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**CLINICAL RESEARCH**
*Heart failure/cardiomyopathy*

# Refining the prognostic impact of functional mitral regurgitation in chronic heart failure

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**Aims** Significant efforts are currently undertaken to reduce functional mitral regurgitation (FMR) in patients with chronic heart failure in the hope to improve prognosis. We aimed to assess the prognostic impact of FMR in heart failure with reduced ejection fraction (HFrEF) under optimal medical therapy (OMT) and various conditions of HFrEF. We further intended to identify a heart failure phenotype, where FMR is most likely a driving force and not a mere bystander of the disease.

**Methods and results** We prospectively included 576 consecutive HFrEF patients into our long-term observational study. Functional [i.e. New York Heart Association (NYHA) class], echocardiographic, invasive haemodynamic, and biochemical (i.e. NT-proBNP, MR-proANP, MR-proADM, CT-proET-1, copeptin) measurements were performed at baseline. During a median follow-up of 62 months (interquartile range 52–76), 47% of patients died. Severe FMR was a significant predictor of mortality [hazard ratio (HR) 1.76, 95% confidence interval (CI) 1.34–2.30; $P < 0.001$], independent of clinical (adjusted HR 1.61, 95% CI 1.22–2.12; $P = 0.001$), and echocardiographic (adjusted HR 1.46, 95% CI 1.09–1.94; $P = 0.01$) confounders, OMT (adjusted HR 1.81, 95% CI 1.25–2.63; $P = 0.002$), and neurohumoral activation (adjusted HR 1.38, 95% CI 1.03–1.84; $P = 0.03$). Subanalysis revealed that severe FMR was associated with poor outcome in an intermediate-failure phenotype of HFrEF i.e. patients with NYHA class II (adjusted HR 2.17, 95% CI 1.07–4.44; $P = 0.03$) and III (adjusted HR 1.80, 95% CI 1.17–2.77; $P = 0.008$), moderately reduced left ventricular function (adjusted HR 2.37, 95% CI 1.36–4.12; $P = 0.002$), and within the second quartile (871–2360 pg/mL) of NT-proBNP (adjusted HR 2.16, 95% CI 1.22–3.86; $P = 0.009$).

**Conclusion** In a patient cohort under OMT, the adverse prognostic impact of FMR is given predominantly in a sub-cohort of a specific intermediate-failure phenotype—well-defined functionally, haemodynamically, biochemically, and morphologically.

**Keywords** Functional mitral regurgitation • HFrEF • Prognosis



## Introduction

Chronic heart failure (HF) is frequently accompanied by functional mitral regurgitation (FMR)[1] 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.[2,3] The pathophysiologic effects of FMR are not well understood, presumably volume overload on a failing ventricle increases diastolic wall stress[4] and consequently stimulates further maladaptation including up-regulation of pro-hypertrophic and anti-apoptotic signalling[5] and neurohumoral activation leading to further ventricular dilatation and failure.[1,6] 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.

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Nevertheless, driven by recent advances in percutaneous MV repair (PMVR), significant efforts are currently undertaken to reduce FMR in patients with HF in the hope to improve prognosis.[8] Similar to HF patients without FMR, it is recommended to prescribe optimized guideline-directed HF therapy (OMT) targeting LV dysfunction including cardiac resynchronization therapy.[2–4] However, whether OMT is able to counterbalance maladaptive processes and the adverse effects of FMR on long-term survival remain unknown.[9] Likewise, the impact of MV repair on outcome in HF patients with severe FMR by interruption of the presumed maladaptive effects is unknown[3] and several randomized clinical trials (MITRA-FR, RESHAPE-HF, COAPT) are underway to test this hypothesis. These studies are designed to cover a broad spectrum of patients with advanced HF, though it is hardly conceivable that all patients will equally benefit from MV repair. In order to successfully tackle outcome, a more profound understanding of the association between FMR and long-term mortality in patients with various stages of HF seems necessary in order to identify those that will benefit most from MV repair. We therefore aimed to assess the independent prognostic impact of FMR on long-term mortality in patients with chronic HF under optimized OMT encompassing functional, haemodynamic, biochemical and echocardiographic markers. We further intended to identify a HF phenotype, where FMR is most likely a driving force of the disease.

# Methods

## Study population

We enrolled consecutive adult patients with HF with reduced ejection fraction (HFrEF) who presented to our HF clinic at the Vienna General Hospital, a university-affiliated tertiary centre in this observational, non-interventional study as previously described.[10] Heart failure with reduced ejection fraction was defined in line with the guidelines as history of HF signs and symptoms as well as a LV ejection fraction (LVEF) below 40%.[3] As the investigated population already received OMT at index time, there is a portion of patients in New York Heart Association (NYHA) stage I and improved ejection fraction > 40%. All patients who underwent a comprehensive echocardiographic exam at our institution were included, patients with more than mild aortic or mitral stenosis or ≥ moderate primary mitral regurgitation were excluded. The study was approved by the Ethics Committee of the Medical University of Vienna.

