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RESEARCH ARTICLE

Impact of mitral regurgitation in patients with worsening heart failure: insights from BIOSTAT-CHF

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Aims Few data regarding the prevalence and prognostic impact of mitral regurgitation (MR) in patients with worsening chronic or new-onset acute heart failure (HF) are available. We investigated the role of MR in the BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF).

Methods and results We performed a retrospective *post-hoc* analysis including patients from both the index and validation BIOSTAT-CHF cohorts with data regarding MR status. The primary endpoint was a composite of all-cause death or HF hospitalization. Among 4023 patients included, 1653 patients (41.1%) had moderate–severe MR. Compared to others, patients with moderate–severe MR were more likely to have atrial fibrillation and chronic kidney disease and had larger left ventricular (LV) dimensions, lower LV ejection fraction (LVEF), worse quality of life, and higher plasma concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP). A primary outcome event occurred in 697 patients with, compared to 836 patients without, moderate–severe MR [Kaplan–Meier 2-year estimate: 42.2% vs. 35.3%; hazard ratio (HR) 1.28; 95% confidence interval (CI) 1.16–1.41; log-rank $P < 0.0001$]. The association between MR and the primary endpoint remained significant after adjusting for baseline variables and the previously validated BIOSTAT-CHF risk score (adjusted HR 1.11; 95% CI 1.00–1.23; $P = 0.041$). Subgroup analyses showed a numerically larger impact of MR on the primary endpoint in patients with lower LVEF, larger LV end-diastolic diameter, and higher plasma NT-proBNP.

Conclusions Moderate–severe MR is common in patients with worsening chronic or new-onset acute HF and is strongly associated with outcome, independently of other features related to HF severity.

Keywords Mitral regurgitation • Heart failure • Valvular heart disease • Mortality • Hospitalization

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Introduction

Heart failure (HF) remains a major cause of morbidity and mortality worldwide.[1,2] In particular, the prognosis of patients with worsening HF leading to hospitalizations or emergency visits is poor, with high rates of rehospitalization and mortality.[3–6]

Mitral regurgitation (MR) is the most common valvular heart disease in HF patients, affecting almost one-third of patients with chronic HF and about half of those with acute HF.[7–9] Accordingly, it has emerged as a therapeutic target in HF patients.[10,11] However, randomized trials with percutaneous treatment of functional MR yielded different results and the subsets of patients who may benefit more from this treatment remain uncertain.[12–16] Previous studies demonstrated the prognostic impact of MR in patients with HF.[17–28] However, only few studies included patients with worsening chronic or new-onset acute HF and/or with preserved left ventricular ejection fraction (LVEF).[19,20,28–30] Thus, further assessment of the impact of MR on outcomes of HF patients seems warranted.

The aim of this study was to assess the prognostic impact of MR in a selected population with worsening chronic or new-onset acute HF enrolled in the large, prospective, multicentre BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF), focussed on guideline-directed medical therapy optimization.[31]

Methods

Study design and study population

We retrospectively analysed data from BIOSTAT-CHF, a multicentre European study enrolling patients with new-onset or worsening chronic HF between 2010 and 2014.[31–33] It included an index cohort of 2516 patients enrolled from 69 centres in 11 European countries and a validation cohort of 1738 patients from six centres in Scotland. Patients from the index cohort had symptoms of new-onset or worsening chronic HF, confirmed either by LVEF ≤40% or B-type natriuretic peptide (BNP) >400 pg/mL and/or N-terminal pro-BNP (NT-proBNP) >2000 pg/mL and were treated with oral or intravenous furosemide ≥40 mg/day or equivalent at inclusion. Patients from the validation cohort had an HF diagnosis based on left ventricular (LV) dysfunction or a previous admission for HF requiring diuretic treatment and had to be treated with furosemide ≥20 mg/day or equivalent. The study was approved by the ethics committees of all participating centres and all patients provided written informed consent.

For the purposes of the present study, the index and validation cohorts were merged ($n = 4254$ patients). Patients without echocardiography performed at inclusion ($n = 180$) and patients with available echocardiography but without information on MR ($n = 51$) were excluded. Therefore, a total of 4023 patients were included in the final analysis.

