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Predictors of Persistence of Functional Mitral Regurgitation after Cardiac Resynchronization Therapy

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Abstract:

Background: Functional mitral regurgitation (FMR) commonly occurs in dilated cardiomyopathy. Cardiac resynchronization therapy (CRT) is an effective approach; however, some cases continue to experience persistent or worsening mitral regurgitation (MR), underscoring the need to identify predictive factors. **Methods:** This prospective study followed 100 adults with non-ischemic dilated cardiomyopathy indicated for CRT. Baseline evaluations included demographics, comorbidities, laboratory tests, ECG, and detailed echocardiography with multiparametric MR grading. Follow-up at 3 and 6 months included repeat assessments, NYHA class, 6-minute walk test, and imaging. Logistic regression was employed to recognize variables associated with MR improvement or persistence post-CRT. **Results:** CRT improved functional status and exercise capacity, evidenced by reduced NYHA class and increased 6-minute walk distance. Echocardiography showed enhanced ejection fraction and fractional shortening, with reductions in left atrial size and ventricular dimensions (EDD, EDV, ESD, ESV). Tenting height and area also decreased. Most cases exhibited reduced MR severity. No significant predictors were identified pre-CRT. Post-CRT, MR improvement was associated with smaller end-systolic volume, higher fractional shortening, larger mid-diastolic mitral annular area, increased regurgitation, and wider vena contracta. Persistent MR was more common in older cases and those with larger baseline MR jet area, higher EDV, elevated heart rate, enlarged left atrium, prolonged PR interval, and wider QRS duration. **Conclusion:** In non-ischemic dilated cardiomyopathy, FMR improvement after CRT is mainly linked to reverse remodeling and residual MR severity. Baseline clinical and echocardiographic variables can help identify cases at risk for persistent MR, enabling personalized management strategies.

Keywords: Functional mitral regurgitation, cardiac resynchronization therapy, echocardiography, predictors, reverse remodeling.

Introduction

Functional mitral regurgitation (FMR) is commonly observed in cases with left ventricular (LV) dysfunction and remodeling, occurring in both ischemic and non-ischemic heart diseases. The prevalence of FMR in heart failure (HF) cases varies between 20% and 50%, with approximately 40% of these individuals exhibiting moderate to severe mitral regurgitation (SMR) (1). This contributes to the development of HF, which carries a mortality rate of 15-40% within the first year. As a result, significant attention has been given to the advancement of optimal methods for assessing and classifying the severity of FMR, as well as the development of effective treatment strategies to improve patient outcomes in those with significant FMR (1,2). However, there remains a gap in evidence regarding treatment recommendations for FMR (3).

As per the latest guidelines, surgical intervention is recommended for cases with severe secondary mitral regurgitation undergoing coronary artery bypass grafting, provided they have an LV ejection fraction above 30%. In cases where revascularization is not advised, the preferred treatment approach is medical therapy, in accordance with HF management protocols (4). However, for cases with HF and FMR who qualify for cardiac resynchronization therapy (CRT), CRT may lead to a reduction in the severity of FMR (5).

Unfortunately, in a subset of CRT cases, significant MR persists and worsens overtime. Thus, it is essential to study the parameters which determine the occurrence of persistent FMR. To achieve this, the Echocardiogram is classically the primary diagnostic tool of assessment for guide quantification and management of this disease (5,6).

This research is intended to identify the parameters that predict persistence of FMR among cases who underwent recent CRT to improve survival and reduce mortality of those cases.

Methodology

This prospective cohort study was conducted at the Cardiology Department of El Sheikh Zayed Specialized Hospital, which is renowned for its comprehensive care and advanced therapeutic interventions. The study involved 100 cases who were considered appropriate candidates for CRT. Before their inclusion, informed consent was obtained from all participants, ensuring their understanding of the study and their voluntary participation. Each participant was assigned a unique identification code to protect their confidentiality and ensure anonymity. The study protocol underwent rigorous review and received approval from the Research Ethics Committee of the Faculty of Medicine, Benha University, ensuring that all ethical standards were maintained throughout the research process. The study was conducted from May 2024 to February 2025.

Eligibility Criteria

Participants eligible for inclusion in the study were adult cases aged over 18 years who presented with non-ischemic dilated cardiomyopathy and had a left ventricular ejection fraction (LVEF) ≤ 35%. They were also required to have been on optimal medical therapy for at least 4 weeks, allowing for stabilization before further interventions. Additionally, they had to have sinus rhythm, left bundle branch block (LBBB), and a QRS duration ≥ 120 ms, and they had to experience severe limitations in physical activity, specifically NYHA class III or IV, despite receiving optimal medical treatment. Cases who did not meet these criteria were excluded from the study. This included those with NYHA class I, QRS duration < 120 ms, ischemic cardiomyopathy, LVEF > 35%, non-LBBB patterns, or non-sinus rhythm, as these factors could interfere with the outcomes of CRT.

Study Procedure

History and Physical Examination:

The study commenced with a detailed history and physical examination of each participant. This included gathering demographic data and relevant lifestyle factors, alongside an in-depth assessment of HF presentation. Specific attention was given to pulmonary venous congestion, systemic venous congestion, and low cardiac output symptoms. Furthermore, risk factors associated with co-morbidities such as diabetes mellitus, hypertension, dyslipidemia, and obesity were thoroughly evaluated. A complete physical examination was conducted, encompassing both general and cardiopulmonary assessments to establish a baseline health status for each patient.