## Clinical definitions and follow-up

Baseline examination included medical history, detailed assessment of current medication, electrocardiogram recording, and a transthoracic echocardiogram. Cardiovascular risk factors were recorded according to the respective guidelines.[11] According to the standard operating procedure of our HF outpatient clinic and in agreement with the ESC guidelines,[3] dosage of medical therapy was pro-actively increased in all enrolled patients until the maximal recommended dosage was reached or a further increase was no longer possible due to the clinical characteristics of the patient (systolic blood pressure < 90 mmHg, heart rate < 60 bpm, potassium level > 5.0 mmol/L). Intensified guideline-directed therapy was defined if ≥ 50% of the recommended dosages of renin-angiotensin system (RAS) antagonists with a concomitant dosage of ≥ 50% of the recommended dosages of beta blockers were reached and mineralocorticoid antagonist therapy was prescribed if indicated according to the guidelines.[3] Response to cardiac resynchronization therapy was defined as improvement of EF by more than 15% or reduction in LV end-diastolic diameter by more than 15%.[12] Estimated glomerular filtration rate was calculated by using the Cockcroft–Gault formula. All-cause mortality was selected as primary endpoint. Mortality was determined via retrieval query of the Austrian Death Registry. Austrian law stipulates that all deaths of Austrian citizens (also in foreign countries, if reported to Austrian officials) have to be recorded in the central Austrian death registry, allowing almost complete follow up of all patients.[13]

## Echocardiographic and haemodynamic assessments

Standard echocardiograms were performed using commercially available equipment (Vivid5 and Vivid7, GE-Healthcare, and Acuson Sequoia, Siemens). 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) ≥ 62 mm for women and ≥ 69 mm for men.[14] Left ventricular ejection fraction was calculated using the biplane Simpson method and semi-quantitative assessment of right heart function were performed by experienced readers using multiple acoustic windows and graded as normal, mild, mild-to-moderate, moderate, moderate-to-severe, and severe. Mitral regurgitation was graded by an integrated approach comprising MV morphology, width of the proximal regurgitant jet, proximal flow convergence, and pulmonary venous flow pattern. Valvular stenosis and regurgitation were quantified using an integratively and graded as none, mild, mild-to-moderate, moderate, moderate-to-severe, and severe according to the guidelines.[15,16] Systolic pulmonary artery pressures were calculated by adding the peak tricuspid regurgitation (TR) systolic gradient to the estimated central venous pressure. Invasive haemodynamic assessment was recorded in all patients, who underwent clinically indicated right-heart catheterization at time of study enrolment. Haemodynamics were performed using a 7F-Swan-Ganz catheter (Edwards Lifesciences, Austria) via jugular or femoral access. Pressures were documented as average of eight measurements over eight consecutive heart cycles using CathCorLX (Siemens AG, Berlin, Germany).

## Laboratory measurements

Routine laboratory parameters were analysed from venous blood samples according to the local laboratory's standard procedure at study enrolment. Neurohormones were used to illustrate the haemodynamic and volume state of the cardiovascular system as both are directly related to FMR. All of them are already proven to be excellent markers of outcome in stable chronic systolic HF.[10,17] NT-proBNP and MR-proANP have been already tested in primary MR.[18] Markers for myocardial stretch were chosen specifically with respect to possible complementary information they might provide in FMR.[19] Functional mitral regurgitation directs an unloading of the ventricle (the main trigger for NT-proBNP) at the expense of the left atrium (the main trigger for MR-proANP) and therefore, from a mechanistically perspective, the combination of both might better reflect the haemodynamic alteration of the regurgitant lesion. MR-proADM was chosen due to its properties as a peripheral vasodilator regulating afterload[20] and Copeptin as well as CT-proET-1 as the direct counter-regulatory hormones. CT-pro-ET1 was used because of its endothelial release in response to shear stress and its association with MR severity.[21] Copeptin was used due to its independent and incremental prognostic value to NT-proBNP.[10] NT-proBNP measurements were performed in heparin plasma using the Elecsys Systems (Roche Diagnostics, Mannheim, Germany). MR-proANP, MR-proADM, CT-proET-1, and Copeptin were measured in EDTA plasma using specific sandwich immunoassays (BRAHMS, Hennigsdorf/Berlin, Germany).

