Long-term Follow-up Outcomes and Prognosis Predictors of Non-Ischemic Functional Mitral Regurgitation in Patients with Heart Failure: A Retrospective Cohort study

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Research Article

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Abstract

Purpose:

Non-ischemic Functional Mitral Regurgitation (FMR) is accompanied by dire long-term consequences. The treatment revolves around correcting the underlying LV dysfunction. This study reports long-term follow-up outcomes and prognosis predictors of non-ischemic FMR.

Methods:

We enrolled 200 patients with at-least-moderate non-ischemic FMR, undergoing medical treatment and/or cardiac resynchronization therapy (CRT) between 2003 and 2019. MR severity and LV 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 (52%) men and 96 (48%) women with the median age of 61 years (IQR 50-70) at diagnosis and the median follow-up of 2 years (IQR 1-4), were enrolled. The all-cause mortality, all-cause rehospitalization, and need for heart transplantation were significantly associated with lower LVEF and TAPSE at diagnosis (P-value<0.05). Furthermore, baseline MR severity was significantly associated with the incidence of stroke (P-value =0.026) and the all-cause rehospitalization (P-value<0.001).

The MR severity, NYHA classification, LVEDD, and TAPSE improved at the follow-up (P-value<0.001). ACEi/ARB (P-value =0.008), Nitrate (P-value =0.001), and Hydralazine (P-value =0.006) were associated with MR severity improvement.

CRT (HR=0.22, P-value=0.008) and Hydralazine (HR=0.25, P-value=0.038) were the independent negative predictors of all-cause mortality. Ultimately, a significant difference was observed between survival free of all causes according to the LVEF (P-value=0.041).

Conclusion:

We detected a significant decline in MR severity and NYHA classification during follow-up. Overall, the FMR-associated mortality risk will be significantly reduced by closely sticking to the treatment guidelines in a tertiary heart center.

Introduction

Functional mitral regurgitation (FMR) occurs in the aftermath of left ventricular (LV) remodeling in the absence of mitral valve (MV) structural pathologies. FMR is prevalent, particularly in patients with ischemic and non-ischemic cardiomyopathies (CMP) [1]. FMR brings about poor prognosis and dire long-term consequences in patients with the underlying etiologies of ischemic and non-ischemic CMP, as it

triples the heart failure risk (HF) and doubles the five-year mortality rate [2, 3]. Although medical and surgical treatments are both indicated for FMR, there remain controversies and concerns regarding treatment effectiveness [4]. The more the severity of HF, the more prevalent the FMR. To give an instance, one-third of the patients with advanced HF are diagnosed with moderate to severe FMR.

Treatment in FMR focuses mainly on halting and/or reversing LV remodeling. The 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. Thus, surgical MV repair is indicated in severe cases with persistent symptoms despite appropriate medical treatment or in patients in whom cardiac surgery or CABG is otherwise indicated [5].

In the present study, we decided to report long-term follow-up outcomes and prognosis predictors of non-ischemic FMR in Iranian HF patients referred to Rajaie Cardiovascular Medical and Research Center (CMRC) for medical treatment and/or CRT between 2003 and 2019.

Methods

Eligibility:

In this cohort study, we retrospectively enrolled all eligible at-least moderate non-ischemic FMR patients, referred to Rajaie CMRC for medical treatment and/or CRT between 2003 and 2019 using the electronic database of Rajaei CMRC. The inclusion criteria were as follows: Patients over 18 years of age diagnosed with at least moderate non-ischemic FMR using coronary angiography or CT angiography, in whom the epicardial coronary arteries were normal or contained nonsignificant/mild lesions incapable of explaining MR severity. The exclusion criteria were as follows: 1. Primary MR 2. MR, secondary to ischemia or rheumatic heart disease. 3. Patients who lack complete echocardiographic examination in the first visit or follow-ups. An ultimate sample size of 200 patients met the inclusion criteria.