Laboratory Investigations:

Participants underwent a comprehensive set of laboratory tests. These tests included cardiac enzymes such as CK and CK-MB to assess myocardial injury, kidney function tests (creatinine, urea, and BUN), and fasting blood glucose levels. Liver function tests, which included AST, ALT, GGT, ALP, total bilirubin, total protein, and albumin, were performed to monitor hepatic health. A lipid profile, including measurements of total cholesterol, triglycerides, HDL, and LDL, was also conducted to evaluate cardiovascular risk. Inflammatory markers, including CRP and LDH, were measured to assess the inflammatory status, which is often elevated in HF.

Electrocardiography (ECG):

A standard 12-lead ECG was obtained at baseline, prior to the implantation of the CRT device. Follow-up ECGs were taken at both the 3- and 6-m marks, with the device temporarily set to "CRT-off" in order to assess intrinsic conduction. The key intervals measured included the PR interval, the intrinsic QRS duration, and the QRS axis. Recordings were made at a paper speed of 25 mm/s and a gain of 10 mm/mV. Following each "off" recording, CRT programming was restored to "on" to continue therapy.

Echocardiographic Examination:

Transthoracic echocardiography was performed using a GE Vivid 9 Dimension machine, and measurements included left ventricular volumes and dimensions, such as LVEDD and LVESD. Ejection fraction was calculated using 2D biplane Simpson’s and M-mode tracings. Additional parameters such as LV sphericity index, left atrial volume, right ventricular end-diastolic diameter (RVEDD), and mitral annulus diameter were also recorded. Tenting height and area, as well as interpapillary distance, were measured along with PML/AML tethering angles and lengths. LV dyssynchrony was quantified through tissue Doppler imaging, and diastolic filling time was assessed using pulsed-wave Doppler.

MR Assessment:

Mitral regurgitation (MR) severity was assessed using a multiparametric approach. The vena contracta width (VCW) was measured at its narrowest point, and the jet area to left atrial (LA) area ratio was calculated. Effective regurgitant orifice area (EROA) was estimated using the proximal isovelocity surface area (PISA) method with a Nyquist limit between 30-60 cm/s. MR severity was classified on a scale from 1+ to 4+, depending on jet area size.

CRT Implantation:

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CRT devices were implanted through subclavian or axillary venous access, with leads positioned according to standard procedures. The right atrial and right ventricular leads were placed according to established guidelines, while the left ventricular lead was advanced through the coronary sinus and into the posterolateral vein, which was selected based on individual venous anatomy. Lead placement was confirmed fluoroscopically, and all leads were subsequently connected to the CRT generator. Following implantation, atrioventricular and interventricular delays were optimized using echocardiographic and device-based algorithms to ensure maximal resynchronization.

Outcome Measures

The response to CRT was assessed using echocardiographic measures such as a ≥ 15% reduction in left ventricular end-systolic volume (LVESV) and/or an increase in ejection fraction (LVEF) greater than 5% at the 6-m follow-up. In addition, cases who responded to CRT were expected to show clinical improvements, including at least one NYHA class improvement, an increased 6-minute walk distance, fewer HF-related hospitalizations, and improved quality of life. Nonresponders were defined as those who showed less than 15% LVESV reduction, ≤ 5% LVEF increase, no improvement in LV dyssynchrony, and no change in clinical symptoms or hospitalization rates.

Follow-Up

Cases were followed up regularly to monitor CRT-related complications, such as coronary sinus injury, pneumothorax, phrenic nerve pacing, and infections. These complications were closely tracked during follow-up visits at 3 and 6 m. At each follow-up, clinical status was assessed, including NYHA class and 6-minute walk distance, while adverse events were documented. ECGs were taken with CRT "off" to reassess intrinsic conduction, and echocardiography was repeated to monitor changes in LV/LA volumes, ejection fraction, dimensions, MR grade, and other important parameters. These measurements were compared to pre-CRT values to determine the overall response to therapy.

Approval code: MS 38-7-2023

Statistical Analysis

Data analysis was performed using SPSS v28 software. The normality of data distribution was evaluated using the Shapiro-Wilks test and histograms. Parametric quantitative data were presented as means and standard deviations, and comparisons were made using unpaired t-tests. Qualitative variables were presented as frequencies and percentages, and the Chi-square test was used for their analysis. A two-tailed P value of < 0.05 was considered statistically significant. Additionally, logistic regression was employed to evaluate the relationship between dependent and independent variables in a multivariate context.

Results

Table 1 presents the baseline characteristics of the study participants. The cases' ages ranged from 30 to 65 years, with a mean age of 46 ± 10.87 years. The cohort was predominantly male, with 73 males (73%) and 27 females (27%). The participants' weights ranged from 57 to 95 kg, with an average of 76.2 ± 11.68 kg. Their heights varied from 1.57 to 1.75 meters, with a mean height of 1.7 ± 0.06 meters. The body mass indices (BMIs) ranged from 18.61 to 38.54 kg/m², with a mean of 27.9 ± 4.78 kg/m². Regarding medical history, 25% of the cases were smokers, 53% had hypertension, 48% had diabetes, and

27% had hyperlipidemia. According to the NYHA classification, 72% of the cases were in class III and 28% in class IV. The results of the 6-minute walk test varied between 70 and 250 meters, with an average of 164.6 ± 51.63 meters. Prior to CRT, MR severity was mild in 17% of the cases, moderate in 45%, and severe in 38%. **Fig. 1**.