## Statistical methods

Continuous data were presented as median and interquartile range (IQR) and discrete data were presented as count and percentage. Cox proportional hazard regression analysis was applied to assess the effect of severe FMR (dichotomous: severe vs. non-severe FMR) on survival. First we conducted an unadjusted model with FMR as a single exploratory variable and in order to account for potential confounding effects, we adjusted for a clinical confounder cluster (encompassing: age, sex, ischaemic aetiology of HF, serum creatinine, and NT-proBNP), an echocardiographic confounder cluster (encompassing: LV end-diastolic diameter, LV function, severe TR), an optimal medical therapies cluster (encompassing: intensified guideline-directed therapy, implanted cardioverter defibrillator, and response to cardiac resynchronization therapy), and a neurohumoral activation cluster (encompassing: NT-proBNP, MR-proANP, MR-proADM, CT-proET-1, and Copeptin). The discriminatory power of the respective clusters was assessed using Harrell's C-statistic. In order to test for interactions between severe FMR and all above named variables, we used Cox proportional hazard regression models with FMR, a variable in question and the interaction between both variables. We tested for collinearity in the multivariable model using the variance inflation factor. The proportional hazards assumption was tested and satisfied in all cases using Schoenfeld residuals. Cox survival curves adjusted for all variables in the clinical confounder cluster were presented according to FMR severity (no/mild, moderate, severe). Sub-group analysis was performed to assess the impact of severe FMR on outcome in various stages of HF categorized by functional status (NYHA class), echocardiographic parameters [LV function, LV, and left atrium (LA) size] and biochemical markers (NT-proBNP, MR-proANP, MR-proADM, CT-proET-1, and Copeptin). Two-sided *P*-values < 0.05 were used to indicate statistical significance. The STATA11 software package (StataCorp, College Station, TX, USA) and SPSS 24.0 (IBM Corp, New York, NY, USA) were used for all analyses.

# Results

## Baseline characteristics

We enrolled a total of 576 patients with HF. Median age was 58 (IQR 50–64), 83% ($n = 476$) were male. The median NT-proBNP was 2360 pg/mL (IQR 867–5163) and LV function was significantly reduced (≥moderate) in 84% ($n = 484$) of patients. Forty-one percent of patients ($n = 236$) were in NYHA functional class III and 21% ($n = 121$) in NYHA class IV. Regarding HF therapy, 551 patients (96%) received RAS antagonists up-titrated to a median dose of 100% of the maximal guideline recommended dosages, 410 patients (71%) received beta-blockers up-titrated to a median dose of 50% of the maximal guideline recommended dosages, 189 patients (33%) were treated with a mineralocorticoid receptor antagonist. Fifty-five patients (10%) underwent cardiac resynchronization therapy with a response rate of 52%. Detailed baseline characteristics of the entire study population are displayed in *Table 1*.

## Severity of functional mitral regurgitation and outcome

Detailed baseline characteristics according to severity of mitral regurgitation are presented in *Table 1*. Briefly, with increasing FMR severity levels of NT-proBNP (mild/noMR: 1556 pg/mL [IQR 440–3670], moderate MR: 2672 pg/mL [IQR 1243–5649], severe MR: 4262 pg/mL [IQR 2317–7527]; $P < 0.001$), NYHA class ($P < 0.001$), and prevalence of atrial fibrillation [mild/noMR: 48 patients (17%), moderate MR: 37 (20%), severe MR: 34 (29%); $P = 0.05$] increased, while LV function decreased ($P < 0.001$). Vice-versa severity of FMR gradually increased with rising NYHA class ($P < 0.001$; *Figure 1A*) as well as levels of NT-proBNP ($P < 0.001$; *Figure 1B*). During a median follow-up time of 62 months (IQR 52–76 months), 47% of patients ($n = 271$) died. Adjusted survival curves demonstrated a significant increase of mortality with increasing FMR severity (*Figure 2*, $P < 0.001$). We observed an hazard ratio (HR) of 1.76 [95% confidence interval (CI) 1.34–2.30; $P < 0.001$] comparing patients with severe FMR to patients with non-severe FMR. This result remained virtually unchanged after multivariable adjustment using a clinical confounder cluster, an echocardiographic confounder cluster, an optimal medical therapies cluster, and a neurohumoral activation cluster encompassing various neurohumoral pathways in HF (*Table 2*). Furthermore, we did not observe any significant interaction between severe FMR and ischaemic or non-ischaemic FMR (*P*-for-interaction = 0.57). Additionally, we did not observe any significant interactions between severe FMR and any other variables included in the multivariable model and we did not detect a significant collinearity in our multivariable models.

## Severe functional mitral regurgitation and New York Heart Association functional class

We further assessed the incremental prognostic value of severe FMR in various stages of HF. We observed a significant association between severe FMR and long-term mortality in patients with NYHA functional class II (adjusted HR 2.17, 95% CI 1.07–4.44; $P = 0.03$) and class III (adjusted HR 1.80, 95% CI 1.17–2.77; $P = 0.008$), whereas no statistically significant association was present in NYHA class I ($P = 0.73$) and IV ($P = 0.71$; *Table 3*).