The variables recorded were NYHA class, echocardiographic parameters (LVEF, LVEDD, LVESD, LVVI, LA size, RV size, TAPSE, MR severity, TR severity, and sPAP), baseline characteristics (age, gender, BMI, and BSA), comorbidities like hypertension, medications prescribed (ACEi, ARB, beta-blocker, Nitrate, diuretic, Digoxin, and Hydralazine), CRT insertion. The endpoint outcomes 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 patients' records. MR severity criteria is summarized as: 1. Mild: VCW $\leq$ 0.3 cm, PISA radius absent or $\leq$ 0.3 cm, Normal LV and LA size, EROA < 0.2 cm, RVol < 30 ml, RF < 30%. 2. Moderate: intermediate values and EROA 0.20-0.39 cm, RVol 30-59 ml, RF 30-49%. 3. Severe: Flail leaflet, VCW $\geq$ 0.7 cm, PISA radius $\geq$ 1.0 cm, EROA $\geq$ 0.4 cm, RVol $\geq$ 60 ml, RF $\geq$ 50%. TR severity criteria is summarized as: 1. Mild: VCW $\leq$ 0.3 cm, PISA radius <0.3 cm, Normal RV and RA size, EROA <

0.2 cm^2, RVol < 30 ml. 2. Moderate: intermediate values and VCW 0.3-0.69 cm, EROA 0.20-0.40 cm, RVol 30-44 ml. 3. Severe: Flail leaflet, VCW ≥ 0.7 cm, PISA radius > 0.9 cm, EROA > 0.4 cm^2, RVol ≥ 45 ml [6].

Follow-up data:

All enrolled patients had been followed up after at least six months of the first visit, and the data were recorded in the database. The follow-up data were insufficient for certain patients, and those patients were contacted for a follow-up visit. In the follow-up visits, the symptoms of the patients, NYHA classification, follow-up echocardiographic examination, and medication dosage adjustment were recorded.

Statistics:

The normality of the data was evaluated using the Kolmogorov-Smirnov test. Continuous variables are indicated as mean (SD) or median (IQR), and the difference between subgroups was analyzed using t-test or Mann-Whitney U test for two subgroups and ANOVA or Kruskal-Wallis test for more than two subgroups. Wilcoxon signed-rank test was employed to compare the change in the continuous data of the first visit and the follow-up. Sankey diagrams were utilized to visualize the difference in the data from the first visit to the follow-up. Categorical data are expressed as percentages and are compared using the Chi-squared test. The endpoints were all-cause mortality, stroke, and the need for heart transplantation. Using multivariate modeling, a Cox proportional hazards analysis was employed to identify the survival predictors. The results were expressed as Hazard Ratio (HR) and 95% CI. The survival analysis was carried out using the Kaplan-Meier method, censoring patients at the time of the last follow-up, and survival and event-free survival based on the LVEF, MR severity, and NYHA classification were measured using the long-rank test. All data analysis was conducted by SPSS version 25 (SPSS, Inc, Chicago, IL), and the significance level was set to <0.05.

Ethics:

This study adheres to the Helsinki statement and is approved by the institutional ethics review board of the Rajaei CMCR. All patients' data is kept confidential. Since this study is retrospective, the need for written consent was waived.

Results

Baseline characteristics and endpoint outcomes:

From 2003 until 2019, 200 non-ischemic CMP patients were enrolled in this study. (The normality study indicated that the data does not follow a normal distribution; hence, we used non-parametric tests). The median age was 61 years (IQR 50-70 years) at diagnosis. The median follow-up duration was 2 years (IQR 1-4 years). 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, clinical and echocardiographic data are shown 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-value=0.023). Also, all-cause mortality was significantly associated with lower LVEF (P-value=0.007) and lower TAPSE at diagnosis (P-value<0.001) (Table 1). Although MR severity at diagnosis was not significantly associated with all-cause mortality, it was significantly associated with the incidence of stroke (P-value =0.026) and the all-cause rehospitalization (P-value<0.001). Moreover, all-cause rehospitalization was significantly associated with lower LVEF (P-value=0.04) and LVEF<30% at diagnosis (P-value=0.014) but was not significantly associated with any medication and NYHA classification at diagnosis. Furthermore, the need for heart transplantation was significantly associated with lower LVEF (P-value =0.029) and lower TAPSE (P-value =0.039) at diagnosis; however, the association of the need for heart transplantation was not significant with the MR severity at diagnosis, NYHA classification at diagnosis, or any other echocardiographic or clinical data or medications.

The MR severity, NYHA classification, LVEDD, and TAPSE at the follow-up, improved compared to the time of diagnosis after the precisely guideline-directed medical treatment (P-value<0.001) (Table 2). Of all the treatments, ACEi/ARB (P-value =0.008), Nitrate (P-value =0.001), and Hydralazine (P-value =0.006) were associated with MR severity change since the first visit (Table 3). Sankey diagrams representing the improvements of the follow-up MR severity and NYHA classification are shown in Figure 1.

