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RESEARCH ARTICLE

Prevalence, clinical characteristics and outcomes of heart failure patients with or without isolated or combined mitral and tricuspid regurgitation: An analysis from the ESC-HFA Heart Failure Long-Term Registry

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Aim Mitral regurgitation (MR) and tricuspid regurgitation (TR) are common in patients with heart failure (HF). The aim of this study was to investigate prevalence, clinical characteristics and outcomes of patients with or without isolated or combined MR and TR across the entire HF spectrum.

Methods and results The ESC-HFA EORP HF Long-Term Registry is a prospective, multicentre, observational study including patients with HF and 1-year follow-up data. Outpatients without aortic valve disease were included and stratified according to isolated or combined moderate/severe MR and TR. Among 11 298 patients, 7541 (67%) had no MR/TR, 1931 (17%) isolated MR, 616 (5.5%) isolated TR and 1210 (11%) combined MR/TR. Baseline characteristics were differently distributed across MR/TR categories. Compared to HF with reduced ejection fraction, HF with mildly reduced ejection fraction was associated with a lower risk of isolated MR (odds ratio [OR] 0.69; 95% confidence interval [CI] 0.60–0.80), and distinctly lower risk of combined MR/TR (OR 0.51; 95% CI 0.41–0.62). HF with preserved ejection fraction (HFpEF) was associated with a distinctly lower risk of isolated MR (OR 0.42; 95% CI 0.36–0.49),

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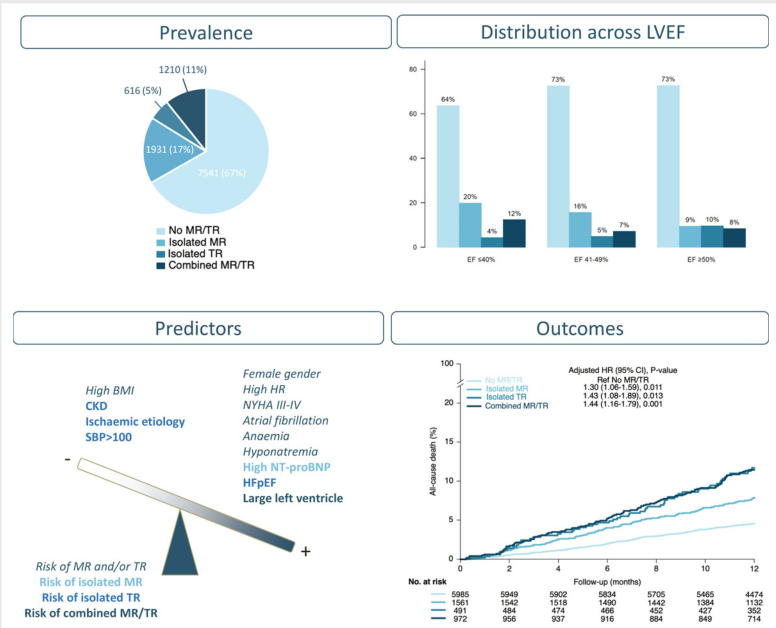
and combined MR/TR (OR 0.59; 95% 0.50–0.70), but a distinctly increased risk of isolated TR (OR 1.94; 95% CI 1.61–2.33). All-cause death, cardiovascular death, HF hospitalization and combined outcomes occurred more frequently in combined MR/TR, isolated TR and isolated MR versus no MR/TR. The highest incident rates were observed in isolated TR and combined MR/TR.

Conclusion In a large cohort of outpatients with HF, prevalence of isolated and combined MR and TR was relatively high. Isolated TR was driven by HFpEF and was burdened by an unexpectedly poor outcome.

Graphical Abstract



Heart failure with or without isolated or combined mitral and tricuspid regurgitation: The ESC Heart Failure Long-Term Registry. BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio/heart rate; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; TR, tricuspid regurgitation. [Correction added on 26 July 2023, after first online publication: Graphical Abstract caption has been added in this version.]

Keywords Heart failure • Mitral regurgitation • Tricuspid regurgitation • Left ventricular ejection fraction

Introduction

Mitral regurgitation (MR) and tricuspid regurgitation (TR) are the most prevalent valvular heart diseases (VHD) in patients with chronic heart failure (HF).[1,2] Commonly, they are secondary to structural alterations of the myocardial geometry, and can present as isolated or combined.[3,4] The pathophysiology of secondary MR and TR is complex.[2] Left ventricular remodelling leading to mitral leaflet tethering, left atrial dilatation causing mitral annular dysfunction, and ventricular dyssynchrony are the main mechanisms of secondary MR. MR can cause pulmonary hypertension, right ventricular overload and TR. Rarely, MR and TR can coexist without influencing each other, especially when atrial disorders (i.e. atrial fibrillation) or different concomitant causes (i.e. pacemaker lead) are present. However, MR can be isolated and also TR can be observed in the absence of MR.

Several data are available on the epidemiology and survival of HF patients with or without MR[5–9] and with or without TR.[10–13] However, these two VHD have been analysed separately in previous studies. There is lack of data regarding isolated or combined MR and TR profiles and their impact on prognosis across the entire HF spectrum, including different groups based on left ventricular ejection fraction (LVEF). Characterizing MR and TR according to LVEF category is important because these VHD are highly dependent on cardiac structure. Notably, secondary MR and TR are treatable with surgical or catheter-based interventions, but the characteristics of patients in the community with the greatest potential benefit from these interventions remain poorly understood. The European Society of Cardiology-Heart Failure Association EURObservational Research Programme HF Long-Term (ESC-HFA EORP HF-LT) Registry is a large prospective registry with data from patients with HF from multiple European and ESC affiliated countries. In this analysis, we investigated prevalence, clinical characteristics, and outcomes of outpatients with HF with or without isolated or combined moderate/severe MR and TR.

Methods

Study population

The ESC-HFA EORP HF-LT Registry is a prospective, multicentre, multinational, observational registry including patients with acute and chronic HF from 133 participating centres across 21 European and ESC affiliated countries. Patients were enrolled in the following countries: Lithuania and Sweden (northern countries); Bosnia and Herzegovina, Bulgaria, Czech Republic, Hungary, Latvia, Poland, Romania and Slovakia (eastern countries); Austria and France (western countries); Greece, Italy, Portugal, Serbia, Slovenia, Spain and Turkey (southern countries); Israel (Middle East), and Egypt (North Africa). There were no specific exclusion criteria other than patient age, which was required to be higher than 18 years. Further details on the registry protocol have been described elsewhere.[14] From the overall population enrolled between March 2011 and September 2018, for the purpose of the present analyses, only data on outpatients with HF and with complete echocardiographic data regarding MR and TR were included. Patients with concomitant aortic valve disease (i.e. moderate/severe aortic regurgitation and moderate/severe aortic stenosis) were excluded.

