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ORIGINAL PAPER

Prevalence and clinical outcomes of isolated or combined moderate to severe mitral and tricuspid regurgitation in patients with cardiac amyloidosis

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Aims

Evidence on the epidemiology and prognostic significance of mitral regurgitation (MR) and tricuspid regurgitation (TR) in patients with cardiac amyloidosis (CA) is scarce.

Methods and results

Overall, 538 patients with either transthyretin (ATTR, $n = 359$) or immunoglobulin light-chain (AL, $n = 179$) CA were included at three Italian referral centres. Patients were stratified according to isolated or combined moderate/severe MR and TR. Overall, 240 patients (44.6%) had no significant MR/TR, 112 (20.8%) isolated MR, 66 (12.3%) isolated TR, and 120 (22.3%) combined MR/TR. The most common aetiologies were atrial functional MR, followed by primary infiltrative MR, and secondary TR due to right ventricular (RV) overload followed by atrial functional TR. Patients with isolated or combined MR/TR had a more frequent history of heart failure (HF) hospitalization and atrial fibrillation, worse symptoms, and higher levels of NT-proBNP as compared to those without MR/TR. They also presented more severe atrial enlargement, atrial peak longitudinal strain impairment, left ventricular (LV) and RV systolic dysfunction, and higher pulmonary artery systolic pressures. TR carried the most advanced features. After adjustment for age, sex, CA subtypes, laboratory, and echocardiographic markers of CA severity, isolated TR and combined MR/TR were independently associated with an increased risk of all-cause death or worsening HF events, compared to no significant MR/TR [adjusted HR 2.75 (1.78–4.24) and 2.31 (1.44–3.70), respectively].

Conclusion

In a large cohort of patients with CA, MR, and TR were common. Isolated TR and combined MR/TR were associated with worse prognosis regardless of CA aetiology, LV, and RV function, with TR carrying the highest risk.

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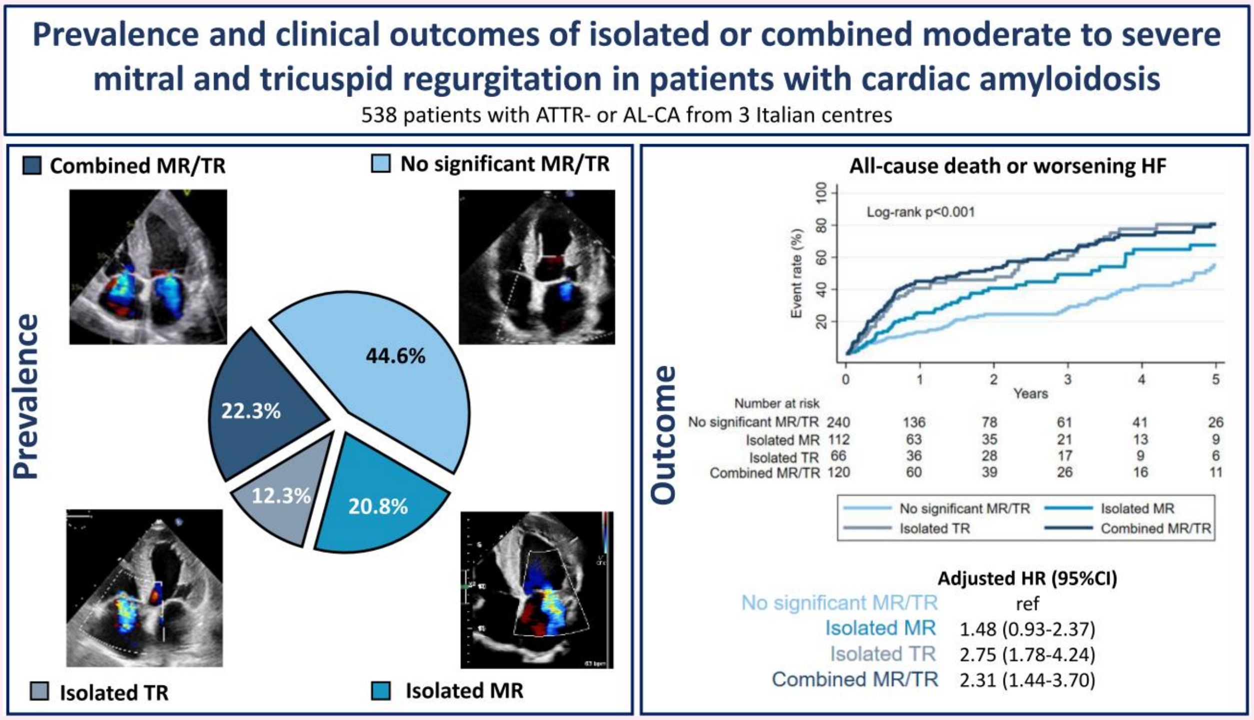
Graphical Abstract



