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ORIGINAL RESEARCH

Severity of Functional Mitral Regurgitation on Admission for Acute Decompensated Heart Failure Predicts Long-Term Risk of Rehospitalization and Death

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BACKGROUND: Functional mitral regurgitation (FMR) has emerged as a therapeutic target in patients with chronic heart failure and left ventricular systolic dysfunction. The significance of FMR in acute decompensated heart failure remains obscure. We systematically investigated the prevalence and clinical significance of FMR on admission in patients admitted with acute decompensated heart failure and left ventricular systolic dysfunction.

METHODS AND RESULTS: The study was a single-center, retrospective review of patients admitted with acute decompensated heart failure and left ventricular systolic dysfunction between 2012 and 2017. Patients were divided into 3 groups of FMR: none/mild, moderate, and moderate-to-severe/severe FMR. The primary outcome was 1-year post-discharge all-cause mortality. We also compared these groups for 6-month heart failure hospitalization rates. Of 2303 patients, 39% (896) were women. Median left ventricular ejection fraction was 25%. Four hundred and fifty-three (20%) patients had moderate-to-severe/severe FMR, which was independently associated with 1-year all-cause mortality. Moderate or worse FMR was found in 1210 (53%) patients and was independently associated with 6-month heart failure hospitalization. Female sex was independently associated with higher severity of FMR.

CONCLUSIONS: More than half of patients hospitalized with acute decompensated heart failure and left ventricular systolic dysfunction had at least moderate FMR, which was associated with increased readmission rates and mortality. Intensified post-discharge follow-up should be undertaken to eliminate FMR amenable to pharmacological therapy and enable timely and appropriate intervention for persistent FMR. Further studies are needed to examine sex-related disparities in FMR.

Key Words: acute decompensated heart failure ■ functional mitral regurgitation ■ sex-related disparities

Mitral regurgitation (MR) is the most common valvular heart disorder with an estimated prevalence of ≈1.7% in the United States, further increasing to ≈9.3% in those over 75 years of age.[1] Mitral regurgitation has traditionally been classified as primary or degenerative, when the principal defect lies in the anatomy of the mitral valve apparatus itself and secondary or functional, when the abnormality lies in the left ventricle or perhaps the left atrium and annulus.[2,3] Functional mitral regurgitation (FMR) is more common than degenerative MR and has been studied mostly in chronic stable heart failure.[1,4–9] The COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial was the first to demonstrate a reduction in all-cause

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CLINICAL PERSPECTIVE

What Is New?

- More than half of all patients presenting with acute decompensated heart failure have at least moderate functional mitral regurgitation.
- Presence of higher severity functional mitral regurgitation on admission for acute decompensated heart failure bears long-term prognostic significance.
- Female sex is associated with increased odds of higher severity functional mitral regurgitation.

What Are the Clinical Implications?

- The detection of higher severity mitral regurgitation during heart failure admission should trigger intensified postdischarge follow-up with particular emphasis on optimization of guideline-directed medical therapy.
- Reassessment of mitral regurgitation and functional status should occur once comprehensive medical therapy has been optimized to allow appropriate and timely evaluation for device-based heart failure therapies.
- Further studies are needed to examine the sex-related disparities in functional mitral regurgitation.

Nonstandard Abbreviations and Acronyms

ADHF	acute decompensated heart failure
FMR	functional mitral regurgitation
GDMT	guideline-directed medical therapy
HFH	heart failure hospitalizations
LVSD	left ventricular systolic dysfunction
MR	mitral regurgitation
PH	proportional hazards
TTE	transthoracic echocardiogram

mortality as well as heart failure hospitalizations (HFH) following a reduction in FMR severity with use of percutaneous transcatheter edge-to-edge repair of the mitral valve.[10] FMR has since been regarded as a therapeutic target in patients with chronic heart failure.

Although we have advanced our understanding of FMR in chronic heart failure, there still remains a paucity of data pertaining to FMR in the setting of acute decompensated heart failure (ADHF).[11–14] Patients presenting with ADHF are in a state of increased ventricular loading conditions[15] and it remains unclear whether FMR in this setting is simply a marker of preload and after-load mismatch or if it also carries any long-term prognostic significance. Notably, FMR in the setting of ADHF is highly susceptible to pharmacological optimization.[16]

Accordingly, we sought to systematically investigate the prevalence and prognostic significance of FMR at the time of admission in a cohort of 2303 patients hospitalized with ADHF and left ventricular systolic dysfunction (LVSD) defined as left ventricular ejection fraction (LVEF) of 50% or less.

METHODS

Disclosure

The data, analytic methods, and study materials used in this study will not be made available to other researchers.

Study Design

A retrospective review of patients admitted to Montefiore Medical Center between January 1, 2012 and December 31, 2017 with a diagnosis of ADHF (using *International Classification of Diseases, Ninth Revision* [*ICD-9*] and *Tenth Revision* [*ICD-10*] codes-428, 428:21, 428:22, 428:23, 428:40, I50.9, I50.21, I50.23, I50.41), and LVSD (defined as LVEF <50% on a transthoracic echocardiogram (TTE) performed on admission), was conducted. Baseline demographic, clinical, laboratory, and echocardiographic data were manually retrieved from the electronic medical record system of Montefiore Health system, the largest health care provider in Bronx, New York, with an integrated electronic medical record shared by all its campuses. The investigational review board for Montefiore Medical Center/Albert Einstein College of Medicine approved the study protocol. Given the retrospective nature of this study, informed consent was not required.

The primary outcome was 1-year post-discharge all-cause mortality. We also compared the 3 groups of FMR for 6-month HFH rates.

Study Population

All patients aged 18 years or above were eligible for inclusion. Patients were excluded if they did not have a TTE performed within the first 72 hours of index admission or if upon review their TTE showed LVEF of >50% or if it was an incomplete or poor-quality study. We based our LVEF cutoff on the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial inclusion criteria. We did so to include all patients who could be candidates for contemporary transcatheter edge-to-edge repair, if appropriate.