Data collection and follow-up

Demographic, clinical and echocardiographic data were collected, and details on HF management were recorded. A transthoracic echocardiography examination was performed at enrolment and presence of moderate/severe MR and/or moderate/severe TR was assessed. Patients were followed up in accordance with the standard of care at each participating centre. A follow-up visit or a telephone call at 12 months after the entry visit was mandatory for all patients to obtain information on morbidity and mortality. During the course of the year patients were followed up according to the usual practice of the respective centres.

The registry was approved by local ethics committees as required in each country and informed consent forms were signed by all participants. To ensure data quality and consistency, training meetings were organized for the investigators and data sources were verified by EORP monitors in a random sample of 5% of the enrolled patients.

Statistical analysis

Descriptive analyses were summarized and stratified by MR/TR categories: no MR or TR, isolated MR, isolated TR and combined MR and TR. Continuous variables are presented as median and interquartile range (IQR). For comparisons of continuous variables, the ANOVA test was used. Categorical variables are presented as number and percentages and statistical analyses were performed using chi-squared test.

Logistic regression models were fitted including several independent variables, and each MR/TR category as dependent variable. A univariate analysis was performed with the purpose of identifying characteristics associated with undetected MR/TR. A multivariable analysis was performed to assess possible pathophysiological drivers of MR/TR. Independent variables, selected based on clinical judgment, were: female sex, old age (≥65 years), high body mass index (BMI ≥25 kg/m^2), LVEF groups (HF with reduced LVEF: ≤40%; HF with mildly reduced LVEF: 41–49%; HF with preserved LVEF: ≥50%), HF duration >12 months, previous HF hospitalization, ischaemic aetiology of HF, New York Heart Association (NYHA) class III/IV, history of atrial fibrillation, history of coronary artery disease, peripheral artery disease, diabetes mellitus, chronic obstructive pulmonary disease, prior stroke or transient ischaemic attack, low estimated glomerular filtration rate (eGFR<60 ml/min/1.73 m^2), low sodium (<135 mmol/L), anaemia (haemoglobin <12 g/dl in women and <13 g/dl in men), high N-terminal pro-B-type natriuretic peptide (NT-proBNP ≥ median value), high heart rate (≥70 bpm), high systolic blood pressure (≥100 mmHg), large left ventricle (left ventricular end-diastolic diameter [LVEDD] ≥60 mm). Results are reported as odds ratio (OR) and 95% confidence interval (CI).

At 1-year follow-up the following clinical outcomes were assessed: all-cause death, all-cause death or HF hospitalization, cardiovascular (CV) death or HF hospitalization, CV death, and first HF hospitalization. The outcomes are presented as cumulative incidence rates (number of events/100 patients/year) and by using Kaplan–Meier curves stratified by MR/TR categories. To assess the association between MR/TR category (as independent variable) and outcomes (dependent variables), multivariable Cox proportional hazard regression models were used, with the same variables adopted in the logistic regression analysis for adjustments. The proportional hazards assumption was investigated using the scaled Schoenfeld residuals. HF duration and NYHA class exhibited non-proportional hazards and were included as strata variables in the model. Results were reported as hazard ratio (HR) and 95% CI.

To avoid bias due to data missing not at random, missing baseline covariates were handled by multiple imputation by chained equations[15] for 15 datasets and 15 iterations. The primary outcome, CV death or first rehospitalization for HF at follow-up, was included as the Nelson–Aalen estimator. Valve disease was not imputed. For patients with hospitalization during follow-up but missing information on date, the time to hospitalization was imputed with half the time to last follow-up.

All analyses were performed using R version 4.2.1 (2022-06-23 ucrt) (R Core Team 2019) with a level of significance set to 5%, two-sided.

Results

A total of 25 261 patients were enrolled in the ESC-HFA EORP HF-LT Registry, 14 742 of whom were outpatients. Among them, 11 298 had complete data on MR and TR and did not have significant concomitant aortic valve disease, and were therefore included in the present analysis.

Baseline characteristics

Among included patients, 7541 (67%) had no MR or TR, 1931 (17%) had isolated MR, 616 (5.5%) had isolated TR and 1210 (11%) had combined MR/TR. The prevalence of isolated MR decreased

