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RESEARCH ARTICLE

Impact of mitral regurgitation in patients with acute heart failure: insights from the RELAX-AHF-2 trial

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Aims The impact of mitral regurgitation (MR) in patients hospitalized for acute heart failure (AHF) is not well established. We assessed the role of MR in patients enrolled in the Relaxin in Acute Heart Failure 2 (RELAX-AHF-2) trial.

Methods and results Patients enrolled in RELAX-AHF-2 with available data regarding MR status were included in this analysis. Baseline characteristics, in-hospital data, and clinical outcomes through 180-day follow-up were evaluated. The impact of moderate/severe MR was assessed. Among 6420 AHF patients with known MR status, 1810 patients (28.2%) had moderate/severe MR. Compared to patients with no/mild MR, those with moderate/severe MR were more likely to have history of heart failure (HF), prior HF hospitalization, more comorbidities, symptoms/signs of HF, lower left ventricular ejection fraction and higher N-terminal pro-B-type natriuretic peptide levels. Moderate/severe MR was associated with longer length of hospital stay, higher rates of residual dyspnoea, increased jugular venous pressure through the index hospitalization and a higher unadjusted risk of the composite of cardiovascular (CV) death or rehospitalization for HF/renal failure (RF) through 180 days (crude hazard ratio [HR] 1.15, 95% confidence interval [CI] 1.03–1.27, $p = 0.01$). The association between moderate/severe MR and poorer outcomes was not maintained in a multivariable model including several covariates of interest (adjusted HR 1.03, 95% CI 0.91–1.17, $p = 0.65$). Similar findings were observed for HF/RF rehospitalization alone.

Conclusions In patients with AHF, moderate/severe MR was associated with a worse clinical profile but did not have an independent prognostic impact on clinical outcomes.

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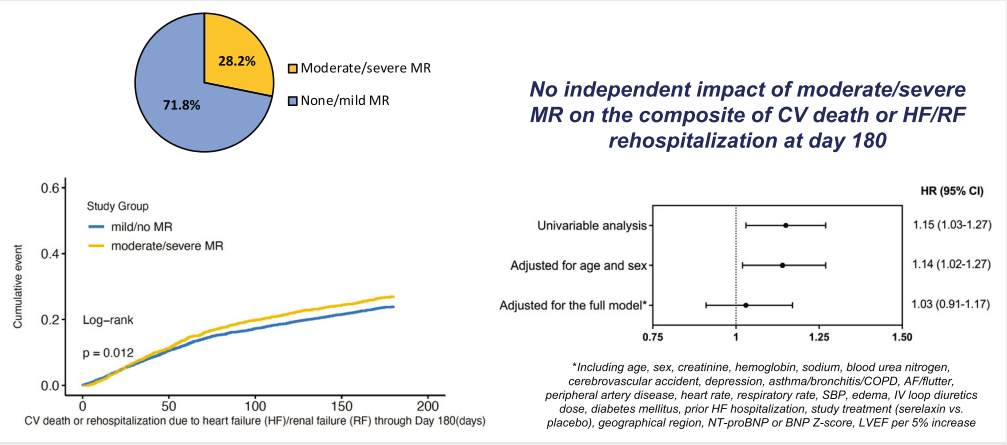
Graphical Abstract



Impact of mitral regurgitation (MR) in patients with acute heart failure (HF): an analysis on 6420 patients from RELAX-AHF-2. AF, atrial fibrillation; BNP, B-type natriuretic peptide; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; HR, hazard ratio; IV, intravenous; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RF, renal failure; SBP, systolic blood pressure.

Keywords Acute heart failure • Hospitalization • Mitral regurgitation • Mortality • Outcomes • Valvular heart disease

Introduction

Hospitalization for acute heart failure (AHF) is associated with high subsequent mortality and rehospitalization rates.[1] Mitral regurgitation (MR) represents the most common valvular heart disease in patients with heart failure (HF), with moderate-to-severe MR affecting up to half of patients hospitalized for AHF.[2–4] Several studies have demonstrated the prognostic impact of MR in HF, either in the acute or chronic setting, but they were characterized by relatively limited sample size and/or predominant inclusion of patients with reduced left ventricular ejection fraction (LVEF).[2,5–18] Recently, an analysis of the Atherosclerosis Risk in Communities (ARIC) study on 3878 patients with AHF showed a significant impact of moderate/severe MR on 1-year mortality among patients with LVEF <50%.[2] Another recent single-centre, retrospective analysis on 2303 patients with AHF and LVEF <50% demonstrated that moderate or higher MR on admission was associated with higher 6-month HF rehospitalization and 1-year mortality.[19] Hence, MR may be an important prognostic marker as well as a potential target and thus influence management and outcomes in patients hospitalized for AHF.

Further assessment of the impact of MR in a large, well-characterized cohort of patients with AHF, including patients with both reduced and preserved LVEF, is needed. We analysed the clinical profile and prognostic impact of MR from the Relaxin in Acute Heart Failure 2 (RELAX-AHF-2) randomized controlled trial.