## Severe functional mitral regurgitation and echocardiographic indicators in heart failure

Severe FMR was associated with outcome in patients with moderately reduced LV function (LVEF 30–40%; adjusted HR 2.37, 95% CI 1.36–4.12; $P = 0.002$) but not in patients with severely reduced LV function (LVEF < 30%; HR 1.31, 95% CI 0.95–1.81; $P = 0.10$; *Table 3*). Comparably, severe FMR was associated with poor prognosis in patients with smaller LV size (≤moderately dilated LV: adjusted HR 2.00, 95% CI 1.39–2.87; $P < 0.001$ vs. severely dilated LV: adjusted HR 1.41, 95% CI 0.92–2.16; $P = 0.11$) and smaller LA size [LA diameter ≤ 64 mm (i.e. median): adjusted HR 2.45, 95% CI 1.50–4.01; $P < 0.001$ vs. LA diameter > 64 mm: adjusted HR 1.31, 95% CI 0.93–1.83; $P = 0.12$] as well as in patients without severe TR (≤moderate TR: adjusted HR 1.65, 95% CI 1.23–2.22; $P = 0.001$ vs. severe TR: adjusted HR 2.17, 95% CI 0.70–6.73; $P = 0.18$).

## Severe functional mitral regurgitation and neuro-humoral pathways in heart failure

The predictive value of FMR severity remained independent of neurohumoral activation encompassing NT-proBNP, MR-proANP, MR-proADM, CT-proET-1, and copeptin (*Table 2*).

Analogously to NYHA functional class and echocardiographic markers, severe FMR was associated with poor outcome in patients

**Table 1 Baseline characteristics of total study population (*n* = 576) according to severity of mitral regurgitation**

| | Total study population (*n* = 576) | No/mild MR (*n* = 272) | Moderate MR (*n* = 185) | Severe MR (*n* = 119) | *P*-value |
|---|---|---|---|---|---|
| Baseline characteristics | | | | | |
| Age, median years (IQR) | 58 (50–64) | 57 (49–63) | 59 (51–66) | 58 (50–64) | 0.11 |
| Male sex, *n* (%) | 476 (83) | 234 (86) | 143 (77) | 99 (83) | 0.053 |
| BMI, kg/m$^2$ (IQR) | 26 (24–29) | 27 (24–29) | 26 (24–28) | 26 (24–28) | **0.02** |
| Systolic blood pressure, mmHg (IQR) | 115 (100–130) | 120 (104–135) | 115 (100–120) | 103 (91–120) | **0.001** |
| Ischaemic aetiology of HF, *n* (%) | 225 (39) | 105 (39) | 79 (43) | 35 (29) | 0.35 |
| Hypertension, *n* (%) | 284 (49) | 148 (54) | 94 (51) | 42 (35) | **0.02** |
| Diabetes, *n* (%) | 130 (23) | 71 (26) | 41 (22) | 18 (15) | 0.06 |
| Hypercholesterolaemia, *n* (%) | 234 (41) | 123 (45) | 76 (41) | 35 (29) | **0.01** |
| Left bundle branch block, *n* (%) | 112 (19) | 60 (22) | 33 (18) | 19 (16) | 0.94 |
| Atrial fibrillation, *n* (%) | 119 (21) | 48 (17) | 37 (20) | 34 (29) | **0.05** |
| NYHA functional class | | | | | **<0.001** |
| NYHA I, *n* (%) | 66 (11) | 40 (15) | 17 (9) | 9 (8) | |
| NYHA II, *n* (%) | 153 (27) | 82 (30) | 55 (30) | 16 (13) | |
| NYHA III, *n* (%) | 236 (41) | 119 (44) | 69 (37) | 48 (40) | |
| NYHA IV, *n* (%) | 121 (21) | 31 (11) | 44 (24) | 46 (39) | |
| Creatinine, mg/dL (IQR) | 1.2 (1.0–1.4) | 1.2 (1.0–1.3) | 1.2 (1.0–1.4) | 1.3 (1.1–1.5) | **0.005** |