Other exclusion criteria included patients with repaired/unrepaired congenital heart disease, rheumatic heart disease with involvement of the mitral valve, degenerative mitral valve disease, evidence of prior mitral valve

surgery or transcatheter mitral valve procedure, a left ventricular assist device, or orthotopic heart transplant. To avoid inclusion of acute ischemic mitral regurgitation, we excluded patients who underwent coronary revascularization during index admission.[17] To preclude undue confounding from abnormal volume status not primarily due to heart failure, we also excluded patients with end-stage renal disease on renal replacement therapy.

Echocardiographic Analysis of FMR

We used the electronic medical record to obtain clinical reports of the previously interpreted TTE from each patient's index admission. All TTE readers at our institution follow the American Society of Echocardiography guidelines.[18]

FMR grading was based on a validated multi-integrative method and classified from grade 0 to grade 4 as per American Society of Echocardiography guidelines.[18] In our laboratory, disagreements regarding FMR grading are routinely adjudicated by 2 senior echocardiographers (C.T. and M.J.G). The study cohort was categorized into 3 groups based on FMR severity noted on their index admission TTE report: none/mild (grade 0 and 1), moderate (grade 2), and moderate-to-severe/severe FMR (grade 3 and 4).

Outcomes Assessment

We used the electronic medical record to determine survival status at 1 year as well as to detect HFH using the same *ICD* codes listed previously.

Patients who died during index hospitalization, were discharged to hospice care, had no follow-up with our health care system after index admission, or who underwent advanced heart failure therapies or mitral valve interventions (repair/replacement) during index admission were excluded from all time-to-event analyses. Patients who underwent advanced heart failure therapies (left ventricular assist device implant or heart transplant) or mitral valve interventions during follow-up period were censored on the date of the procedure, as these procedures would be considered definitive treatments for FMR.

Statistical Analysis

Continuous data are displayed as median (interquartile range 25%, 75%) and were compared using the Kruskal-Wallis rank test. A post hoc Dunn test for pairwise comparison was also performed. Categorical data are shown as absolute numbers (percentage) and were compared using the chi-square test unless otherwise specified. Generalized ordered logistic regression models were used to identify independent predictors of higher FMR severity.

One-year postdischarge all-cause mortality was presented using Kaplan-Meier analysis and compared using log-rank test for trends followed by multivariable Cox proportional hazards regression analysis. Variables with more than one-third missing data points were excluded from this analysis. Variables that have shown to influence outcomes after discharge were examined in a univariate analysis: age, sex, etiology of cardiomyopathy, NT-proBNP (N-terminal pro-B-type natriuretic peptide) level on admission, diabetes, atrial fibrillation, predischarge creatinine, presence of chronic resynchronization therapy device, guideline-directed medical therapy (GDMT) at discharge (beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, diuretics, and angiotensin receptor neprilysin inhibitors) and echocardiographic parameters (left ventricular ejection fraction, left ventricle internal diameter at end diastole and at end systole, left atrial diameter, mitral valve E max velocity).[12,14] The purposeful selection of variables methods was then used.[19] Variables with a univariate $P<0.2$ were entered into an initial model after which a reduced model was derived with all covariates with a $P<0.05$. Variables included in the final model were age, etiology of cardiomyopathy being non-ischemic, NT-proBNP per 1000 units, and beta blocker, angiotensin-converting enzyme inhibitors, and angiotensin receptor blocker prescription on discharge. We performed an objective analysis of the proportional hazards (PH) assumption based on the Schoenfeld residuals with a *P-value* >0.1 suggesting that PH assumption is reasonable and a *P*-value of <0.05 suggesting that PH assumption was violated. Results of the final model are presented as hazard ratios (HR) with 95% CIs.

When analyzing HFH, since death after discharge from index admission but before HFH could be a competing event with HFH, we used competing events regression to estimate the cumulative incidence of HFH after index admission.[20,21] A multivariable competing risk regression was performed and variables included were chronic kidney disease, etiology of cardiomyopathy (non-ischemic), NT-proBNP per 1000 units, and angiotensin-converting enzyme inhibitor prescription on discharge. All statistical analyses were performed using commercially available software (Stata/SE 15.0, StataCorp, College Station, TX).

RESULTS

We found 2748 unique admissions for ADHF with LVSD during the study period. Of these, 445 were excluded based on the study exclusion criteria (Figure 1). Of the 2303 patients included in the study cohort, 1407 (61%) were men. With regard to MR severity, 1093 (47%) had none/mild FMR, 757 (33%) had moderate FMR, and 453 (20%) had moderate-to-severe/severe FMR (Figure 1). As such 53% of patients had moderate or worse FMR.