Survival analysis:

Using a multivariate Cox regression, it was observed that CRT (HR=0.22, 95% CI 0.072-0.675, P-value=0.008) and Hydralazine (HR=0.25, 95% CI 0.067-0.928, P-value=0.038) were the independent negative predictors of all-cause mortality (Table 4). Figure 2 indicates the echocardiographic images of one of the patients undergoing CRT before and after CRT implantation (video accessible in the supplementary section).

During a median 2-year (IQR 1.00-4.00) follow-up, 29 death occurred. The Kaplan-Meier survival curves in Figure 3 indicate the survival free of all-cause mortality (95% CI 8.57-10.38), the survival free of cardiac mortality (95% CI 8.72-10.53), the survival free of stroke (95% CI 10.31-12.06), the survival free of all-cause rehospitalization (95% CI 3.76-4.69), the survival free of heart transplantation (95% CI 11.30-11.95), and the survival free of composite (95% CI 7.67-9.67) endpoint (all-cause mortality, the need for heart transplantation, and stroke combined) for all the patients. Furthermore, the survival curves in Figure 4 show the survival free of all-cause mortality for patients with severe (95% CI 7.45-11.65) and moderate-to-severe MR at diagnosis (95% CI 8.64-11.62), for patients with of LVEF<30% (95% CI 7.25-9.21) and LVEF≥30% (95% CI 10.34-11.99) at diagnosis and eventually for patients with NYHA class Ⅲ or Ⅳ (95% CI 8.43-11.00) and NYHA class Ⅰ or Ⅱ (95% CI 6.37-7.97). A significant difference was observed between survival free of all causes according to the LVEF (Log Rank Test P-value=0.041) (Figure 4a).

Discussion

FMR plays a vital role in the prognosis of HF patients as it poses much more adverse outcomes to these patients [7-10]. Kajimoto et al., in a study in 2017, indicated that although ischemic FMR is significantly associated with higher mortality risk, this is not true in non-ischemic FMR [11]. Thus, it is crucial to determine whether the underlying etiology is ischemic or non-ischemic.

This present study focused only on at-least-moderate non-ischemic FMR patients. According to the results of this observational follow-up study, by guideline-directed treatment in patients with non-ischemic FMR patients, a clinically and statistically improvement in patients' symptoms, MR severity, and NYHA classification was observed. Moreover, the addition of CRT to the treatment plan significantly diminished the mortality risk. Also, among all the medications, Hydralazine was proposed as an effective potential medication in preventing mortality. Hence, CRT and Hydralazine are suggested as independent negative prognostic predictors. The all-cause mortality was significantly associated with LVEF and TAPSE measured at the time of diagnosis. In the survival analysis, although the LVEF<30% compared to the LVEF≥30% was significantly linked to lower survival, severe MR compared to moderate-to-severe MR and the NYHA classes or compared to NYHA classes or were not accompanied in significantly lower survival.

In our study, in concert with the results of previous studies, moderate-to-severe and severe MR were not associated with increments in all-cause mortality. However, lower age at diagnosis was associated with increased mortality, contrasting the results Agricola et al. obtained [2].

Furthermore, in our study, by employing multivariate regression analysis, neither MR severity nor NYHA classifications were not independent predictors of mortality, as is supported by the study conducted by Mowakeaa et al. [12]. However, Agricola et al. has stated otherwise, reflecting the need for further investigations in future studies [2].

Receiving CRT was shown in our study to be of great significance in preventing mortality and is determined as an independent negative prognostic predictor for mortality. This result is corroborated with the study by van der Bijl et al., in which the CRT ameliorated the FMR severity [13].

Limitations:

The retrospective enrollment of the patients in the study is a limitation, as we cannot assure the exact time before the study when they got diagnosed with FMR. Also, due to the study's observational nature, we cannot generalize the outcomes to the population, and further observations and trial studies are required. Furthermore, the number of patients receiving CRT and Hydralazine was small in proportion to the total patients, which might affect the power of distinguishing the mortality predictors. Last but not least, the data of MR severity and NYHA classification is missed at follow-up for some participants and particularly the before-death follow-up data of those who did not survive.

Conclusion

This study demonstrates that by delicately observing the guideline-directed treatment in a professional tertiary Heart center, we can significantly reduce the mortality risk associated with FMR. 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.