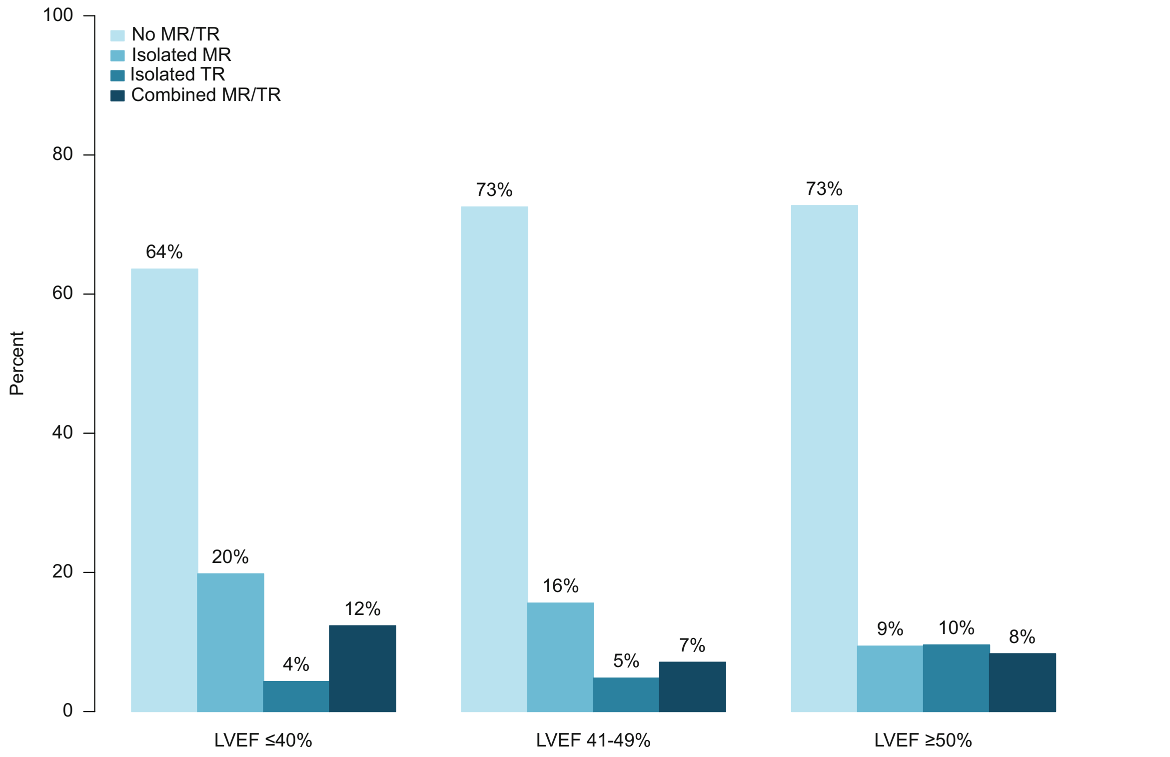


Figure 1 Distribution of mitral (MR) and tricuspid regurgitation (TR) categories across heart failure phenotypes. Prevalence of isolated MR, isolated TR and combined MR/TR are reported according to heart failure phenotypes (left ventricular ejection fraction [LVEF] ≥50%, 41–49%, ≤40%).

across LVEF groups: 20% in HF with reduced ejection fraction (HFrEF), 16% in HF with mildly reduced ejection fraction (HFmrEF) and 9% in HF with preserved ejection fraction (HFpEF). A similar pattern was observed for combined MR/TR (12% in HFrEF, 7% in HFmrEF and 8% in HFpEF). Conversely, prevalence of isolated TR increased through LVEF categories: 4% in HFrEF, 5% in HFmrEF and 10% in HFpEF (*Figure 1*).

Baseline characteristics and outpatient visit data stratified by MR/TR categories are reported in *Tables 1* and *2*, respectively. Almost all demographic, clinical, echocardiographic and laboratory variables were differently distributed across groups.

Association between baseline characteristics and risk of mitral and/or tricuspid regurgitation

Unadjusted and adjusted association between selected baseline characteristics and MR/TR categories are reported in *Figures 2* and *3*, respectively. In univariable analysis, multiple variables were associated with both isolated MR, isolated TR and combined MR/TR. Notable variables included female sex, old age, and multiple factors associated with more advanced HF and congestion, such as lower sodium and haemoglobin, higher NT-proBNP and NYHA class III–IV (vs. I–II). In addition, history of atrial fibrillation was associated with all MR/TR categories, most strongly with isolated TR (*Figure 2*). Compared to HFrEF, HFmrEF was associated with a lower risk of MR (OR 0.69; 95% CI 0.60–0.80), and distinctly lower risk of combined MR/TR (OR 0.51; 95% CI 0.41–0.62) but similar risk of isolated TR (OR 0.98; 95% CI 0.76–1.26). HFpEF was associated with a distinctly lower risk of isolated MR (OR 0.42; 95% CI 0.36–0.49), and combined MR/TR (OR 0.59; 95% 0.50–0.70), but a distinctly increased risk of isolated TR (OR 1.94; 95% CI 1.61–2.33) (*Figure 2*). Consistent with these findings, a larger LVEDD was associated with an increased likelihood of isolated MR and combined MR/TR but with a decreased likelihood of isolated TR.

In multivariable analysis, the associations between clinical characteristics and MR/TR were overall similar as in univariable analysis. The pattern for LVEF categories was similar although ORs were slightly closer to 1.0. LVEDD was more strongly associated with MR and MR/TR, suggesting it is a strong independent driver of MR and combined MR/TR. Notably, presence of MR was associated with an increased risk of TR and vice versa, while signs of MR (i.e. murmur) at baseline visit and valvular aetiology were associated with an increased risk of both MR and TR. On the other hand, prior valvular surgery was associated with an increased likelihood of having TR, but did not affect the risk of MR (online supplementary *Figure S1*).

Table 1 Baseline characteristics

Variable	Overall ($n = 11\,298$)	No MR/TR ($n = 7541$)	Isolated MR ($n = 1931$)	Isolated TR ($n = 616$)	Combined MR/TR ($n = 1210$)	*p*-value
Age (years)	65 [56–74]	65 [56–73]	66 [57–74]	69 [60–77]	67 [58–76]	<0.001
Female sex	3210 (28)	1970 (26)	586 (30)	259 (42)	395 (32)	<0.001
Region						<0.001
Eastern	2050 (18)	1152 (15)	373 (19)	120 (19)	405 (33)	
Northern	659 (5.8)	435 (5.8)	98 (5.1)	36 (5.8)	90 (7.4)	
Southern	6338 (56)	4555 (60)	1035 (54)	340 (55)	408 (34)	
Western	703 (6.2)	530 (7)	93 (4.8)	34 (5.5)	46 (3.8)	
Middle East	449 (4)	303 (4)	63 (3.3)	35 (5.7)	48 (4)	
North Africa	498 (4.4)	96 (1.3)	183 (9.5)	29 (4.7)	190 (15.7)	
Other	601 (5.3)	470 (6.2)	86 (4.5)	22 (3.6)	23 (1.9)	
BMI (kg/m^2)	28 [25–31]	28 [25–31]	27 [24–30]	26 [24–30]	27 [24–30]	<0.001
NYHA class III or IV	2938 (26)	1510 (20)	604 (31)	256 (42)	568 (47)	<0.001
HF phenotypes						<0.001
HFrEF	7329 (65)	4660 (62)	1450 (75)	316 (52)	903 (75)	
HFmrEF	1707 (15)	1238 (16)	266 (14)	82 (13)	121 (10)	
HFpEF	2202 (20)	1601 (21)	207 (11)	211 (35)	183 (15)	
HF history >12 months	5702 (53)	4090 (56)	836 (45)	270 (47)	506 (45)	<0.001
Previous HF hospitalization	5414 (48)	3554 (47)	925 (48)	338 (55)	597 (50)	0.001
HF aetiology						<0.001
Ischaemic	4923 (44)	3318 (44)	891 (46)	202 (33)	512 (43)	
Hypertension	858 (7.6)	580 (7.7)	120 (6.2)	61 (9.9)	97 (8)	
Dilated cardiomyopathy	3339 (30)	2287 (30)	594 (31)	103 (17)	355 (29)	
Valve disease	777 (6.9)	374 (5.0)	154 (8.0)	133 (21.6)	116 (9.6)	
Other	1394 (12)	975 (13)	172 (8.9)	117 (19)	130 (11)	
History of AF	4047 (36)	2335 (31)	690 (36)	382 (62)	640 (53)	<0.001
Diabetes mellitus	3644 (32)	2443 (32)	579 (30)	220 (36)	402 (33)	0.036
History of CAD	5093 (45)	3383 (45)	916 (48)	230 (37)	564 (47)	<0.001
Prior stroke/TIA	996 (8.8)	633 (8.4)	171 (8.9)	59 (9.6)	133 (11)	0.027
Peripheral artery disease	1231 (11)	765 (10)	228 (12)	82 (13)	156 (13)	0.002
Prior valve surgery	1009 (8.9)	625 (8.3)	125 (6.5)	153 (25)	106 (8.8)	<0.001
Hypertension	6640 (59)	4372 (58)	1124 (58)	374 (61)	770 (64)	0.002
COPD	1537 (14)	983 (13)	266 (14)	96 (16)	192 (16)	0.024
Devices						<0.001
No	7367 (65)	5017 (67)	1197 (62)	368 (60)	785 (65)	
PM	598 (5.3)	340 (4.5)	90 (4.7)	85 (14)	83 (6.9)	
CRT-P	234 (2.1)	148 (2.0)	41 (2.1)	13 (2.1)	32 (2.7)	
CRT-D	1234 (11)	726 (9.6)	283 (15)	69 (11)	156 (13)	
ICD	1844 (16)	1297 (17)	318 (16)	78 (13)	151 (12)	