Methods

Study design and study population

The design of the RELAX-AHF-2 trial (ClinicalTrials.gov NCT01870778) has been described previously.[20,21] Briefly, RELAX-AHF-2 was a multicentre, randomized, double-blind, placebo-controlled phase 3 trial enrolling 6545 patients who were hospitalized with AHF between 2 October 2013 and 1 February 2017 at 546 centers in 35 countries. The trial was approved at each participating centre and written consent was obtained from all participants. The inclusion criteria identified patients ≥18 years with all of the following at study entry: dyspnoea; pulmonary congestion on chest radiograph; elevated B-type natriuretic peptide (BNP) ≥500 pg/ml or N-terminal pro-BNP (NT-proBNP) ≥2000 pg/ml (BNP ≥750 pg/ml or NT-proBNP ≥3000 pg/ml for patients ≥75 years of age or with atrial fibrillation); systolic blood pressure (SBP) ≥125 mmHg; mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥25 and ≤75 ml/min/1.73 m^2); and persistent HF symptoms after initial intravenous loop diuretic treatment (equivalent to ≥40 mg of furosemide). Detailed inclusion and exclusion criteria have been previously reported.[20,21] Eligible patients were randomized within 16 h of presentation to receive either intravenous serelaxin (30 μg/kg/day) for 48 h or placebo, in addition to standard care. Serelaxin had a neutral effect on the RELAX-AHF-2 co-primary endpoints (cardiovascular [CV] death through day 180 and worsening HF [WHF] through day 5) and on key secondary outcomes.[20] Hence, the two treatment arms were pooled for the present analysis.

Definitions and clinical assessment

In RELAX-AHF-2, details on the presence and severity of MR at the latest available echocardiography prior to study enrolment (history of MR) were collected. Severity of MR was reported as none, mild, moderate, or severe, in line with available recommendations.[22,23] Details on MR aetiology, MR mechanisms or methods of MR quantification were not collected. Of note, severe MR for which surgical or percutaneous intervention was indicated was an exclusion criterion.[20,21] Only patients with available data on MR status were included in the present analysis ($n = 6420$).

As previously described, patients enrolled in RELAX-AHF-2 were assessed daily during the index hospitalization and physical examination, vital signs and laboratory tests were recorded through day 5, at discharge and at day 14.[20,21] The simplified Modification of Diet in Renal Disease formula was used to calculate eGFR. Worsening renal function (WRF) was defined as any rise in creatinine ≥0.3 mg/dl from baseline through day 5.[24,25] Diuretic response was defined as weight change in kg from baseline to day 5 per 40 mg of intravenous furosemide or equivalent administered during the corresponding period.[26] In a pre-specified subset of patients, selected biomarkers were analysed at the central laboratory on blood samples collected at different time points during the index hospitalization and at day 14. After discharge, enrolled patients were followed up at pre-specified clinic visits through day 180.[20,21]

Study endpoints

The main outcome of this analysis was the time to the first event of the composite endpoint of CV death or rehospitalization for HF or renal failure (RF) through day 180. Other outcomes of interest were the two components of the composite endpoint, all-cause mortality through day 180, and WHF through day 5. An independent Clinical Events Committee reviewed and adjudicated all deaths and rehospitalization events through day 180 according to pre-specified criteria.[20,21]

Statistical analysis

Continuous variables are presented as median (interquartile range [IQR]) and were compared with the Kruskal–Wallis test. Categorical variables are presented as number and percentages and were compared with the chi-square test. Baseline characteristics, in-hospital data and clinical outcomes were compared in patients with moderate/severe MR versus those with no/mild MR. In secondary analyses, baseline characteristics and clinical outcomes were evaluated across all four MR groups (no MR, mild MR, moderate MR, and severe MR). The first occurrence of the study endpoint was evaluated in patients with moderate/severe MR or no/mild MR using the Kaplan–Meier method (log-rank test). Kaplan–Meier curves for all endpoints were also compared in all four MR groups (no MR, mild MR, moderate MR, and severe MR).

Cox proportional hazards regression analysis was performed to assess the impact of moderate/severe MR, as compared to no/mild MR, on study endpoints. Such impact was evaluated by means of univariable analysis and two multivariable models adjusting the presence of moderate/severe MR for age and sex (model 1) and for several covariates of interest (model 2), as previously reported.[24] The following variables were included for the composite endpoint at day 180, HF/RF rehospitalization at day 180, and WHF at day 5: age; sex; creatinine; haemoglobin; sodium; blood urea nitrogen (BUN); prior cerebrovascular accident; depression; airway disease (asthma, bronchitis or chronic obstructive pulmonary disease [COPD)]; history of atrial fibrillation or flutter; peripheral artery disease; heart rate; respiratory rate; SBP; oedema; intravenous loop diuretics total dose (in furosemide units) at baseline; history of diabetes mellitus; prior HF hospitalization; study treatment arm (serelaxin vs. placebo); geographical region; composite of NT-proBNP or BNP Z-score; and LVEF (per 5% increase). In the full multivariable model for CV mortality and all-cause mortality at 180 days, four variables (history of atrial fibrillation or flutter, depression, geographical region, and heart rate) were dropped from the reported variable set and body mass index (BMI) was added, as previously described.[24] Results of the Cox regression analyses are reported as hazard ratio (HR) and 95% confidence interval (CI).

Subgroup analysis was performed to assess the impact of moderate/severe MR on the composite endpoint at day 180, HF/RF rehospitalization at day 180 and CV death at day 180 in subgroups of interest by means of univariable Cox regression. Univariable and multivariable Cox regression analyses were also performed to evaluate the impact of severe MR versus no/mild/moderate MR and the impact of any MR (mild, moderate or severe) versus no MR.

All reported p-values are 2-sided, and a p-value <0.05 was considered statistically significant. Analyses were performed using R statistical software version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

Of the 6545 patients enrolled in RELAX-AHF-2, 6420 (98.1%) had available data regarding MR and were included in this analysis. Severe, moderate and mild MR were reported in 290 (4.5%), 1520 (23.7%) and 1579 (24.6%) patients, respectively, whereas 3031 patients (47.2%) had no MR.