Abbreviations

MI=myocardial infarction

HF=heart failure

ACE-I= Angiotensin-Converting Enzyme (ACE) inhibitors

ARBs=angiotensin receptor blockers

BMI=body mass index

CABG=coronary artery bypass grafting

CRT=cardiac resynchronization therapy

CMP=cardiomyopathy

FMR=Functional Mitral Regurgitation

LV=left ventricle

LVEF=left ventricular (LV) ejection fraction

LVEDV = LV end-diastolic volume

LVEDD = LV end-diastolic diameter

NYHA=New York Heart Association

RV=right ventricle

sPAP=systolic pulmonary artery pressure

TR=tricuspid regurgitation

TAPSE=tricuspid annular plane systolic excursion

Declarations

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Conflict of interests: The authors declare no conflict of interest.

Author Contributions

SH and ST contributed to the study conception and design. Material preparation and data collection were performed by ZN, NN, AA, AAG, MY, and MMP. Analysis was performed by AR and YP. The first draft of the manuscript was written by AR and YP, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval:

This study adheres to the Helsinki statement and is approved by the institutional ethics review board of the Rajaei CMCR. All patients' data is kept confidential. Since this study is retrospective, the need for written consent was waived.

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Tables

Table1- Baseline characteristics, clinical and echocardiographic data

Variables	All patients (n=200)	Survivors (n=171, 85.5%)	Non-survivors (n=29, 14.5%)	P-value
Age at diagnosis (years), median (IQR)	61.00 (25.00-75.00)	61.00 (52.00-70.50)	57.00 (39.50-68.00)	0.044
Female, n (%)	96 (48%)	79 (46.2%)	17 (58.6%)	NS
Male, n (%)	104 (52%)	92 (53.8%)	12 (41.4%)	NS
BMI (Kg/m^2), median (IQR)	26.64 (23.43-30.29)	26.76 (23.68-30.66)	25.71 (22.21-29.01)	NS
BSA (m^2), median (IQR)	1.78 (23.64-1.96)	1.80 (1.67-1.97)	1.70 (1.57-1.90)	0.055
Diagnosed with HTN, n (%)	77 (38.5%)	70 (40.9%)	7 (24.1%)	NS
Stroke, n (%)	5 (2.5%)	5 (2.5%)	0 (0%)	NS
Heart transplantation	5 (2.5%)	4 (2.3%)	1 (3.4%)	NS
NYHA classification				
Class Ⅱ	19 (9.5%)	17 (9.9%)	2 (6.9%)	NS
Class Ⅲ	86 (43%)	75 (43.9%)	11 (37.9%)	NS
Class Ⅱ or Ⅲ	95 (47.5%)	79 (46.2%)	16 (55.2%)	NS
MR severity at diagnosis				
Moderate, n (%)	133 (66.5%)	111 (64.9%)	22 (75.9%)	NS
Moderate-to-severe, n (%)	31 (15.5%)	26 (15.2%)	5 (17.2%)	NS
Severe, n (%)	36 (18%)	34 (19.9%)	2 (6.9%)	NS
TR severity at diagnosis				
Mild, n (%)	69 (34.5%)	59 (34.5%)	10 (34.5%)	NS
Moderate, n (%)	108 (54%)	92 (53.8%)	16 (55.2%)	NS
Moderate-to-severe, n (%)	15 (7.5%)	14 (8.2%)	1 (3.4%)	NS
Severe, n (%)	8 (4%)	6 (3.5%)	2 (6.9%)	NS
LVEF (%), median (IQR)	20.00 (15.00-30.00)	20.00 (15.00-35.00)	15.00 (10.00-20.00)	0.007
LVEDD (cm), median (IQR)	6.20 (4.20-6.90)	6.20 (5.60-6.90)	6.40 (5.35-7.40)	NS
LVESD (cm), median (IQR)	5.30 (4.20-6.00)	5.35 (4.20-5.92)	5.30 (4.25-6.65)	NS
LVVI (mL/m2), median	102.00 (84.00-	101.50 (84.75-	139.00 (75.00-	NS