Definitions and study endpoints

Patients underwent two-dimensional transthoracic echocardiography at inclusion using a commercially available echocardiography (3.5 MHz probe). MR was identified and evaluated using two-dimensional and colour Doppler echocardiography.[34] According to the study protocol, only the presence of moderate or severe MR at baseline echocardiography (as compared to no or mild MR) was recorded. Both patients with primary and secondary MR were enrolled, but detailed data on MR mechanism or aetiology were not collected. Quantification of LV diameters, LVEF according to the modified Simpson rule, and left atrium diameter was also performed. LV remodelling was evaluated according to the relative wall thickness and LV mass index as previously reported.[35] Baseline clinical characteristics, quality of life (QoL) measures and laboratory data at inclusion, and clinical outcomes at follow-up were also analysed.

The primary endpoint was the composite of all-cause mortality or HF hospitalization. Secondary outcomes of interest were all-cause mortality and cardiovascular (CV) mortality as individual endpoints.

Statistical analyses

Continuous variables are presented as mean ± standard deviation or median (interquartile range, IQR), as appropriate, and were compared with the unpaired Student's *t*-test or the Mann–Whitney U test, respectively. Categorical variables are presented as number and percentages and were compared with the χ^2 test. Baseline characteristics, echocardiography data, QoL measures, laboratory data, primary and secondary endpoints were compared between patients with vs. without moderate–severe MR. The first occurrence of the primary and secondary endpoint was evaluated in patients with or without moderate–severe MR using the Kaplan–Meier method (log-rank test). For all evaluated endpoints, follow-up was censored at 2 years. Cox proportional hazards regression analysis was also performed to assess the prognostic impact of moderate–severe MR on primary and secondary endpoints. Such impact was evaluated by means of univariable analysis and multiple multivariable models adjusting the presence of MR for the following covariates of interest: age and sex (demographic model); primary ischaemic HF aetiology, peripheral oedema, New York Heart Association (NYHA) class, and previous HF hospitalization in last year (clinical model); and the already validated BIOSTAT-CHF risk prediction models.[32] Results of the Cox regression analyses are reported as unadjusted or adjusted hazard ratio (HR) and 95% confidence interval (CI). Subgroup analysis was also performed to evaluate the impact of moderate–severe MR on the primary endpoint in subgroups of interest by means of multivariable Cox regression adjusted for age and sex.

All reported *P*-values are 2-sided, and a $P < 0.05$ was considered statistically significant.

Statistical analyses were performed using STATA version 13.0 (STATA Corp., College Station, TX, USA) and R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline patient characteristics

Among the 4023 patients included in the present study, 1653 patients (41.1%) had moderate–severe MR and 2370 patients (58.9%) had no moderate–severe MR at baseline. Baseline characteristics of the study population are reported in *Table 1*. Compared to patients with no or mild MR, patients with moderate–severe MR were less likely to be men and to have a history of ischemic heart disease, myocardial infarction, percutaneous coronary intervention, prior valve surgery, peripheral artery disease, diabetes mellitus, and chronic obstructive pulmonary disease. They were more likely to have history of atrial fibrillation, HF hospitalization in