As compared to patients with no/mild MR, patients with moderate/severe MR were older and more frequently of white race and from Eastern Europe (*Table 1*). Regarding medical history, patients with moderate/severe MR were less likely to have diabetes mellitus and more likely to have atrial fibrillation, COPD, chronic kidney disease, history of myocardial infarction, prior coronary artery bypass graft, prior percutaneous coronary intervention (PCI), ischaemic HF aetiology, prior history of HF, prior HF hospitalization and had higher New York Heart Association (NYHA) class. Patients with moderate/severe MR also had lower weight, BMI and SBP, higher degrees of dyspnoea on exertion, peripheral oedema, and jugular venous pulse (JVP), higher NT-proBNP, BUN and urea/creatinine ratio values, and lower eGFR and LVEF, as compared with the no/mild MR group. Regarding baseline therapy, beta-blockers, mineralocorticoid receptor antagonists (MRA), digoxin, oral loop diuretics, cardiac resynchronization therapy and implantable cardioverter defibrillator were used more commonly in patients with moderate/severe MR, whereas calcium channel blockers were used less frequently.

Detailed baseline characteristics across the four MR groups (no MR, mild MR, moderate MR and severe MR) are reported in online supplementary *Table S1*.

Table 1 Baseline characteristics in patients with moderate/severe vs. no/mild mitral regurgitation

Variable	No/mild MR (n = 4610)	Moderate/severe MR (n = 1810)	p-value	n
Demographics				
Age (years)	74.0 [66.0; 81.0]	75.0 [67.0; 81.0]	**0.014**	6420
Female sex	1844 (40.0)	745 (41.2)	0.410	6420
White race	4185 (90.8)	1716 (94.8)	**<0.001**	6420
Geographical region			**<0.001**	6420
America/other	1177 (25.5)	206 (11.4)		
Eastern Europe	1733 (37.6)	1057 (58.4)		
Western Europe	1700 (36.9)	547 (30.2)		
Medical history				
Hypertension	4134 (89.7)	1632 (90.3)	0.540	6416
Diabetes mellitus	2187 (47.5)	767 (42.4)	**<0.001**	6417
Atrial fibrillation	2153 (46.8)	1127 (62.4)	**<0.001**	6404
Peripheral artery disease	602 (13.2)	253 (14.1)	0.355	6353
COPD	705 (15.4)	315 (17.5)	**0.044**	6390
CKD (baseline eGFR <60 ml/min/1.73 m^2)	3135 (68.1)	1294 (71.6)	**0.007**	6412
Smoking history			**0.009**	6390
Current	531 (11.6)	164 (9.1)		
Former	1584 (34.6)	618 (34.2)		
Never	2469 (53.9)	1024 (56.7)		
Depression	445 (9.68)	158 (8.75)	0.271	6400
Cerebrovascular accident	695 (15.1)	300 (16.6)	0.150	6408
Hyperthyroidism	147 (3.20)	69 (3.82)	0.248	6404
Hypothyroidism	494 (10.8)	199 (11.0)	0.801	6403
Prior CABG	615 (13.4)	325 (18.0)	**<0.001**	6413
Prior PCI	1055 (23.0)	494 (27.5)	**<0.001**	6383
History of myocardial infarction	1389 (30.4)	720 (40.1)	**<0.001**	6362
Prior history of HF	3187 (69.2)	1588 (87.7)	**<0.001**	6416
Primary ischaemic HF aetiology	1641 (51.6)	922 (58.1)	**<0.001**	4768
Prior HF hospitalization	2121 (50.0)	1168 (66.3)	**<0.001**	5999
NYHA class (1-month prior to index admission)			**<0.001**	4672
I	160 (5.2)	49 (3.1)		
II	1271 (40.9)	544 (34.7)		
III	1349 (43.4)	797 (50.9)		
IV	326 (10.5)	176 (11.2)		
Cardiac resynchronization therapy	142 (3.1)	111 (6.2)	**<0.001**	6405
Implantable cardioverter defibrillator	346 (7.5)	225 (12.5)	**<0.001**	6413
Physical examination and vital signs				
Body mass index (kg/m^2)	29.3 [25.6; 33.7]	28.0 [24.9; 32.1]	**<0.001**	6296
Weight (kg)	83.0 [70.0; 97.0]	79.0 [68.6; 92.0]	**<0.001**	6414
Systolic blood pressure (mmHg)	140 [130; 151]	136 [130; 145]	**<0.001**	6419
Diastolic blood pressure (mmHg)	80.0 [70.0; 89.0]	79.0 [70.0; 87.0]	**0.026**	6419
Heart rate (bpm)	80.0 [70.0; 92.0]	80.0 [70.0; 91.0]	0.751	6418
Respiratory rate (breaths/min)	21.0 [18.0; 24.0]	21.0 [18.0; 24.0]	0.791	6356
Dyspnoea on exertion			**<0.001**	5987
None	17 (0.40)	5 (0.30)		
Mild	175 (4.07)	44 (2.60)		
Moderate	1790 (41.7)	626 (37.0)		
Severe (including dyspnoea at rest)	2313 (53.9)	1017 (60.1)		
Oedema			**0.019**	6017
None	681 (15.8)	222 (13.0)		
1+	1309 (30.3)	497 (29.2)		
2+	1473 (34.1)	622 (36.5)		
3+	852 (19.7)	361 (21.2)		

Table 1 (Continued)