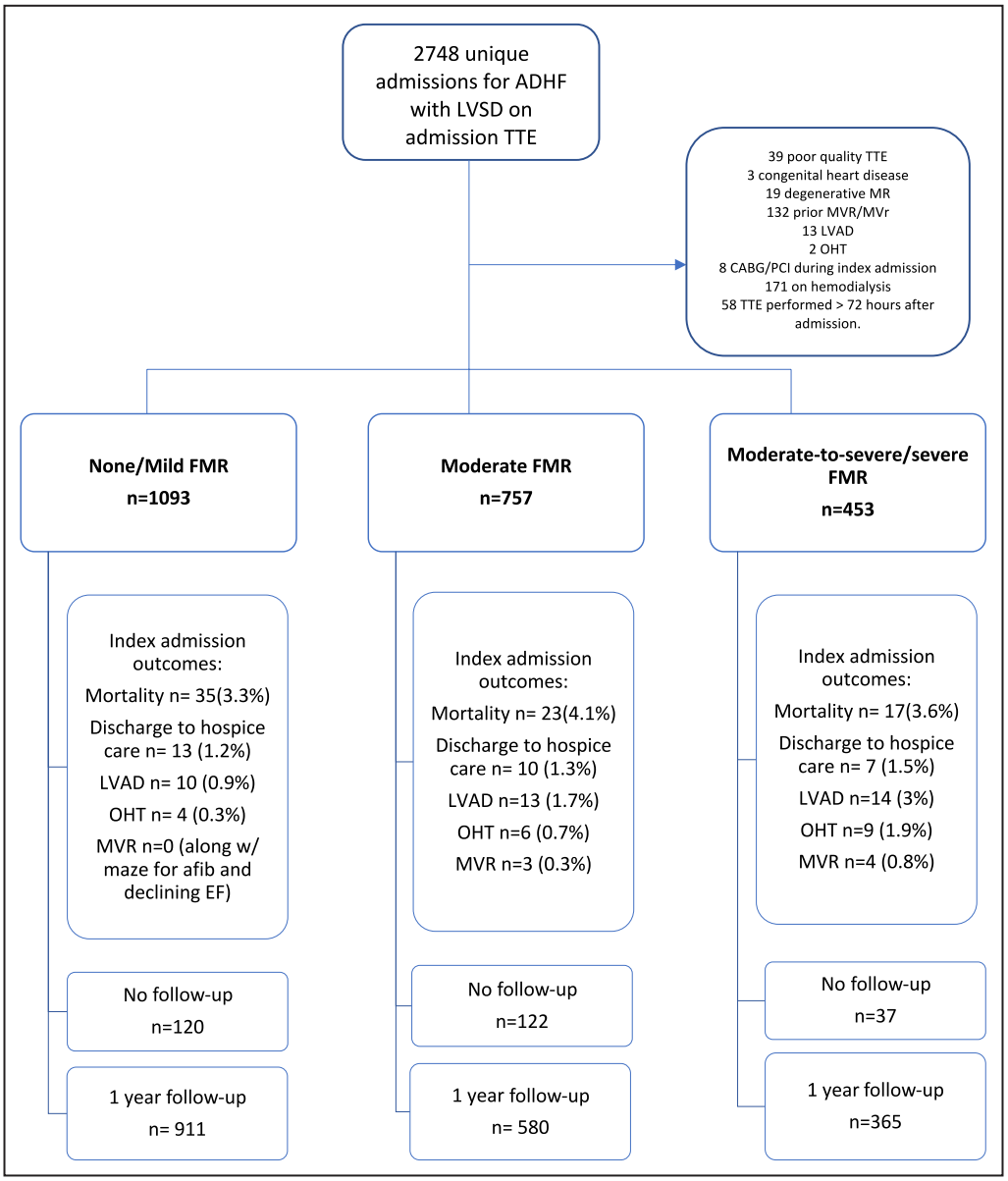

Figure 1. Flow chart depicting study cohort selection.
Flow diagram depicting selection of study cohort after application of predefined exclusion criteria followed by classification of all patients into 3 groups based on functional mitral regurgitation severity. Also summarizing exclusion criteria applied based on outcomes at discharge from index admission, including those who had no postdischarge follow-up. All remaining patients were included in time-to-event analyses. ADHF indicates acute decompensated heart failure; CABG, coronary artery bypass graft; FMR, functional mitral regurgitation; LVAD, left ventricular assist device; LVSD, left ventricular systolic dysfunction; MR, mitral regurgitation; MVR, mitral valve repair/replacement; OHT, orthotopic heart transplant; PCI, percutaneous coronary intervention; and TTE, transthoracic echocardiogram.

Baseline Characteristics

Baseline demographics as well as clinical, laboratory, and echocardiographic data of different FMR groups are detailed in Table 1, with post hoc pairwise comparisons for continuous variables depicted in Figure 2.

Patients with higher severity (moderate or moderate-to-severe/severe) FMR were older, had higher NT-proBNP levels on admission, and were more likely to be female (Figure 3, Table S1) and to have atrial fibrillation and diabetes when compared with patients with none/mild FMR (Table 1). There were no significant differences in the prevalence of chronic kidney disease between the moderate-to-severe/severe, moderate, and none/mild FMR groups, respectively (Table 1). A significantly greater percentage of patients in the moderate-to-severe/severe FMR group had a cardiac

Table 1. Baseline Clinical Characteristics and Laboratory and Echocardiographic Parameters of Patients in the 3 Groups of FMR

	None/mild FMR (n=1093)	Moderate FMR (n=757)	Moderate-to-severe/ severe FMR (n=453)	*P* value
Age, y (IQR)	65 (54, 76)	68 (57, 80)	68 (57, 79)	<0.001
Female sex, n (%)	371 (34)	320 (42)	205 (45)	<0.001
Ethnicity, n (%)				
Hispanic	301 (28)	210 (28)	150 (33)	0.18
Non-Hispanic	660 (60)	467 (61)	250 (55)	
Unknown	132 (12)	80 (11)	53 (12)	
Race, n (%)				
Black	422 (39)	303 (40)	182 (40)	0.36
White	214 (20)	154 (20)	68 (15)	
Asian	19 (2)	9 (1)	6 (1)	
Other (American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander)	333 (30)	221 (30)	151 (33)	
Unknown	105 (9)	70 (9)	46 (11)	
Mean arterial pressure, mm Hg (IQR)*	93 (82, 104)	93 (82, 103)	90 (81, 101)	0.03
Creatinine, mg/dL (IQR)	1.24 (1, 1.7)	1.3 (1, 1.7)	1.29 (0.98–1.7)	0.49
N-terminal pro-B-type natriuretic peptide, pg/mL (IQR)	4886 (2160, 10 553)	6599 (3367, 14 269)	7000 (3300, 14 200)	<0.001
Left ventricular ejection fraction, % (IQR)	30 (25, 35)	25 (20, 35)	25 (20, 30)	<0.001
Left ventricular end diastolic volume index†, cm^3/m^2 (IQR)	80 (65, 98)	80 (66, 104)	96 (79, 120)	<0.001
LVID at end-diastole, cm (IQR)	5.7 (5.1–6.2)	5.9 (5.2, 6.4)	6.1 (5.5, 6.8)	<0.001
LVID at end-systole, cm (IQR)	4.7 (4–5.5)	5.0 (4.3, 5.7)	5.2 (4.6, 6)	<0.001
Left atrial diameter, cm (IQR)	4.4 (4, 4.9)	4.6 (4.2, 5)	4.8 (4.4, 5.3)	<0.001
Right ventricular systolic pressure†, mm Hg (IQR)	46 (38, 55)	50 (41, 57)	52 (45, 60)	<0.001
MV inflow E wave velocity, cm/s (IQR)	90 (71, 108)	101 (82, 117)	112 (94, 129)	<0.001
MV A max† velocity, cm/s (IQR)	65 (44, 87)	61 (44, 81)	62 (47, 83)	0.25
E/A† (IQR)	1.3 (0.88, 2)	1.49 (1.48, 1.5)	1.74 (1.35, 2.4)	<0.001
Atrial fibrillation, n (%)	228 (21)	182 (24)	129 (28)	0.005
Diabetes, n (%)	176 (16)	305 (40)	178 (39)	<0.001
Chronic kidney disease, n (%)	233 (21)	176 (23)	84 (19)	0.154
Nonischemic cardiomyopathy, n (%)	586 (54)	307 (41)	294 (65)	<0.001
Severe tricuspid regurgitation, n (%)	50 (5)	63 (8)	83 (18)	<0.001
Cardiac resynchronization therapy device, n (%)	73 (7)	75 (10)	51 (11)	0.005

