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Original Article

Long-term Adverse Events of Nonischemic Functional Mitral Regurgitation in Patients With Heart Failure

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ABSTRACT

Background: Nonischemic functional mitral regurgitation (FMR) is accompanied by dire long-term consequences. The treatment revolves around correcting the underlying left ventricular dysfunction. This study reports the long-term adverse outcomes of nonischemic FMR.

Methods: We enrolled 200 patients with at-least-moderate nonischemic FMR undergoing medical treatment and/or cardiac resynchronization therapy between 2003 and 2019. MR severity and left ventricular dysfunction parameters were obtained. The endpoint outcomes were all-cause mortality, stroke, all-cause rehospitalization, and the need for heart transplantation.

Results: Two hundred participants, 104 men (52%) and 96 women (48%), with a median age of 61 years (interquartile range [IQR], 50-70) at diagnosis and a median follow-up of 2 years (IQR, 1-4), were enrolled. All-cause mortality, all-cause rehospitalization, and need for heart transplantation were significantly associated with lower left ventricular ejection fraction and tricuspid annular plane systolic excursion (TAPSE) at diagnosis ($P < 0.05$). Baseline MR severity was significantly associated with stroke ($P = 0.026$) and all-cause rehospitalization ($P < 0.001$).

MR severity, New York Heart Association (NYHA) classification, left ventricular end-diastolic diameter, and TAPSE improved at follow-up ($P < 0.001$). ACEi/ARB ($P = 0.008$), nitrate ($P = 0.001$), and hydralazine ($P = 0.006$) were associated with MR severity improvement. A significant difference was observed between survival free of all-cause mortality according to left ventricular ejection fraction ($P = 0.041$).

Conclusions: We reported freedom from all-cause mortality, cardiac mortality, and composite endpoints (all-cause mortality, heart transplantation, and stroke) in nonischemic FMR patients. We detected a significant decline in MR severity and NYHA classification during follow-up. Overall, the FMR-associated mortality risk can be significantly reduced by adhering to treatment guidelines in a tertiary heart center. ***(Iranian Heart Journal 2024; 25(1): 27-41)***

KEYWORDS: Nonischemic functional mitral regurgitation, MR severity, NYHA classification, Heart failure, CRT

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Functional mitral regurgitation (FMR) occurs in the aftermath of left ventricular (LV) remodeling in the absence of mitral valve structural pathologies. FMR is prevalent, particularly in patients with ischemic and nonischemic cardiomyopathy. [1] FMR causes poor prognosis and dire long-term consequences in patients with the underlying etiologies of ischemic and nonischemic cardiomyopathy since it triples the heart failure risk and doubles the 5-year mortality rate. [2,3] Although medical and surgical treatments are both indicated for FMR, controversies and concerns persist regarding treatment effectiveness. [4] Higher severity of heart failure is allied to higher prevalence of FMR. For instance, one-third of patients with advanced heart failure are diagnosed with moderate-to-severe FMR.

Treatment of FMR focuses on halting and/or reversing LV remodeling. Treatment options revolve around correcting the underlying LV dysfunction. Hence, guideline-directed pharmacologic medical treatment and/or cardiac resynchronization therapy (CRT) are the treatments of choice. Surgical mitral valve repair is indicated in severe cases with persistent symptoms despite appropriate medical treatment or in patients in whom cardiac surgery or coronary artery bypass grafting is otherwise indicated. [5]

In the present study, we report the long-term adverse events of nonischemic FMR in Iranian heart failure patients referred to Rajaie Cardiovascular Medical and Research Center (RCMRC) for medical treatment and/or CRT between 2003 and 2019.

METHODS

Eligibility

The present cohort study retrospectively enrolled all eligible at-least-moderate nonischemic FMR patients referred to RCMRC for medical treatment and/or CRT between 2003 and 2019 using the electronic database of RCMRC.

The inclusion criteria were as follows: 1) age over 18 years of age; 2) diagnosis with at-least-moderate nonischemic FMR using coronary angiography or computed tomography (CT) angiography in whom the epicardial coronary arteries were normal or contained nonsignificant/mild lesions incapable of explaining MR severity; and 3) receiving the guideline-directed medical treatment according to the updated version of the European Society of Cardiology guidelines for the treatment of heart failure available at each time. (The latest version was published in 2021. [6])

The exclusion criteria were as follows: 1) primary MR; 2) MR secondary to ischemia or rheumatic heart disease; 3) lacking complete echocardiographic examinations at the first visit or follow-ups. An ultimate sample size of 200 patients met the inclusion criteria.

The variables recorded were the New York Heart Association (NYHA) functional class, echocardiographic parameters (left ventricular ejection fraction [LVEF], left ventricular end-diastolic diameter [LVEDD], left ventricular end-diastolic volume [LVEDV], left ventricular end-systolic diameter [LVESD], left ventricular volume index [LVVI], left atrial size, right ventricular (RV) size, tricuspid annular plane systolic excursion [TAPSE], MR severity, tricuspid regurgitation (TR) severity, and systolic pulmonary artery pressure [sPAP]), baseline characteristics (age, sex, body mass index [BMI], and body surface area [BSA]), comorbidities (hypertension, medications, including angiotensin-converting enzyme inhibitors [ACEis], angiotensin receptor blockers [ARBs], β-blockers, nitrate, diuretics, digoxin, and hydralazine), and CRT. The endpoint outcomes (adverse events) were all-cause mortality, stroke, all-cause rehospitalization, and the need for heart transplantation.

Echocardiographic Study

MR severity, TR severity, LV dysfunction, and LV remodeling parameters (LVEF, LVEDD, and LVESD), and chamber volumes were extracted from the patients' records.

A summary of the MR severity criteria is as follows : 1) mild: vena contracta width (VCW) ≤ 0.3 cm, proximal isovelocity surface area (PISA) radius absent or ≤ 0.3 cm, normal LV and left atrial size, effective regurgitant orifice area (EROA) < 0.2 cm, regurgitant volume (RVol) < 30 mL, and RF < 30%; 2) moderate: intermediate values and EROA = 0.20-0.39 cm, RVol = 30-59 mL, and RF = 30-49%; and 3) severe: flail leaflets, VCW ≥ 0.7 cm, PISA radius ≥ 1.0 cm, EROA ≥ 0.4 cm, RVol ≥ 60 mL, and RF ≥ 50%.