| Estimated GFR, mL/min/1.73 m$^2$ (IQR) | 75 (58–94) | 79 (61–99) | 71 (59–88) | 68 (53–86) | **<0.001** |
| Blood urea nitrogen, mg/dL (IQR) | 20 (17–30) | 20 (15–25) | 21 (17–30) | 25 (20–38) | **<0.001** |
| Neurohormones | | | | | |
| NT-proBNP, pg/mL (IQR) | 2360 (867–5163) | 1556 (440–3670) | 2672 (1243–5649) | 4262 (2317–7527) | **<0.001** |
| MR-proANP, pmol/L (IQR) | 275 (131–479) | 184 (86–360) | 293 (187–468) | 479 (298–745) | **<0.001** |
| MR-proADM, nmol/L (IQR) | 0.67 (0.42–1.06) | 0.59 (0.38–0.92) | 0.72 (0.45–1.03) | 0.96 (0.55–1.66) | **<0.001** |
| Copeptin, pmol/L (IQR) | 11.3 (5.8–21.8) | 9.5 (5.1–17.7) | 11.3 (5.9–21.4) | 18.8 (9.1–35.3) | **<0.001** |
| CT-pro-ET1, pmol/L (IQR) | 62 (31–106) | 55 (29–90) | 65 (31–106) | 90 (45–157) | **<0.001** |
| Echocardiographic characteristics | | | | | |
| Left ventricular end-diastolic diameter, mm (IQR) | 64 (58–71) | 60 (54–68) | 66 (59–71) | 68 (62–75) | **<0.001** |
| Left ventricular function | | | | | **<0.001** |
| Moderately reduced (EF 30–40%), *n* (%) | 159 (28) | 84 (31) | 51 (28) | 24 (20) | |
| Severely reduced (LVEF <30%), *n* (%) | 325 (56) | 112 (41) | 122 (66) | 91 (76) | |
| Left ventricular ejection fraction, % (IQR) | 27 (20–35) | 32 (22–40) | 26 (20–33) | 25 (15–30) | **0.006** |
| Left atrial diameter, mm (IQR) | 64 (57–71) | 59 (53–67) | 65 (60–71) | 72 (64–77) | **<0.001** |
| Right ventricular end-diastolic diameter, mm (IQR) | 36 (31–42) | 34 (30–38) | 36 (32–42) | 41 (36–46) | **<0.001** |
| Tricuspid regurgitation (≥ moderate), *n* (%) | 111 (19) | 10 (4) | 39 (21) | 62 (52) | **<0.001** |
| Medication | | | | | |
| RAS antagonist, *n* (%) | 551 (96) | 235 (86) | 181 (98) | 115 (97) | 0.09 |
| Percent of maximal recommended dose, median % | 100% | 100% | 100% | 100% | 0.15 |
| Beta-blockers, *n* (%) | 410 (71) | 199 (73) | 139 (75) | 72 (61) | **0.01** |
| Percent of maximal recommended dose, median % | 50% | 50% | 50% | 44% | 0.66 |
| Mineralocorticoidantagonist, *n* (%) | 189 (33) | 78 (29) | 62 (34) | 49 (41) | 0.052 |
| Intensified guideline-directed therapy, *n* (%) | 216 (38) | 111 (41) | 71 (38) | 34 (29) | 0.07 |
| Furosemide, *n* (%) | 429 (74) | 182 (67) | 139 (75) | 108 (91) | **<0.001** |
| Amiodarone, *n* (%) | 110 (19) | 37 (14) | 39 (21) | 34 (29) | **0.002** |
| Rhythm devices | | | | | |
| Implanted cardioverter defibrillator, *n* (%) | 69 (12) | 25 (9) | 32 (17) | 12 (10) | **0.03** |
| Pacemaker, *n* (%) | 100 (17) | 37 (14) | 36 (19) | 27 (23) | 0.06 |
| Cardiac resynchronization therapy, *n* (%) | 55 (10) | 27 (10) | 15 (8) | 13 (11) | 0.46 |
| Haemodynamic characteristics | (*n* = 150) | (*n* = 42) | (*n* = 53) | (*n* = 55) | |
| mPAP, mmHg (IQR) | 38 (31–43) | 38 (31–43) | 36 (31–40) | 40 (34–43) | 0.26 |
| PAWP, mmHg (IQR) | 23 (20–26) | 24 (21–26) | 22 (20–26) | 22 (20–26) | 0.80 |
| Cardiac index, l/min/m$^2$ (IQR) | 1.8 (1.5–2.1) | 1.7 (1.5–2.1) | 1.8 (1.7–2.1) | 1.8 (1.5–2.1) | 0.58 |