FMR indicates functional mitral regurgitation; IQR, interquartile range; LVID, left ventricular internal diameter; and MV, mitral valve.
*Measured on the day of index admission.
†More than one-third missing data points.

resynchronization therapy device in place at the time of index admission when compared with patients with moderate and none/mild FMR, respectively (Table 1).

Using generalized ordered logistic regression analysis, female sex was associated with significantly increased odds of presence of moderate-to-severe/severe FMR (odds ratio, 1.81; 95% CI, 1.49–2.19; *P*<0.001; Table S2). There were no significant racial or ethnic differences between the FMR groups (Table 1).

Echocardiographic Parameters

Patients with moderate-to-severe/severe FMR were found to have larger left ventricular chamber sizes (diameter at end-diastole 6.1 cm versus 5.9 cm versus 5.7 cm, *P*<0.001, diameter at end-systole 5.2 cm versus 5 cm versus 4.7 cm, *P*<0.001), lower LVEF (25% versus 25% versus 30%, *P*<0.001) and higher median mitral valve inflow E wave velocities (112 cm/s versus 101 cm/s versus 90 cm/s, *P*<0.001) when compared with patients with moderate and none/mild FMR, respectively (Table 1, Figure 2).

Notably, patients with moderate-to-severe/severe FMR were also more likely to have severe tricuspid regurgitation (Table 1).

Seventy-five (3.3%) patients died during the index hospitalization and 30 patients (1.3%) were discharged

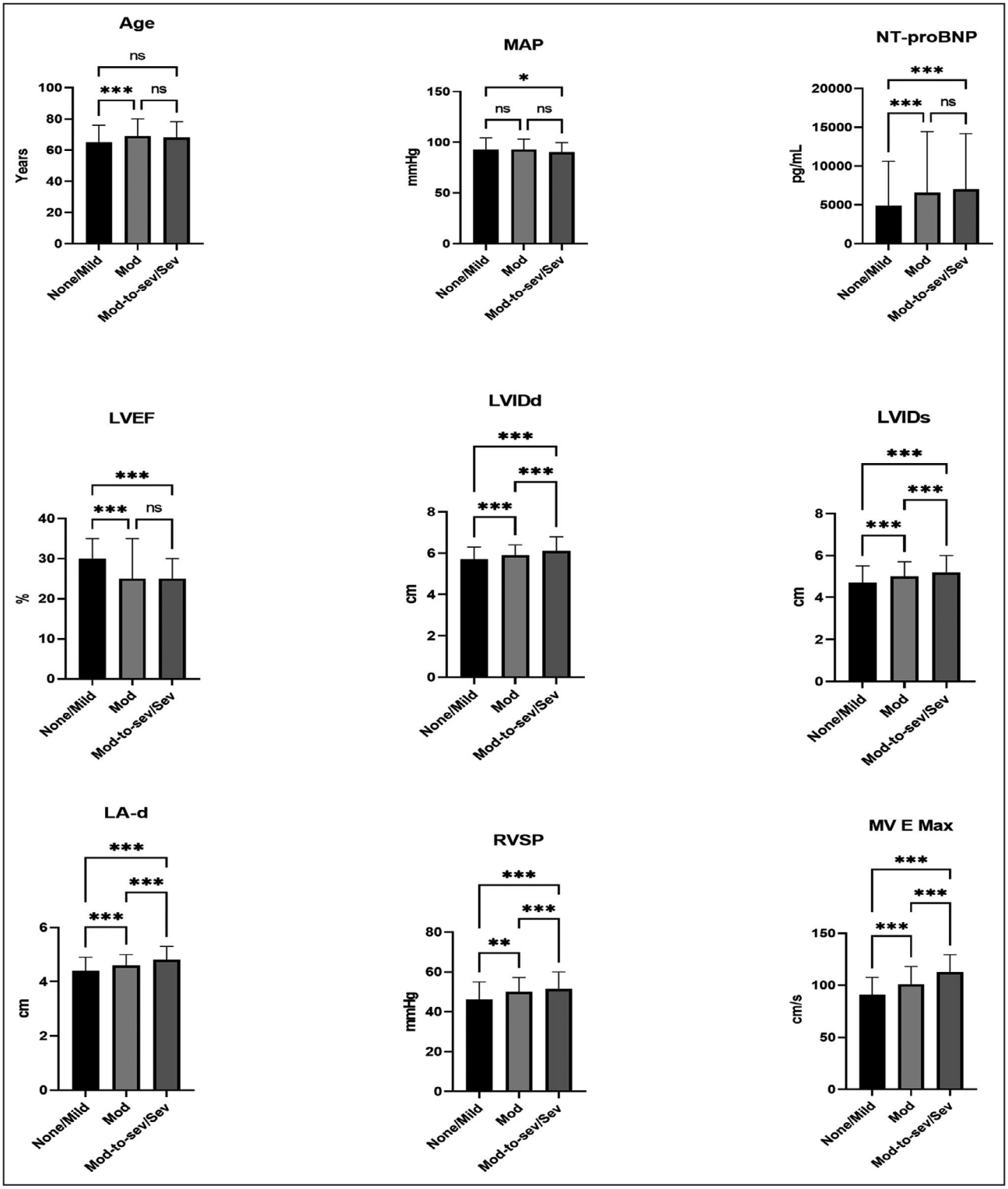

Figure 2. Pairwise comparisons for continuous variables using post hoc Dunn test across 3 groups of functional mitral regurgitation.