Table 2 shows the baseline echocardiographic data before CRT implantation. The LVEF ranged from 15% to 35%, with a mean of 25.84 ± 5.87%. The left atrial (LA) size ranged from 4.12 to 5.9 cm, with a mean of 4.89 ± 0.45 cm. The end-diastolic diameter (EDD) ranged from 6 to 6.7 mL, with an average of 6.3 ± 0.21 mL. The end-diastolic volume (EDV) varied from 182 to 450 mL, with a mean of 312.38 ± 79.79 mL. The end-systolic volume (ESV) ranged from 118 to 261 mL, with a mean of 188.2 ± 42.59 mL. The fractional shortening (FS) ranged from 10% to 17%, with a mean of 13.6 ± 2.27%. The tenting height ranged from 3.4 to 7.7 mm, with an average of 6.67 ± 0.9 mm, and the tenting area varied from 0.63 to 4.1 cm², with a mean of 3.72 ± 1.02 cm².

Table 3 reports the improvements observed after the CRT procedure. There was a significant improvement in the NYHA classification (P < 0.05). Before CRT, 72% of the cases were in NYHA class III, and 28% were in class IV. After CRT, 33% of the cases were in class I, 29% in class II, 22% in class III, and 16% in class IV. The 6-minute walk test scores significantly increased from a mean of 164.62 ± 51.63 meters before CRT to 325.89 ± 72.22 meters post-CRT (P < 0.001). Regarding MR severity, 46% of cases had mild MR, 19% had moderate MR, 21% had severe MR, and 14% had no MR after CRT. **Fig. 2-3**.

Table 4 shows the post-CRT echocardiographic results. The EF post-CRT ranged from 19% to 48%, with a mean of 32.16 ± 8.37%. The LA size ranged from 3.4 to 4.4 cm, with an average of 3.84 ± 0.29 cm. The EDD ranged from 4.5 to 6.7 mL, with a mean of 5.6 ± 0.6 mL. The EDV varied from 164 to 385 mL, with a mean of 271.42 ± 62.82 mL. The ESV ranged from 52 to 228 mL, with a mean of 146.52 ± 52.89 mL. The FS ranged from 15% to 25%, with a mean of 19.78 ± 3.27%. The tenting height ranged from 3 to 7.74 mm, with a mean of 6.03 ± 1.38 mm, and the tenting area ranged from 0.6 to 4.1 cm², with a mean of 2.85 ± 1.6 cm².

Table 5 illustrates the electrocardiographic response to CRT. The EF and FS were significantly higher at 3 to 6 m post-CRT compared to baseline (P < 0.05). There were significant reductions in LA size, EDD, EDV, ESD, ESV, tenting height, and tenting area post-CRT compared to baseline (P < 0.05). **Fig. 4**.

Logistic regression analysis revealed that baseline (pre-CRT) factors were not predictive of MR improvement (all P ≥ 0.97). However, post-CRT echocardiographic measures, including reduced end-systolic volume, increased fractional shortening, a larger mid-diastolic annular area, a higher regurgitant fraction, and a wider vena contracta, were significantly associated with MR improvement (P ≤ 0.002). These findings suggest that ventricular reverse remodeling and the residual severity of MR after CRT are key determinants of MR improvement. These results are illustrated in **Fig. 5**.

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Table 1: Baseline characteristics of the included cases.

Age (years)	Mean± SD	46 ± 10.87
	Range	30 – 65
Sex	Male	73 (73%)
	Female	27 (27%)
Weight (Kg)	Mean± SD	76.2 ± 11.68
	Range	57 – 95
Height (m)	Mean± SD	1.7 ± 0.06
	Range	1.57 - 1.75
BMI (Kg/m^2)	Mean± SD	27.9 ± 4.78
	Range	18.61 - 38.54
Smoking	Frequency (Percentage)	25 (25%)
HTN	Frequency (Percentage)	53 (53%)
DM	Frequency (Percentage)	48 (48%)
Hyperlipidaemia	Frequency (Percentage)	27 (27%)
NYHA classification	III	72 (72%)
	IV	28 (28%)
6 Minute Walk Test	Mean± SD	164.6 ± 51.63
	Range	70 - 250
MR grade	Mild	17(17%)
	Moderate	45(45%)
	Severe	38(38%)

HTN; hypertension, DM; diabetes mellitus, NYHA; New York heart classification, MR; mitral regurgitation.

Table 2: Echocardiographic data of the included cases before CRT implantation.

Variables		Total (n=100)
EF (%)	Mean± SD	25.84±5.87
	Range	15-35
LA	Mean± SD	4.89 ±0.45
	Range	4.12-5.9
EDD (mL)	Mean± SD	6.3±0.21
	Range	6-6.7
EDV (mL)	Mean± SD	312.38±79.79
	Range	182-450
ESD (mL)	Mean± SD	4.94±0.31
	Range	4.5-5.5
ESV (mL)	Mean± SD	188.2±42.59
	Range	118-261
FS (%)	Mean± SD	13.6±2.27
	Range	10-17
Tenting height (mm)	Mean± SD	6.67±0.9
	Range	3.4-7.7
Tenting area (cm2)	Mean± SD	3.72±1.02
	Range	0.63-4.1

EF; Ejection fraction, LA; left atrium, EDD; end-diastolic diameter, EDV; end-diastolic volume, ESD; end-systolic dimension, ESV; end-systolic volume, F; Fractional shortening.