Bold values indicates statistical significance.
IQR, interquartile range; HF, heart failure; NYHA, New York Heart Association; GFR, glomerular filtration rate; EF, ejection fraction; LVEF, left ventricular EF; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure.

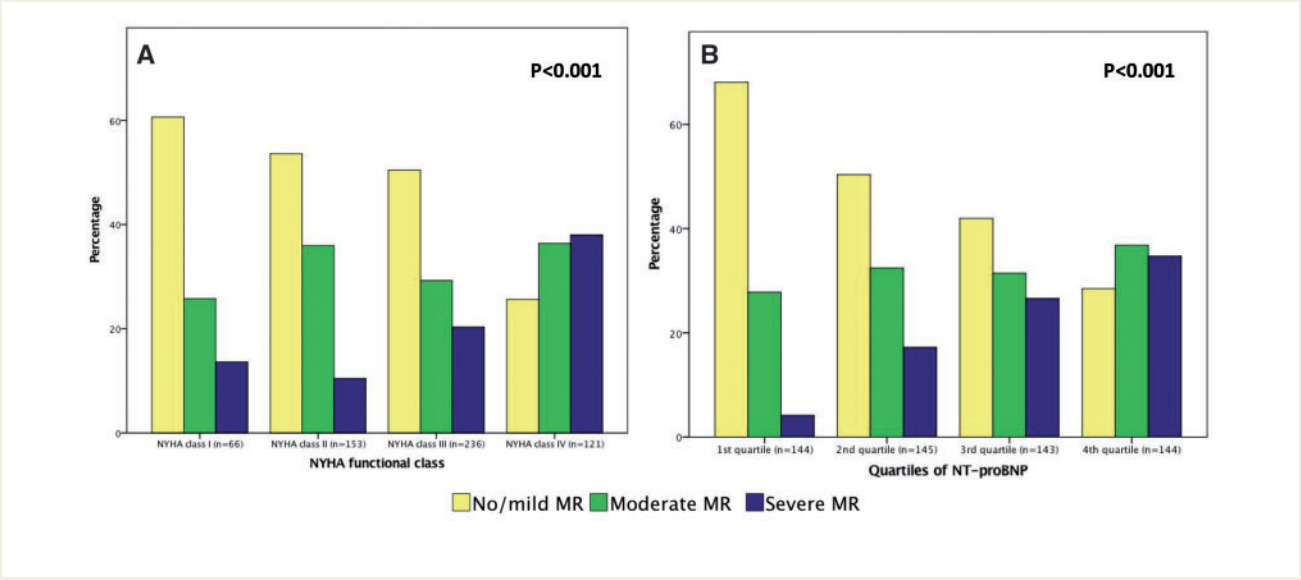


**Figure 1** Prevalence of functional mitral regurgitation according to NYHA functional class (*A*; $P < 0.001$) and quartiles of NT-proBNP (*B*; $P < 0.001$). NYHA, New York Heart Association; MR, mitral regurgitation.

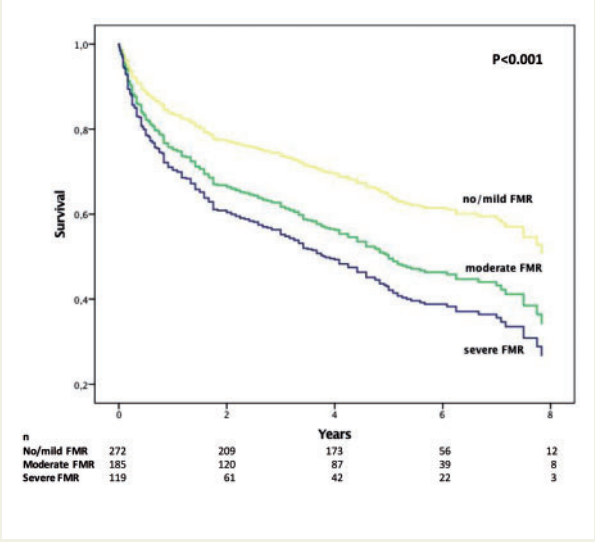


**Figure 2** Adjusted survival curves of long-term mortality according to severity of mitral regurgitation ($P < 0.001$) adjusted for the clinical confounder model (i.e. age, sex, ischaemic aetiology of heart failure, serum creatinine, and NT-proBNP). FMR, functional mitral regurgitation.

within the 2nd quartile of NT-proBNP (adjusted HR 2.16, 95% CI 1.22–3.86; $P = 0.009$), while no association was present in the 1st ($P = 0.56$), 3rd ($P = 0.26$), and 4th quartile ($P = 0.43$, *Table 3*). Additionally, severe FMR was associated with impaired survival within the 1st quartile (adjusted HR 1.49, 95% CI 1.04–2.12; $P = 0.03$) and 2nd quartile (adjusted HR 1.62, 95% CI 1.05–2.48; $P = 0.03$) of MR-proADM, within the 2nd quartile (adjusted HR 1.50, 95% CI 1.10–2.06; $P = 0.01$) and 3rd quartile (adjusted HR 1.34, 95% CI 1.00–1.80; $P = 0.05$) of Copeptin, and within the 1st quartile (adjusted HR 1.47, 95% CI 1.06–2.02; $P = 0.02$) and 2nd quartile (adjusted HR 1.89, 95% CI 1.29–2.76; $P = 0.001$) of CT-pro-ET1. No association between outcome and FMR could be established for quartiles of MR-proANP. Results of the univariable and multivariable Cox regression analysis per quartile of neurohumoral marker are displayed in Supplementary material online, *Table S1*.

## Severe functional mitral regurgitation and haemodynamic indicators of heart failure

Invasive haemodynamic assessment was available in a total of 150 patients and results are presented in *Table 1*. The median mean pulmonary artery pressure was 38 mmHg (IQR 31–43) and the median wedge was 23 mmHg (IQR 20–26). Severe FMR was associated with impaired survival in patients with increased mean pulmonary artery pressure [≥42 mmHg (3rd tertile): adjusted HR 3.10, 95% CI 1.29–7.43; $P = 0.011$ vs. 2nd tertile: $P = 0.69$ and 1st tertile $P = 0.90$] and increased pulmonary artery wedge pressure [≥26 mmHg (3rd tertile): adjusted HR 3.60, 95% CI 1.42–9.15; $P = 0.007$ vs. 2nd tertile: $P = 0.87$ and 1st tertile $P = 0.34$].