A summary of the TR severity criteria is as follows: 1) mild: VCW ≤ 0.3 cm, PISA radius <0.3 cm, normal RV and right atrial size, EROA < 0.2 cm^2, and RVol < 30 mL; 2) moderate: intermediate values and VCW = 0.3-0.69 cm, EROA = 0.20-0.40 cm, and RVol = 30-44 mL; and 3) severe: flail leaflets, VCW ≥ 0.7 cm, PISA radius > 0.9 cm, EROA > 0.4 cm^2, and RVol ≥ 45 mL. [7]

Follow-Up Data

All the enrolled patients had a follow-up of at least 6 months after the first visit, and their data were recorded in the database. The follow-up data were insufficient for some patients, who were subsequently contacted for a follow-up visit. In the follow-up visits, the symptoms of the patients, NYHA classification, follow-up echocardiographic examinations, and medication dosage adjustments were recorded.

Statistical Analysis

The normality of the data was evaluated using the Kolmogorov-Smirnov test. Continuous variables were indicated as the mean (the standard deviation [SD]) or the median (the interquartile range [IQR]), and the difference between subgroups was analyzed using the *t* or Mann-Whitney *U* test for 2 subgroups and ANOVA or the Kruskal-Wallis test for more than 2 subgroups. The Wilcoxon signed-rank test was employed to compare the change in the continuous data of the first visit and the follow-up. Alluvial diagrams were utilized to visualize the difference in the data from the first visit to the follow-up. Categorical data were expressed as percentages and were compared using the χ^2 test. The endpoints were all-cause mortality, stroke, and the need for heart transplantation. Via multivariate modeling, a Cox proportional hazards analysis was performed to identify survival predictors. The results were expressed as the hazard ratio (HR) and the 95% confidence interval (CI). The survival analysis was carried out using the Kaplan-Meier method after censoring patients at the time of the last follow-up. Survival and event-free survival based on LVEF, MR severity, and NYHA classification were measured using the log-rank test. All data analyses were conducted with SPSS (SPSS, Inc, Chicago, IL), version 22, and R version 4.2.1. The significance level was set at a *P* value of less than 0.05.

Ethics

The current study adhered to the Helsinki Statement and was approved by the Ethics Review Board of RCMRC. All the patients' data are kept confidential. Since this study is retrospective, the need for written consent was waived.

RESULTS

Baseline Characteristics and Endpoint Outcomes

From 2003 through 2019, 200 nonischemic cardiomyopathy patients were enrolled in this study. (The normality study indicated that the data did not follow a normal distribution; hence, non-parametric tests were used.) The median age of the study population was 61 years (IQR, 50-70 y) at

diagnosis. The median follow-up duration was 2 years (IQR, 1-4 y). The endpoint outcomes comprised all-cause mortality, stroke, all-cause rehospitalization, and the need for heart transplantation and occurred in 29 (14.5%), 5 (2.5%), 135 (67.5%), and 5 (2.5%) patients, respectively. The median number of rehospitalizations for all the participants was 1.00 (IQR, 0.00-4.00). Of the 29 deaths, 26 (89.7%) were cardiac deaths. A summary of the baseline characteristics and clinical and echocardiographic data is presented in Table 1. Of the 200 participants, 104 (52%) were male, and 96 (48%) were female.

All-cause mortality was significantly increased with LVEF < 30% at diagnosis (P = 0.023). In addition, all-cause mortality was significantly associated with lower LVEF (P = 0.007) and lower TAPSE at diagnosis (P < 0.001) (Table 1). While MR severity at diagnosis was not significantly associated with all-cause mortality, it was significantly associated with stroke (P = 0.026) and all-cause rehospitalization (P < 0.001). Moreover, all-cause rehospitalization was significantly associated with lower LVEF (P = 0.04) and LVEF < 30% at diagnosis (P = 0.014) but was not significantly associated with any medication and NYHA classification at diagnosis. The need for heart transplantation was significantly associated with lower LVEF (P = 0.029) and lower TAPSE (P = 0.039) at diagnosis. Nonetheless, the association of the need for heart transplantation was not significant with MR severity at diagnosis, NYHA classification at diagnosis, or any other echocardiographic or clinical data or medications.

MR severity, NYHA classification, LVEDD, and TAPSE at follow-up improved compared with the time of diagnosis after the precisely guideline-directed medical treatment (P < 0.001, P < 0.001, P = 0.043, and P = 0.036, respectively) (Table 2). Of all the treatments, ACEis/ARBs (P = 0.008), nitrate (P =0.001), and hydralazine (P = 0.006) were significantly associated with MR severity changes from the first visit to follow-up (Table 3). Alluvial diagrams representing the improvements in the follow-up MR severity and NYHA classification are illustrated in Figure 1.

Survival Analysis

The Cox regression analysis showed that none of the covariates was significantly associated with all-cause mortality (Table 4). The model was adjusted for age, sex, BSA, MR severity, TR severity, LVEF, NYHA classification, ACEi/ARBs, diuretics, β-blockers, mineralocorticoid receptor antagonists, digoxin, nitrate, hydralazine, and CRT. During a median 2-year (IQR, 1.00-4.00) follow-up, 29 deaths occurred. The Kaplan-Meier survival curves in Figure 2 indicate the survival free of all-cause mortality, the survival free of cardiac mortality, and the survival free of composite endpoints (all-cause mortality, the need for heart transplantation, and stroke combined) for all the patients. One- and 5-year freedom from all-cause mortality was 93% (95% CI, 89.5 to 96.6) and 82.6% (95% CI, 75.8 to 90.1), respectively. Additionally, 1- and 5-year freedom from the composite endpoints was 92% (95% CI, 88.3 to 95.8) and 78.4% (95% CI, 71.2 to 86.2), respectively.

The survival curves in Figure 3 show the survival free of all-cause mortality for patients with LVEF < 30% and LVEF ≥ 30% at diagnosis, for patients with severe and moderate-to-severe MR at diagnosis, and for patients with NYHA functional class I or II and NYHA functional class III or IV. A significant difference was observed between the survival free of all causes according to LVEF strata (log rank test P = 0.041) (Fig. 3a). Nevertheless, no significant difference was observed according to the MR strata (log rank test P = 0.27) or the NYHA strata (log rank test P = 0.28) (Fig. 3b and 3c).