Table 1 Baseline clinical characteristics

	Overall (n = 4023)	Moderate or severe MR (n = 1653)	No or mild MR (n = 2370)	P-value
Age (years)	70.8 ± 11.7	70.6 ± 11.8	71.0 ± 11.6	0.279
Male sex	2843 (70.7)	1139 (68.9)	1704 (71.9)	**0.040**
BMI (kg/m^2)	28.3 ± 5.9	27.4 ± 5.5	28.9 ± 6.1	**<0.001**
HF hospitalization in last year	1184 (29.6)	528 (32.1)	656 (27.9)	**0.004**
Primary ischaemic HF aetiology	2125 (61.2)	822 (56.1)	1303 (64.8)	**<0.001**
Smoking				0.849
Past	1705 (42.5)	698 (42.4)	1007 (42.6)	
Current	561 (14.0)	225 (13.7)	336 (14.2)	
Medical history				
Hypertension	2438 (60.7)	974 (59.1)	1464 (61.8)	0.081
Diabetes mellitus	1301 (32.4)	501 (30.3)	800 (33.4)	**0.019**
Atrial fibrillation	1810 (45.1)	799 (48.5)	1011 (42.8)	**<0.001**
Myocardial infarction	1711 (42.6)	651 (39.4)	1060 (44.8)	**0.001**
PCI	809 (20.2)	298 (18.1)	511 (21.7)	**0.005**
CABG	704 (17.5)	278 (16.8)	426 (18.0)	0.339
Prior valvular surgery	272 (6.8)	92 (5.6)	180 (7.6)	**0.012**
Peripheral artery disease	609 (15.3)	218 (13.3)	391 (16.7)	**0.003**
COPD	716 (17.9)	270 (16.4)	446 (18.9)	**0.044**
Stroke	520 (13.0)	195 (11.8)	325 (13.8)	0.073
Current malignancy	163 (4.1)	60 (3.6)	103 (4.4)	0.257
CKD	1390 (34.8)	610 (37.0)	780 (33.2)	**0.012**
Device therapy				**0.001**
Pacemaker	280 (7.0)	112 (6.8)	168 (7.1)	
ICD	248 (6.2)	121 (7.3)	127 (5.4)	
CRT-P	66 (1.6)	33 (2.0)	33 (1.4)	
CRT-D	202 (5.0)	104 (6.3)	98 (4.1)	
NYHA functional class				**0.014**
I	70 (1.8)	25 (1.5)	45 (1.9)	
II	1511 (38.2)	578 (35.5)	933 (40.1)	
III	1880 (47.5)	805 (49.4)	1075 (46.2)	
IV	498 (12.6)	222 (13.6)	276 (11.9)	
Clinical profile				
Peripheral oedema	1022 (29.6)	438 (30.7)	584 (28.8)	0.209
Hepatomegaly	397 (10.2)	210 (13.1)	187 (8.2)	**<0.001**
SBP (mmHg)	125 ± 22	123 ± 21	127 ± 22	**<0.001**
DBP (mmHg)	73 ± 14	73 ± 13	72 ± 14	0.120
HR (bpm)	78 ± 19	79 ± 19	77 ± 18	**<0.001**
Type of visit				0.124
Inpatient hospitalization	2462 (61.2)	1035 (62.6)	1427 (60.2)	
Outpatient clinic	1561 (38.8)	618 (37.4)	943 (39.8)	
HF therapy				
ACEi/ARB use	2884 (71.8)	1171 (71.0)	1713 (72.4)	0.347
β-blocker use	3172 (79.0)	1329 (80.6)	1843 (77.9)	**0.037**
MRA use	1803 (44.9)	838 (50.8)	965 (40.8)	**<0.001**
Loop diuretic use	3988 (99.3)	1642 (99.6)	2346 (99.1)	0.083
Digoxin use	764 (19.0)	375 (22.7)	389 (16.4)	**<0.001**

Data are presented as n (%) and mean ± standard deviation.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; DBP, diastolic blood pressure; HF, heart failure; HR, heart rate; ICD, implantable cardioverter-defibrillator; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.

the last year, and chronic kidney disease, had higher heart rate and more advanced symptoms as shown by their higher NYHA functional class. β-blockers were more frequently used at baseline in patients with, compared to those without, moderate–severe MR, whereas use of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) was similar between groups.

Detailed baseline characteristics in the index cohort and validation cohort are reported in online supplementary *Tables S1* and *S2*, respectively.

Echocardiographic data, laboratory findings, and quality of life measures

Echocardiographic, laboratory, and QoL characteristics are reported in *Table 2*. Mean LVEF was lower in patients with moderate–severe MR compared to those with no or mild MR. Accordingly, patients with moderate-to-severe MR were more likely to have HF with reduced ejection fraction (HFrEF; LVEF <40%) rather than with mid-range (HFmrEF; LVEF 40–49%) or preserved LVEF (HFpEF; LVEF ≥50%). Moreover, mean LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), and left atrium diameter were greater in patients with, compared to those without, moderate–severe MR.