Table 3: Clinical outcomes of the included cases after CRT implantation.

Variables		Total (n=100)		P value
		Before CRT implantation	**3-6 M after CRT implantation**	
NYHA classification	I	0(0%)	33 (33%)	<0.001*
	II	0(0%)	29(29%)	<0.001*
	III	72(72%)	22(22%)	<0.001*
	IV	28(28%)	16(16%)	<0.001*
6 Minute Walk Test	Mean± SD	164.62±51.63	325.89±72.22	<0.001*
	Range	70-250	195-450	
MR grade	Mild	17(17%)	46(46%)	<0.001*
	Moderate	45(45%)	19(19%)	<0.001*
	Severe	38(38%)	21(21%)	0.001*
	No	0(0%)	14(14%)	<0.001*

NYHA; New York Heart Association, CRT; Cardiac resynchronization therapy, MR; mitral regurgitation, *; statistically significant as p value <0.05.

Table 4: Echocardiographic data of the included cases after CRT implantation.

Variables		Total (n=100)		P value
		Before CRT implantation	**3-6 M after CRT implantation**	
EF (%)	Mean± SD	25.84±5.87	32.16±8.37	<0.001*
	Range	15-35	19-48	
LA	Mean± SD	4.89 ±0.45	3.84±0.29	<0.001*
	Range	4.12-5.9	3.4-4.4	
EDD (mL)	Mean± SD	6.3±0.21	5.6±0.6	<0.001*
	Range	6-6.7	4.5-6.7	
EDV (mL)	Mean± SD	312.38±79.79	271.42±62.82	<0.001*
	Range	182-450	164-385	
ESD (mL)	Mean± SD	4.94±0.31	4.29±0.45	<0.001*
	Range	4.5-5.5	3.5-5	
ESV (mL)	Mean± SD	188.2±42.59	146.52±52.89	<0.001*
	Range	118-261	52-228	
FS (%)	Mean± SD	13.6±2.27	19.78±3.27	<0.001*
	Range	10-17	15-25	
Tenting height (mm)	Mean± SD	6.67±0.9	6.03±1.38	<0.001*
	Range	3.4-7.7	3-7.74	
Tenting area (cm2)	Mean± SD	3.72±1.02	2.85±1.6	<0.001*
	Range	0.63-4.1	0.6-4.1	

EF; Ejection fraction, LA; left atrium, EDD; end-diastolic diameter, EDV; end-diastolic volume, ESD; end-systolic dimension, ESV; end-systolic volume, FS; Fractional shortening, *; statistically significant as p value <0.05.

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Table 5: Electrocardiographic response to CRT.

ECG		Total (n=100)			P value
		Before CRT implantation	**Immediately after CRT implantation**	**3-6 M after CRT implantation**	
HR (bpm)	Mean± SD	87.03±10.1	98.31±14.05	83.96±8.47	<0.001*
	Range	70-106	75-120	70-100	
	P value	P1 <0.001*, P2=0.021*, P3<0.001*			
PR Interval	Mean± SD	160.49±23.53	126.43±15.86	120.46±11.89	<0.001*
	Range	120-200	70-150	100-140	
	P value	P1<0.001*, P2<0.001*, P3=0.003*			
QRS width (on)	Mean± SD	152.89±15.23	128.46±20.55	125.24±21.17	<0.001*
	Range	125-180	91-160	90-160	
	P value	P1<0.001*, P2<0.001*, P3=0.276			
QRS width (off)	Mean± SD	152.43±16.63	133.96±19.48	136.77±19.47	<0.001*
	Range	125-180	100-170	100-170	
	P value	P1<0.001*, P2<0.001*, P3=0.309			

HR; heart rate, *; statistically significant as p value <0.05, P1; p value between before CRT implantation and immediately after CRT implantation, P2; p value between before CRT implantation and 3-6 M after CRT implantation, P3; p value between immediately after CRT implantation and 3-6 M after CRT implantation.

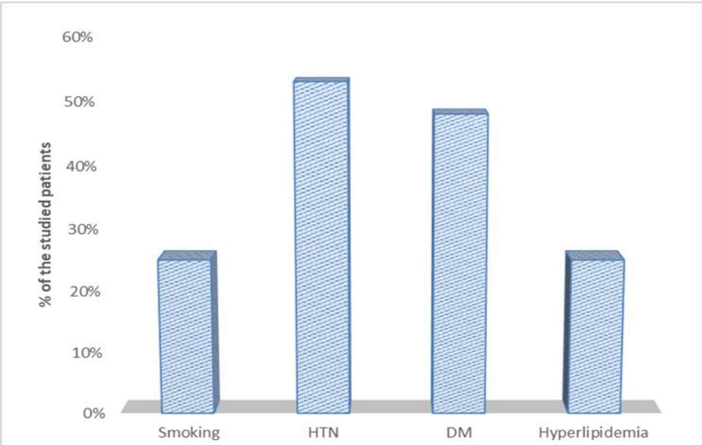

Figure 1: Risk factors of the studied patients before implantation.