(IQR)	155.00)	151.50)	173.00)	
LA area (cm^2), median (IQR)	24.00 (20.25-28.00)	24.00 (20.00-28.00)	25.00 (20.50-27.00)	NS
LA size (cm), median (IQR)	4.20 (3.80-4.70)	4.20 (3.72-4.70)	4.20 (3.90-4.55)	NS
RV size (cm), median (IQR)	3.30 (2.90-3.70)	3.30 (2.90-3.70)	3.20 (2.70-3.75)	NS
sPAP (mm Hg), median (IQR)	40.00 (30.00-50.00)	40.00 (30.00-50.00)	40.00 (30.00-50.00)	NS
TAPSE (mm), median (IQR)	17.00 (14.00-20.00)	18.00 (14.00-20.00)	14.00 (13.00-16.00)	<0.001
S' velocity (m/s), median (IQR)	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, n (%)	183 (91.5%)	157 (91.8%)	26 (89.7%)	NS
ACEi, n (%)	137 (68.5%)	118 (69%)	19 (65.5%)	NS
ARB, n (%)	46 (23%)	39 (22.8%)	7 (24.1%)	NS
Diuretic, n (%)	166 (83%)	140 (81.9%)	26 (89.7%)	NS
Beta-blocker, n (%)	189 (94.5%)	161 (94.2%)	28 (96.6%)	NS
Nitrate, n (%)	11 (5.5%)	10 (5,8%)	1 (3.4%)	NS
Hydralazine, n (%)	13 (6.5%)	9 (5.3%)	4 (13.8%)	0.016
MRA, n (%)	144 (72%)	121 (70.8%)	23 (79.3%)	NS
Digoxin use, n (%)	43 (21.5%)	31 (18.1%)	12 (41.4%)	NS
VKA, n (%)	46 (23%)	38 (22.2%)	8 (27.6%)	NS
NOAC, n (%)	20 (10%)	20 (11.7%)	0 (0%)	NS
LVEF<30%, n (%)	136 (68%)	111 (64.9%)	25 (86.2%)	0.023
LVEF≥30%, n (%)	64 (32%)	60 (35.1%)	4 (13.8%)	0.023

Table 2-Comparison of clinical and echocardiographic outcomes between the first visit and follow-up

Variables	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, n (%)	0 (0%)	19 (9.5%)	<0.001
Mild-to-moderate, n (%)	0 (0%)	19 (9.5%)	
Moderate, n (%)	133 (66.5%)	88 (44%)	
Moderate-to-severe, n (%)	31 (15.5%)	23 (11.5%)	
Severe, n (%)	36 (18%)	35 (17.5%)	
Echocardiographic data			
LVEF (%), median (IQR)	20.00 (15.00-30.00)	20.00 (15.00-35.00)	NS
LVEDD (cm), median (IQR)	6.20 (4.20-6.90)	6.10 (5.32-6.90)	0.043
LVESD (cm), median (IQR)	5.30 (4.20-6.00)	5.10 (4.10-6.00)	NS
LVVI (mL/m2), median (IQR)	102.00 (84.00-155.00)	102.00 (88.00-139.00)	NS
LA area (cm^2), median (IQR)	24.00 (20.25-28.00)	24.00 (21.00-29.00)	NS
LA size (cm), median (IQR)	4.20 (3.80-4.70)	4.30 (3.80-4.80)	NS
RV size (cm), median (IQR)	3.30 (2.90-3.70)	3.20 (2.90-3.80)	NS
sPAP (mm Hg), median (IQR)	40.00 (30.00-50.00)	39.50 (30.00-50.00)	NS
TAPSE (mm), median (IQR), mean (SD)	17.00 (14.00-20.00), 17.25 (4.49)	17.00 (14.50-19.00), 16.79 (4.03)	0.036
S' velocity (m/s), median (IQR)	9.00 (8.00-11.00)	9.00 (7.00-10.00)	NS

Table 3- The crosstabulation table showing the association between the MR severity change during the follow-up time and the medications administered

Medications	P-value
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
Beta-blockers	0.848

Table 4- The all-cause mortality independent predictors (Multivariate analysis adjusted by MR severity, LVEF, NYHA, ACEi/ARBs, Diuretics, Beta-blockers, MRA, Digoxin, and Nitrate)

