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Clinical Implications of Functional Mitral Regurgitation Severity in Patients with Heart Failure with Reduced Ejection Fraction (HFrEF)

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ABSTRACT

Background: An estimated 64.3 million people are living with heart failure worldwide. Functional MR in chronic HFrEF reflects primarily the severity of LV dysfunction and is not related to structural alterations of the mitral valvular apparatus. FMR in patients with HFrEF independently of the etiology of HFrEF and its underlying mechanisms, contributes to progression of the symptoms of HF and is independent predictor of worse clinical outcomes.

Objective: The purpose of this study was to assess the severity of functional mitral regurgitation (FMR) and its clinical implications in patients with chronic heart failure with reduced ejection fraction (HFrEF). **Methods:** We enrolled 146 consecutive adult patients with CHF with reduced ejection fraction (HFrEF) who presented to outpatient clinics. All patients underwent clinical and physical examination. Baseline examination included medical history, detailed assessment of current medication, electrocardiogram recording, transthoracic echocardiogram and comorbidities. Heart failure with reduced ejection fraction was defined in line with the new guidelines as history of HF signs and symptoms as well as a LV ejection fraction (LVEF) below 40%. Cardiovascular risk factors were recorded according to the respective guidelines. FMR was defined and graded according to the ESC/EACTS Guidelines for the management of valvular heart disease. The extent of FMR was assessed at baseline and after a median follow-up period of 4 years in 146 consecutive HFrEF patients (left ventricular ejection fraction <40%). All of the patients received the heart failure (HF) medications in agreement with 2016 and 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Major adverse cardiac events were defined as a composite of all-cause death and the need for admission for HF. **Results:** A total of 146 chronic HFrEF patients (mean age of 63±11 years, 62% male, mean LVEF of 25±11%) of which 19% patients had severe FMR at baseline, with a mean EROA of 31.4±2.7 mm² and a mean Reg Vol of 45.9±5.3 ml. There was a significant interaction between FMR and NYHA functional class in predicting death or need for hospitalization, (P < 0.0001 for the interaction term FMR NYHA III-IV). During a median follow-up period of 4.2 (IQR 3.1-5.8) years, the primary endpoint occurred in 52 (36%) patients (21 HF admissions, and 31 deaths). There was a strong graded association between the presence and degree of FMR and risk of death or admission (P < 0.0001) at 4 years follow-up period. Regarding HF therapy, 129 patients (88%) received RAAS antagonists, 17 patients (12%) received ARNI, 86 patients (59%) received beta-blockers, 75 patients (51%) were treated with MRA. 31 patients (21%) underwent cardiac resynchronization therapy (CRT) with a response rate of 64%. 24 patients (16%) underwent ICD implantation. **Conclusion:** Guideline-directed medical therapy is the first-line treatment for chronic HF patients who also have FMR. After this first-line approach, surgical or MitraClip transcatheter therapy can be considered in patients with persistent severe and symptomatic FMR in order to improve symptoms, quality of life and functional status.

Keywords: Functional Mitral Regurgitation Severity, Heart Failure, Reduced Ejection Fraction (HFrEF).

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1. BACKGROUND

The heart failure syndrome has first been described as an emerging epidemic about 25 years ago. Today, because of a growing and ageing population, the total number of heart failure patients still continues to rise (1-4). An estimated 64.3 million people are living with heart failure worldwide (5). Functional mitral regurgitation is a ventricular disease that occurs despite a structurally normal mitral valve (MV). LV dysfunction and remodelling lead to apical and posterior displacement of the papillary muscles causing leaflet