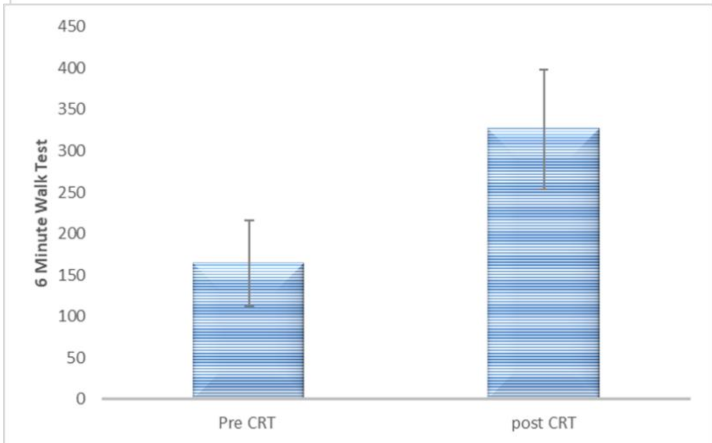

Figure 2: 6 Minute Walk Test of the studied patients before and after CRT implantation.

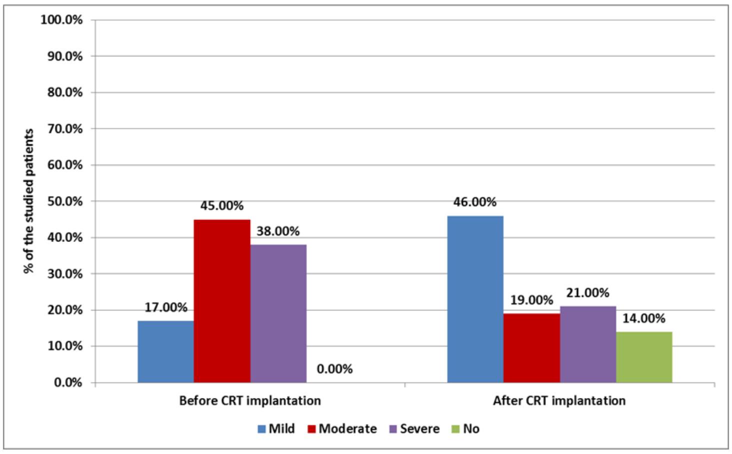

Figure 3: MR grade of the studied patients before and after CRT implantation.

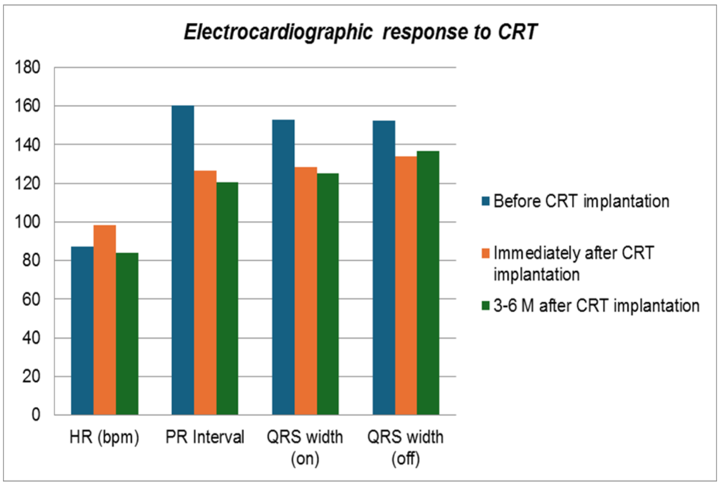

Figure 4: Echocardiographic data of the included cases after CRT implantation.

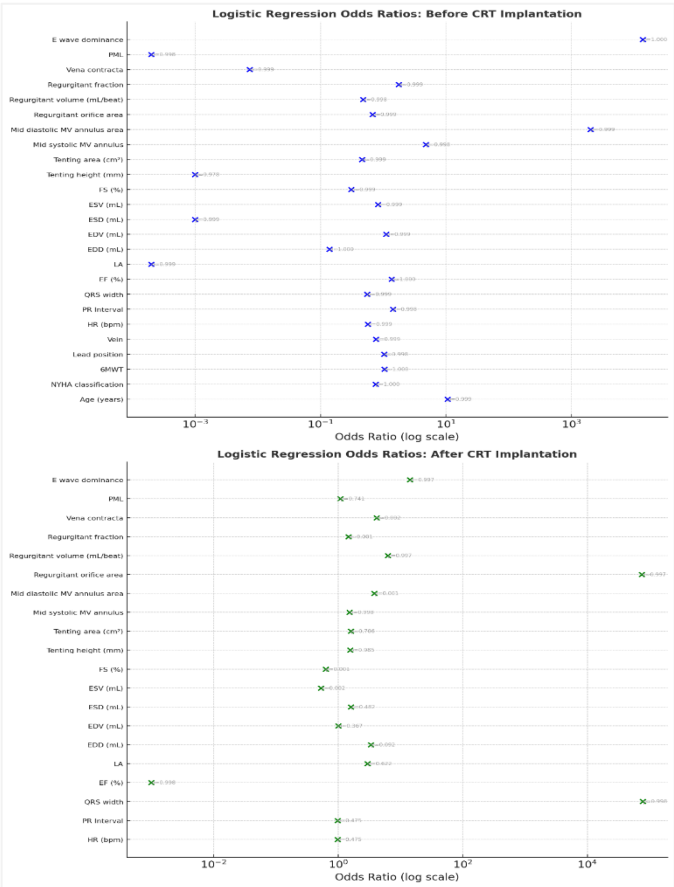

Figure 5: Logistic regression analysis for prediction of improved MR.