	HR	95% CI	P-value
CRT	0.22	0.072-0.675	0.008
Hydralazine	0.25	0.067-0.928	0.038

Figures

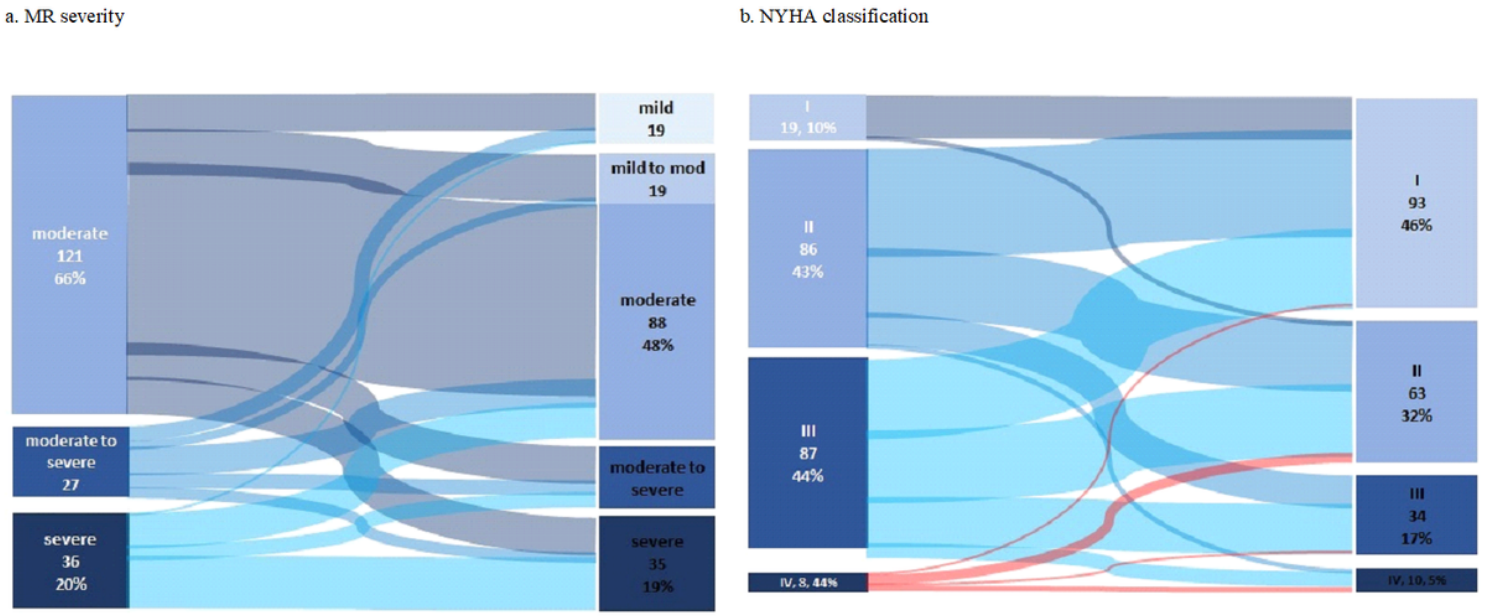

Figure 1

The Sankey Diagrams of the data comparison between the first visit and the follow-up. a. MR severity. b. NYHA classification