	No/mild MR (n = 4610)	Moderate/severe MR (n = 1810)	p-value	n
Jugular venous pulse			**<0.001**	5515
<6 cm	1161 (29.3)	356 (22.8)		
6–10 cm	1837 (46.4)	760 (48.7)		
>10 cm	958 (24.2)	443 (28.4)		
Orthopnoea			0.235	6015
None	175 (4.1)	51 (3.0)		
1 pillow (10 cm)	708 (16.4)	294 (17.3)		
2 pillows (20 cm)	2053 (47.6)	817 (48.0)		
>30°	1377 (31.9)	540 (31.7)		
Rales			0.053	
None	275 (6.4)	83 (4.9)		
Rales <1/3	1698 (39.4)	684 (40.2)		
Rales 1/3–2/3	1987 (46.1)	815 (47.9)		
Rales >2/3	353 (8.2)	120 (7.0)		
Laboratory values				
NT-proBNP (pg/ml)	5831 [3432; 9331]	6534 [3839; 12 119]	**<0.001**	5141
BNP (pg/ml)	1111 [751; 1869]	1242 [775; 1824]	0.318	1279
Blood urea nitrogen (mg/dl)	23.8 [18.5; 31.7]	25.2 [19.6; 33.6]	**<0.001**	6139
Creatinine (μmol/L)	114 [97.0; 141]	114 [97.2; 140]	0.200	6404
eGFR (ml/min/1.73 m^2)	51.9 [40.0; 63.0]	50.0 [40.0; 61.0]	**0.026**	6403
Urea/creatinine (ratio)	75.2 [60.8; 92.6]	78.3 [63.1; 97.5]	**<0.001**	6135
Sodium (mmol/L)	140 [137; 142]	140 [137; 142]	0.669	6352
Potassium (mmol/L)	4.30 [3.90; 4.70]	4.30 [3.93; 4.74]	**0.032**	6293
Haemoglobin (g/L)	127 [113; 140]	126 [113; 140]	0.669	6377
Echocardiographic data				
MR degree			**<0.001**	6420
No MR	3031 (65.7)	0 (0.0)		
Mild MR	1579 (34.3)	0 (0.0)		
Moderate MR	0 (0.0)	1520 (84.0)		
Severe MR	0 (0.0)	290 (16.0)		
LVEF at index hospitalization (%)	40.0 [30.0; 50.0]	35.0 [26.0; 45.0]	**<0.001**	6012
LVEF categories			**<0.001**	6012
HFrEF (LVEF <40%)	2061 (48.1)	1064 (61.5)		
HFmrEF (LVEF 40–49%)	969 (22.6)	354 (20.5)		
HFpEF (LVEF ≥50%)	1252 (29.2)	312 (18.0)		
Aortic stenosis	399 (8.7)	237 (13.1)	**<0.001**	6406
Aortic regurgitation	687 (14.9)	698 (38.8)	**<0.001**	6402
Baseline medical therapy				
ACEi or ARBs	3036 (69.9)	1197 (68.7)	0.371	6084
Beta-blockers	3170 (73.0)	1407 (80.8)	**<0.001**	6084
MRA	1139 (26.2)	693 (39.8)	**<0.001**	6084
Calcium channel blockers	1104 (25.4)	318 (18.3)	**<0.001**	6084
Digoxin	473 (10.9)	345 (19.8)	**<0.001**	6084
Oral loop diuretics	2650 (61.0)	1323 (75.9)	**<0.001**	6084
Oral loop diuretics total daily dose (mg)	40.0 [20.0; 80.0]	40.0 [20.0; 80.0]	0.739	3945

Data are presented as n (%) or median [interquartile range]. p-values < 0.05 were considered statistically significant and are reported in bold.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CABG, coronary artery bypass graft; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention.

Table 2 In-hospital data

Variable	No/mild MR ($n = 4610$)	Moderate/severe MR ($n = 1810$)	p-value	n
Diuretic doses and length of stay				
Total IV loop diuretics dose through day 5 (mg)	160 [60.0; 280]	160 [60.0; 280]	0.736	6420
Total oral loop diuretics dose through day 5 (mg)	270 [180; 420]	280 [180; 440]	**0.033**	6403
Length of ICU and/or CCU stay (days)	2.00 [0.00; 4.00]	2.00 [0.00; 4.00]	0.200	6420
Length of hospital stay (days)	6.80 [5.02; 10.0]	6.90 [5.14; 9.89]	**0.039**	6420
Diuretic response and congestion status at day 5				
Weight loss at day 5 (% change)	−3.00 [−5.10; −1.00]	−2.80 [−5.00; −1.10]	0.082	5898
Diuretic response through day 5 (kg of weight change per 40 mg of furosemide)	−0.64 [−1.40; -0.21]	−0.60 [−1.27; −0.23]	0.440	5154
Haemoconcentration (increase of haemoglobin) at day 5	1780 (48.1)	696 (44.5)	**0.021**	5267
Dyspnoea on exertion at day 5			**<0.001**	6358
None	1527 (33.5)	469 (26.1)		
Mild	1994 (43.7)	815 (45.3)		
Moderate	676 (14.8)	356 (19.8)		
Severe (including dyspnea at rest)	362 (7.9)	159 (8.8)		
Orthopnoea (2 pillows or >30°) at day 5	678 (14.8)	256 (14.2)	0.550	6366
Oedema (any degree) at day 5	1474 (32.3)	609 (33.8)	0.258	6368
Jugular venous pulse at day 5			**0.007**	5958
<6 cm	3394 (79.2)	1268 (75.8)		
6–10 cm	558 (13.0)	269 (16.1)		
>10 cm	334 (7.8)	135 (8.1)		
Rales (any degree) at day 5	1091 (23.9)	425 (23.6)	0.816	6367
Any sign of congestion at day 5	1950 (44.4)	793 (46.4)	0.172	6095
Change in vital signs at day 5 (% change from baseline)				
Systolic blood pressure	−10.87 [−18.52; −3.23]	−10.34 [−17.01; −4.00]	0.354	6076
Diastolic blood pressure	−9.09 [−20.00; 2.13]	−7.89 [−18.18; 1.75]	0.055	6075
Heart rate	−7.69 [−18.37; 1.69]	−7.41 [−17.33; 1.64]	0.592	6048
Respiratory rate	−16.67 [−28.00; −5.26]	−18.18 [−30.00; −6.25]	**0.006**	5626
Change in renal function at day 5 (% change from baseline) and WRF				
Creatinine	3.77 [−10.02; 20.0]	0.87 [−11.45; 16.5]	**<0.001**	5418
eGFR	−4.08 [−18.95; 13.1]	−1.07 [−16.07; 15.5]	**<0.001**	5356
Blood urea nitrogen	19.2 [−7.14; 55.2]	12.0 [−13.18; 39.6]	**<0.001**	5127
Urea/creatinine (ratio)	14.8 [−4.94; 39.4]	9.01 [−9.34; 32.6]	**<0.001**	5106
WRF through day 5	1343 (29.2)	446 (24.7)	**<0.001**	6404