tethering and reduced closing forces (3, 6-8) Chronic heart failure (HF) is frequently accompanied by functional mitral regurgitation (FMR) caused by left ventricular (LV) remodelling and subsequent papillary muscle displacement resulting in mitral valve (MV) leaflet tethering, dilatation, and flattening of the mitral annulus and reduced closing forces (1, 7). With left chambers enlargement, the mitral annulus dilates and loses its saddle shape, resulting in increased mitral leaflet stress and failure of coaptation. LV desynchrony may be an additional mechanism of FMR due to wall motion abnormalities involving the papillary muscles, with further leaflet dysfunction and retraction. Isolated left atrial enlargement, generally associated with atrial fibrillation, may be an additional, though uncommon, cause of FMR due to annulus dilatation (7, 8, 10). Functional mitral regurgitation can be classified as having an ischaemic or non-ischaemic etiology, the former being the most common and occurring after myocardial infarction. Non-ischaemic FMR can be caused by idiopathic dilated cardiomyopathy, long-standing hypertension, and myocarditis. Functional mitral regurgitation is associated with HF symptoms, increased hospitalization rates and worse long-term prognosis of patients with chronic HF (1, 7, 8). However, it remains debated whether FMR is a central driving force of HF progression or rather a bystander, reflecting the severity of the disease.

2. OBJECTIVE

The purpose of this study was to assess the severity of functional mitral regurgitation (FMR) and its clinical implications in patients with chronic heart failure with reduced ejection fraction (HFrEF).

3. PATIENTS AND METHODS

We enrolled consecutive adult patients with HF with reduced ejection fraction (HFrEF) who presented to outpatient clinics. All patients underwent clinical and physical examination. Baseline examination included medical history, detailed assessment of current medication, electrocardiogram recording, transthoracic echocardiogram and comorbidities (chronic obstructive pulmonary disease, chronic kidney disease, hypertension or use of antihypertensive medications, and diabetes mellitus). Heart failure with reduced ejection fraction was defined in line with the new guidelines as history of HF signs and symptoms as well as a LV ejection fraction (LVEF) below 40%. Cardiovascular risk factors were recorded according to the respective guidelines. The extent of FMR was assessed at baseline and after a median follow-up period of 48 months in 146 consecutive chronic HFrEF patients (left ventricular ejection fraction <40%). Severe mitral regurgitation criteria based on 2D echocardiography was defined according to the ESC/EACTS Guidelines for the management of valvular heart disease. All of the patients received the heart failure (HF) medications in agreement with 2016 and 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Major adverse cardiac events

Demographics	
Age	63 ± 11
Male gender	91 (62%)
Female gender	55 (38%)
Risk factors	
Hypertension	115 (79%)
Obesity	81 (55%)
Dyslipidemia	105 (72%)
Current Smoking	68 (47%)
Family history for cardiovascular disease	86 (59%)
Comorbidity	
Diabetes Mellitus	75 (51%)
Atrial fibrillation	66 (45%)
Chronic renal failure	38 (26%)
Chronic obstructive pulmonary disease	29 (20%)
Peripheral vascular disease	84 (57%)
Heart Failure	
Ischemic etiology	91 (62%)
Prior hospitalization	78 (53%)
LVEF, %	25 ± 11
NYHA functional class >2	96 (66%)
Drugs and Devices	
ACEi/ARBs	129 (88%)
ARNI	17 (12%)
Beta-blockers	86 (59%)
MRA	75 (51%)
SGLT-2 inhibitors	14 (10%)
Digoxin	82 (56%)
Diuretics	106 (73%)
Nitrates	80 (55%)
NOACs	58 (40%)
ICD	24 (16%)
Cardiac resynchronization therapy (CRT)	31 (21%)

Table 1. Patient demographic, risk factors, clinical and comorbidity characteristics

were defined as a composite of all-cause death and the need for admission for HF.

Standard echocardiograms were performed using commercially available equipment (Epic-7, Philips and Vivid5 and Vivid7, GE-Healthcare). Cardiac morphology was assessed using diameters in standard four- and two-chamber views. Severe LV dilatation was defined as left ventricular end-diastolic diameter (LVEDD) ≥ 61 mm for women and ≥ 65 mm for men. Left ventricular ejection fraction was calculated using the biplane (A4C and A2C) Simpson method and/or dynamic heart model (DHM by Philips). Functional mitral regurgitation was graded quantitatively according to effective regurgitant orifice area (EROA (2D PISA, mm), Regurgitant volume (mL/beat) and Regurgitant fraction (%) and semiquantitatively according to vena contracta width (VC mm) pulmonary vein flow pattern, mitral inflow-peak E velocity and TVI mitral/TVI aortic. Systolic pulmonary artery pressures were calculated by adding the peak tricuspid