Prevalence and clinical outcomes of isolated or combined moderate to severe mitral and tricuspid regurgitation in patients with cardiac amyloidosis. AL, immunoglobulin light chains; ATTR, transthyretin; CA, cardiac amyloidosis; HR, hazard ratio; MR, mitral regurgitation; TR, tricuspid regurgitation

Keywords cardiac amyloidosis • valvular heart disease • mitral regurgitation • tricuspid regurgitation • prognosis

Introduction

Cardiac amyloidosis (CA) is an infiltrative disease caused by the deposition of misfolded fibrillar proteins, namely, transthyretin (ATTR) or immunoglobulin light chains (AL).[1–3] Infiltration of ventricular walls typically produces left ventricular (LV) hypertrophy, myocardial stiffening, diastolic dysfunction with restrictive physiology, and preserved LV ejection fraction (LVEF).[4–6]

For a long time, CA has been an underdiagnosed cause of heart failure (HF).[4,7] More recently the prevalence of CA has been redefined.[7–9] Advances in non-invasive diagnostic techniques, an increased awareness of the disease, and the gain of interest related to the novel therapeutic options led to a dramatic rise in the diagnosis of CA.[10]

Valvular heart disease (VHD) is highly prevalent in patients with HF.[11,12] Several studies have described an association between CA and aortic stenosis, and aortic stenosis is now considered a red flag for CA.[2,8,13–16] More recently, worsening of mitral regurgitation (MR) and tricuspid regurgitation (TR) during follow-up emerged as having a major prognostic role in the natural history of ATTR-CA.[17] In patients with CA, MR, and TR can be considered as a comorbidity, a consequence of elevated filling pressures, atrial enlargement and dysfunction, or a consequence of amyloid deposition with thickened leaflets, and significantly contribute to exercise limitation and dyspnoea. MR and TR can be isolated or combined. If combined, TR can be a consequence of MR due to post-capillary pulmonary hypertension. However, MR and TR can also coexist because of the parallel deposition of amyloid that alters the structure of the entire valve apparatus and the bi-atrial enlargement/dysfunction.[17–20]

So far, few data are available regarding prevalence, aetiologies of MR and TR in patients with CA and their association with outcomes.[21] Furthermore, there is a lack of evidence regarding the significance of combined MR and TR in this setting. Thus, this study aims at investigating prevalence and clinical outcomes of patients with CA with or without isolated or combined moderate/severe MR and TR.

Methods

Study population

Consecutive patients diagnosed with AL- or ATTR-CA from 2011 to March 2022 at three Italian referral Centres (Cardiology Department, Fondazione Toscana Gabriele Monasterio, Pisa; Cardiology, ASST Spedali Civili and University of Brescia, Brescia; Cardiovascular Department, Azienda Sanitaria Universitaria Integrata, Trieste) and with complete echocardiographic data regarding MR and TR were included (14 patients excluded due to missing data). CA was diagnosed according to guidelines.[1,2,22–24]

Data collection and follow-up

Patients' data including demographics, medical history, physical examination, laboratory, and echocardiographic findings were extracted from electronic health records. Echocardiographic measurements were performed by trained cardiac sonographers in agreement with the American Society of Echocardiography and the European Association of Cardiovascular Imaging recommendations.[25] 2D speckle-tracking echocardiography was available in a subset of patients. In patients with atrial fibrillation, flutter,