# Discussion

This long-term observational study shows, for the first time, the prognostic significance of FMR in a large contemporary heart failure cohort under guideline-directed HF therapy. The main findings are (i) the adverse prognostic impact of FMR remains despite guideline directed medical therapy, (ii) the confirmation of rising FMR prevalence with increasing HF severity, (iii) the prognostic impact of severe FMR is given in a sub-cohort of a specific intermediate-failure

**Table 2 Crude and multivariable Cox regression model assessing the impact of severe of mitral regurgitation (severe functional mitral regurgitation vs. non-severe functional mitral regurgitation) on long-term mortality ($n = 576$/events = 271)**

| | HR | 95% CI | *P*-value | C-statistic |
|---|---|---|---|---|
| Crude model | 1.76 | 1.34–2.30 | **<0.001** | 0.55 |
| Clinical confounder cluster[a] | 1.61 | 1.22–2.12 | **0.001** | 0.64 |
| Echocardiographic confounder cluster[b] | 1.46 | 1.09–1.94 | **0.01** | 0.62 |
| Optimal medical therapies cluster[c] | 1.81 | 1.25–2.63 | **0.002** | 0.61 |
| Neurohumoral activation cluster[d] | 1.38 | 1.03–1.84 | **0.03** | 0.65 |

Bold values indicates statistical significance.
HR, hazard ratio; CI, confidence interval.
[a]Adjusted for: age, sex, ischaemic aetiology of heart failure, serum creatinine and NT-proBNP.
[b]Adjusted for: LV end-diastolic diameter, LV function, severe tricuspid regurgitation.
[c]Adjusted for: intensified guideline-directed therapy, implanted cardioverter defibrillator, and response to cardiac resynchronization therapy.
[d]Adjusted for: NT-proBNP, MR-proANP, MR-proADM, CT-proET-1, and Copeptin.

**Table 3 Impact of severe mitral regurgitation on outcome compared with the remaining study population by various subgroups of heart failure defined functionally by New York Heart Association stage, biochemically by quartiles of NT-proBNP, and echocardiographically by left ventricular ejection fraction**

| Subgroups | Patients/events | Crude HR (95% CI) | *P*-value | Adjusted HR (95% CI)[a] | *P*-value |
|---|---|---|---|---|---|
| NYHA functional class | | | | | |
| NYHA I | 66/22 | 1.20 (0.40–3.55) | 0.75 | 0.83 (0.27–2.49) | 0.73 |
| NYHA II | 153/58 | 1.89 (0.95–3.77) | 0.07 | 2.17 (1.07–4.44) | **0.03** |
| NYHA III | 236/110 | 1.81 (1.18–2.79) | **0.007** | 1.80 (1.17–2.77) | **0.008** |
| NYHA IV | 121/81 | 1.02 (0.65–1.60) | 0.93 | 1.09 (0.69–1.72) | 0.71 |
| Echocardiographic LV function | | | | | |
| Moderately reduced (LVEF 30–40%) | 159/76 | 2.15 (1.25–3.69) | **0.006** | 2.37 (1.36–4.12) | **0.002** |
| Severely reduced (LVEF <30%) | 325/171 | 1.29 (0.94–1.79) | 0.12 | 1.31 (0.95–1.81) | 0.10 |
| Quartiles of NT-proBNP (pg/mL) | | | | | |
| 1st quartile (<863 pg/mL) | 144/39 | 0.43 (0.06–3.17) | 0.41 | 0.56 (0.07–4.05) | 0.56 |
| 2nd quartile (871–2360 pg/mL) | 145/64 | 2.07 (1.19–3.62) | **0.01** | 2.16 (1.22–3.86) | **0.009** |
| 3rd quartile (2368–5159 pg/mL) | 143/67 | 1.33 (0.78–2.26) | 0.30 | 1.36 (0.79–2.32) | 0.26 |
| 4th quartile (>5167 pg/mL) | 144/101 | 1.17 (0.78–1.76) | 0.45 | 1.18 (0.78–1.77) | 0.43 |

Bold values indicates statistical significance.
NYHA, New York Heart Association; HR, hazard ratio; CI, confidence interval; LV, left ventricular; LVEF, LV ejection fraction.
[a]Adjusted for: age, sex, and ischaemic aetiology of heart failure.

phenotype—well-defined functionally, haemodynamically, biochemically, and morphologically, and (iv) once the transition to a full-grown HF phenotype has been completed, severe MR might be no longer of prognostic significance.