Regarding laboratory data, patients with moderate–severe MR had higher values of serum creatinine, urea, and plasma NT-proBNP, and lower estimated glomerular filtration rate compared to those with no or mild MR. Regarding QoL measures, the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score, KCCQ overall summary score, and EuroQol-5 Dimension (EQ-5D) visual analogue scale score were lower among patients with moderate–severe MR compared to those with no or mild MR (*Table 2*).

Detailed echocardiographic, laboratory and QoL data in the index cohort and validation cohort are reported in online supplementary *Tables S3* and *S4*, respectively.

Clinical outcome

A primary outcome event at 2 years occurred in 697 patients (42.2%) with moderate–severe MR and in 836 patients (35.3%) without moderate–severe MR. Accordingly, the 2-year incidence of

Table 2 Baseline echocardiographic data, laboratory characteristics, and quality of life measures

	Overall (*n* = 4023)	Moderate or severe MR (*n* = 1653)	No or mild MR (*n* = 2370)	*P*-value
Echocardiographic data				
LVEF (%)	35 (25–42)	30 (25–38)	35 (30–45)	**<0.001**
LVEF categories				**<0.001**
HFrEF (LVEF <40%)	2514 (66.7)	1215 (77.5)	1299 (59.0)	
HFmrEF (LVEF 40–49%)	679 (18.0)	220 (14.0)	459 (20.8)	
HFpEF (LVEF ≥50%)	577 (15.3)	132 (8.4)	445 (20.2)	
LV remodelling				**<0.001**
Normal geometry	440 (18.5)	175 (15.8)	265 (20.8)	
Concentric remodelling	143 (6.0)	36 (3.3)	107 (8.4)	
Concentric hypertrophy	509 (21.4)	186 (16.8)	323 (25.3)	
Eccentric hypertrophy	1290 (54.2)	708 (64.1)	582 (45.6)	
LVEDD (mm)	59 (52–65)	62 (56–68)	57 (50–63)	**<0.001**
LVESD (mm)	49 (41–56)	52 (44–58)	46 (39–54)	**<0.001**
Left atrium diameter (mm)	46 (42–51)	48 (44–53)	45 (40–50)	**<0.001**
Laboratory data				
Haemoglobin (g/dL)	13.3 (11.9–14.5)	13.2 (11.9–14.4)	13.3 (11.9–14.6)	0.202
Creatinine (μmol/L)	100 (82–128)	104 (83–133)	98 (81–125)	**<0.001**
eGFR CKD-EPI (mL/min/1.73 m^2)	60 (44–78)	57 (42–76)	61 (45–79)	**<0.001**
Urea (mmol/L)	9.6 (7.0–15.1)	10.7 (7.5–17.1)	9.2 (6.8–13.8)	**<0.001**
Sodium (mmol/L)	139 (137–141)	139 (137–142)	139 (137–141)	0.606
NT-proBNP (ng/L)	2080 (824–4868)	2847 (1211–6100)	1632 (590–4025)	**<0.001**
QoL measures				
KCCQ clinical summary score	48 (30–69)	45 (27–65)	49 (31–70)	**<0.001**
KCCQ overall summary score	48 (32–67)	46 (31–65)	49 (33–68)	**<0.001**
EQ-5D index value	0.72 (0.57–0.84)	0.72 (0.57–0.84)	0.74 (0.57–0.84)	0.168
EQ-5D VAS	55 (45–70)	52 (40–70)	59 (45–70)	**0.003**

Data are presented as *n* (%) and median (Q25–Q75).
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; EQ-5D, EuroQol-5 Dimension; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; QoL, quality of life; VAS, visual analogue scale.