Pairwise comparisons of continuous variables across 3 groups of functional mitral regurgitation using post hoc Dunn test. LA-d indicates left atrial diameter; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal diameter at end-diastole; LVIDs, left ventricular internal diameter at end-systole; MAP, mean arterial pressure; Mod, moderate; Mod-to-sev/Sev, moderate-to-severe/severe; MV E max, mitral valve maximum E velocity; NT-proBNP, N-terminal pro B-type natriuretic peptide; and RVSP, right ventricular systolic pressure. ns: not significant or $P \geq 0.05$; *:P <0.05 to 0.01; **:P <0.01 to 0.001, significant; ***:P<0.0.001, significant.

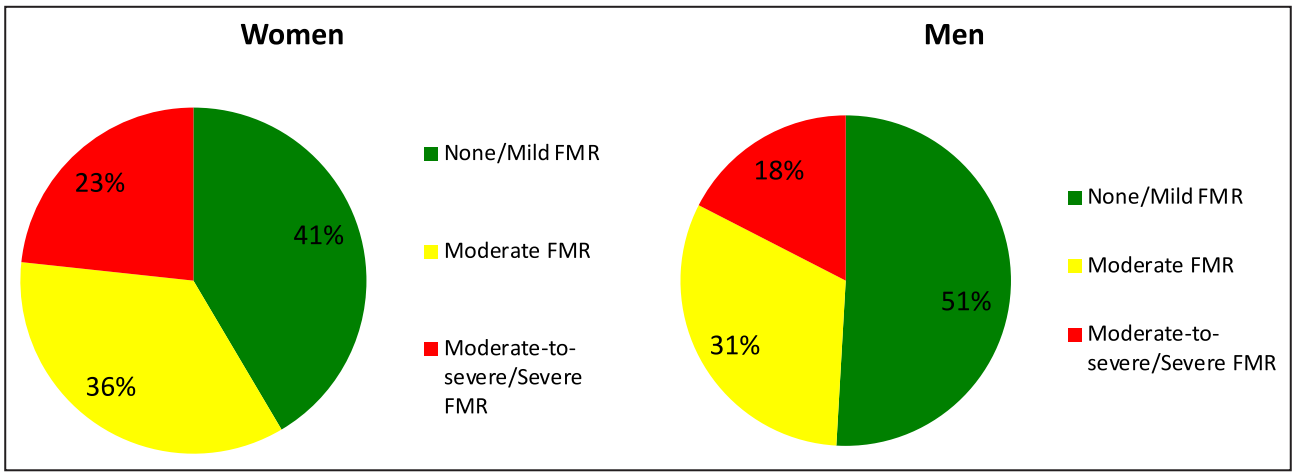

Figure 3. Sex distribution of functional mitral regurgitation.
Figure depicting distribution of functional mitral regurgitation severity among females vs males. Females were more likely to have moderate-to-severe/severe FMR (24% vs 18%, *P*<0.001). FMR indicates functional mitral regurgitation.

to hospice care. These patients were excluded from time-to-event analyses (Figure 1).

Thirty-seven (1.6%) patients received a left ventricular assist device, 19 (0.8%) underwent orthotopic heart transplant, and 7 (0.3%) underwent mitral valve repair/replacement (Figure 1) during index admission and were excluded from further analyses.

We looked for prescriptions of GDMT and found no significant differences in the discharge prescription rates of beta- blockers or angiotensin-converting enzyme inhibitors/angiotensin receptor blockers between the 3 FMR groups (Table 2). However, patients with higher severity of FMR on index admission were more likely to receive a discharge prescription of diuretics (*P*<0.01) and mineralocorticoid receptor antagonists (*P*=0.009). Angiotensin receptor neprilysin inhibitors were only prescribed to 2 patients in our cohort. Similarly, a small percentage of patients in all 3 groups were prescribed the combination of hydralazine-isosorbide dinitrate.

Post-discharge Outcomes

Two hundred and seventy-nine (12%) patients had no further follow-up with our health care system after discharge from index admission and were excluded from further analyses (Figure 1). Importantly, the rate of such loss to follow-up was similar between the none/mild and moderate-to-severe/severe FMR groups (13% versus 10%, *P*=0.18).

During follow-up, 4.5% patients in the moderate-to-severe/severe FMR group received cardiac resynchronization therapy device implant compared with 4.5% in the moderate FMR group and 4.9% patients in the none/mild FMR group (*P*=0.9). Two patients received a left ventricular assist device and 3 underwent mitral valve repair/replacement during the follow-up period and were censored on the day of the procedure.

One-year all-cause mortality was 13.4% in patients with moderate-to-severe/severe FMR, 13.2% in patients with moderate FMR, and 9.8% in patients with none/mild FMR (unadjusted log-rank test for trends *P*=0.036, Figure 4). After adjusting for covariates, the relative risk

Table 2. Guideline-Directed Medical Therapy Prescribed at Discharge Was Comparable Between the 3 Groups of FMR Except in Case of Diuretics

Discharge medications	None/mild FMR (n=911)	Moderate FMR (n=580)	Moderate-to-severe/ severe FMR (n=365)	*P* value
Beta-blockers, n (%)	793 (89)	519 (93)	325 (90)	0.3
Angiotensin-converting enzyme inhibitors, n (%)	508 (72)	312 (72)	217 (75)	0.2
Angiotensin receptor blockers, n (%)	134 (15)	87 (15)	51 (14)	0.9
Angiotensin receptor neprilysin inhibitors, n (%)	2 (0.2)	0 (0)	0 (0)	0.3
Mineralocorticoid receptor antagonists, n (%)	228 (26)	164 (31)	122 (33)	0.009
Diuretic, n (%)	711 (81)	496 (89)	313 (88)	<0.001
Isosorbide dinitrate/hydralazine, n (%)	57 (6.5)	49 (8.3)	18 (5)	0.08

FMR indicates functional mitral regurgitation.