Figure 2a

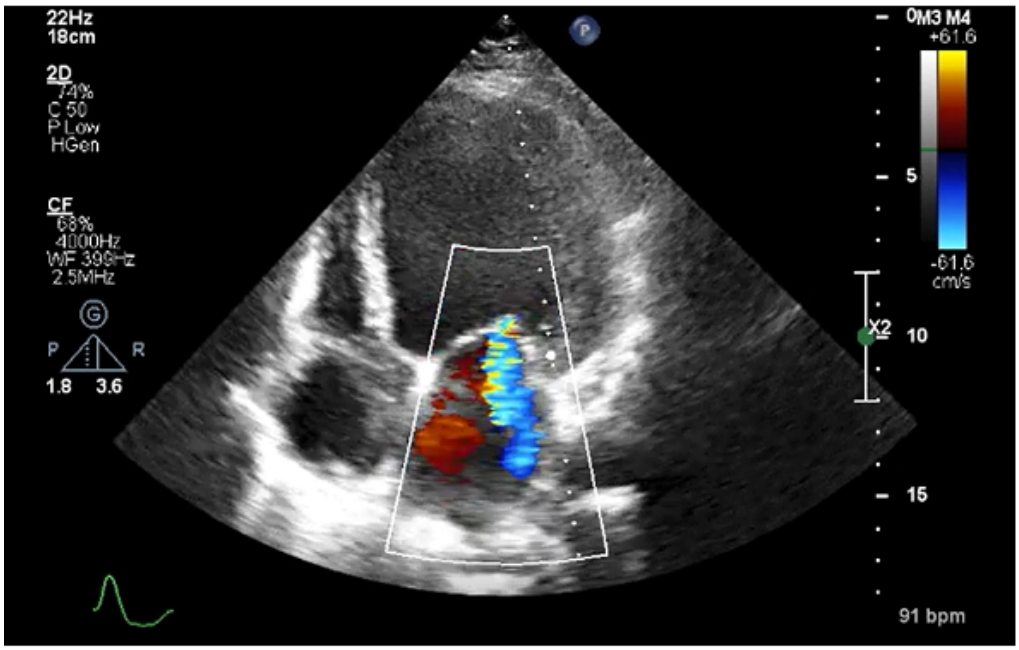

Figure 2b

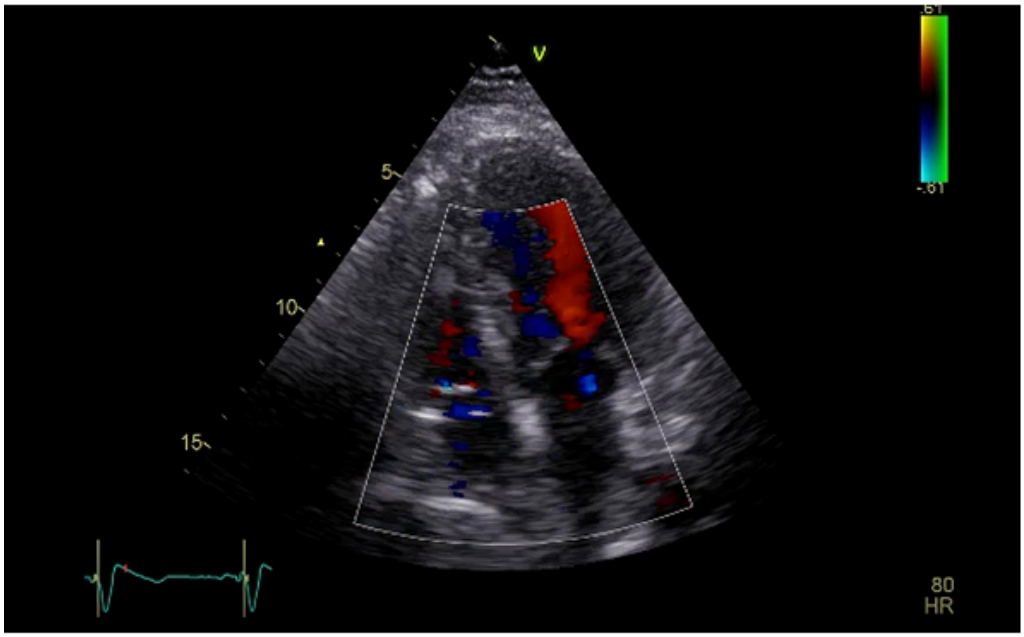

Figure 2

Color Doppler Transthoracic Echocardiographic images of one of the patients undergoing CRT. a. Before CRT implantation; Note the regurgitant jet. b. After CRT implantation.