Data are presented as n (%) or median [interquartile range]. p-values < 0.05 were considered statistically significant and are reported in bold. Doses of loop diuretics are furosemide equivalent.
CCU, coronary care unit; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; IV, intravenous; MR, mitral regurgitation; WRF, worsening renal function.

In-hospital treatment and outcomes

Key in-hospital data are summarized in *Table 2*. Total oral loop diuretics dose through day 5 ($p = 0.033$) and length of hospital stay ($p = 0.039$) were slightly higher in patients with moderate/severe MR, as compared to those with no/mild MR, whereas total intravenous loop diuretics dose through day 5 was similar between groups. There were no significant differences between patients with moderate/severe MR and those with no/mild MR in terms of weight loss, diuretic response, orthopnoea, peripheral oedema, rales and the presence of any sign of congestion, all assessed at day 5. On the other hand, patients with moderate/severe MR less frequently had haemoconcentration (defined as an increase of haemoglobin from baseline) ($p = 0.021$) and had higher degrees of dyspnoea on exertion ($p < 0.001$) and higher degrees of JVP ($p = 0.007$) at day 5. The reduction in respiratory rate from baseline to day 5 was significantly higher among patients with moderate/severe MR ($p = 0.006$), whereas changes in SBP and heart rate were not significantly different. As compared to patients with no/mild MR, those with moderate/severe MR had a smaller decrease in eGFR ($p < 0.001$) and a smaller increase in serum creatinine ($p < 0.001$), BUN ($p < 0.001$) and urea/creatinine ratio ($p < 0.001$) from baseline to day 5. WRF through day 5 occurred more frequently in the no/mild MR group ($p < 0.001$) (*Table 2*).

Further details on symptoms and signs of congestion, vital signs, laboratory data and biomarker data in patients with

Table 3 Number of events (%) and Cox regression analyses for the impact of moderate/severe mitral regurgitation on all study endpoints

Endpoint	No. of events (event rates)		Moderate/severe MR vs. no/mild MR, HR (95% CI), *p*-value		
	No/mild MR (*n* = 4610)	Moderate/severe MR (*n* = 1810)	Univariable analysis	Multivariable model 1 (adjusted for age and sex)	Multivariable model 2 (full model)[a]
Composite endpoint at day 180	1092 (23.7)	485 (26.8)	1.15 (1.03–1.27), *p* = 0.01	1.14 (1.02–1.27), *p* = 0.02	1.03 (0.91–1.17), *p* = 0.65
HF/RF rehospitalization at day 180	827 (17.9)	385 (21.3)	1.20 (1.06–1.36), *p* = 0.003	1.20 (1.06–1.35), *p* = 0.003	1.06 (0.91–1.22), *p* = 0.47
CV death at day 180	391 (8.5)	172 (9.5)	1.11 (0.93–1.33), *p* = 0.25	1.10 (0.92–1.31), *p* = 0.32	1.02 (0.83–1.25), *p* = 0.89
All-cause death at day 180	510 (11.1)	223 (12.3)	1.10 (0.94–1.29), *p* = 0.23	1.08 (0.92–1.27, *p* = 0.33	1.04 (0.87–1.25), *p* = 0.68
Worsening HF at day 5	339 (7.4)	130 (7.2)	0.96 (0.79–1.18), *p* = 0.72	0.96 (0.78–1.17), *p* = 0.65	0.88 (0.69–1.13), *p* = 0.32

BNP, B-type natriuretic peptide; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; HF, heart failure; HR, hazard ratio; IV, intravenous; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RF, renal failure.

[a]Composite endpoint at day 180, HF/RF rehospitalization at day 180, and worsening HF at day 5 were adjusted for: creatinine (μmol/L); haemoglobin (g/L); sodium (mmol/L); blood urea nitrogen (mg/dl); cerebrovascular accident; depression; asthma/bronchitis/COPD; atrial fibrillation/flutter; peripheral artery disease; heart rate (bpm); respiratory rate (breaths/min); systolic blood pressure (mmHg); oedema; IV loop diuretics total dose (in furosemide units) at baseline; history of diabetes mellitus; prior HF hospitalization; actual study treatment (serelaxin vs. placebo); grouped geographical region; composite of NT-proBNP or BNP Z-score; sex; age (years); LVEF per 5% increase.