Variables are reported as *n* (%) or median [interquartile range].
AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; 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; ICD, implantable cardioverter-defibrillator; MR, mitral regurgitation; NYHA, New York Heart Association; PM, pacemaker; TIA, transient ischaemic attack; TR, tricuspid regurgitation.

Association between mitral and/or tricuspid regurgitation and clinical outcomes

Long-term follow-up was available in 9009 patients. Median follow-up was 12.2 (IQR 11.8–13.5) months. All-cause death occurred more frequently in patients with combined MR/TR, isolated TR and isolated MR as compared to no MR/TR (13.3/100 patients/year [adjusted HR 1.45; 95% CI 1.17–1.80] vs. 12.8/100 patients/year [adjusted HR 1.42; 95% CI 1.07–1.88] vs. 9.9 /100 patients/year [adjusted HR 1.29; 95% CI 1.06–1.58] vs. 5/100 patients/year) with incidence rates similarly higher in combined MR/TR and isolated TR as compared to isolated MR (*Figure 4*). A similar pattern was observed for all-cause death or HF hospitalization. On the other hand, for CV death or HF hospitalization, CV death, and HF hospitalization alone, highest incident rates were observed in isolated TR versus combined MR/TR and isolated MR (*Figure 5* and online supplementary *Table S1*).

Table 2 Outpatient visit data

Variable	Overall ($n = 11\,298$)	No MR/TR ($n = 7541$)	Isolated MR ($n = 1931$)	Isolated TR ($n = 616$)	Combined MR/TR ($n = 1210$)	p-value
Heart rate (bpm)	70 [62–80]	70 [61–78]	72.0 [63–81]	70.0 [65–82]	75 [66–88]	<0.001
Systolic BP (mmHg)	120 [110–136]	120 [110–137]	120 [110–135]	120 [105–131]	120 [108–134]	<0.001
Pulmonary rales	1583 (14)	798 (11)	340 (18)	122 (20)	323 (27)	<0.001
S3 gallop	621 (5.5)	280 (3.7)	158 (8.2)	48 (7.8)	135 (11)	<0.001
JVP >6 mm	1331 (12)	551 (7.4)	283 (15)	169 (29)	328 (28)	<0.001
Hypoperfusion	236 (2.1)	83 (1.1)	60 (3.1)	26 (4.2)	67 (5.6)	<0.001
Pleural effusion	392 (3.5)	184 (2.5)	72 (3.8)	58 (9.5)	78 (6.6)	<0.001
Cold	253 (2.2)	97 (1.3)	56 (2.9)	24 (3.9)	76 (6.4)	<0.001
Hepatomegaly	952 (8.5)	354 (4.7)	172 (9.0)	149 (24)	277 (23)	<0.001
Murmur	2776 (25)	867 (11)	1060 (55)	122 (20)	727 (60)	<0.001
Peripheral oedema	2211 (20)	1120 (15)	406 (21)	200 (33)	485 (40)	<0.001
Serum creatinine (mg/dl)	1.1 [0.9–1.4]	1.1 [0.9–1.3]	1.1 [0.9–1.4]	1.2 [0.9–1.6]	1.2 [1–1.5]	<0.001
eGFR (ml/min/1.73 m^2)	71 [52–91]	74 [55–93]	68 [50–86]	59 [42–81]	63 [46–81]	<0.001
Sodium (mEq/L)	140 [137–142]	140 [138–142]	139 [137–141]	139 [137–141]	139 [136–141]	<0.001
Haemoglobin (g/dl)	13 [12–15]	14 [12–15]	13 [12–14]	13 [11–14]	12.9 [11–14]	<0.001
BNP (pg/ml)	279 [105–676]	180 [78–452]	458 [230–863]	548 [258–964]	690 [395–946]	<0.001
NT-proBNP (pg/ml)	1273 [492–3200]	1060 [385–2605]	1880 [825–3876]	2826 [1015–5218]	2451 [860–6682]	<0.001
ECG						<0.001
Sinus rhythm	6779 (63)	4957 (69)	1101 (60)	203 (34)	518 (47)	
Atrial fibrillation/flutter	2295 (21)	1284 (18)	383 (21)	249 (42)	379 (34)	
Other	1672 (16)	979 (14)	340 (19)	140 (24)	213 (19)	
QRS duration (ms)	118 [98–144]	113 [98–140]	120 [100–150]	120 [98–152]	120 [100–146]	<0.001
LVEF (%)	35 [28–45]	37 [30–47]	33 [25–40]	40 [29–55]	32 [25–41]	<0.001
LVEDD (mm)	60 [53–66]	59 [53–65]	63 [58–70]	55 [48–63]	63 [56–70]	<0.001
Mean PAP[a] (mmHg)	27 [20–37]	26 [18–35]	27 [21–35]	34 [27–43]	32 [26–45]	<0.001
RASI	9493 (84)	6437 (85)	1632 (84)	453 (74)	971 (80)	<0.001
Beta-blocker	9561 (85)	6485 (86)	1635 (85)	460 (75)	981 (81)	<0.001
MRA	6132 (54)	3867 (51)	1179 (61)	339 (55)	747 (62)	<0.001
Diuretic	8712 (77)	5549 (74)	1583 (82)	532 (86)	1048 (87)	<0.001
Ivabradine	786 (7)	538 (7.1)	150 (7.8)	20 (3.2)	78 (6.4)	0.001
Digoxin	2115 (19)	1122 (15)	396 (20)	189 (31)	408 (34)	<0.001

Variables are reported as n (%) or median [interquartile range].
BNP, B-type natriuretic peptide; BP, blood pressure; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; JVP, jugular venous pressure; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAP, pulmonary artery pressure; RASI, renin–angiotensin system inhibitor; TR, tricuspid regurgitation.
[a]Assessed by right heart catheterization.