Table 1: Baseline Characteristics, Clinical, and Echocardiographic Data

Variable[1]	All Patients (n=200)	Survivors (n=171, 85.5%)	Non-Survivors (n=29, 14.5%)	*P* value
Age at diagnosis, y	61.00 (25.00-75.00)	61.00 (52.00-70.50)	57.00 (39.50-68.00)	0.044*
Female	96 (48%)	79 (46.2%)	17 (58.6%)	NS
BMI, kg/m^2	26.64 (23.43-30.29)	26.76 (23.68-30.66)	25.71 (22.21-29.01)	NS
BSA, m^2	1.78 (23.64-1.96)	1.80 (1.67-1.97)	1.70 (1.57-1.90)	0.055
HTN	77 (38.5%)	70 (40.9%)	7 (24.1%)	NS
NYHA Classification				
Class Ⅰ	19 (9.5%)	17 (9.9%)	2 (6.9%)	NS
Class Ⅱ	86 (43%)	75 (43.9%)	11 (37.9%)	
Class Ⅲ or Ⅳ	95 (47.5%)	79 (46.2%)	16 (55.2%)	
MR Severity at Diagnosis				
Moderate	133 (66.5%)	111 (64.9%)	22 (75.9%)	NS
Moderate to severe	31 (15.5%)	26 (15.2%)	5 (17.2%)	
Severe	36 (18%)	34 (19.9%)	2 (6.9%)	
TR Severity at Diagnosis				
Mild	69 (34.5%)	59 (34.5%)	10 (34.5%)	NS
Moderate	108 (54%)	92 (53.8%)	16 (55.2%)	
Moderate to severe	15 (7.5%)	14 (8.2%)	1 (3.4%)	
Severe	8 (4%)	6 (3.5%)	2 (6.9%)	NS
LVEF, %	20.00 (15.00-30.00)	20.00 (15.00-35.00)	15.00 (10.00-20.00)	0.007*
LVEDD, cm	6.20 (4.20-6.90)	6.20 (5.60-6.90)	6.40 (5.35-7.40)	NS
LVESD, cm	5.30 (4.20-6.00)	5.35 (4.20-5.92)	5.30 (4.25-6.65)	NS
LVVI, mL/m^2	102.00 (84.00-155.00)	101.50 (84.75-151.50)	139.00 (75.00-173.00)	NS
LA area, cm^2	24.00 (20.25-28.00)	24.00 (20.00-28.00)	25.00 (20.50-27.00)	NS
LA size, cm	4.20 (3.80-4.70)	4.20 (3.72-4.70)	4.20 (3.90-4.55)	NS
RV size, cm	3.30 (2.90-3.70)	3.30 (2.90-3.70)	3.20 (2.70-3.75)	NS
sPAP, mm Hg	40.00 (30.00-50.00)	40.00 (30.00-50.00)	40.00 (30.00-50.00)	NS
TAPSE, mm	17.00 (14.00-20.00)	18.00 (14.00-20.00)	14.00 (13.00-16.00)	<0.001*
S′ velocity, m/s	9.00 (8.00-11.00)	9.00 (8.00-11.00)	9.00 (7.00-10.00)	NS
CRT, n (%)	28 (14%)	20 (11.7%)	8 (27.6%)	0.023*
Medications Administered at Diagnosis				
ACEi/ARB	183 (91.5%)	157 (91.8%)	26 (89.7%)	NS
ACEi	137 (68.5%)	118 (69%)	19 (65.5%)	NS
ARB	46 (23%)	39 (22.8%)	7 (24.1%)	NS
Diuretic	166 (83%)	140 (81.9%)	26 (89.7%)	NS
β-blocker	189 (94.5%)	161 (94.2%)	28 (96.6%)	NS
Nitrate	11 (5.5%)	10 (5,8%)	1 (3.4%)	NS
Hydralazine	13 (6.5%)	9 (5.3%)	4 (13.8%)	0.016*
MRA	144 (72%)	121 (70.8%)	23 (79.3%)	NS
Digoxin	43 (21.5%)	31 (18.1%)	12 (41.4%)	NS
VKA	46 (23%)	38 (22.2%)	8 (27.6%)	NS
NOAC	20 (10%)	20 (11.7%)	0 (0%)	NS
LVEF<30%	136 (68%)	111 (64.9%)	25 (86.2%)	0.023*

ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BMI: body mass index; BSA: body surface area; CABG: coronary artery bypass grafting; CRT: cardiac resynchronization therapy; CMP: cardiomyopathy; EF: ejection fraction; FMR: functional mitral regurgitation; HF: heart failure; HTN: hypertension; IQR: interquartile range; LA: left atrial; LV: left ventricle; LVEDD: LV end-diastolic diameter; LVEDV: LV end-diastolic volume; LVEF: LV ejection fraction; LVVI: LV volume index; MI: myocardial infarction; MR: mitral regurgitation; MRA: mineralocorticoid receptor antagonists; NOAC, Non-vitamin K Antagonist Oral Anticoagulant; NS, not significant; NYHA: New York Heart Association; RV: right ventricle; sPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation; VKA: vitamin-K antagonist

[1] Data are presented as median (IQR) or n (%).

* $P < 0.05$

Table 2: Comparison of Clinical and Echocardiographic Outcomes Between the First Visit and Follow-Up.

Variable[1]	First visit	Follow-Up	*P* value
NYHA Classification			
Class Ⅰ	19 (9.5%)	93 (46.5%)	<0.001*
Class Ⅱ	86 (43%)	63 (31.5%)	
Class Ⅲ	87 (43.5%)	34 (17%)	
Class Ⅳ	8 (4%)	10 (5%)	
MR Severity			
Mild	0 (0%)	19 (9.5%)	<0.001*
Mild to moderate	0 (0%)	19 (9.5%)	
Moderate	133 (66.5%)	88 (44%)	
Moderate to severe	31 (15.5%)	23 (11.5%)	
Severe	36 (18%)	35 (17.5%)	
Echocardiographic Data			
LVEF, %	20.00 (15.00-30.00)	20.00 (15.00-35.00)	NS
LVEDD, cm	6.20 (4.20-6.90)	6.10 (5.32-6.90)	0.043*
LVESD, cm	5.30 (4.20-6.00)	5.10 (4.10-6.00)	NS
LVVI, mL/m^2	102.00 (84.00-155.00)	102.00 (88.00-139.00)	NS
LA area, cm^2	24.00 (20.25-28.00)	24.00 (21.00-29.00)	NS
LA size, cm	4.20 (3.80-4.70)	4.30 (3.80-4.80)	NS
RV size, cm	3.30 (2.90-3.70)	3.20 (2.90-3.80)	NS
sPAP, mm Hg	40.00 (30.00-50.00)	39.50 (30.00-50.00)	NS
TAPSE, mm	17.00 (14.00-20.00)	17.00 (14.50-19.00)	0.036*
S′ velocity, m/s	9.00 (8.00-11.00)	9.00 (7.00-10.00)	NS

IQR: interquartile range; LA: left atrial; LV, left ventricle; LVEDD: LV end-diastolic diameter; LVEDV: LV end-diastolic volume; LVEF: LV ejection fraction; LVVI: LV volume index; MI: myocardial infarction; MR: mitral regurgitation; NS: not significant; RV: right ventricle; sPAP: systolic pulmonary artery pressure

[1] Data are presented as median (IQR) or n (%).