CV death at day 180 and all-cause death at day 180 were adjusted for: creatinine (μmol/L); haemoglobin (g/L); sodium (mmol/L); blood urea nitrogen (mg/dl); asthma/bronchitis/COPD; peripheral artery disease; respiratory rate (breaths/min); systolic blood pressure (mmHg); body mass index (kg/m^2); oedema; IV loop diuretics total dose (in furosemide units) at baseline; history of diabetes mellitus; prior HF hospitalization; actual study treatment (serelaxin vs. placebo); composite of NT-proBNP or BNP Z-score; sex; age (years); LVEF per 5% increase.

moderate/severe MR versus no/mild MR at different time points during the index hospitalization are reported in online supplementary *Tables S2–S5*. Higher degrees of dyspnoea on exertion and JVP were reported in patients with moderate/severe MR at all time points (online supplementary *Table S2*), and the reduction in respiratory rate from baseline was larger in patients with moderate/severe MR at all time points (online supplementary *Table S3*). The significant differences between moderate/severe MR and no/mild MR groups in the percent change of creatinine, eGFR, BUN and urea/creatinine ratio were observed in most of the time points (online supplementary *Table S4*). Regarding biomarkers, a significantly lower decrease of NT-proBNP from baseline to day 2, day 5 and day 14, and a significantly lower decrease of serum soluble suppression of tumorigenicity 2 from baseline to day 2 and day 5 were observed in patients with moderate/severe MR (online supplementary *Table S5*).

Clinical outcomes

Number of patients with clinical events, event rates and results of the Cox regression analyses are reported in *Table 3*. The composite endpoint of CV death or HF/RF rehospitalization through day 180 occurred in 26.8% of patients with moderate/severe MR as compared to 23.7% of patients with no/mild MR (unadjusted HR 1.15, 95% CI 1.03–1.27, $p = 0.01$). The Kaplan–Meier curves for the composite endpoint differed significantly between the two groups (log-rank *p*-value = 0.012) (*Figure 1*). The significant impact of moderate/severe MR on the composite endpoint was maintained after multivariable adjustment in one model including only age and sex (HR 1.14, 95% CI 1.02–1.27, $p = 0.02$), but not in another model including more variables (model 2; HR 1.03, 95% CI 0.91–1.17, $p = 0.65$).

Moderate/severe MR was not associated with a significantly higher risk of CV mortality or all-cause mortality through day 180 and WHF through day 5 (*Table 3* and *Figure 1*). The impact of moderate/severe MR on the composite endpoint was mainly driven by the higher rate of HF/RF rehospitalization at day 180. This event occurred in 21.3% of the patients with moderate/severe MR versus 17.9% of those with no/mild MR (unadjusted HR 1.20, 95% CI 1.06–1.36, $p = 0.003$) (*Table 3* and *Figure 1*). Similar to the composite endpoint, the higher risk of HF/RF rehospitalization at day 180 in patients with moderate/severe MR was confirmed after multivariable adjustment for age and sex (HR 1.20, 95% CI 1.06–1.35, $p = 0.003$), but not after adjustment in the full multivariable model (HR 1.06, 95% CI 0.91–1.22, $p = 0.47$).

At subgroup analyses, moderate/severe MR was associated with a higher risk of the composite endpoint, HF/RF rehospitalization and CV mortality at day 180 in the subgroup of patients with LVEF <50%, and with a higher risk of the composite endpoint and HF/RF rehospitalization at day 180 in the subgroup of patients with eGFR ≥45 ml/min/1.73 m^2. However, *p*-values for the interaction between moderate/severe MR and LVEF subgroups (<50% vs.