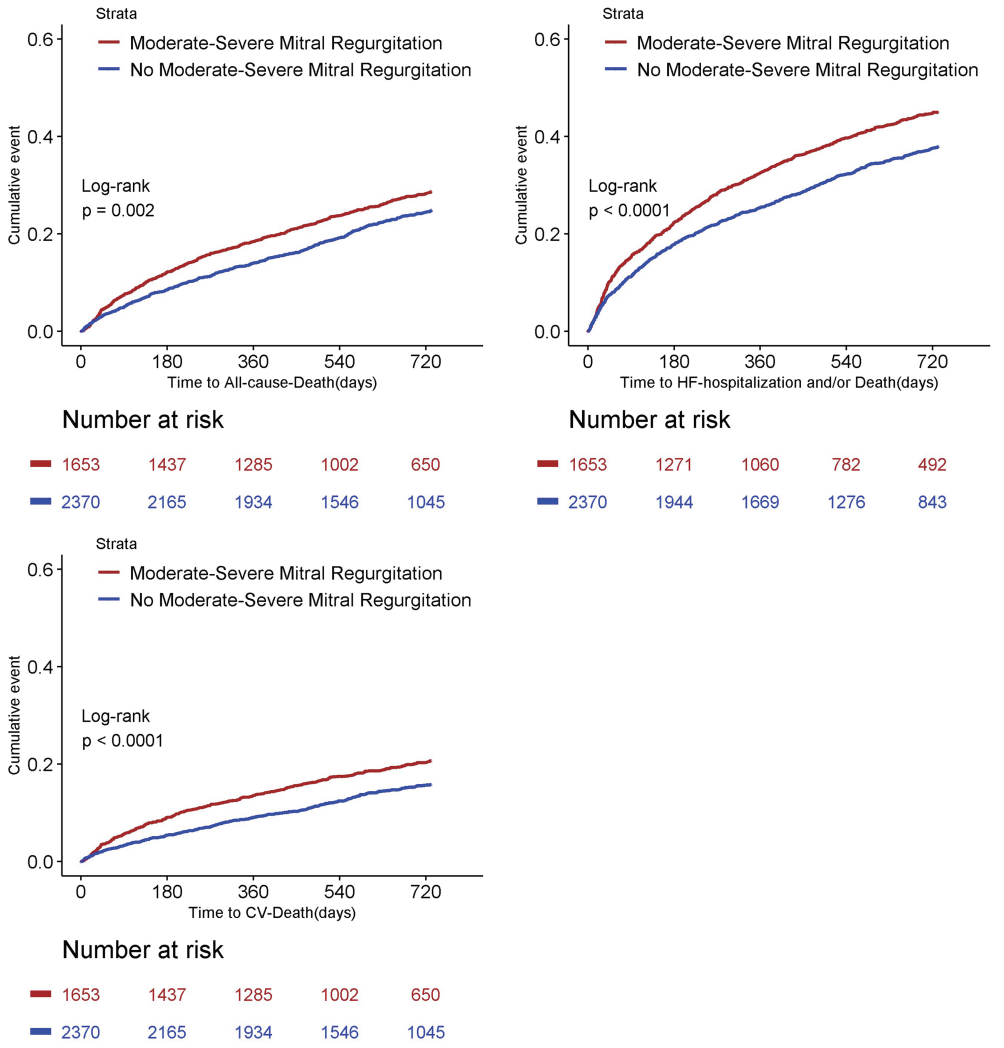

Figure 1 Kaplan–Meier curves for clinical outcomes in patients with vs. without moderate–severe mitral regurgitation. The figure shows Kaplan–Meier curves for 2-year all-cause mortality (upper left panel), cardiovascular (CV) mortality (lower panel), and the combined endpoint of all-cause mortality or heart failure (HF) hospitalization (upper right panel) in patients with vs. without moderate–severe mitral regurgitation.

the primary endpoint was higher in patients with moderate–severe MR compared to those with no moderate–severe MR at Kaplan–Meier analysis (log-rank $P < 0.0001$; *Figure 1*). The 2-year incidence of both individual secondary endpoints was higher in patients with moderate–severe MR compared to the others (*Figure 1*): all-cause death (26.3% vs. 22.6%; log-rank $P = 0.002$) and CV death (18.3% vs. 13.7%; log-rank $P < 0.0001$).