Discussion

The main findings of the present study of a large cohort of outpatients with HF were the following: (i) the prevalence of isolated MR, isolated TR and combined MR/TR were of 17%, 5.5% and 11% respectively, with different distribution across LVEF categories; (ii) HFrEF was associated with isolated MR and combined MR/TR and HFpEF was associated with isolated TR; (iii) several demographic, clinical, echocardiographic and laboratory variables were identified as possible risk factors for MR and/or TR; and (iv) the relative risk of 1-year clinical events increased in patients with versus those without MR and/or TR with the highest incident rates observed in patients with isolated TR and/or combined MR/TR (*Graphical Abstract*).

Prevalence of mitral and tricuspid regurgitation

Previous studies reported a high prevalence – up to 40% – of moderate/severe secondary MR in patients with HF.[1,5,16] The prevalence of moderate/severe MR appears higher in patients with HFrEF compared with other LVEF categories.[1,7] Our results are in line with these previous findings. However, additional and novel information regarding MR/TR is provided especially with regard to their combination and to the distribution of valve disease across the three LVEF categories, i.e. HFrEF, HFmrEF, and HFpEF.

Patients with combined moderate/severe MR/TR accounted for more than one third of the total patients with moderate/severe MR. The three LVEF categories demonstrated qualitative and distinct

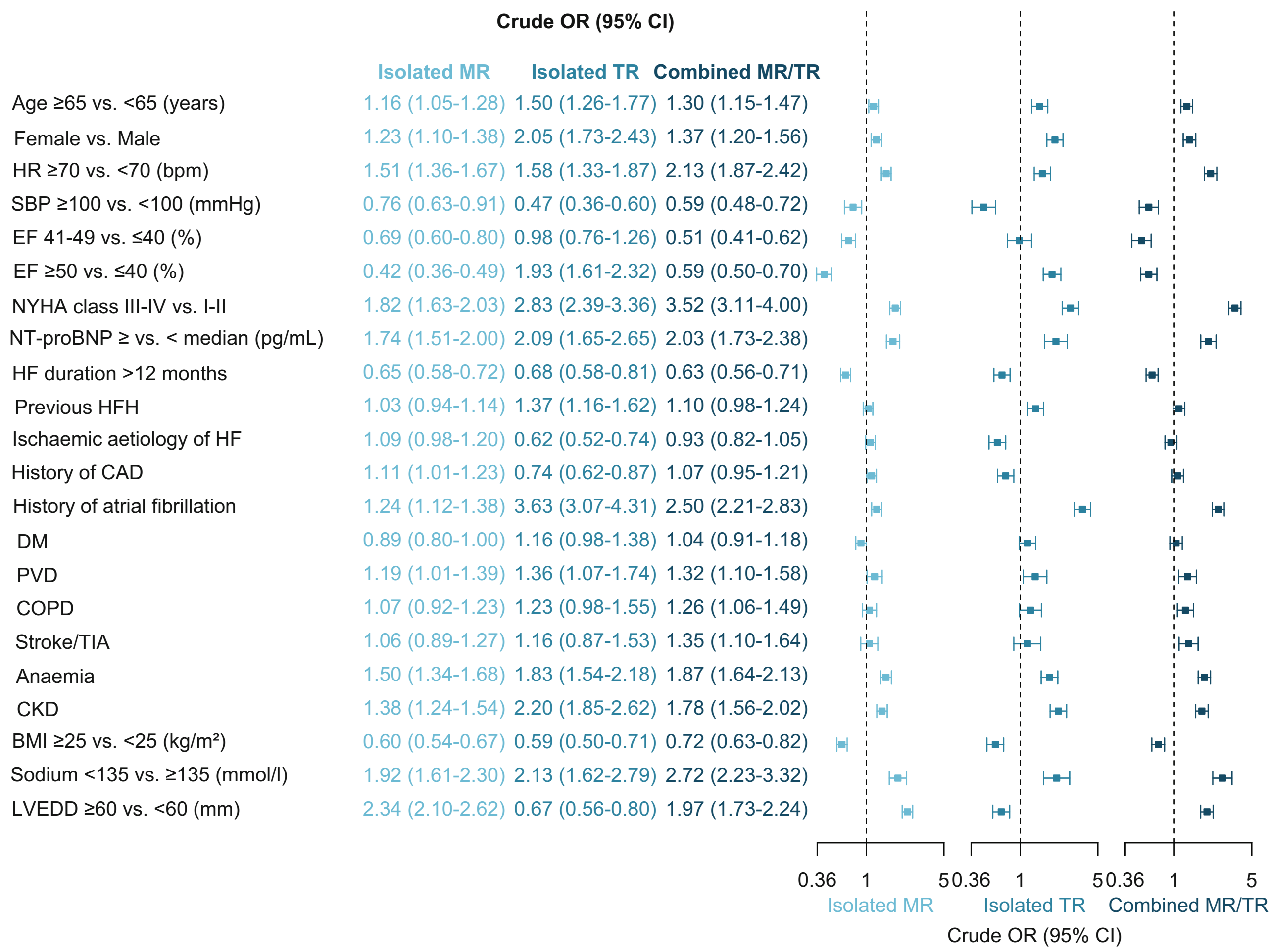


Figure 2 Crude association between baseline characteristics and mitral (MR) and tricuspid regurgitation (TR). Forest plots showing relative risk (odds ratio [OR] and 95% confidence interval [CI]) of isolated MR, isolated TR and combined MR/TR for selected demographic, clinical, echocardiographic and laboratory variables are reported. BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; EF, ejection fraction; HF, heart failure; HFH, heart failure hospitalization; HR, heart rate; LVEDD, left ventricular end-diastolic diameter; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PVD, peripheral vascular disease; SBP, systolic blood pressure; TIA, transient ischaemic attack.

differences in MR vs. TR. Isolated MR was more common in HFrEF and HFmrEF, which is consistent with left ventricular dilatation and systolic dysfunction, whereas combined MR/TR was more common in HFrEF only, consistent with greater severity of HF and greater structural impact of MR on the tricuspid valve and annulus. Indeed, combined MR/TR probably represents, in most of the cases, an advanced stage of left ventricular impairment.[2,15]