*$P < 0.05$

Table 3: Association Between the MR Severity Change (from baseline to follow-up) and the Medications Administered

Medication	*P* value[1]
ACEi/ARB	0.008*
Nitrate	0.001*
Hydralazine	0.006*
NOAC	0.781
VKA	0.904
Digoxin	0.121
Diuretics	0.277
MRA	0.153
β-blockers	0.848

ACE-I: Angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonists; NOAC: Non-vitamin K antagonist oral anticoagulant; VKA: vitamin-K antagonist

[1] the χ^2 test

*$P < 0.05$

Table 4: Cox Regression of the Predictors of All-Cause Mortality

Variable	HR[1]	95% CI	*P* value
Age	0.969	0.939-1.001	0.059
Sex (female)	2.476	0.817-7.505	0.109
BSA	0.124	0.012-1.225	0.074
HTN	0.798	0.274-2.327	0.680
MR severity[2]	-	-	0.264
TR severity[2]	-	-	
LVEF	0.970	0.916-1.028	0.302
NYHA[2]	-	-	0.414
ACEi/ARBs	0.314	0.060-1.654	0.172
Diuretic	1.318	0.309-5.624	0.709
β-blocker	1.286	0.132-12.540	0.829
MRA	0.977	0.298-3.203	0.969
Digoxin	1.322	0.507-3.449	0.568
Nitrate	0.458	0.018-11.924	0.639
CRT	1.802	0.628-5.176	0.274
Hydralazine	0.830	0.089-7.710	0.870

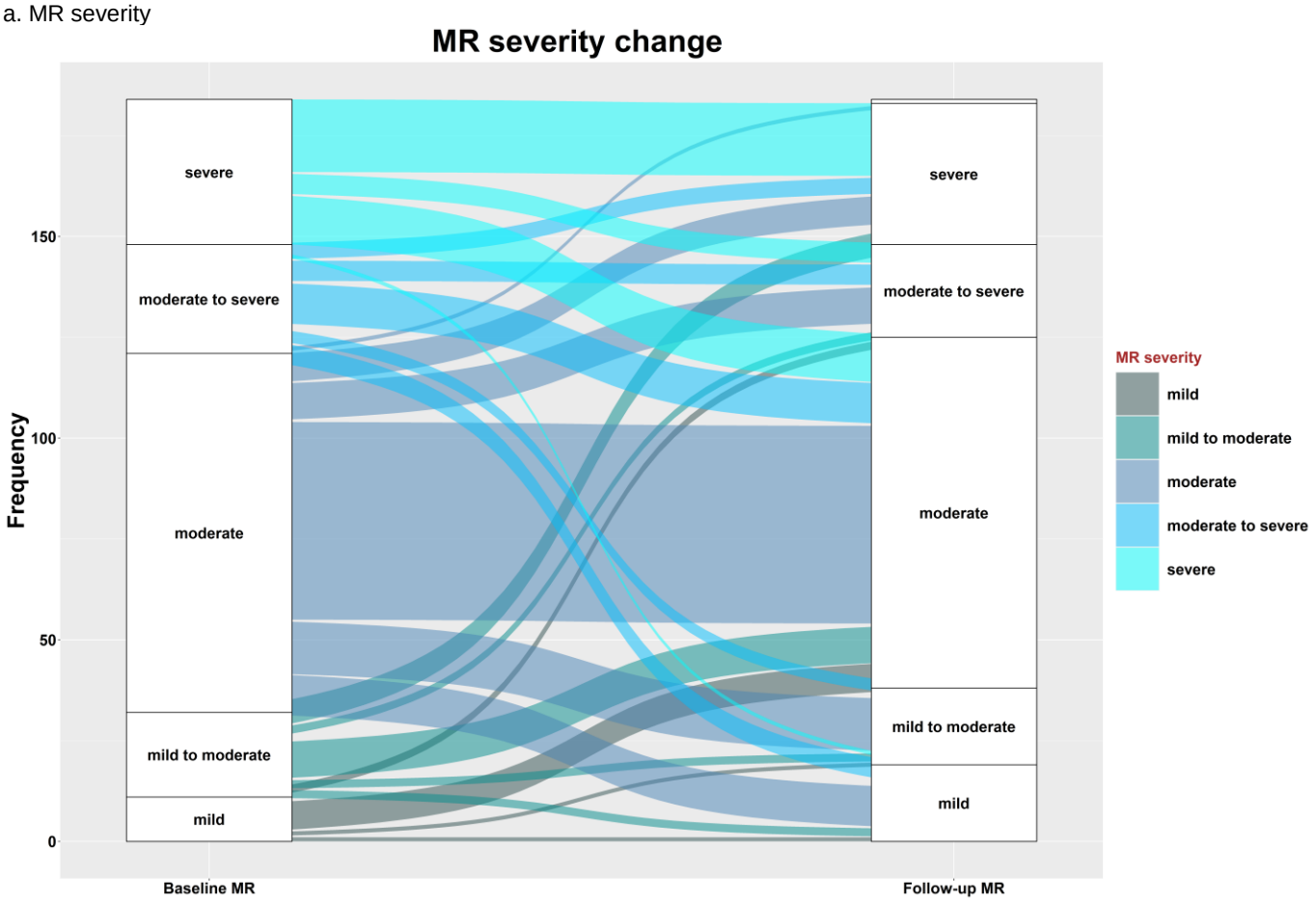
BSA: body surface area; CRT: cardiac resynchronization therapy; CI: confidence interval; HR: hazard ratio; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; MRA: mineralocorticoid receptor antagonists; NYHA; New York Heart Association; TR; tricuspid regurgitation

*$P < 0.05$

[1] Adjusted for age, sex, BSA, MR severity, TR severity, LVEF, NYHA, ACEi/ARBs, diuretics, β-blockers, MRA, digoxin, nitrate, hydralazine, and CRT.