Univariable Cox regression analysis confirmed the significant association between moderate–severe MR and the primary endpoint, all-cause death, and CV death. As shown in *Table 3*, the significant impact of moderate–severe MR on the primary endpoint was confirmed also after multivariable adjustment for different models including, respectively, age and sex (model 1); primary ischaemic HF aetiology, peripheral oedema, NYHA class, and previous HF hospitalization in last year (model 2); and the BIOSTAT-CHF risk prediction score (model 3). The risk of both individual secondary endpoints remained higher in patients with moderate–severe MR also after multivariable adjustment for model 1 and model 2 (*Table 3*). After adjustment for model 3, moderate–severe MR remained significantly associated with CV death, but not with all-cause death.

In subgroup analyses, the impact of moderate–severe MR on the primary endpoint was significant for both patients with and without HF hospitalization in previous year, with and without ischaemic HF aetiology, with or without history of atrial fibrillation, and with estimated glomerular filtration rate ≤60 and >60 mL/min/1.73 m^2. On the other hand, the impact of moderate–severe MR on the primary endpoint was significant only in patients with NYHA class I–II and III, in the two lowest LVEF tertiles (≤30% and 31–39%), in the two largest LVEDD tertiles (56–63 mm and ≥64 mm), and in the highest NT-proBNP tertile (≥3621 pg/mL) (*Figure 2*). Kaplan–Meier curves for the primary endpoint according to LVEF subgroups are

Table 3 **Cox regression models for the impact of moderate–severe mitral regurgitation on 2-year combined endpoint (all-cause death or heart failure hospitalization), all-cause death and cardiovascular death**

	Combined endpoint		All-cause death		CV death	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Univariable analysis	1.28 (1.16–1.41)	**<0.001**	1.22 (1.08–1.39)	**0.002**	1.40 (1.19–1.63)	**<0.001**
Multivariable model 1 (adjusted for age and sex)	1.30 (1.18–1.44)	**<0.001**	1.25 (1.10–1.42)	**<0.001**	1.43 (1.22–1.67)	**<0.001**
Multivariable model 2 (adjusted for primary ischaemic HF aetiology, peripheral oedema, NYHA class, and previous HF hospitalization in last year)	1.23 (1.09–1.38)	**<0.001**	1.19 (1.03–1.38)	**0.017**	1.40 (1.17–1.67)	**<0.001**
Multivariable model 3 (adjusted for BIOSTAT-CHF risk prediction models)[a]	1.11 (1.00–1.23)	**0.041**	1.08 (0.95–1.22)	0.249	1.22 (1.04–1.43)	**0.014**

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.
[a]In multivariable model 3, moderate-to-severe mitral regurgitation was adjusted for the BIOSTAT-CHF risk prediction models, including the following covariates: age, HF hospitalization in last year, systolic blood pressure, peripheral oedema, log-NT-proBNP, haemoglobin, sodium, high-density lipoprotein, and use of beta-blockers at baseline for the combined endpoint; age, log-urea, log-NT-proBNP, haemoglobin, and use of beta-blockers at baseline for all-cause death and CV death; age, HF hospitalization in last year, systolic blood pressure, peripheral oedema, and estimated glomerular filtration rate for HF hospitalization.