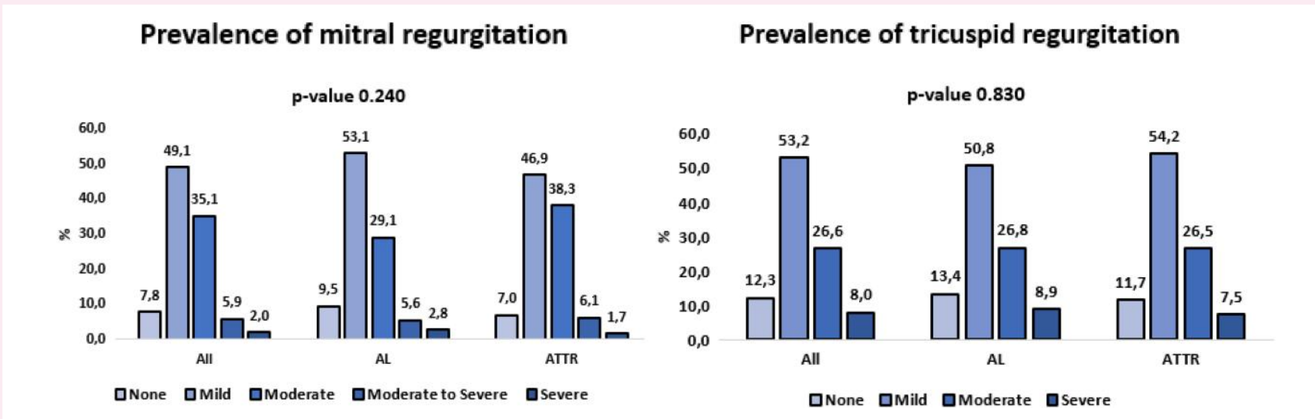


Figure 1 Prevalence of mitral and tricuspid regurgitation in the whole population and stratified by CA subtypes (ATTR- vs. AL-). AL, immunoglobulin light chains; ATTR, transthyretin.

or tachycardia, left atrium (LA) strain analysis was limited to LA peak atrial longitudinal strain (PALS) measurement. The high prevalence of atrial fibrillation in patients with VHD and CA limited the comparison of data on LA peak contraction strain (LA-PACS). Thus, only data on LA-PALS were reported.

Patients were followed-up in accordance with the standard of care at each participating centre. According to routine clinical practice, clinical follow-up assessment was scheduled every 6 months. Data regarding outcomes were collected during follow-up using electronic health records, chart review, and patient reporting or phone calls to patients or relatives. This study complied with the Declaration of Helsinki.

Valvular regurgitation assessment

A baseline echocardiography was recorded at CA diagnosis. MR and TR grades were assessed in accordance with European recommendations.[26,27] Accordingly, MR was classified as 'none', 'mild', 'moderate', 'moderate to severe', and 'severe'. Tricuspid regurgitation was classified as 'none', 'mild', 'moderate', and 'severe'. In the present analysis, patients were classified in MR/TR categories by the presence of significant MR and/or TR at baseline echocardiography. A significant MR was $\geq$ moderate and a significant TR was $\geq$ moderate, as previously defined.[28] Accordingly, 4 groups were identified: (i) no significant MR or TR; (ii) isolated MR; (iii) isolated TR; and (iv) combined MR/TR. Aetiologies of MR and TR were classified based on echocardiographic findings, using a previous description of atrio-ventricular (AV) valve apparatus in patients with CA that was confirmed on histology.[17]

Outcomes

The primary outcome was the composite of all-cause death and worsening HF. Worsening HF included both HF hospitalization and urgent HF visits requiring intravenous drugs.[29,30] The secondary outcomes were all-cause death and worsening HF as separate endpoints. Patients with ATTR-CA who were enrolled in clinical trials, or who initiated disease-modifying therapy (i.e. tafamidis or patisiran) were censored on the date that they were enrolled or started treatment. Patients undergoing valvular surgical or percutaneous interventions during follow-up were censored at the date of procedure.

Statistical analysis

Descriptive analyses were stratified by MR/TR categories. The normal distribution of continuous variables was explored through the Shapiro–Wilk test. Continuous variables were reported as mean ± standard deviation (SD) or median and the interquartile range (IQR). For comparisons of continuous variables, the analysis of variance (ANOVA) test was used. Categorical variables are presented as number and percentages and statistical analyses were performed using chi-squared test.