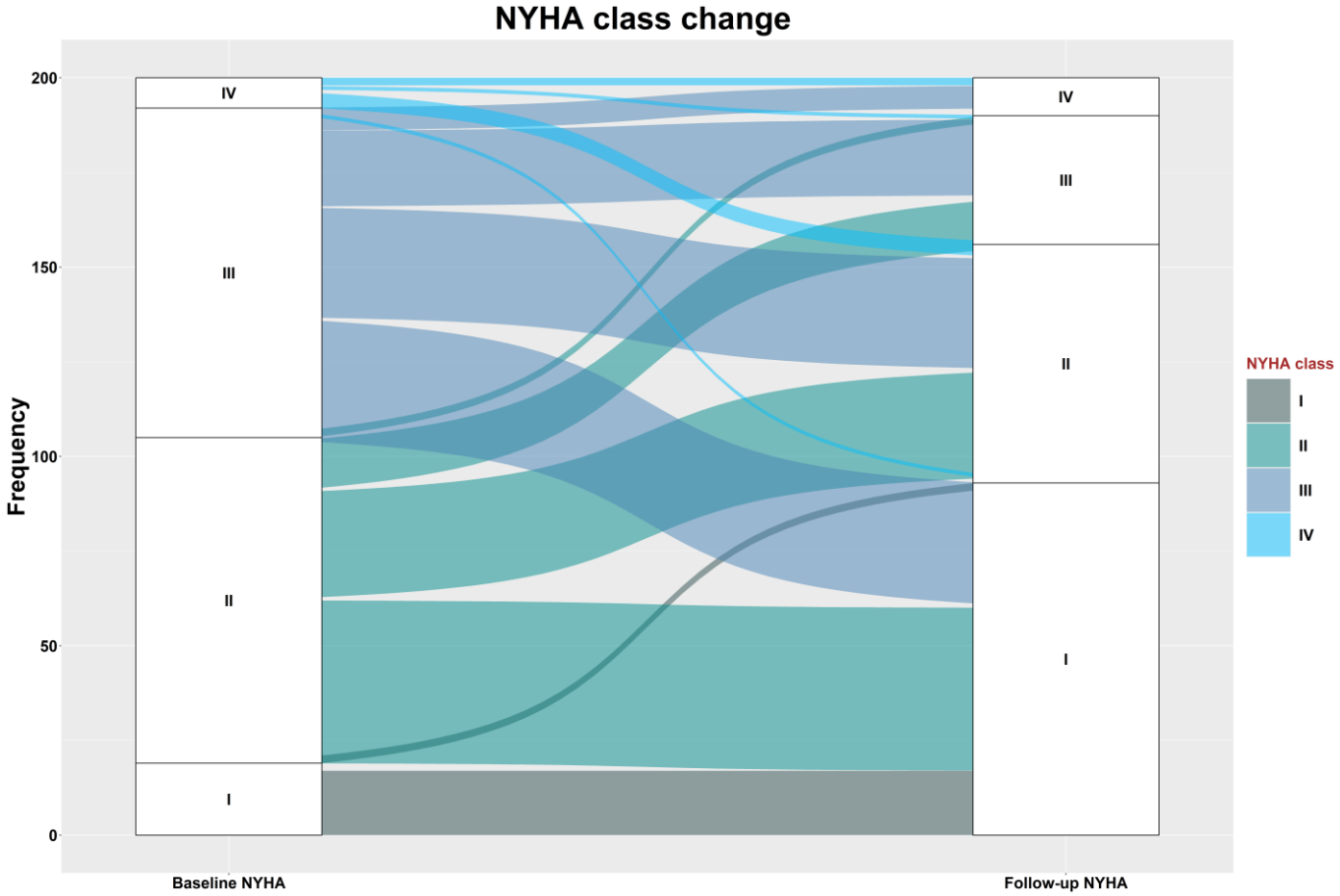
[2] HR was available for each level of this variable (mild, moderate, severe, and 1, 2, 3, and 4). As they were all nonsignificant, the HR and 95% CI of the levels were not reported separately to make the table as brief as possible.

a. MR severity



MR: mitral regurgitation

b. NYHA classification



NYHA: New York Heart Association

Figure 1: The images present alluvial diagrams of the data comparison between the first visit and the follow-up as follows: a) MR severity and b) NYHA classification.