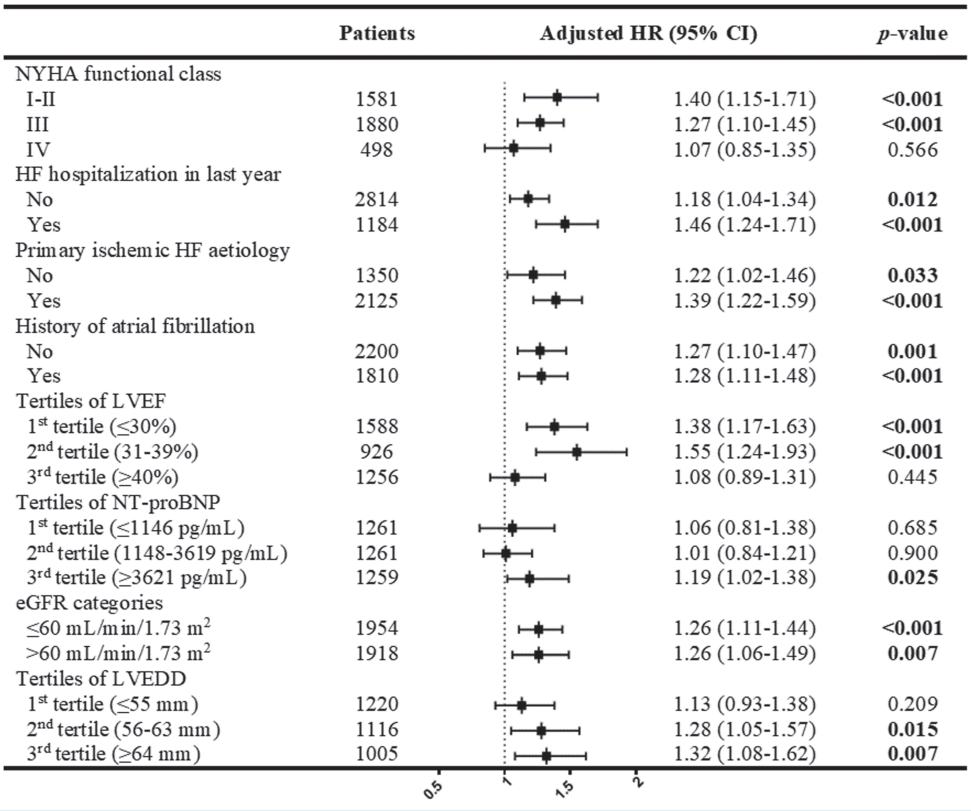

Figure 2 Impact of moderate–severe mitral regurgitation on 2-year primary endpoint in subgroups of interest. The figure shows the impact of moderate–severe mitral regurgitation on 2-year all-cause mortality or heart failure (HF) hospitalization at 2 years according to relevant subgroups. Such impact was evaluated by means of multivariable Cox regression adjusted for age and sex, and results are presented as adjusted hazard ratios (HR) and 95% confidence intervals (CI). eGFR, estimated glomerular filtration rate; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

reported in online supplementary *Figure S1*, confirming the significant impact of moderate–severe MR in the two lowest LVEF tertiles (≤30% and 31–39%) but not in the highest one (LVEF ≥40%). Furthermore, the significant impact of moderate–severe MR on the primary endpoint in the highest NT-proBNP tertile was observed only in patients with history of atrial fibrillation (online supplementary *Table S5*).

Discussion

Our study shows that moderate–severe MR is associated with an increased risk of death or HF hospitalizations in patients with worsening chronic HF or new-onset acute HF enrolled in BIOSTAT-CHF. The prognostic impact of moderate–severe MR is additive to a validated risk model including relevant clinical and laboratory features and seems to be more pronounced in patients with HFrEF, larger LV dimensions, higher plasma NT-proBNP, and NYHA class I to III. To the best of our knowledge, this is the largest study available exploring the prognostic impact of MR on clinical outcomes in patients with HF. Our cohort included more than 4000 well-phenotyped patients with worsening chronic or new-onset acute HF enrolled in a prospective study.