Variable	Grade I FMR (n = 45)	Grade II FMR (n = 34)	Grade III FMR (n = 40)	Grade IV FMR (n = 27)	P for trend
Age (years)	61.2 ± 11.4	59.8 ± 10.0	60.4 ± 9.8	57.9 ± 10.4	0.26
Men	30 (66.6)	23 (67.6)	22 (55.0)	16 (59.2)	0.831
NYHA Class I-II	36 (80.0)	18 (52.9)	28 (70.0)	14 (51.8)	
NYHA Class III-IV	9 (20.0)	16 (47.0)	12 (30.0)	13 (48.1)	<0.0001
Ischaemic etiology	24 (53.3)	27 (79.4)	23 (57.5)	17 (62.9)	0.742
Atrial fibrillation	18 (40.0)	14 (41.2)	19 (47.5)	15 (55.6)	0.094
Chronic kidney disease	10 (39.2)	7 (20.6)	13 (32.5)	8 (29.6)	0.884
COPD	4 (8.9)	7 (20.6)	10 (25.0)	8 (29.7)	0.347
Beta-blockers	29 (65.3)	20 (58.6)	22 (54.9)	15 (54.7)	0.048
ACEi/ARBs	40 (90.0)	29 (85.1)	37 (91.5)	23 (84.4)	0.655
MRA	35 (77.7)	22 (64.7)	33 (82.5)	25 (92.6)	0.637
ICD	5 (14.2)	7 (19.8)	7 (17.5)	5 (17.5)	0.544
CRT	4 (8.9)	6 (17.6)	8 (20.0)	5 (18.5)	0.903
LV EF (%)	31.7 ± 6.2	28.9 ± 7.7	27.5 ± 7.4	25.9 ± 6.1	<0.0001
LVEDD (mm)	65.2 ± 7.9	69.5 ± 8.1	70.6 ± 8.6	71.4 ± 9.3	<0.0001
LAD (mm)	43.3 ± 6.4	47.4 ± 7.8	48.5 ± 7.0	51.9 ± 6.5	<0.0001

Table 2. Baseline characteristics according to the degree of functional mitral regurgitation

regurgitation (TR) systolic gradient to the estimated central venous pressure.

The study population was categorized into 4 groups: patients with Grade I FMR, Grade II FMR, Grade III FMR, and Grade IV FMR. Comparisons across groups were performed by χ^2 test for categorical variables and analysis of variance (ANOVA) for continuous variables, and the P-value for trend is shown. Kaplan-Meier curves were constructed to display survival-free from death or admission during the follow-up hospitalization. Patients were censored at the time of death, admission.

4. RESULTS

The patient's demographic, risk factors, clinical and comorbidity characteristics are shown in Table 1. A total of 146 chronic HFrEF patients (mean age of 63 ± 11 years, 62% male, mean LVEF of $25 \pm 11\%$) of which 19% patients had severe FMR at baseline, with a mean EROA of 31.4 ± 2.7 mm and a mean Reg Vol of 45.9 ± 5.3 m. Patients with severe FMR were more likely to be male (59.2% vs 40.8%, $p = 0.026$) and to have atrial fibrillation (55.6% vs 44.4%, $p = 0.094$), a lower LVEF (25.9 ± 6.1 vs 28.1 ± 7.2 , $p = 0.001$), more dilated LV (LV end-diastolic diameter: 69.6 ± 12.4 vs 64.5 ± 8.9 P = 0.001), EROA was an independent predictor of the primary outcome (OR 1.23, 95% CI 1.08-1.54, $p = 0.039$) and patients with severe FMR had a lower survival free of events during the follow-up period (log-rank $p = 0.012$). Regarding HF therapy, 129 patients (88%) received RAAS antagonists, 17 patients (12%) received ARNI, 86 patients (59%) received beta-blockers, 75 patients (51%) were treated with MRA. 31 patients (21%) underwent cardiac resynchronization therapy with a response rate of 64%. 24 patients (16%) underwent ICD implantation.