Data on TR epidemiology in HF are more limited than on MR.[10,11,13,17] In a large single-centre study, including unselected patients undergoing echocardiography, LVEF seemed to decrease with increasing TR severity and prevalence of moderate/severe TR was around 10%.[11] A similar prevalence was observed in a large cohort of patients with HF stratified by TR severity, but in this study the rate of left ventricular dysfunction numerically decreased with increasing of TR grade.[13] In other studies, focusing on HFrEF populations, the prevalence of moderate/severe TR was roughly 20% suggesting a possible prevalent role of HFrEF in TR aetiology.[10,12] Our study included a large series of patients with HF enrolled independently of their LVEF. It therefore yields data regarding the prevalence of TR across the different categories of HF. The prevalence of isolated TR was distinctly higher among patients with HFpEF as compared to those with HFmrEF and HFrEF, and HFpEF was associated with a distinct and independent increased risk of isolated TR (OR 1.94 in univariable and 1.53 in multivariable analysis). In these patients, two different pathophysiological mechanisms need to be recognized. On one hand, post-capillary pulmonary hypertension secondary to HFpEF may lead to right ventricular overload and TR. Second, atrial fibrillation, which is a common comorbidity in HFpEF, may lead to right atrial remodelling, and subsequently tricuspid annular dilatation and TR.[18] Accordingly, atrial fibrillation was associated with a larger than two-fold increase in the likelihood of TR.

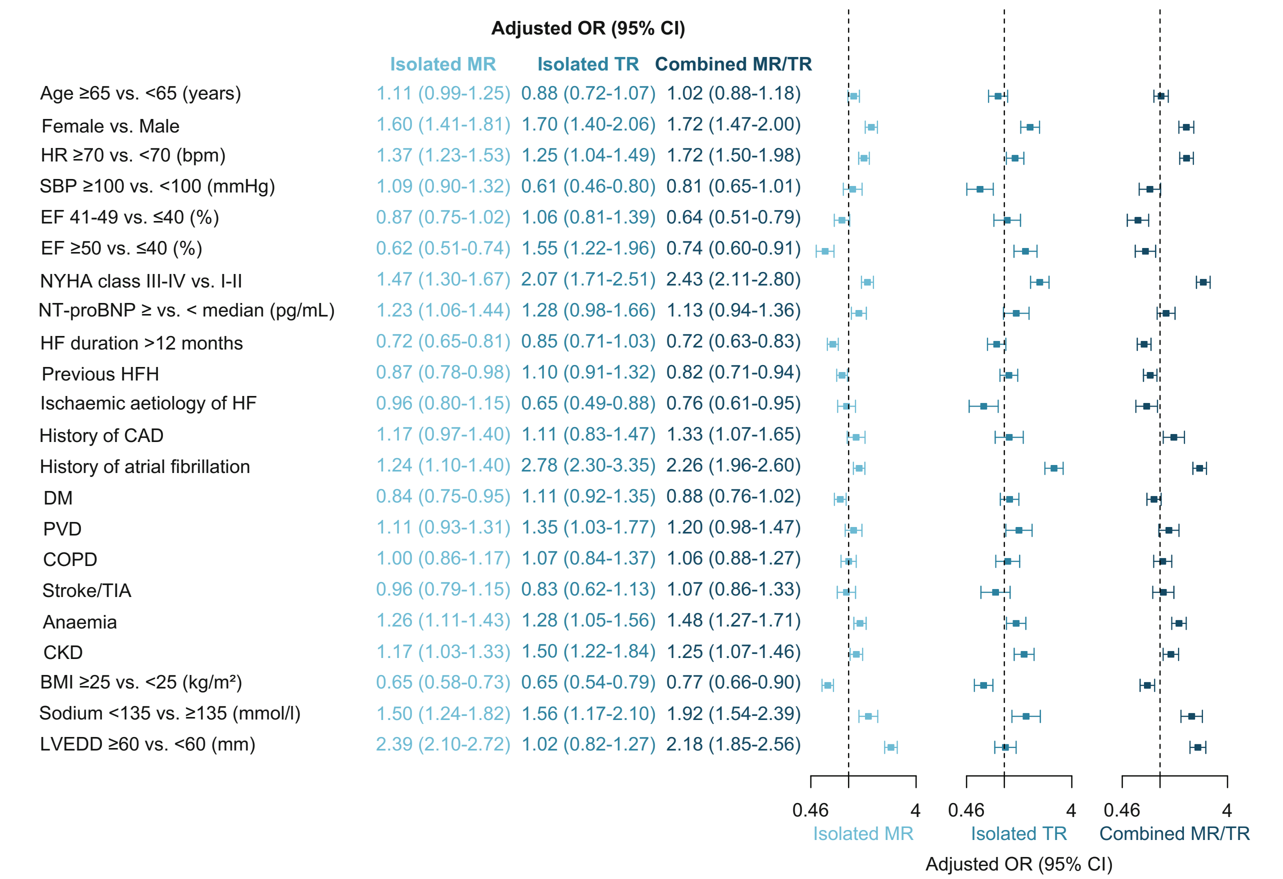


Figure 3 Adjusted association between baseline characteristics and mitral (MR) and tricuspid regurgitation (TR). Forest plots showing adjusted relative risk (odds ratio [OR] and 95% confidence interval [CI]) of isolated MR, isolated TR and combined MR/TR for selected demographic, clinical, echocardiographic and laboratory variables are reported. BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; EF, ejection fraction; HF, heart failure; HFH, heart failure hospitalization; HR, heart rate; LVEDD, left ventricular end-diastolic diameter; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PVD, peripheral vascular disease; SBP, systolic blood pressure; TIA, transient ischaemic attack.

Clinical characteristics of patients with mitral and/or tricuspid regurgitation

In this study, several risk factors were identified as independently associated with the likelihood of having isolated MR, isolated TR, or combined MR/TR. Among them, NYHA class III/IV, atrial fibrillation, high heart rate, low sodium, anaemia, low eGFR and low BMI have been already identified as markers of HF severity and outcome.[1] Atrial fibrillation has a particular important role in this setting as it can be the consequence or cause of MR and TR and can induce a vicious circle leading to HF and VHD progression.[19–22]

In addition, the specific link between isolated TR and HFpEF adds novel information to a growing body of evidence suggesting that HFpEF is distinct from HFrEF and HFmrEF. Consistently, our data showed also a higher prevalence of female sex and higher age as well as, as in most studies, higher prevalence of hypertension, atrial fibrillation and chronic kidney disease, lower prevalence of ischaemic heart disease, higher risk of non-CV events, and poorer response to neurohormonal modulator drugs, in patients with TR versus those with MR and MR/TR and those without VHD.[23,24]

Importantly, previous valve surgery was considerably more frequent in patients with isolated TR as compared to other categories. Indeed, it can lead to TR even if TR was not significant at the time of left-sided valve intervention.[22] This information, from the patient history, has to be carefully considered as an important risk factor for TR in HF patients.