Prevalence of moderate–severe MR was 41%, in line with previous studies reporting rates ranging from 29% to 53% in patients with HF.[7–9,22,23] These studies also showed an association between MR and poor prognosis, with a correlation between MR severity and poorer outcomes.[4,17,18,21–24,26,28] However, available evidence was mainly derived from relatively small and/or single-centre studies on unselected HF populations including mostly patients with reduced LVEF and stable clinical conditions.[17,18,22,23] In contrast, our analysis includes mostly patients with worsening HF and with a wide range of LVEF. Our data may be compared with those of a recent analysis of the Atherosclerosis Risk in Communities (ARIC) study showing a significant impact of moderate or severe MR on 1-year mortality in a community-derived cohort of 3878 patients hospitalized for HF and with echocardiographic data available.[20] The prevalence of moderate or severe MR was 44.5% and it was independently associated with increased 1-year mortality (odds ratio 1.30; 95% CI 1.16–1.45).[20] Our study confirms and extends these results to the European population enrolled in BIOSTAT-CHF. The analysis of the ARIC cohort had only 1-year all-cause mortality as endpoint, whereas we were able to confirm the independent value of MR also for the combined endpoint of all-cause death or HF hospitalization and with a 2-year follow-up. In addition, the value of MR was additive compared with a risk prediction model already validated and strongly associated with outcome.[32]

In subgroup analyses, we noted an association between moderate–severe MR and the primary endpoint only in patients with HFrEF. Accordingly, moderate–severe MR emerged as a predictor of prognosis in patients with dilated left ventricles (LVEDD >56 mm). Similar results were also found in the ARIC analysis where moderate or severe MR was an independent predictor of 1-year mortality only in patients with LVEF <50%.[20] These findings may be related to the different mechanisms and pathogenesis of MR in patients with normal or reduced LVEF so that the contribution of MR, as well as that of LV remodelling, is larger in patients with a reduced LVEF.[11,29,36,37]

Our analysis of a large study group allowed the assessment of the role of MR according to the severity of HF. In our study, the prognostic impact of moderate–severe MR on clinical outcome seemed more evident in patients with NT-proBNP ≥3619 pg/mL and, consistently, in those with reduced LVEF and larger LV volumes. In the study by Goliasch *et al.*,[23] the prognostic impact of severe MR was predominantly observed in a specific phenotype characterized by NYHA class II and III, moderately increased NT-proBNP and LVEF between 30% and 40%. This result may reflect a different patient population. The study by Goliasch *et al.*[23] included only patients with HFrEF and they were younger than in our study, on optimal medical therapy and with a lower burden of comorbidities. Furthermore, in their subgroup analysis the authors evaluated the impact of severe MR, rather than moderate or severe MR, on a different endpoint (all-cause mortality). Finally, the number of patients included in the subgroups and consequently the number of events were much lower compared to our population, hence potentially impacting statistical power.

Consistent with previous data,[22,23] in our study the prognostic impact of MR seemed to be less pronounced in patients with NYHA class IV. These data may be explained by the relatively small number of patients with NYHA class IV in our study. However, Bursi *et al.*[22] showed that the impact of MR on outcomes was not evident in a subgroup of patients with advanced HF. Thus, severe HF symptoms might be a marker of an advanced stage of HF and treating MR in NYHA class IV patients could be futile from a prognostic point of view. Patients in NYHA class IV have been reported to have a poor outcome after percutaneous mitral valve repair.[38,39] In a recent analysis from the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial, no differences were observed in the impact of percutaneous MR treatment on outcomes in patients with NYHA class IV compared to the other classes.[40] However, patients with non-ambulatory NYHA class IV were excluded from COAPT but included in BIOSTAT-CHF.[6,41]

Limitations

The present study is a *post-hoc* retrospective analysis of a database collected in a large, prospective, multicentre, observational study of patients with worsening chronic or new-onset acute HF. Its main limitations are the lack of a central core-laboratory analysis of echocardiographic images and hence the lack of detailed data regarding MR severity and aetiology. Thus, we could not investigate the influence of these important variables on patients' outcome. However, a strong, independent, impact of moderate–severe MR on the outcome of patients with worsening chronic or new-onset acute HF was shown by our study, despite its intrinsic limitations, and these data may have a major impact for patients' assessment and possibly treatment indications. Furthermore, the sample size was relatively small in some subgroups of interest (i.e. HFpEF), thus preventing us from performing detailed sub-analyses in such subgroups.

Conclusions

In patients with worsening chronic or new-onset acute HF, moderate–severe MR is highly prevalent and has a strong impact on clinical outcome, independently of other relevant variables related with patients' outcomes and HF severity.

Supplementary Information

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

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