Discussion

This research was designed to examine the factors that predict the persistence of FMR in cases who underwent recent CRT aimed at improving survival and reducing mortality. Additionally, the study sought to identify the patient characteristics and echocardiographic indicators that could predict the recurrence of FMR after CRT [4].

In this study, significant improvement in NYHA classification was observed after CRT (P<0.05). Prior to implantation, 72 (72%) cases were classified as NYHA class III, and 28 (28%) cases were in class IV. After implantation, the distribution shifted with 33 (34%) cases in class I, 29 (30%) in class II, 22 (22%) in class III, and 16 (16%) in class IV. Furthermore, the post-CRT 6-minute walk test showed a notable increase compared to the pre-CRT test (325.89±72.22 vs. 164.62±51.63, P<0.001). A significant relationship between NYHA classification and 6-minute walk test results was found, with a higher 6-minute walk test score observed in cases with improved NYHA status compared to those without improvement (P<0.001).

Similarly, Al-Mashat and co-authors investigated whether changes in perfusion gradients were related to improvements in HF symptoms after CRT. In their follow-up study of 19 HF cases who had received CRT, they found that 13 out of 19 (68%) cases experienced improvement in NYHA classification. However, five cases (26%) showed no improvement, and one patient's symptoms worsened post-CRT. Additionally, no correlation was found between NYHA classification and the 6-minute walk test (P = 0.07) [7].

Consistent with our findings, van Bommel and co-authors investigated the role of CRT as a potential therapeutic approach for HF cases with moderate to severe FMR and those with high operative risk. The study, which involved 85 cases categorized into two groups (MR improvers, n=42, and MR non-improvers, n=43), showed a remarkable improvement in the cases' functional status, as measured by the NYHA class. Specifically, the cases experienced a significant improvement in their functional class, with a noticeable decrease in severity from 3.1 ± 0.3 to 2.1 ± 0.7 at 6 months following CRT, reflecting a substantial enhancement in their overall clinical condition (P<0.001) [8].

In a similar vein, Solis and co-authors explored the effects of CRT on 34 cases suffering from functional MR. Their findings demonstrated a clear clinical improvement, with cases showing an increase in their functional capacity as indicated by a change in the NYHA functional class (P<0.0001). Additionally, they reported a significant improvement in the 6-minute walk test, with the cases walking a greater distance after CRT, increasing from 284 ± 143 meters to 408 ± 100 meters, highlighting the positive impact of the treatment (P=0.001) [9].

In terms of changes in HR, our results showed a noticeable and significant increase immediately following CRT implantation when compared to the measurements taken before the procedure. However, over the following 3 to 6 months after the procedure, HR dropped significantly, showing a marked decrease when compared to both pre-CRT values and immediate post-CRT readings (P=0.021, <0.001). In addition to the HR changes, we also observed a significant reduction in the PR interval, which was evident both right after the CRT implantation and at the 3 to 6 month follow-up, when compared to the values measured before the procedure (P<0.001, <0.001). This reduction was even more pronounced when comparing the 3 to 6 month post-CRT data to the immediate post-CRT measurements (P=0.003). Furthermore, the width of the QRS complex also showed a significant decrease immediately following CRT implantation and continued to show a reduction at the 3 to 6 month mark (P<0.05), with no notable difference between these two post-implantation time points.

On the other hand, in a study by Solis and co-authors, no meaningful change in HR was observed in their 34 cases with functional MR before and after CRT. The HR remained almost the same, with no significant reduction or increase, changing from 70 ± 11 bpm to 69 ± 10 bpm (P=0.8) [9].

In contrast to our findings, Fantoni and colleagues conducted an investigation into the long-term effects of CRT on heart rate variability and overall heart rate in cases with severe heart failure symptoms. Their study revealed that CRT led to a noticeable reduction in the lowest recorded heart rate, which decreased from 63 ± 9 beats per minute to 58 ± 7 beats per minute ($p < 0.001$). Additionally, the typical heart rate, measured as the average over time, also saw a reduction from 76 ± 10 beats per minute to 72 ± 8 beats per minute ($p < 0.01$) [10].

In our investigation, notable improvements in left ventricular function were observed following CRT, with increases in both ejection fraction and fractional shortening. At the same time, there were significant reductions in left atrial dimensions, as well as in volumes at both end-diastolic and end-systolic points. Furthermore, mitral valve tenting height and area decreased considerably. A marked reduction in MR severity was also evident during follow-up.

Similarly, Mihos and co-authors explored the effects of CRT after inferior myocardial infarction on SMRs and mitral valve geometry. Their findings revealed that CRT led to a significant decrease in MR severity, along with improvements in left ventricular shape. Specifically, they observed a notable reduction in the MR jet area/left atrial area ratio from 33.2% to 25.8% (P=0.06) and a decrease in MR grade from 2.3 to 1.8 (P=0.05) during follow-up, signifying improved mitral valve function post-therapy [11].

