous studies based on recent cohorts.[15,20] The observed prevalence of severe pulmonary hypertension, significant TR, and RV dysfunction is lower than other studies, possibly because at our centers, patients tend to be referred and offered surgery early in their clinical presentation.[28]

PROGNOSTIC IMPACT OF CARDIAC INVOLVEMENT IN PRIMARY MR. The prognostic value of separate extra-MV cardiac involvements has been explored in different studies of patients with severe primary MR. Tribouilloy et al[19] concluded that LV end-systolic diameter is an independent predictor of overall mortality, and Wang et al[23] reported in a population with both primary and functional MR that impaired LV function and LV enlargement were predictors of early and late mortality, respectively. However, in the present study, group 0 and group 1 did not significantly differ in terms of survival. The prevalence of LV dysfunction in our cohort, and particularly within group 1, was relatively low (with LV ejection fraction ≥50% even in patients with values less than the cutoff of 60%) and might explain this finding. Group 1 seems therefore to be represented mainly by patients with LV dilatation, which with these criteria might reflect a physiological adaptation mechanism to the volume overload. Importantly, LA involvement (group 2, presence of atrial fibrillation or severe LA dilatation) and pulmonary vasculature or tricuspid valve involvement (group 3, severe pulmonary hypertension or significant TR) showed significant associations with mortality. Previous studies demonstrated the negative impact of atrial fibrillation,[17,29] severe pulmonary hypertension,[16,23] and significant TR[24,25] on survival after MV repair, but the evidence for severe LA enlargement is limited.[15,30] Current guidelines[3,4] therefore recommend that surgery for severe primary MR may be considered in patients with LA volume index ≥60 mL/m^2 in sinus rhythm (Class 2a indication). However, the results of the present study show that patients in groups 2 and 3 have a similarly poor prognosis, suggesting that severe LA dilatation deserves more clinical attention, as it is not just a benign compensatory phenomenon. Also, subclinical atrial fibrillation (often underdiagnosed) is strongly associated with LA size,[15] and therefore incorporating LA size in clinical decision making could be of further value. Undoubtedly, patients with impaired RV function (group 4) showed the worst prognosis, in line with initial studies focusing on RV dysfunction in severe patients with primary MR.[26,31]

Studies combining all separate extra-MV cardiac involvement parameters are limited. The MIDA registry included patients with isolated degenerative MR and proposed a mortality risk score. This risk score included several parameters: age ≥65 years, presence of symptoms, history of atrial fibrillation, LA diameter ≥55 mm, RV systolic pressure >50 mm Hg, LV end-systolic diameter ≥40 mm, and LV ejection fraction ≤60%.[5] However, the risk score does not include RV dysfunction, which in our study was an important predictor of survival. Furthermore, the

MIDA registry mostly includes patients with flail leaflets with very severe MR. In the present study, an intuitive classification system is proposed including the anatomical and functional extent of extra-MV cardiac involvement, tested in a large, real-world, multicenter cohort of patients with moderate to severe and severe primary MR. This study highlights the association among severe LA dilatation (group 2), severe pulmonary hypertension, significant TR (group 3), RV dysfunction (group 4), and mortality. Therefore, identification of extra-MV cardiac involvement as suggested in this study can be easily performed and could be taken into consideration in patient management.

STUDY LIMITATIONS. First, the patients in this study underwent surgery at 2 tertiary referral centers, and the association between the cardiac involvement groups and mortality in the natural course of primary MR (medical therapy) could not be evaluated. In addition, the results might not be applicable to different clinical settings (with high rates of MV replacement). Furthermore, to include widely and consistently available parameters, this novel classification system included only standard echocardiographic measures and a history of atrial fibrillation. TAPSE was therefore the only measure used for the assessment of RV function. Although TAPSE takes into account only tricuspid lateral annular displacement, it is a measure that is easy to obtain, is less dependent on image quality, has been validated in large patient cohorts,[13] and is also specifically performed in patients with MV disease.[32] Biomarkers, such as pro-brain natriuretic peptide, or advanced echocardiographic parameters such as LV global longitudinal strain (with intervendor variability issues) were also not included. Finally, all-cause mortality was chosen as the outcome because this is the most robust endpoint and considering the difficulty of obtaining detailed information on cause of death and registration of other cardiovascular events (aside from reoperation).

CONCLUSIONS

Extra-MV cardiac involvement is frequently present in patients with severe primary MR and was included in a novel classification system in which particularly atrial fibrillation and severe LA dilatation (group 2), pulmonary hypertension or significant TR (group 3), and RV dysfunction (group 4) were independently associated with all-cause mortality. Incorporating this classification system into clinical decision making might help improve risk stratification and optimal timing for surgery in these patients.

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ADDRESS FOR CORRESPONDENCE: Dr Nina Ajmone Marsan, Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, the Netherlands. E-mail: n.ajmone@lumc.nl.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Proper risk stratification and timely indication for surgery in patients with severe primary MR remain a clinical challenge. In the present study, an intuitive classification system for these patients is proposed, including the anatomical and functional extent of extra-MV cardiac involvement, and tested in a large, real-world, multicenter cohort. Atrial fibrillation, severe LA dilatation (group 2), pulmonary hypertension or significant TR (group 3), and RV dysfunction (group 4) were independently associated with all-cause mortality. Incorporating this novel classification system into clinical decision making might therefore help improve management and optimal timing for surgery in these patients.

TRANSLATIONAL OUTLOOK: Larger prospective studies should further confirm the findings of the present study as well as the prognostic value of the classification system based on extra-MV cardiac involvement. The concept of this new classification system, which is comprehensive of additional characteristics such as severe LA dilatation and RV dysfunction, but also simple and intuitive, will favor its application in clinical practice.

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KEY WORDS mitral valve surgery, primary mitral regurgitation, survival

APPENDIX For a supplemental table, please see the online version of this paper.

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