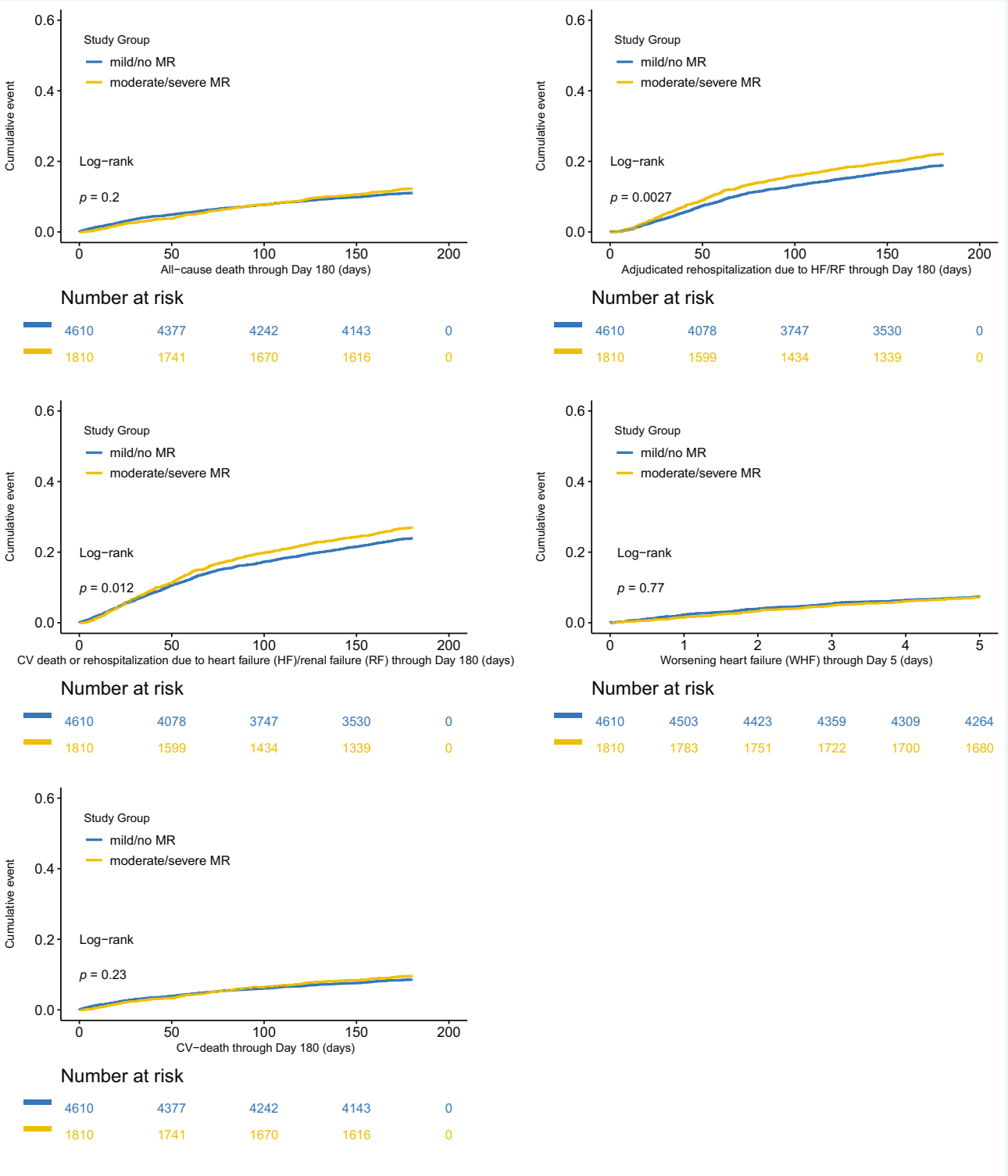


Figure 1 Kaplan–Meier curves for all endpoints in patients with moderate/severe versus no/mild mitral regurgitation (MR). The figure shows Kaplan–Meier curves for all-cause mortality through day 180, heart failure/renal failure (HF/RF) rehospitalization through day 180, composite of cardiovascular (CV) death or HF/RF rehospitalization through day 180, CV death through day 180, and worsening heart failure (WHF) through day 5 in patients with moderate/severe MR versus those with no/mild MR. The log-rank *p*-value is also reported.

Table 4 Impact of moderate/severe vs. no/mild mitral regurgitation on clinical outcomes in subgroups of interest

Subgroups	No. of events (%) in moderate/severe MR	No. of events (%) in no/mild MR	Moderate/severe MR vs. no/mild MR within each subgroup, HR (95% CI), *p*-value	*p*-value for interaction[a]
Composite endpoint of CV death or rehospitalization due to HF/RF through day 180				
LVEF subgroups				0.39
LVEF <50%	385/1418 (27.1)	691/3030 (22.8)	1.22 (1.08–1.38), $p = 0.002$	
LVEF ≥50%	75/312 (24.0)	285/1252 (22.8)	1.08 (0.83–1.39), $p = 0.58$	
eGFR subgroups				0.28
eGFR <45 ml/min/1.73 m^2	248/741 (33.5)	569/1799 (31.6)	1.07 (0.93–1.25), $p = 0.35$	
eGFR ≥45 ml/min/1.73 m^2	237/1067 (22.2)	521/2805 (18.6)	1.21 (1.04–1.41), $p = 0.02$	
HF/RF rehospitalizations through day 180				
LVEF subgroups				0.67
LVEF <50%	304/1418 (21.4)	533/3030 (17.6)	1.25 (1.09–1.44), $p = 0.002$	
LVEF ≥50%	61/312 (19.6)	214/1252 (17.1)	1.17 (0.88–1.55), $p = 0.29$	
eGFR subgroups				0.58
eGFR <45 ml/min/1.73 m^2	201/741 (27.1)	430/1799 (23.9)	1.15 (0.98–1.36), $p = 0.09$	
eGFR ≥45 ml/min/1.73 m^2	184/1067 (17.2)	396/2805 (14.1)	1.24 (1.04–1.47), $p = 0.02$	
CV death through day 180				
LVEF subgroups				0.24
LVEF <50%	143/1418 (10.1)	249/3030 (8.2)	1.23 (1.00–1.51), $p = 0.048$	
LVEF ≥50%	21/312 (6.7)	93/1252 (7.4)	0.91 (0.56–1.46), $p = 0.68$	
eGFR subgroups				0.47
eGFR <45 ml/min/1.73 m^2	92/741 (12.4)	214/1799 (11.9)	1.04 (0.81–1.33), $p = 0.75$	
eGFR ≥45 ml/min/1.73 m^2	80/1067 (7.5)	176/2805 (6.3)	1.19 (0.91–1.55), $p = 0.20$	

CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; RF, renal failure.
[a]*p*-value for interaction = *p*-value for interaction between moderate/severe MR vs. no/mild MR and the subgroup of interest.

≥50%) and between moderate/severe MR and eGFR subgroups (<45 ml/min/1.73 m^2 vs. ≥45 ml/min/1.73 m^2) were not significant (all *p*-values >0.10) (*Table 4*).

Similar findings were observed when severe MR alone was compared with milder degrees of MR, though without reaching statistical significance also at univariable analysis because of the smaller number of events (online supplementary *Table S6* and *Figure S1*). In a further sub-analysis, any MR (mild/moderate/severe MR) was associated with a higher risk of HF/RF rehospitalization at day 180 at univariable analysis and after adjustment for age and sex but not after full multivariable adjustment (online supplementary *Table S7*).

Discussion

Our *post-hoc* analysis of 6420 patients included in the RELAX-AHF-2 trial, one of the largest databases of patients with AHF, shows that moderate/severe MR was associated with more severe HF at the time of admission, higher rates of residual dyspnoea on exertion, increased JVP through hospitalization and longer length of hospital stay, but did not have an independent impact on clinical outcomes. The impact of moderate/severe MR on HF/RF rehospitalization at day 180 and on the composite endpoint of CV death or HF/RF rehospitalization at day 180 was significant at univariable analyses and was maintained after adjustment for age and sex, but not after extensive adjustment in a previously validated multivariable model including several variables of interest (*Graphical Abstract*).[24]

In our study, moderate/severe MR was observed at last available echocardiography before enrolment in 28.2% of patients, a rate that is lower as compared to recent studies in patients with AHF, reporting rates between 36% and 64%.[2,4,19] This discrepancy is likely related to the inclusion criteria of RELAX-AHF-2 which included only patients with a SBP ≥125 mmHg and/or with an eGFR ≥25 ml/min/1.73 m^2. Thus, RELAX-AHF-2 enrolled patients with AHF and a relatively low risk of events whereas the prevalence of MR increases with severity of HF.[21,27] Second, the use of historical data as regards echocardiography may have led to underestimation of the rate and severity of MR since this may be increased in patients with worsening HF as those enrolled in RELAX-AHF-2.