The clinical endpoints were assessed with the Kaplan–Meier method and compared with the log-rank test. To assess the association between MR/TR category (as independent variable) and outcomes (dependent variables), multivariable Cox proportional hazard regression models were used. The following variables, differently distributed at an alpha level of 0.05 and/or judged as clinically relevant, associated with outcome at univariable analysis entered into the multivariable model: age, sex, CA subtypes (AL- vs. ATTR-CA), New York Heart Association (NYHA) functional class, atrial fibrillation, LVEF, LV-global longitudinal strain (GLS), right ventricular (RV) coupling defined as tricuspid annular plane systolic excursion (TAPSE)/pulmonary artery systolic pressure (PASP) ratio.[31] N-terminal pro–B-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin T (hs-TnT) were not included in the main model being the proportion of missing values >10%, but were entered in a further sensitivity analysis (see Supplementary data online, *material*). Moderate to severe aortic stenosis might have a potential role as a confounder even if it was equally distributed among subgroups. Thus, in a sensitivity analysis, the multivariable Cox proportional hazard regression models were repeated after excluding patients with moderate-to-severe aortic stenosis.

Results of the Cox regression analyses are reported as unadjusted or adjusted hazard ratio (HR) and 95% confidence interval (CI). Proportionality assumption was assessed by visual inspection of residuals and met.

Statistical tests were based on a two-sided significance level of 0.05. Statistical analyses were performed using STATA version 16.0 (Stata Corp., College Station, TX, USA).

Results

Out of 552 patients enrolled in the registry, a total of 538 with complete data on MR and TR were included in the present analysis. A similar distribution of MR/TR grade across the whole population and in the subgroups of patients with AL- ($n = 179$) and ATTR-CA ($n = 359$, of whom 13 with hereditary form) was observed (*P*-value 0.240 and 0.830, respectively) (*Figure 1*). Moderate, moderate to severe and severe MR were reported in 35.1, 5.9, and 2% of patients, respectively. Moderate and severe TR was observed in 26.6 and 8% of patients, respectively. *Figure 2* reports different mechanisms/aetiologies underlying moderate to severe MR and moderate to severe TR in the cohort. Primary MR was described in 34% of patients, of whom 60% with an infiltrative cause. Half of patients had secondary MR and the most