In line with our results, Bommel and co-authors, 2011, documented significant reverse remodeling of the left ventricle six m after CRT. This was highlighted by reductions in left ventricular volumes, with a drop in LVEDV from 261±88 mL at baseline to 233±81 mL and LVESV from 205±81 mL to 166±72 mL (both P<0.001). Additionally, a rise in ejection fraction from 23±7% to 30±9% was observed (P<0.001). Notably, 55% of cases demonstrated a significant volumetric response to CRT (≥15% reduction in LVESV). Also, left atrial volume decreased from 103±38 mL to 91±32 mL, and mitral valve tenting area was reduced from 7.2±2.0 cm² to 6.2±2.0 cm² (P<0.001) [8].

Consistent with our observations, Solis and co-authors assessed the impact of CRT on echocardiographic parameters in 34 cases with functional MR. The results indicated a significant increase in ejection fraction following CRT ($P < 0.001$), while both end-diastolic and end-systolic volumes showed notable reductions ($P < 0.001$). Additionally, MR volume was significantly reduced, and left ventricular volumes decreased as well. Tenting volume was reduced from 4.6 ± 2.2 mL to 5.7 ± 2.6 mL ($P < 0.001$) [9].

Additionally, Ypenburg and co-authors analyzed the impact of discontinuing CRT after 6 m on dyssynchrony and MR. They noted acute changes in the mitral valve tenting area, which decreased from 7.8 cm² to 7.2 cm² (P<0.001), correlating with improved coaptation height, suggesting better mitral valve leaflet coaptation post-therapy [12].

In line with our observations, Madaric and co-authors investigated the changes in MR and LV remodeling both at rest and during physical exertion following early and late CRT in 28 cases. Their findings revealed a significant increase in the efficiency of the heart's pumping function after CRT, as reflected by improved measures of LV performance. Additionally, there was a marked reduction in the size of the heart’s chambers, specifically in the LVEDV and LVESV, both of which were significantly smaller following treatment. Moreover, there was a notable reduction in the mitral valve tenting area after a few m, further suggesting improvements in the heart’s structure and function [13].

Our study also used statistical analysis to identify factors associated with the onset of MR. The results indicated that factors like age, characteristics of the MR jet, the size of certain heart structures, heart rate, and electrical conduction time were significant in predicting the likelihood of MR occurrence. Conversely, several other factors, including gender, exercise capacity, and other heart function measures, were not found to be substantial predictors. This emphasizes that MR development can be influenced by specific variables, and not all heart function markers may be reliable indicators.

Supporting our findings, Trepa and co-authors highlighted that electrical conduction time, specifically QRS width, was an important predictor of improvements in MR. However, their study showed that other factors, such as certain heart structure measurements and lead placement, did not appear to significantly impact the outcome. This suggests that while some factors might be influential, others may not play a pivotal role in MR improvements post-therapy [14].

Similarly, Shu and co-authors examined a large group of older individuals and found that the prevalence of valvular conditions, including MR, increased with age. The study demonstrated a significant rise in the occurrence of these conditions as individuals aged, highlighting that older age is a key risk factor for developing MR and other valvular issues. These findings further underline the importance of age as a major factor in the assessment and management of heart conditions [15].

In alignment with our findings, Upadhyay and co-authors found that the severity of baseline MR, changes in MR following CRT, heart chamber size at follow-up, and heart function measures were key predictors of the primary outcome, which included the time to all-cause mortality or the first hospitalization. These findings were supported by multivariate analysis of echocardiographic data. However, in the univariate analysis, they found that only the degree of MR was a significant predictor at baseline, at 6-m follow-up, and in terms of changes from baseline to follow-up [16].

In contrast, Cipriani and co-authors conducted a similar analysis to determine predictors of worsening MR after CRT in a large cohort. Their results showed that heart function was a significant predictor of worsening MR ($p<0.001$), suggesting that left ventricular function plays a critical role in MR progression [17].

Contrasting with our findings, Cabrera-Bueno and co-authors conducted a study to identify independent predictors of persistent significant MR six m after CRT in a smaller group of cases. They found that end-systolic volume was not a significant predictor for MR recurrence. Interestingly, while they disagreed with our results regarding this measure, they agreed with our findings that end-diastolic volume was also an insignificant predictor for MR recurrence [18].

Conclusions

Our study showed that older age, MR jet, EDV, HR LA, PR, QRS width were the only significant predictors for the incidence of MR. Sex, 6-minute walk test, E wave dominance, EDD, EF, FS, LA, mid-diastolic MV annulus, mid systolic MV annulus, MR grade, lead position, regurgitation fraction, orifice area, and volume were insignificant predictors for MR incidence.