During a median follow-up period of 4.2 (interquartile range (IQR) 3.1-5.8) years, the primary endpoint occurred in 52 (36%) patients (21 HF admissions, and 31 deaths). EROA showed independent prediction for the primary endpoint (HR 1.30 [1.05-1.57], $P=0.01$). There

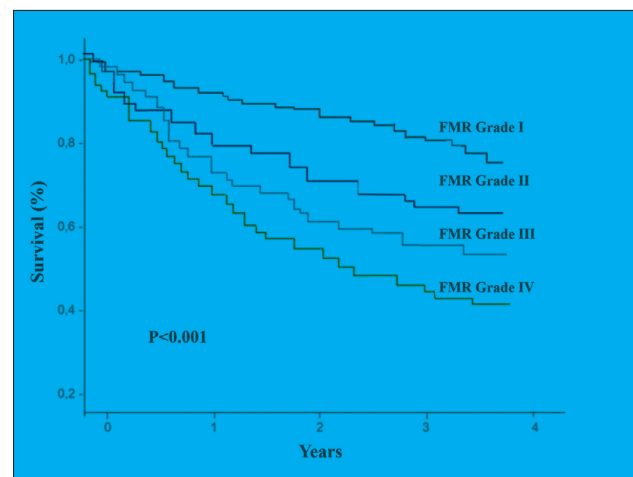


Figure 1. Kaplan-Meier curves shows event free survival according to the presence and severity of mitral regurgitation ($P < 0.001$). FMR: functional mitral regurgitation. Yellow line indicates patients with grade I functional mitral regurgitation, green line indicates patients with grade II functional mitral regurgitation, blue line indicates patients with grade III functional mitral regurgitation, and red line indicates patients with grade IV functional mitral regurgitation.

was a strong graded association between FMR and the long-term risk of death and hospitalization.

There was a significant interaction between FMR and NYHA functional class in predicting death or need for hospitalization, ($P < 0.0001$ for the interaction term FMR NYHA III-IV). Therefore, we stratified the patients into two groups: 96 patients with milder CHF severity (NYHA Class I-II) and 50 patients with advanced CHF symptoms (NYHA Class III-IV).

Among the 96 patients in NYHA I-II, 19 subjects died or hospitalized. Among the 50 patients in NYHA Class III-IV, 33 patients died or hospitalized. FMR was an independent predictor of events. Patients with grade III and IV of FMR were more likely to have a higher NYHA class, worse LV ejection fraction, larger left ventricles, and larger left atria. There was no difference in the prev-

alence of ischaemic etiology, previous history of myocardial infarction, atrial fibrillation at baseline. The baseline characteristics according to the degree of functional mitral regurgitation are shown in Table 2.

Throughout the follow-up, compared with those with Grade I FMR, patients with Grade II FMR had an almost 50% increased risk of dying or admission (unadjusted HR: 1.47, 95% CI: 0.93–2.35, $P = 0.107$), those with Grade III FMR had more than two-fold increased risk (unadjusted HR: 2.72, 95% CI 1.84–3.93, $P < 0.001$), and those with Grade IV FMR had more than three-fold increased risk (unadjusted HR: 3.48, 95% CI: 2.36–5.49, $P < 0.0001$).

There was a strong graded association between the presence and degree of FMR and risk of death or admission ($P < 0.0001$) at 4 years follow-up period, death or admission-free survival was $83.5 \pm 2.7\%$ in patients with Grade I FMR, $65.4 \pm 5.2\%$ in Grade II, $57.1 \pm 4.9\%$ in Grade III, and $44.7 \pm 5.8\%$ in Grade IV (Figure 1).

5. DISCUSSION

Functional mitral regurgitation (FMR) is frequently observed in patients with CHF and left ventricular (LV) systolic dysfunction. Echocardiography is the gold standard for the diagnosis of FMR. An integrative approach using different criteria (qualitative, semi-quantitative and quantitative) is recommended. Comprehensive and standardized 2D and 3D echocardiography is recommended as the key investigation for the assessment of FMR. As well as the determination of the LVEF in patients with heart failure (13–16).