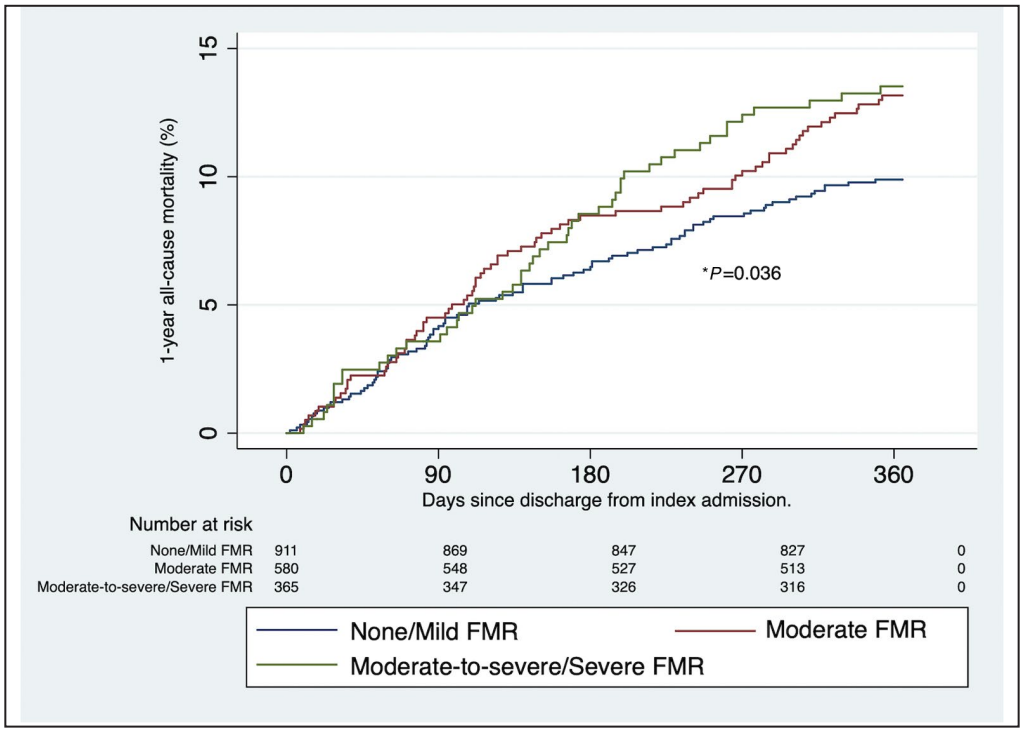

Figure 4. Kaplan-Meier failure curves showing 1-year all-cause mortality across the 3 groups of functional mitral regurgitation.
Test of proportional hazards assumption based on Schoenfeld residuals, *P*=0.2696. Kaplan-Meier failure curve showing estimates of 1-year all-cause mortality across 3 groups of FMR. There was a statistically significant increase in mortality with increasing severity of FMR. FMR indicates functional mitral regurgitation. **P* value was computed using log-rank test for trends.

for all-cause mortality in the first year after admission remained 45% higher for patients with moderate-to-severe/severe FMR on admission compared with those with none/mild FMR (Model 1. HR, 1.45; 95% CI, 1.001–2.08; *P*=0.049; Table S3). Despite graphical representation suggesting otherwise, a test of the PH assumption (based on Schoenfeld residuals) showed that the PH assumption was not violated (*P*=0.2696).

Rates of 6-month HFH were 37% for patients with moderate-to-severe/severe FMR, 39% for patients with moderate FMR, and 33% for patients with none/mild FMR (unadjusted *P*=0.045) (Figure 5). Moderate-to-severe/severe FMR was associated with 25% higher relative risk of HFH when compared with none/mild FMR in a multivariable competing risk regression model (HR, 1.25; 95% CI, 1.006–1.55; *P*=0.043) and moderate FMR was associated with 24% higher relative risk of HFH compared with none/mild FMR (HR, 1.24; 95% CI, 1.03–1.49; *P*=0.02) (Table S4).

Sensitivity Analysis

Given that our study focuses on FMR diagnosed on admission for ADHF, we performed a sensitivity analysis wherein we combined index in-hospital mortalities (n=75) with those that occurred after discharge from index admission (n=215) and found that the relative risk of 1-year all-cause mortality for patients with moderate-to-severe/severe FMR remained significantly greater than for patients with none/mild FMR after adjusting for relevant clinical variables (HR, 1.38; 95% CI, 0.99–1.9; *P*=0.05, Table S5).

DISCUSSION

We examined the prevalence of varying degrees of FMR and their prognostic impact in a large contemporary cohort of patients who presented with ADHF and LVSD. Our principal findings are as follows: (1) the prevalence of moderate or greater FMR was found to be 53%, with 20% of all patients having moderate-to-severe/severe FMR; (2) moderate-to-severe/severe FMR was found to be independently associated with increased 1-year all-cause mortality; and (3) both moderate and moderate-to-severe/severe FMR on index hospitalization were independently associated with increased 6-month rehospitalization rates for HF.

Contemporary evidence suggests a role for novel therapies in mitigating the adverse impact of FMR and

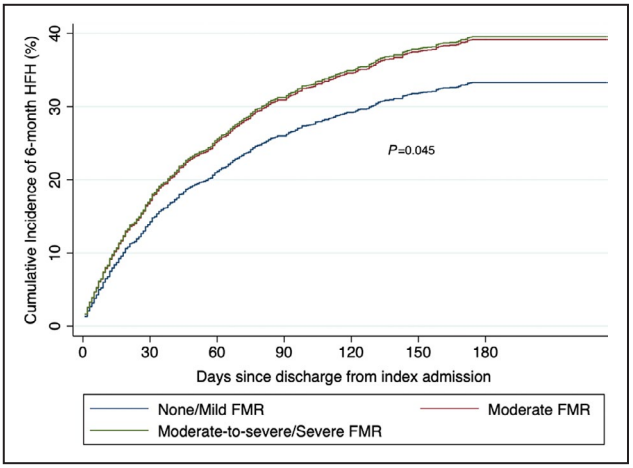

Figure 5. Competing risk regression curves showing cumulative incidence of 6-month heart failure hospitalizations across 3 groups of functional mitral regurgitation.