Figure 2a

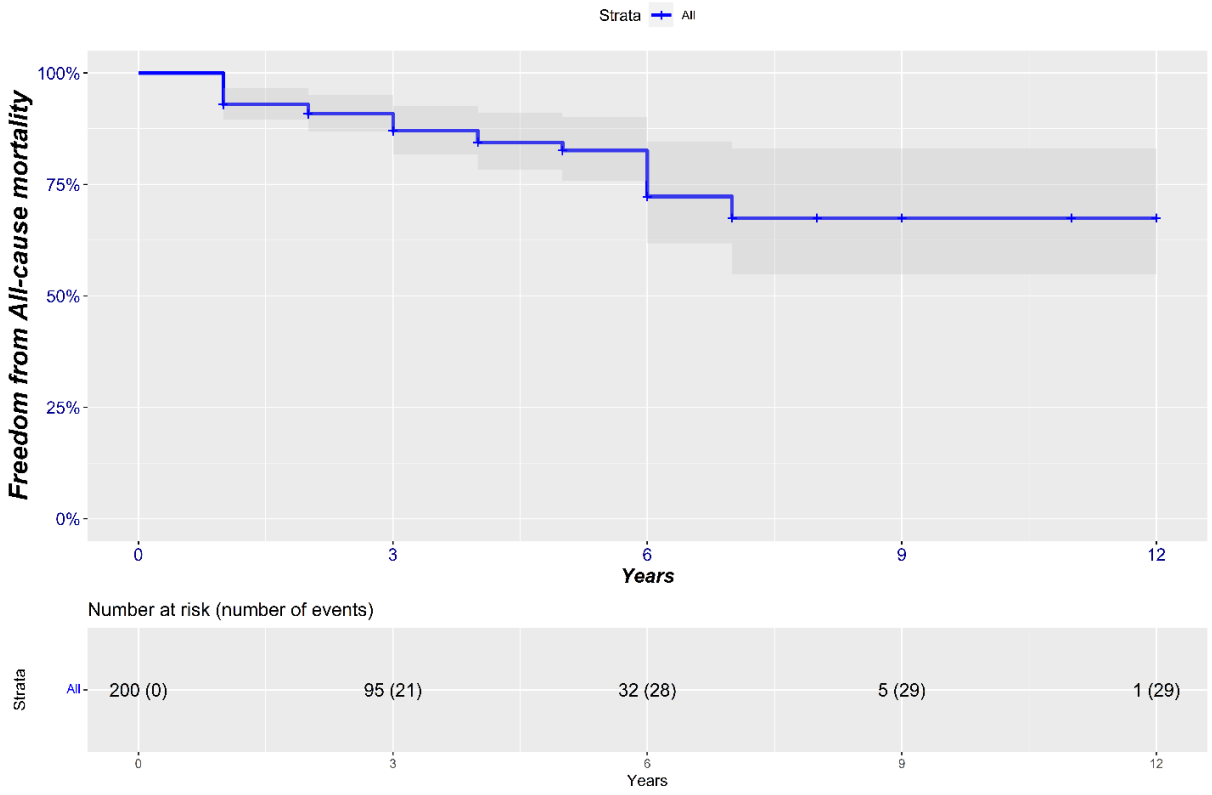


Figure 2b

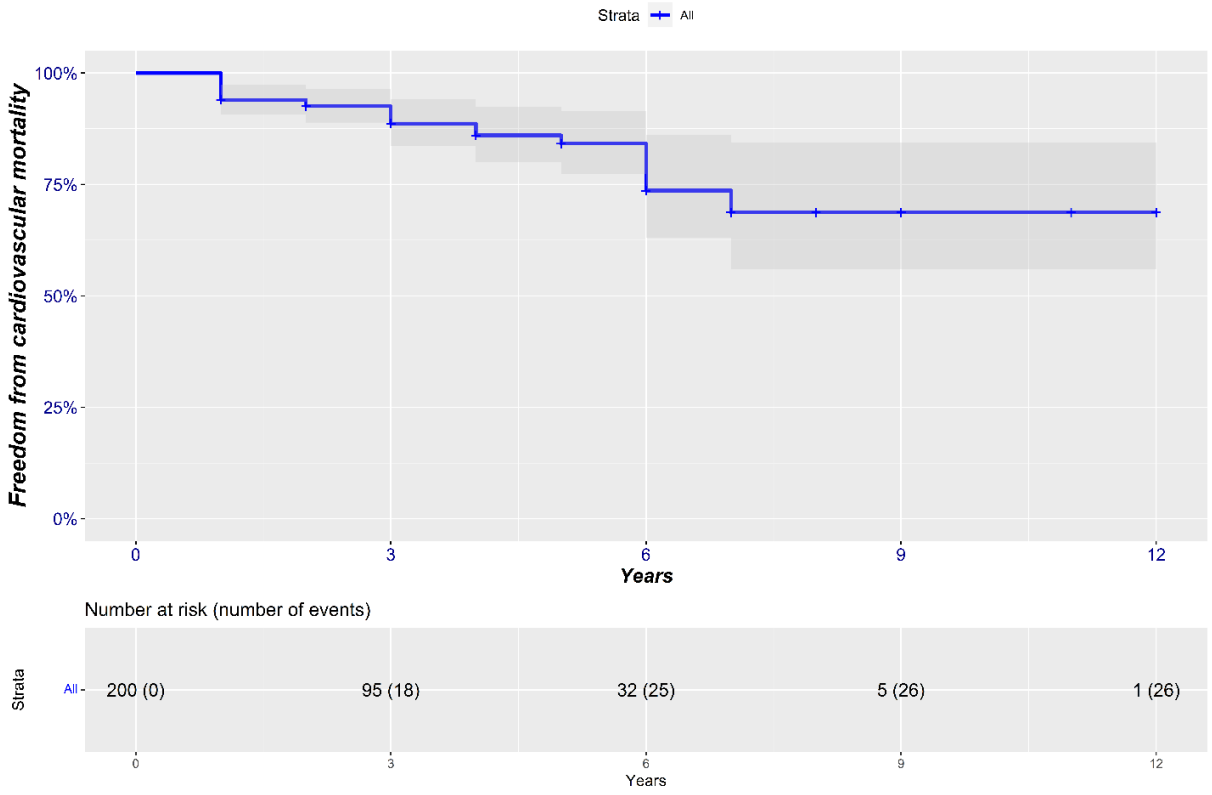


Figure 2c

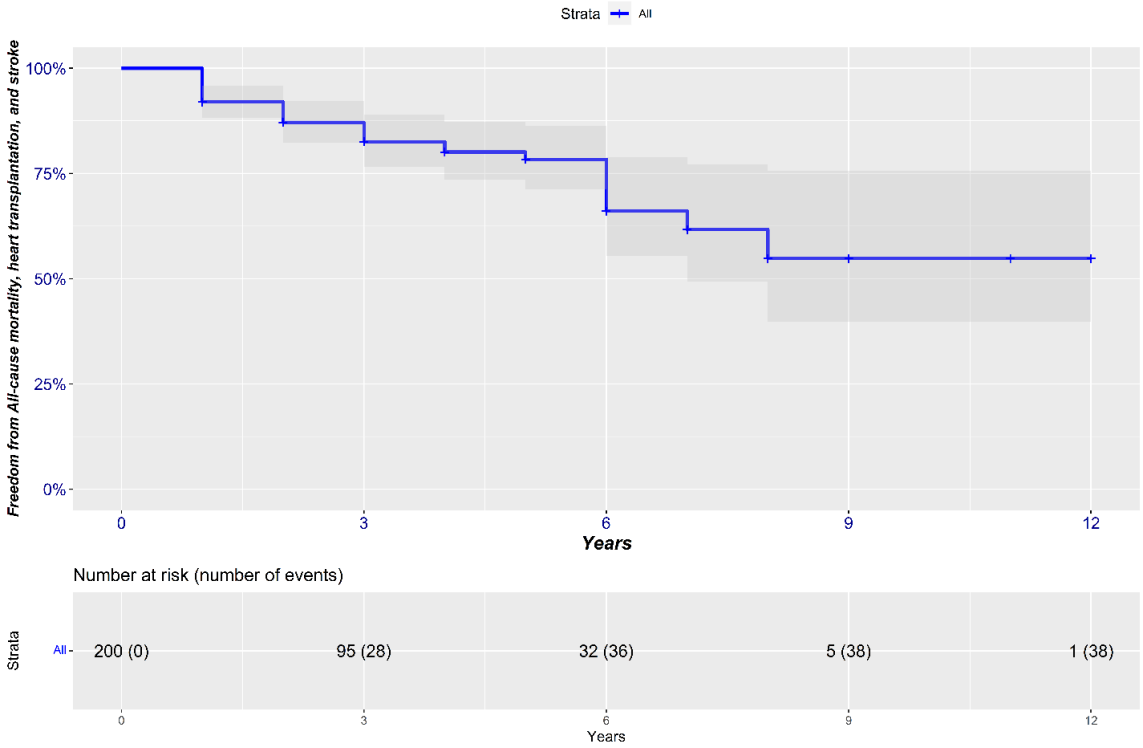
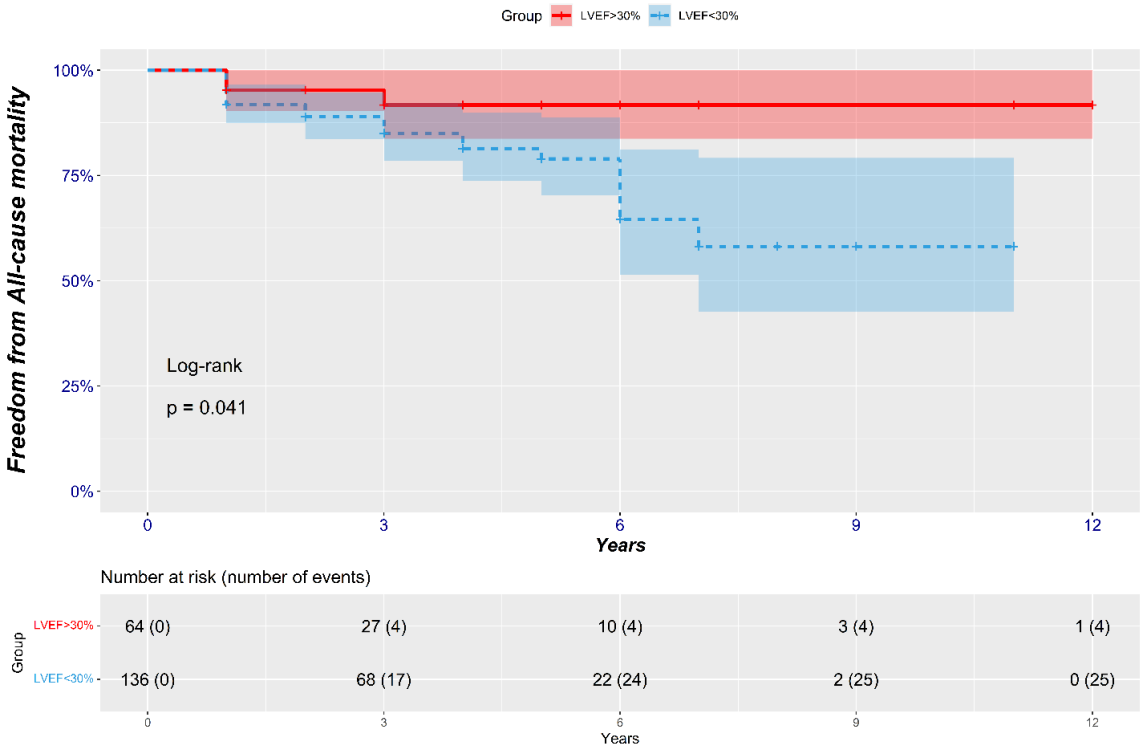


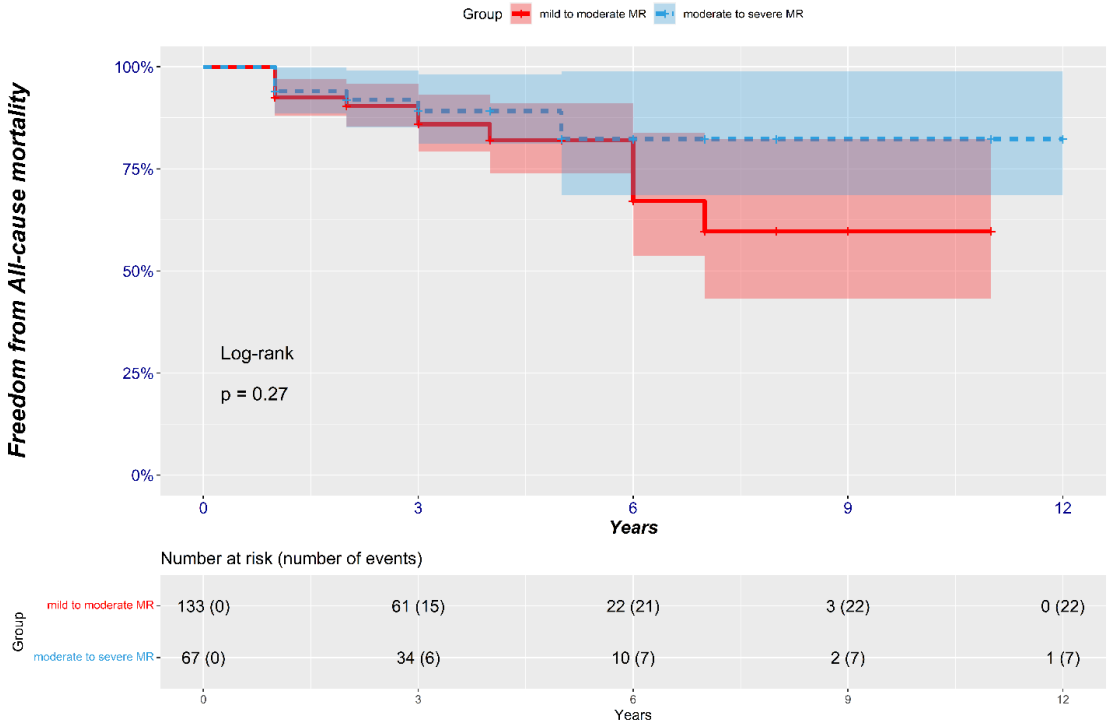
Figure 2: The images present survival curves as follows: a) survival free of all-cause mortality; b) survival free of cardiac mortality; and c) survival free of all-cause mortality, heart transplantation, and stroke.