Thus, HFpEF was a strong and important driver of isolated TR. In addition to prior valve surgery, the other risk factors, such as history of atrial fibrillation and non-ischaemic aetiology of HF, are consistent with the role of HFpEF.

Associations between mitral and/or tricuspid regurgitation and outcomes

In HF populations, both moderate/severe MR and moderate/severe TR were previously found to be associated with an increased risk of adverse outcomes, regardless of other clinical

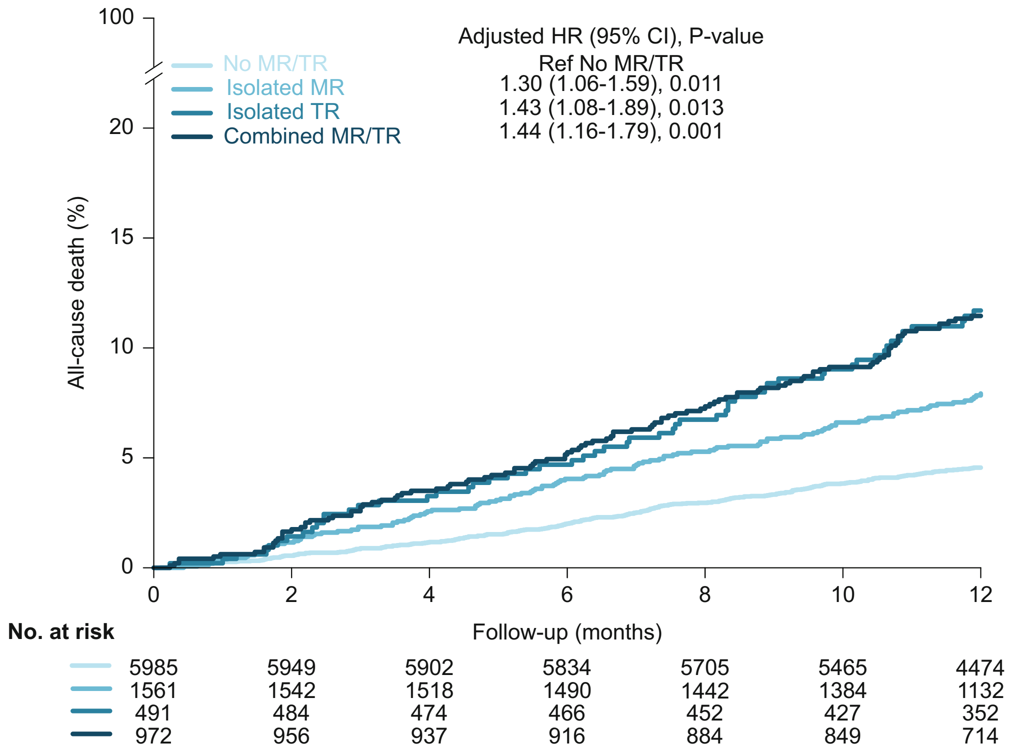


Figure 4 Mortality according to mitral (MR) and tricuspid regurgitation (TR) categories. Kaplan–Meier curves and adjusted relative risk of all-cause death in isolated MR, isolated TR and combined MR/TR are reported. CI, confidence interval; HR, hazard ratio.

and echocardiographic variables.[5–13,17] Only a single-centre study[15] compared long-term survival in patients with no MR/TR versus isolated MR/TR and combined MR/TR in HFrEF patients. Severe combined MR/TR was associated with the worst survival followed by severe isolated MR/TR and no severe MR/TR. However, the authors did not distinguish between isolated MR and isolated TR, probably because in the HFrEF setting isolated TR is very rare.[15] We confirmed previous findings regarding the poorer outcome of patients with MR versus no MR and TR versus no TR.[5,6,11,13] In addition, we specifically compared 1-year clinical events in different MR/TR categories, distinguishing between isolated MR, isolated TR and combined MR/TR across the entire LVEF spectrum. Moreover, we evaluated CV mortality and HF hospitalizations in addition to all-cause mortality. We found similarly high rates of all-cause-death in patients with combined MR/TR and isolated TR followed by a lower rate in those with isolated MR and even lower rate in subjects with no MR/TR. The highest risk of CV death and first HF hospitalization was observed in patients with isolated TR followed by combined MR/TR, followed by isolated MR and finally by no MR/TR. These results were maintained even after adjustment for possible confounders and are novel. Isolated TR should be considered a distinct and specific entity whose one of the main drivers is HFpEF. The particularly poorer outcome associated with this condition deserves attention and might be explained by little awareness and limited therapeutic opportunities available until recently.[25] Interest in isolated TR is currently growing since new catheter-based devices for TR treatment are emerging.[19,26–28] Therefore, greater awareness of isolated TR and further advances in treatments may significantly improve clinical outcome of these patients in the near future.

Limitations

Several limitations should be acknowledged. The study population includes only patients evaluated at cardiology outpatient clinics (rather than other providers). The diagnosis of HF as well as clinical events were not adjudicated. Echocardiography examinations were performed in the context of routine clinical practice and were not centrally analysed by a core laboratory. Data regarding the presence of moderate/severe MR and moderate/severe TR were obtained only at the time of enrolment in the registry and no other information about MR and TR grading or aetiology was collected.

Conclusions

In a large cohort of outpatients with HF, the prevalence of isolated MR and isolated TR was 17% and 5.5% respectively, while combined MR/TR was observed in 11% of patients. HFpEF was one of the main driver of isolated TR. Isolated TR was associated with an unexpectedly poor outcome.