Competing-risks regression curves showing a statistically significant difference in the cumulative incidence of 6-month heart failure hospitalizations across 3 groups of FMR. Death before rehospitalization was regarded as a competing event. FMR indicates functional mitral regurgitation; and HFH, heart failure hospitalizations.

there is a renewed interest in the early identification and characterization of patients with FMR who may be appropriate candidates for such therapies.[22] However, much of our current understanding of FMR is based on studies of patients with chronic heart failure.[13] Very little is known about prevalence and long-term prognostic significance of FMR in ADHF.[12,13,23]

We found that, on admission for ADHF, 53% of our cohort had moderate or moderate-to-severe/severe FMR. Prior studies of FMR in ADHF report a prevalence of moderate or greater FMR ranging from 36% to 45%.[13,14,23] Of note, only one of these studies looked at FMR at the time of admission for ADHF,[23] whereas the others report the prevalence of FMR at varying time points during the admission, that is, after clinical stabilization or before discharge,[13,14] potentially explaining the higher burden of FMR observed in our cohort where all echocardiograms were performed within 72 hours of presentation. FMR grading at our institution was based on the American Society of Echocardiography guidelines throughout the duration of this study.[18,24] This is important to note because the American Heart Association guidelines changed their recommendations for FMR grading in 2014[25] and again in 2017[26]; our findings were not influenced by these changes.

The presence of moderate-to-severe/severe FMR on admission for ADHF was independently associated with 1-year all-cause mortality. This finding is in line with a very recent "real world" report from the ARIC (Atherosclerosis Risk in Communities) study registry also showing that higher severity of mitral regurgitation during an admission for ADHF was associated with increased 1-year mortality in patients with LVEF <50% and over 55 years of age.[14] However, this study did not distinguish the different etiologic types of MR (degenerative versus rheumatic versus functional MR), it included patients on hemodialysis and it could not establish the timing of the echocardiogram used to determine MR severity in relation to the admission for ADHF.

Finally, we report that the presence of moderate or greater FMR on admission for ADHF was independently associated with significantly increased rates of 6-month HFH suggesting that the prognostic importance of significant FMR (moderate or greater) on admission for ADHF may be likened to that of a predischarge NT-proBNP and its presence should guide treatment and followup strategies.[27,28] Although prior studies in patients with chronic heart failure have established that HFH per se is associated with increased morbidity and mortality after discharge,[29] we now demonstrate that this adverse trajectory is *further* worsened by the presence of severe FMR when presenting for HFH.

Collectively, our findings inform that higher severity (moderate or moderate-to-severe/severe) FMR is highly prevalent in patients presenting with ADHF and bears long-term prognostic significance. As such, an admission for ADHF could provide an excellent opportunity for early identification and characterization of patients according to FMR severity to then enable timely interception of its course.[30] Closer follow-up after discharge, including prompt initiation and optimization of novel drug therapies that have shown promise for left ventricular reverse remodeling, such as angiotensin receptor-neprilysin inhibitors[31–33] and SGLT2 (sodium-glucose cotransporter 2) inhibitors,[34] followed by timely and imaging-guided evaluation of residual or persistent FMR, possibly guided by a heart failure specialist, should be the new norm. This approach (except use of SGLT2-inhibitors) is now a Class 1 recommendation in the recently published 2020 American College of Cardiology/American Heart Association guidelines for the management of valvular heart disease.[35] In contrast to the 2017 guidelines,[26] the 2020 guidelines also provide a class 2a, recommendation for percutaneous mitral edge-to-edge repair in patients with chronic FMR, LVSD, and persistent symptoms despite optimal GDMT. Therefore, as our understanding of FMR continues to evolve, a heart team approach—including a heart failure specialist—is increasingly important.[36,37]

Lastly, an intriguing observation in our cohort was that of sex disparities between the groups of FMR. Women made up a significantly larger proportion of all patients with moderate-to-severe/severe FMR

as compared with other groups of FMR. When we compared women and men, 23% of all women had moderate-to-severe/severe FMR compared with 17% of all men and the independent association of female sex with severe FMR was confirmed on multivariable logistic regression. This finding of increased rate of higher severity FMR in women, also observed in the publication examining weighted samples from the ARIC study cohort mentioned previously,[14] is interesting yet at most hypothesis generating at this time. Pending validation in prospective trials, one might speculate that sex-specific diastolic function (with women being more likely to suffer from heart failure with preserved ejection fraction)[38] or different pliability of the mitral annulus could account for this finding.[39] Observational studies have shown that women are more likely to have rheumatic mitral valve disease[40,41]; however, we carefully excluded all cases of rheumatic heart disease. Women are historically underrepresented in clinical trials[42] and our findings should encourage further systematic evaluation of the sex differences in FMR.

Study Limitations

Our study, despite its very large sample size, has the limitations of a retrospective investigation. Most of the patients in our cohort are from Bronx borough where Montefiore Health system has extensive coverage but we are unable to fully account for HFH to hospitals outside our health care system. We included patients with TTEs performed within 72 hours of admission to account for patients admitted on the weekend because complete, protocol-guided TTE exams are not routinely performed on all patients admitted on weekends at our institution. In order to ensure that FMR severity was not simply a reflection of underlying disease severity, we performed a rigorous adjustment analysis to account for all possible confounders. Missing data in our cohort were limited to 3 variables, as indicated in Table 1: left ventricle end diastolic volumes, right ventricular systolic pressure, and mitral valve inflow maximum A velocity. These data were missing at random. We used left ventricular internal diameters in lieu of volumetric measurements. With regard to right ventricular systolic pressure, 20% of our cohort had severe tricuspid regurgitation, thereby precluding measurement of right ventricular systolic pressure. As such, we used presence or absence of severe tricuspid regurgitation and not right ventricular systolic pressure in the final model. As for mitral valve inflow maximum A velocity, this has not been shown to be associated with mitral valve regurgitation. Results of 1-year mortality are presented in the form of unadjusted Kaplan-Meier failure curves show significant crossing of curves. To supplement this, we performed an adjusted Cox proportional hazards model and ensured that the PH assumption was not violated. Finally, although we did have information about guideline directed medical therapy prescribed at discharge from index admission, we did not collect data pertaining to follow-up visits, outpatient titration of GDMT, and follow-up echocardiograms. We also did not ascertain the chronicity of heart failure or FMR at the time of index admission.