List of abbreviations

CRT	Cardiac resynchronization therapy
DM	diabetes mellitus
ECG	Electrocardiography
EDD	end-diastolic diameter
EDV	end-diastolic volume
EF	Ejection fraction
EROA	Effective regurgitant orifice area
ESD	end-systolic dimension
ESV	end-systolic volume
FMR	Functional mitral regurgitation
HF	heart failure
HTN	hypertension
LA	left atrium
LV	left ventricular
LVEDD	GE
LVESV	left ventricular end-systolic volume
MR	mitral regurgitation
MR	mitral regurgitation
NYHA	New York Heart Association
NYHA	New York heart classification
PISA	proximal isovelocity surface area
SMR	severe mitral regurgitation

VCW vena contracta width

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Authors contributed equally to the study**.**

Conflicts of interest
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References

1. Russo E, Russo G, Braccio M, Cassese M. Predictors of persistence of functional mitral regurgitation after cardiac resynchronization therapy: Review of literature. World J Cardiol. 2022; Mar 26;14(3):170–6.
2. Stassen J, Galloo X, Hirasawa K, van der Bijl P, Leon MB, Marsan NA, et al. Interaction between secondary mitral regurgitation and left atrial function and their prognostic implications after cardiac resynchronization therapy. Eur Heart J Cardiovasc Imaging. 2023; Mar 21;24(4):532–41.
3. Okamoto H, Inden Y, Yanagisawa S, Fujii A, Tomomatsu T, Mamiya K, et al. The mechanism and prognosis of acute and late improvement in mitral regurgitation after cardiac resynchronization therapy. Heart Vessels. 2021; Jul;36(7):986–98.
4. Otto, C. M. ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2020; 143.
5. Cormican DS, Drennen Z, Sonny A, Crowley JC, Gil IJN, Ramakrishna H. Functional Mitral Regurgitation in Heart Failure: Analysis of the ESC Multidisciplinary Heart-Team Position Statement and Review of Current Guidelines. J Cardiothorac Vasc Anesth. 2022; Aug;36(8 Pt B): 33 57 –64.
6. Deferm S, Bertrand PB, Verbrugge FH, Verhaert D, Rega F, Thomas JD, et al. Atrial Functional Mitral Regurgitation: JACC Review Topic of the Week. J Am Coll Cardiol. 2019; May 21;73(19):2465–76.
7. Al-Mashat M, Borgquist R, Carlsson M, Arheden H, Jögi J. Pulmonary perfusion and NYHA classification improve after cardiac resynchronization therapy. J Nucl Cardiol.2022; Dec;29(6):2974–83.
8. van Bommel RJ, Marsan NA, Delgado V, Borleffs CJW, van Rijnsoever EPM, Schalij MJ, et al. Cardiac resynchronization therapy as a therapeutic option in cases with moderate-severe functional mitral regurgitation and high operative risk. Circulation. 2011; Aug 23;124(8):912–9.
9. Solis J, McCarty D, Levine RA, Handschumacher MD, Fernandez-Friera L,Chen-Tournoux A, et al. Mechanism of decrease in mitral regurgitation after cardiac resynchronization therapy: optimization of the force-balance relationship.Circ Cardiovasc Imaging.2009; Nov;2(6):444–50.
10. Fantoni C, Raffa S, Regoli F, Giraldi F, La Rovere MT, Prentice J, et al. Cardiac resynchronization therapy improves heart rate profile and heart rate variability of cases with moderate to severe heart failure. J Am Coll Cardiol. 2005; Nov 15;46(10):1875–82.
11. Mihos CG, Yucel E, Capoulade R, Orencole MP, Upadhyay GA, Santana O, et al. Effects of cardiac resynchronization therapy after inferior myocardial infarction on secondary mitral regurgitation and mitral valve geometry. Pacing Clin Electrophysiol. 2018; Feb;41(2): 114 –21 .
12. Ypenburg C, Lancellotti P, Tops LF, Bleeker GB, Holman ER, Piérard LA, et al. Acute effects of initiation and withdrawal of cardiac resynchronization therapy on papillary muscle dyssynchrony and mitral regurgitation. J Am Coll Cardiol.2007; Nov 20;50(21):2071–7.
13. Madaric J, Vanderheyden M, Van Laethem C, Verhamme K, Feys A, Goethals M, et al. Early and late effects of cardiac resynchronization therapy on exercise-induced mitral regurgitation: relationship with left ventricular dyssynchrony, remodelling and cardiopulmonary performance. Eur Heart J. 2007;Sep;28(17):2134–41.
14. Trepa M, Baggen-Santos R, Fontes-Oliveira M, Silveira I, Costa R, Jo&atilde M, et al. Determinants and Clinical Outcomes of Functional Mitral Regurgitation Improvement FollowingCardiac Resynchronization Therapy [Internet].International Cardiovascular Research Journal; [cited 2025 Jun 4] . Report No.2020; 14. Available from: https://brieflands .com/articles/ircrj-100773#abstract
15. Shu C, Chen S, Qin T, Fu Z, Sun T, Xie M, et al. Prevalence and correlates of valvular heart diseases in the elderly population in Hubei, China. Sci Rep.2016; Jun 2;6:27253.
16. Upadhyay GA, Chatterjee NA, Kandala J, Friedman DJ, Park MY, Tabtabai SR, et al. Assessing mitral regurgitation in the prediction of clinical outcome after cardiac resynchronization therapy. Heart Rhythm. 2015; Jun;12 (6): 1201–8.
17. Cipriani M, Lunati M, Landolina M, Proclemer A, Boriani G, Ricci RP, et al. Prognostic implications of mitral regurgitation in cases after cardiac resynchronization therapy. Eur J Heart Fail. 2016; Aug;18(8):1060–8.

18. Cabrera-Bueno F, Molina-Mora MJ, Alzueta J, Pena-Hernandez J,Jimenez-NavarroM,fernandez- Pastor J, et al. Persistence of secondary mitral regurgitation and response to cardiac resynchronization therapy. Eur J Echocardiogr. 2010; Mar;11(2):131–7.

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