Figure 3a



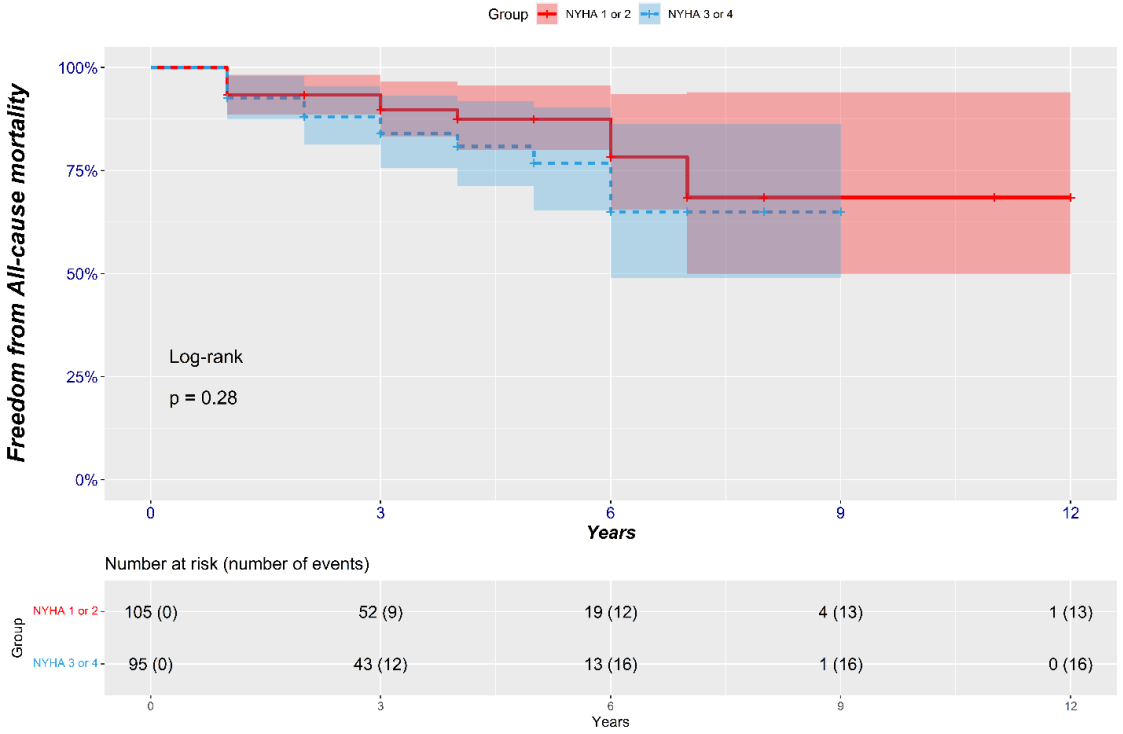
LVEF: left ventricular ejection fraction

Figure 3b



MR: mitral regurgitation

Figure 3c



NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; MR: mitral regurgitation

Figure 3: The images illustrate a) survival free of all-cause mortality according to LVEF, b) survival free of all-cause mortality according to MR severity, and c) survival free of all-cause mortality according to NYHA classification.

DISCUSSION

FMR is crucial to the prognosis of patients with heart failure since it poses additional adverse outcomes to these patients. [8-11] Kajimoto et al [9-12] (2016) stated that FMR was prevalent in patients with heart failure at discharge. FMR, even mild, causes an augmented risk of heart failure rehospitalization and all-cause mortality. In a subsequent study in 2017, Kajimoto et al [12] indicated that although ischemic FMR was significantly associated with higher mortality risk, this was not true in nonischemic FMR. Similarly, Sannio et al, [13] in a meta-analysis in 2017, stated that nonischemic FMR posed a smaller impact on the mortality outcome than ischemic FMR. Thus, it is essential to determine whether the underlying etiology is ischemic or nonischemic.

The present study focused only on patients with at-least-moderate nonischemic FMR. According to this observational follow-up study, by guideline-directed treatment in patients with nonischemic FMR, a clinically and statistically significant improvement in symptoms, MR severity, and NYHA classification was observed. This result is supported by previous evidence, as Agricola et al [2] (2009) showed that adhering to new treatments at the time improved the outcome of FMR patients with LV dysfunction by lowering mortality and rehospitalization rates. Likewise, Nasser et al [14] (2017) gained even better results owing to the updated treatment guidelines insofar as they showed that proper medical management in FMR patients could halt the process of LV remodeling to a great extent. Moreover, adding CRT to the treatment plan significantly diminished the mortality risk. Hence, CRT was suggested as an independent negative prognostic predictor. This result was corroborated by van der Bijl et al, [15] who reported that CRT ameliorated FMR severity in a significant (>40%) portion of their FMR patients. In contrast, in our study, CRT was not significantly associated with all-cause mortality.

In our study, all-cause mortality was significantly associated with LVEF and TAPSE measured at the time of diagnosis. In the survival analysis, LVEF < 30% compared with LVEF ≥ 30% was significantly linked to lower rates of survival free of all-cause mortality. Similarly, Kajimoto et al [9] (2016) indicated that FMR at discharge was associated with lower LVEF in patients with heart failure. Severe MR compared with moderate-to-severe MR and NYHA functional class III or IV compared with NYHA functional class I or II were not accompanied by significantly lower rates of survival free of all-cause mortality, which is in contrast with the results of previous studies. [2, 12, 16] This controversy may arise from the fact that we did not divide our patients into 2 groups of heart failure with either preserved or reduced EF. Further, lower age at diagnosis was associated with increased mortality, contrasting the results reported by Agricola et al. [2]

In our study, neither MR severity nor NYHA classification was an independent predictor of mortality, a finding supported by Mowakeaa et al. [17] However, Agricola et al [2] stated otherwise, reflecting the need for further investigations in future studies.

Limitations

The retrospective enrollment of patients in the present study is a limitation since we cannot ascertain the exact time before the study when they were diagnosed with FMR. Moreover, due to the observational nature of the study, we cannot generalize the outcomes, and further observational and trial studies are required. Furthermore, the number of patients receiving CRT and hydralazine was small in proportion to the total number of studied patients, which might have affected the power of distinguishing mortality predictors. We did

not assess the participants' electrocardiograms; thus, we could not include the data of atrial fibrillation prevalence. Last but not least, the data of MR severity and NYHA classification were missed at follow-up for some participants and particularly the before-death follow-up data of those who did not survive.

CONCLUSIONS

The current study reported the freedom from all-cause mortality, cardiac mortality, and composite endpoints (all-cause mortality, heart transplantation, and stroke) in nonischemic FMR patients. Moreover, we introduced lower LVEF as a critical parameter in determining survival. Overall, we detected a significant decline in MR severity and NYHA classification during follow-up.

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Conflict of Interest
The authors declare no conflicts of interest.

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