CONCLUSIONS

More than half of patients hospitalized with ADHF and LVSD had at least moderate or worse FMR at presentation, which was associated with worse postdischarge outcomes. These findings support the notion that an intensified postdischarge follow-up optimizing ventricular loading conditions to eliminate or substantially reduce FMR could not only help mitigate its adverse effects but also help identify FMR truly refractory to GDMT thereby shortening the time to therapeutic percutaneous intervention in suitable candidates. Further studies are needed to examine sex-related disparities in FMR.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1-S5

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SUPPLEMENTAL MATERIAL

Table S1. Sex distribution across groups of Functional Mitral Regurgitation (FMR).

	Female (%)	Male (%)	P value
FMR Groups			**<0.001**
None/Mild	371 (41)	722 (51)	<0.001
Moderate	320 (36)	437 (31)	0.07
Moderate-to-severe/Severe	205 (23)	248(18)	<0.001

Moderate-to-severe/Severe FMR was significantly more likely to be present in females, while none/mild FMR was more likely to be present in males.

Table S2. Generalized Ordered Logit Estimates to identify independent predictors of greater severity of Functional Mitral Regurgitation (FMR).

Generalized Ordered Logit Estimates	Number of observations	=	2,125
	LR chi2(12)	=	143.28
	Prob > chi2	=	<0.001
Log likelihood = -2140.0637	Pseudo R2	=	0.0324

FMR grades		Odds Ratio	Std. Err.	z	P>z	[95% Conf.	Interval]
None/Mild							
	Female	1.946773	0.1893777	6.85	**<0.001**	1.608838	2.355691
	CKD	0.8844842	0.1005167	-1.08	0.28	0.7078736	1.105158
	CRT	1.110977	0.1878459	0.62	0.534	0.7975954	1.54749
	A-fib	1.488928	0.1602606	3.7	<0.001	1.205743	1.838623
	LVIDd	1.550271	0.0791356	8.59	<0.001	1.402675	1.713399
	NT-proBNP	1.014226	0.0032803	4.37	<0.001	1.007817	1.020676
	_cons	0.0547447	0.0176197	-9.03	<0.001	0.0291327	0.1028734
Moderate							
	Female	1.870066	0.2211658	5.29	<0.001	1.483162	2.3579
	CKD	0.7992596	0.1165057	-1.54	0.124	0.6006352	1.063567
	CRT	0.9599122	0.1891766	-0.21	0.836	0.652348	1.412485
	A-fib	1.578798	0.19979	3.61	<0.001	1.232	2.023216
	LVIDd	1.522789	0.0840258	7.62	<0.001	1.366694	1.696711
	NT-proBNP	1.006585	0.0037703	1.75	0.08	0.9992228	1.014002
	_cons	0.013372	0.0048601	-11.87	<0.001	0.0065588	0.0272627

Female sex was a significant predictor of increasing severity of FMR.

A-fib: atrial fibrillation; CKD: chronic kidney disease (GFR < 60 ml/min/m^2); DM: diabetes mellitus; NT-proBNP: NT pro B-type natriuretic peptide; CRT- cardiac resynchronization therapy; LVIDd: left ventricular internal diameter at end-diastole.

Table S3. Multivariable cox regression model for 1-year all-cause mortality.

	Hazard Ratio	Standard Error	z	p-value	[95% Conf.	Interval]
FMR grade						
Moderate	1.127609	0.1985049	0.68	0.495	0.7985687	1.592225
Moderate-to-severe/Severe	**1.448895**	0.2727794	1.97	**0.049**	**1.001806**	**2.095513**
Age	1.019395	0.0059321	3.3	0.001	1.007835	1.031089
Etiology of cardiomyopathy non-ischemic	0.7034268	0.1118032	-2.21	0.027	0.5151435	0.9605271
NT-proBNP/1000	1.013911	0.0028158	4.97	<0.001	1.008407	1.019444
Discharge beta-blocker	0.6518017	0.133617	-2.09	0.037	0.4361363	0.9741117
Discharge ACEi	0.5835137	0.0956648	-3.29	0.001	0.4231554	0.8046412
Discharge ARB	0.4696092	0.1240232	-2.86	0.004	0.2798565	0.7880212

Severe Functional Mitral Regurgitation (FMR) was significantly associated with increased 1-year all-cause mortality. NT-proBNP: NT pro B-type natriuretic; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

Table S4. Multivariable competing risk regression model for 6-month HFH for moderate or greater FMR compared to none/mild FMR.

	Hazard Ratio	Standard Error	z	p-value	[95% Conf.	Interval]
FMR grade						
Moderate	**1.242537**	0.1155246	2.34	**0.02**	**1.035545**	**1.490904**
Moderate-to-severe/Severe	**1.249608**	0.1376372	2.02	**0.043**	**1.006975**	**1.550703**
CKD	1.364325	0.1342119	3.16	0.002	1.125079	1.654446
Etiology of cardiomyopathy non-ischemic	0.8109301	0.0672733	-2.53	0.012	0.6892381	0.9541082
NT-proBNP	1.004431	0.0023381	1.9	0.058	0.999859	1.009024
Discharge ACEi	0.8638361	0.073577	-1.72	0.086	0.731022	1.02078

Moderate or greater FMR remained significantly associated with increased rates of 6-month hospitalizations for heart failure.

CKD: chronic kidney disease; NT-proBNP: NT pro B-type natriuretic; ACEi: angiotensin-converting enzyme inhibitor.

Table S5. Cox regression analysis model for 1-year all cause mortality including in-hospital mortalities or deaths that occurred during index admission.

	Hazard Ratio	Standard Error	z	p-value	[95% Conf.	Interval]
FMR grade						
Moderate	1.012434	0.1586884	0.08	0.937	0.7446461	1.376524
Moderate-to-severe/Severe	**1.380816**	0.2299527	1.94	**0.05**	**0.9962809**	**1.91377**
Age	1.01842	0.0052505	3.54	<0.001	1.008181	1.028763
Etiology of cardiomyopathy non-ischemic	0.6297143	0.0894539	-3.26	0.001	0.4766794	0.8318801
NT-proBNP	1.013862	0.0024692	5.65	<0.001	1.009034	1.018713
CKD	1.4848	0.2163831	2.71	0.007	1.115888	1.975675