## Functional mitral regurgitation and optimal medical therapy

Heart failure is frequently accompanied by FMR as a consequence of LV remodelling. Optimal medical therapy remains the standard of care and has been shown to influence FMR severity,[22] whereas MV surgery is only recommended in concert with revascularization given evidence of viability or severely symptomatic patients despite OMT.[2] These recommendations are based on expert consensus and rely on the presumed independent contribution of FMR to remodelling and outcome in HFrEF. Multiple studies showed significant association of FMR with survival,[1,23–25] however they did not disclose medical HF-management or up-titration to recommended dosages. Lamas *et al.*[25] investigated on a subgroup of the SAVE trial where patients were randomly assigned to Captopril or Placebo after myocardial infarction, indicating that by design, only roughly half of the patients received angiotensin converting enzyme inhibitors.[25] Moreover, no data on beta-blockers or mineralocorticoid receptor antagonists have been disclosed in this or other studies investigating the impact of FMR.[1,26,27] However, this is a contemporary observation regarding OMT in HF trials and fosters an ongoing discussion regarding the balance between therapeutic effectiveness and financial demands of modern treatments[28] compared with or on top of established therapies. The present study shows an independent and gradually increasing contribution of FMR to worse HFrEF outcome even on top of OMT, and independent of clinical, haemodynamic, echocardiographic and neurohumoral confounders.

## Functional mitral regurgitation in various stages of heart failure

Basic scientific studies investigating the effect of early and late repair of MR suggest a window of opportunity where early repair can reverse the otherwise progressive remodelling.[5,6] Formerly impossible due the inherent invasive nature and excessive risk of perioperative mortality, percutaneous MV repair now opens new low-risk therapeutic options in HFrEF to reduce adverse effects of volume overload by FMR. Improvement with regard to symptomatic status and quality of life (QOL) has been demonstrated for the Mitraclip system in HFrEF, however a clear survival benefit could not been shown so far.[26,29,30] Therefore, with the advent of these new treatment options for FMR, a major challenge for the heart team is the definition of treatment-goals and subsequent allocation to the treatment of choice.

The present study for the first time defines a specific cohort of patients where severe FMR is an independent predictor of outcome despite OMT and auxiliary procedures such as PMVR could potentially reduce the burden of FMR to improve survival. Of note, whereas for instance ACCESS-EU showed a benefit for functional outcome and QOL for the MitraClip system,[26] only 21.9% of FMR patients included had an EF of 30–40% which, from the present analysis, seems to be the window of opportunity to reduce the impact of FMR on survival. However, as LVEF alone is only a modest marker of HF severity, we investigated further surrogates of disease severity to cover the full spectrum of HF. Our data draw a homogenous picture of the particular stage of disease where FMR is predictive and probably intervention might foil its risk. Biochemical markers, NT-proBNP, as the neurohumoral gold standard in HF, but also MR-proADM, CT-pro-ET1 and Copeptin consolidate the evidence that an intermediate-failure phenotype should be targeted for intervention. This is further supported as echocardiographic data show that in those patients with smaller LV/LA size, FMR has more impact on survival. Furthermore, as symptoms are currently the driving force for MV intervention, NYHA functional class is an important issue. Our data show an impact of FMR on survival already in patients with mild symptoms (i.e. NYHA II), with a predominant effect in NYHA class III, and it appears further that the prognostic window is closing in NYHA class IV. Taken together, the impression arises that in terms of prognosis intervention in FMR appears most effective in an intermediate-HFrEF phenotype.

## Functional mitral regurgitation and haemodynamic considerations

Based on our data, severe FMR is only associated with mortality in patients with a significantly increased pulmonary artery pressure or an increased pulmonary artery wedge pressure reflecting a subcohort, where FMR arises in union with severe haemodynamic impairment. Therefore, haemodynamic surrogates appear to more directly reflect the progressive cycle of LV volume overload. This suggests that single echocardiographic determination of the morphologic significance of MV regurgitation may not suffice for a comprehensive clinical decision-making and additional haemodynamic measurement may offer a more complete understanding regarding the prognostic significance of FMR.

# Limitations

The study reflects the experience of a single tertiary care-centre. However, this ensures the inclusion of a homogenous patient population, a consistent quality of imaging procedures and right heart catheterization as well as adherence to a consistent clinical routine. Data on HF hospitalizations proceeding the year of study enrolment—an important additional marker of disease severity in patients with HF—were not available. Moreover, we can exclude that any patient underwent interventional MV repair during study enrolment or follow-up. However, data regarding surgical MV interventions at other centres and myocardial revascularization were not accessible. Further, it has to be mentioned that our data are only hypothesis generating in regard to intervene severe FMR and in the end these conclusions have to be confirmed by large randomized trials. Nevertheless, to the best of our knowledge, these data contain the most comprehensive information on FMR and prognosis at present.

# Conclusions

This long-term observational study for the first time demonstrates the impact of FMR in patients with guideline adherent treatment and fully disclosed medical HF management including percentage of uptitration to recommended dosage regimens. The presented results confirm the rising prevalence of FMR with increasing HF severity and foster the notion that the adverse prognostic impact of FMR is given predominantly in a sub-cohort of a specific intermediate-failure phenotype—well-defined functionally, haemodynamically, biochemically, and morphologically.

# Supplementary material

Supplementary material is available at *European Heart Journal* online.

**Conflict of interest**: none declared.

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