Figure 3a

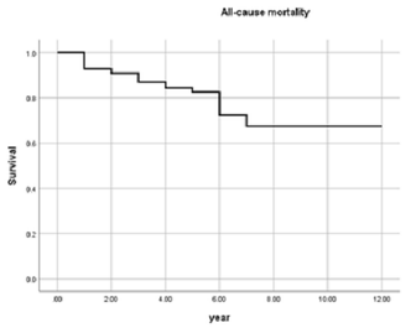

Figure 3b

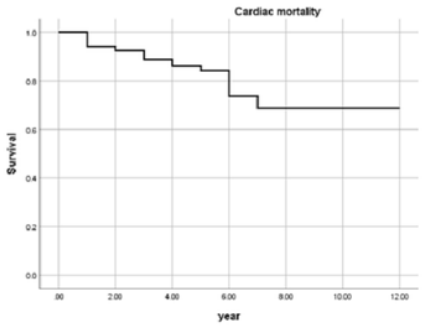

Figure 3c

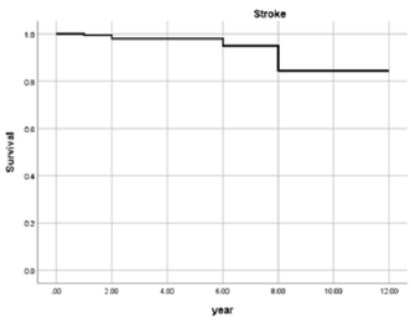

Figure 3d

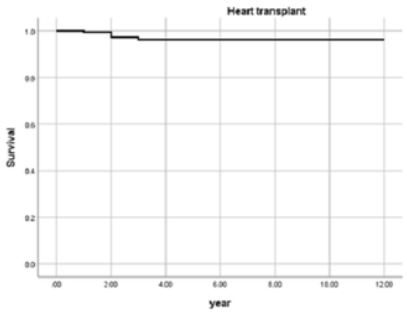

Figure 3e

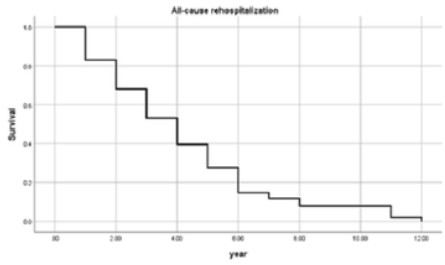

Figure 3f

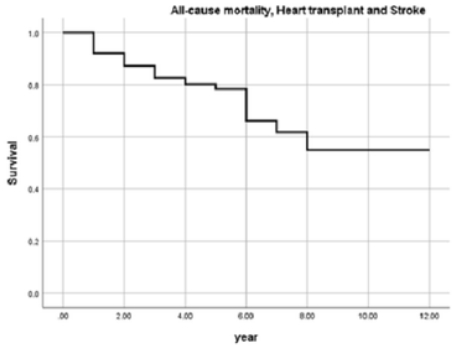

Figure 3

Survival curves. a. Survival free of all-cause mortality. b. Survival free of cardiac mortality. c. Survival free of stroke. d. Survival free of heart transplantation. e. Survival free of all-cause rehospitalization. f. Survival free of all-cause mortality, heart transplantation, and stroke.

Figure 4a

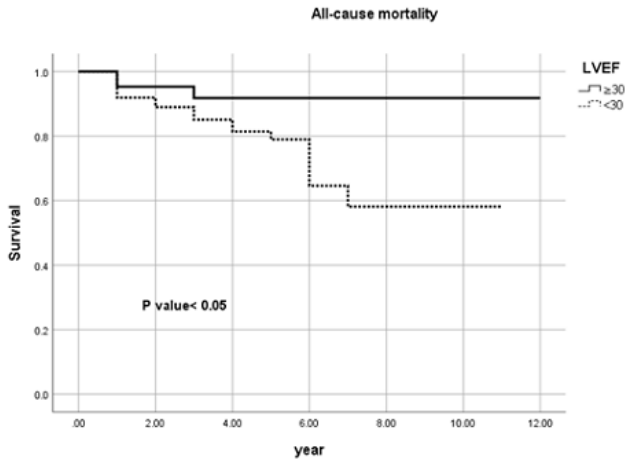

Figure 4c

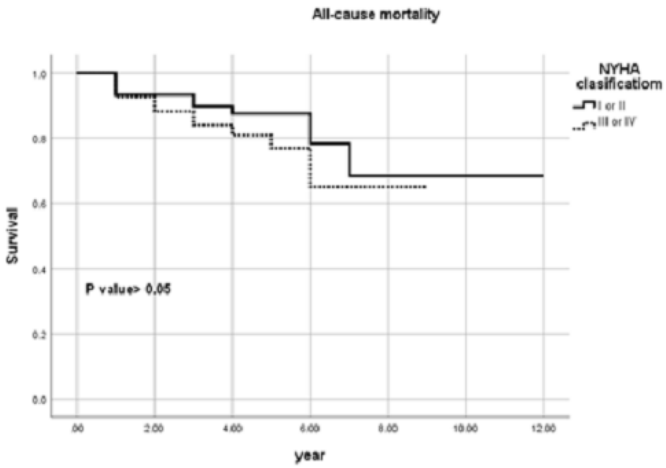

Figure 4b

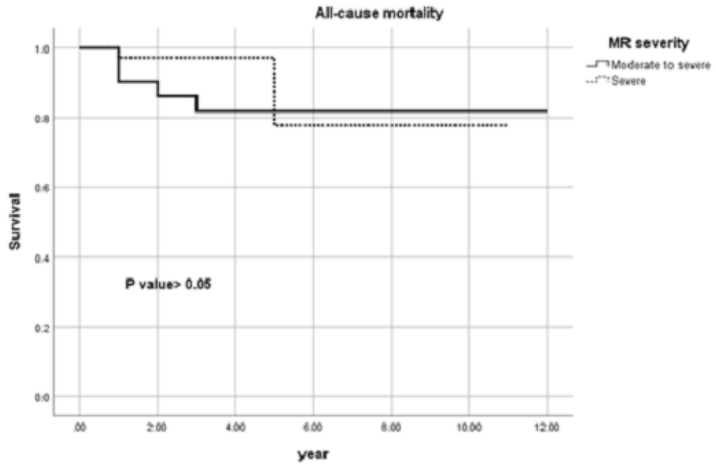

Figure 4

a. Survival free of all-cause mortality according to LVEF. b. Survival free of all-cause mortality according to MR severity. c. Survival free of all-cause mortality according to NYHA classification.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PostCRTMR.avi