CHF is one of the leading causes of death in western countries. Heart failure is frequently accompanied by FMR as a consequence of LV remodelling. The European, American and Japanese new guidelines have recently underscored the importance of the use of guideline-directed medical therapies (GDMT) for treatment of CHF (2–4). The management of symptomatic chronic HF patients with FMR includes GDMT and CRT according to guideline recommendations (2, 3). Pharmacologic therapy comprising of a combination of angiotensin receptor neprilysin inhibitors ACEi/ARBs or ARNI, beta blockers, mineralocorticoid receptor antagonists, SGLT-2 and diuretics represent the recommended pillars in the management of HF with reduced ejection fraction and severe MR (19, 20, 22). Improvement of diastolic LV performance and reduction of FMR severity have been reported with beta-blockers, ARNI and ACEi/ARBs (22, 23). Importantly, in all these studies, FMR improvement was observed in less than half of the population treated with GDMT. After this first-line approach, surgical or transcatheter therapy can be considered in patients with persistent severe and symptomatic FMR. These recommendations are based on trials and expert consensus and rely on the independent contribution of FMR to remodelling and outcome in HFrEF (17). Use of implantable cardiac defibrillators is recommended for primary prevention of sudden cardiac death in patients with previous myocardial infarction and LV systolic dysfunction. Use of cardiac resynchronization therapy among select-

ed patients with LV dysfunction and desynchrony manifested by widening of the QRS complex on electrocardiogram is known to improve secondary MR. Cardiac resynchronization therapy produces marked reductions in LVESD, LVEDD and MR severity amongst responders (26, 31, 35).

The degree of FMR correlated with the severity of LV remodelling and systolic dysfunction, as well as with the severity of symptoms. However, it is difficult to clarify the relative contributions of these variables to the pathogenesis of FMR and CHF (13–15).

Multiple studies provided evidence that FMR has a strong negative impact on clinical outcomes of HF patients. Sanino et al. published meta-analysis, including 53 studies and more than 45 000 patients with ischaemic and non-ischaemic cardiomyopathy, have shown that FMR was associated with an almost two-fold increased risk of all-cause and cardiac mortality and hospitalization due to HF (17).

Functional mitral regurgitation has been shown to have an independent prognostic value that is maintained also after adjustment for demographic, clinical and echocardiographic (i.e. LV end-diastolic diameter, LV function and tricuspid regurgitation) features, and that is correlated with MR severity. Moreover, FMR was found to have an independent prognostic role in specific subgroups of patients with an 'intermediate HF severity phenotype: New York Heart Association (NYHA) class II/III, LV ejection fraction (LVEF) 30–40% (10, 32, 33).

According to the recent valvular guidelines, a weak recommendation (Level of recommendation: Class IIb) exists for surgical intervention in patients with severely symptomatic grade 3 to 4+ secondary MR despite optimum guideline-directed management, treatment of coronary disease and cardiac resynchronization therapy (2, 3, 4). We have demonstrated that the presence and degree of FMR was associated with an almost linear increase in the risk of death or hospitalization at a mean follow-up of 4 years.

Treatment of secondary MR includes addressing concurrent conditions such as atherosclerotic coronary artery disease in the presence of LV dysfunction via percutaneous or surgical revascularization (28–30, 36–41).

6. CONCLUSION

Multimodal imaging and a comprehensive disease-based approach provide the best strategy to establish diagnosis and strategy treatment of heart failure patients with FMR. The management of symptomatic chronic HF patients with FMR includes GDMT and CRT according to guideline recommendations. Guideline-directed medical therapy is the first-line treatment for chronic HF patients who also have FMR. In addition to diuretics, which relieve symptoms, beta-blockers, angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs), or angiotensin receptor-neprilysin inhibitor (ARNI), mineralocorticoid receptor antagonists (MRA) and Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors are recommended for all symptomatic patients with HFrEF. After this first-

line approach, surgical or MitraClip transcatheter therapy can be considered in patients with persistent severe and symptomatic FMR in order to improve symptoms, quality of life and functional status in HF patients. Despite advances in medical therapy and cardiac resynchronization therapy (CRT), outcomes of heart failure (HF) patients remain poor.

Since GDMT can result in improvement in LVEF and reverse remodelling in patients with HFrEF, the trajectory of improvement and recovery of EF has been of interest to determine the types (e.g., device, medical, advanced) and duration of treatment.

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