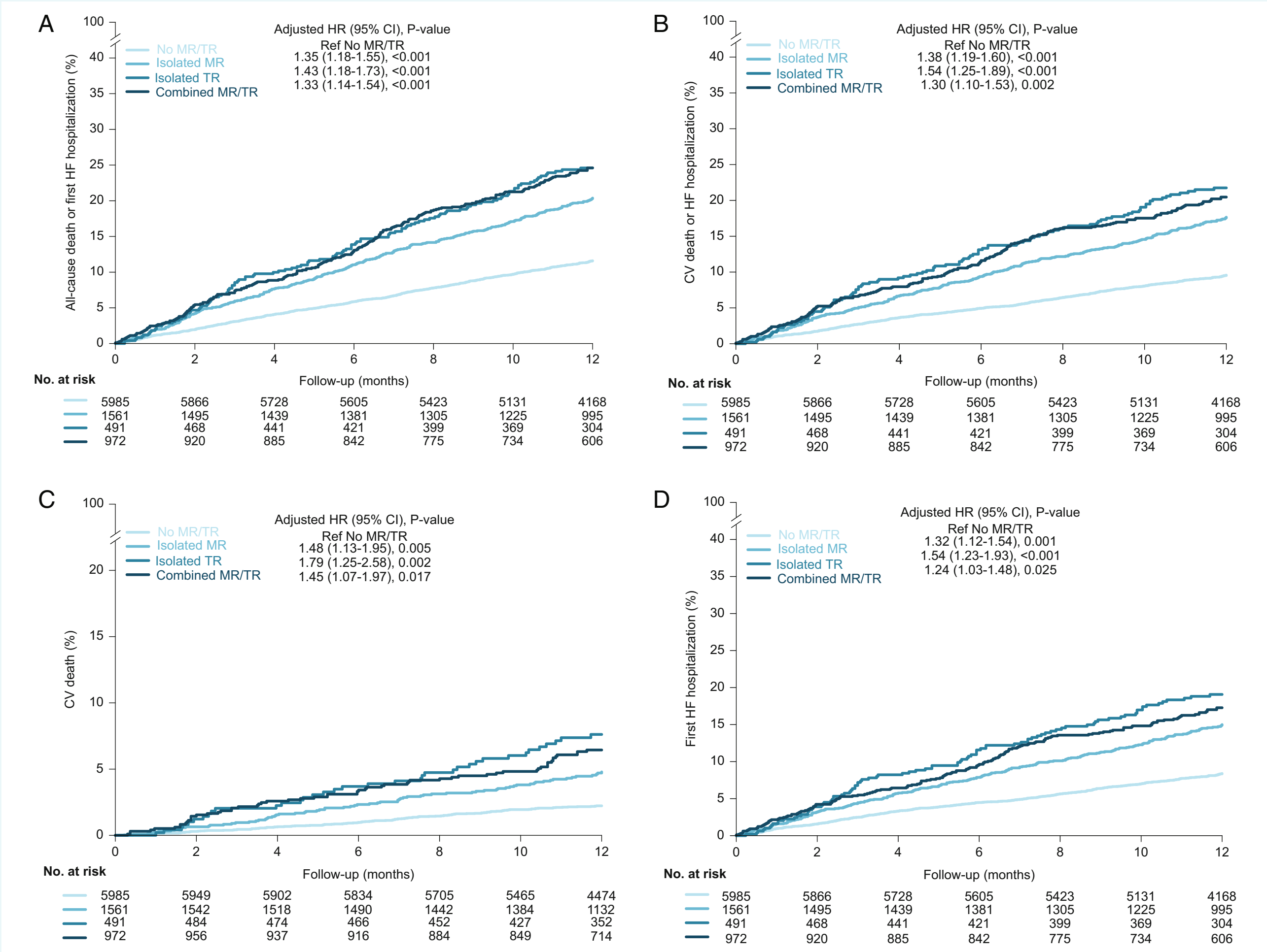


Figure 5 Other clinical outcomes according to mitral (MR) and tricuspid regurgitation (TR) categories. Kaplan–Meier curves and adjusted relative risk of all-cause death or heart failure (HF) hospitalization, cardiovascular (CV) death or HF hospitalization, CV death, and HF hospitalization in isolated MR, isolated TR and combined MR/TR are reported. CI, confidence interval; HR, hazard ratio

Supplementary Information

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

Conflict of interest: M.A.: none related to the present work. Outside the present work: speaker fees from Abbott Vascular and Medtronic. M.G.C.L.: none related to the present work. Outside the present work: speakers honorary and/or consultancy fees from AstraZeneca, Boehringer Ingelheim, Novartis, Rovi, Vifor, Bayer, CareDx, Pfizer, Abbott and Medtronic. S.D.A.: grants and personal fees from Vifor and Abbott Vascular, and personal fees for consultancies, trial committee work and/or lectures from Actimed, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bioventrix, Brahms, Cardiac Dimensions, Cardior, Cordio, CVRx, Edwards, Farraday, Impulse Dynamics, Janssen, Novartis, Occlutech, Pfizer, Respicardia, Servier, Vectorious, and V-Wave. A.J.S.C.: none related to the present work. Outside the present work: consultancy fees from AstraZeneca, Bayer, Boehringer Ingelheim, Edwards, Menarini, Novartis, Nutricia, Servier, Vifor, Abbott, Actimed, Arena, Cardiac Dimensions, Corvia, CVRx, Enopace, ESN Cleer, Faraday, Gore, Impulse Dynamics, Respicardia. M.L.: none related to the present work. Outside the present work: speakers' honoraria from AstraZeneca, Vifor, Boehringer Ingelheim, Novartis, Bayer, Sanofi; consulting from Vifor, Boehringer Ingelheim. T.M.: none related to current work. Outside of current work, speaker honoraria from Boehringer Ingelheim, AstraZeneca, Edwards and Abbott. M.F.P.: none related to the present work. Outside the present work: consultancy, speaker's, institutional fees from AstraZeneca, Boehringer Ingelheim, CHF solution, Menarini, Novartis, Servier. A.P.M.: none related to the present work. Outside the present work: personal fees from Novartis, Bayer, AstraZeneca for participation in study committees. M.M.: none related to the present work. Outside the present work: personal fees of minimal amounts since January 2021 from Amgen, Livanova, and Vifor Pharma as member of Executive or Data Monitoring Committees of sponsored clinical trials; from AstraZeneca, Bayer, Boehringer Ingelheim, Edwards Lifesciences, Roche Diagnostics for participation in advisory boards and/or speeches at sponsored meetings. L.H.L.: none related to the present work. Outside the present work: grants from AstraZeneca, Vifor, Boston Scientific, Boehringer Ingelheim, Novartis, MSD; consulting from Vifor, AstraZeneca, Bayer, Pharmacosmos, MSD, MedScape, Sanofi, Lexicon, Myokardia, Boehringer Ingelheim, Servier, Edwards Life Sciences, Alleviant; speaker's honoraria from Abbott, OrionPharma, MedScape, Radcliffe, AstraZeneca, Novartis, Boehringer Ingelheim, Bayer; Patent: AnaCardio. All other authors have nothing to disclose.

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