In our analysis, moderate/severe MR was associated with longer length of hospital stay and signs of increased residual congestion and/or lower decongestion through the index hospitalization. Indeed, as compared to patients with no/mild MR, those with moderate/severe MR had higher rates of residual dyspnoea on exertion and increased JVP through hospitalization, lower occurrence of haemoconcentration, lower increase of BUN and urea/creatinine

ratio, and a lower rate of WRF at day 5. Haemoconcentration and an increase in serum creatinine occurring late during an AHF hospitalization have been associated with plasma volume reduction and aggressive decongestion and better post-discharge outcomes.[28–31]

Moderate/severe MR was associated with a higher risk of the combined endpoint and of HF/RF rehospitalization at day 180 at univariable analysis and after adjustment for age and sex alone at multivariable analysis. This association remained significant in patients with LVEF <50% or with eGFR ≥45 ml/min/1.73 m^2, although no significant interaction was found with the other LVEF or eGFR subgroups. The prognostic impact of moderate/severe MR on HF/RF rehospitalization at day 180 was lost in a previously validated full multivariable model including history of prior HF hospitalization and other relevant covariates.[24] This finding is consistent with the strong relationship between moderate/severe MR and variables related to HF severity such as HF hospitalization and others included in our previously validated model.[32–35]

Our results at multivariable analysis are at variance with previous studies showing the impact of MR on outcomes in patients with either acute or chronic HF.[2,5–18] However, most of those studies analysed a relatively limited sample size and/or included predominantly patients with reduced LVEF,[5–18] with only a few of them focusing specifically on patients with AHF.[2,19] In contrast, we evaluated the significance of MR in a large, well-characterized, population of patients with AHF enrolled in RELAX-AHF-2. Patients enrolled in clinical trials are, however, highly selected compared to patients in clinical practice with a lower proportion of comorbidities and better adherence to medical treatment. Our findings may be compared with a recent analysis on 3878 patients enrolled in the ARIC study, who were hospitalized for AHF and had available echocardiographic data, demonstrating a significant impact of moderate/severe MR on 1-year mortality.[2] In this study, the prognostic role of moderate/severe MR on 1-year mortality was reported in AHF patients with LVEF <50%, and was confirmed also after multivariable adjustment for several variables of interest (odds ratio 1.30, 95% CI 1.16–1.45, $p < 0.0001$). However, history of prior HF hospitalization was not included in their full multivariable model.[2] Conversely, moderate/severe MR was not independently associated with 1-year mortality in AHF patients with LVEF ≥50%.[2] Furthermore, a recent single-centre, retrospective study on 2303 AHF patients with LVEF <50% confirmed these findings, showing that moderate or higher MR on admission was independently associated with increased 6-month HF rehospitalization and 1-year mortality.[19]

The lack of independent association between moderate/severe MR and clinical outcomes in our study may have multiple explanations. First, historical data may have led to underestimation of MR severity.[15] In contrast, recent studies describing MR in AHF reported details from echocardiography performed during the index hospitalization.[2,4,19] Furthermore, details on MR aetiology and quantification of MR severity were not available, hence we could not differentiate patients with primary and secondary MR or evaluate the impact of quantitative parameters (e.g. effective regurgitant orifice area) on outcomes, as done in previous studies.[18] Lastly, it may well be that MR has a greater impact on HF symptoms and rehospitalizations, as shown by our data, than on mortality alone. Further prospective studies are needed to better characterize the relationship between MR and outcomes in AHF, focusing on serial assessment of MR severity during the hospitalization for AHF and its interplay with treatment, detailing MR aetiology, and evaluating the impact of quantitative MR assessment.

Study limitations

The present study is a *post-hoc* analysis of the RELAX-AHF-2 trial, hence the collection of variables used in this analysis was not designed specifically to evaluate the association between MR and outcomes. Confounding variables that were not identified or considered may have influenced the study results. A major limitation is the lack of a central core-laboratory analysis of echocardiographic images and, therefore, the lack of detailed information regarding MR aetiology and quantitative MR grading. Furthermore, MR status was obtained by local investigators from the last available echocardiography performed prior to study enrolment and not during the index hospitalization with different time intervals between examination and time of randomization, thus potentially influencing the results with respect of the association between MR and outcomes. As previously noted, RELAX-AHF-2 inclusion criteria resulted in the enrolment of a lower risk population as compared to other AHF registry-based studies,[36] whereas inclusion of patients with SBP <125 mmHg or receiving inotropic support may have increased the number of patients with clinical events through follow-up. Finally, follow-up was performed for 180 days in RELAX-AHF-2, thus the impact of MR on long-term outcomes could not be assessed.

Conclusions

In patients with AHF enrolled in RELAX-AHF-2, a history of moderate/severe MR was reported in 28.2% of patients and was associated with a worse clinical profile, longer length of hospital stay, signs of increased residual congestion and less decongestion during the index hospitalization. The relation between moderate/severe MR and the composite of CV death or HF/RF rehospitalization at day 180, significant at univariable analysis, was lost in a multivariable model including several relevant variables.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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