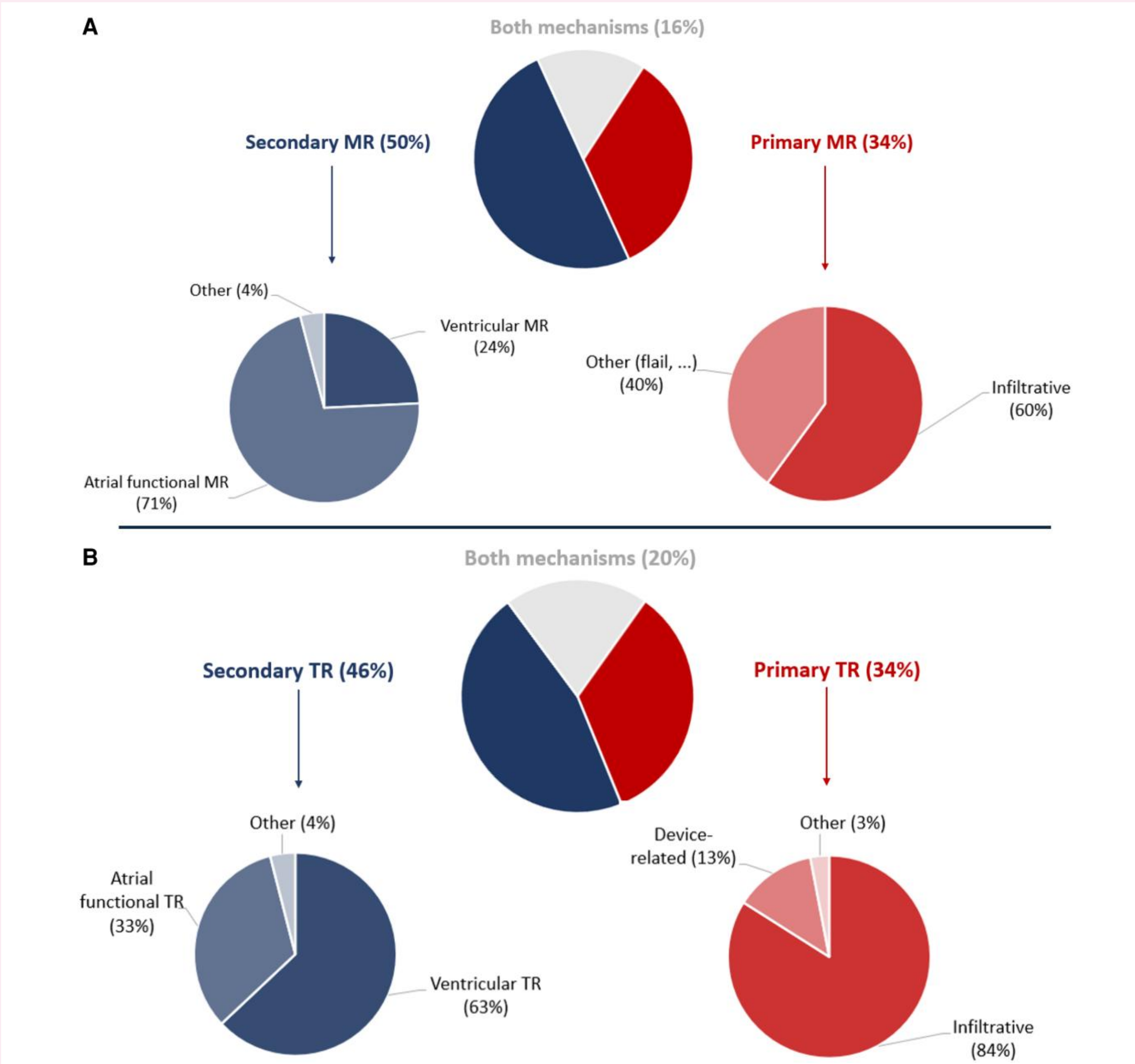


Figure 2 Prevalence of primary and secondary aetiologies of *A*) mitral regurgitation and *B*) tricuspid regurgitation. MR, mitral regurgitation; TR, tricuspid regurgitation.

common cause was atrial functional MR (71%). TR was most frequently secondary (46%) and the most common causes of secondary TR were RV overload (pulmonary hypertension due to left heart disease)/RV dilatation (63%) and atrial functional (33%) (*Figure 2*). About 39 and 45% of patients had thickened MR and TR leaflets, respectively. Overall, 10 patients (4%) underwent correction of MR, of whom five underwent surgery and five percutaneous correction with MitraClip system. The procedures were successful, with $\leq$ mild residual MR in all subjects. No patient underwent correction of TR.

Baseline characteristics

Among included patients, 240 (44.6%) had no significant MR or TR, 112 (20.8%) had isolated MR, 66 (12.3%) had isolated TR, and 120 (22.3%) had combined MR/TR.

Demographic and clinical baseline characteristics stratified by MR/TR categories are reported in *Table 1*. Patients with isolated MR, isolated TR, or combined MR/TR were older, and had lower blood pressure than those with no significant MR/TR, as well as more advanced symptoms (e.g. higher NYHA class), higher rates of previous HF hospitalization and atrial fibrillation. Accordingly, the proportion of patients receiving diuretics was higher among those with isolated or combined MR/TR vs. those with no significant MR/TR. Generally, a progressive worsening from no significant MR/TR to isolated MR, isolated TR and combined MR/TR was observed, with the last two conditions presenting the worst features. *Table 2* reports laboratory and echocardiographic findings of the study population stratified according to MR/TR categories. Patients without significant MR/TR displayed better renal function, lower levels of gamma-glutamyl transpeptidase, lower hs-TnT values, and NT-proBNP concentrations.

Table 1 Baseline clinical characteristics of the study population stratified by MR/TR categories

Variable	No assessed	All (*n* = 538)	No significant MR/TR (*n* = 240)	Isolated MR (*n* = 112)	Isolated TR (*n* = 66)	Combined MR/TR (*n* = 120)	*P* value
Clinical characteristics							
Age (years)	538	75.6 ± 9.9	73.7 ± 10.7	77.8 ± 7.8	74.5 ± 10.1	78.1 ± 8.8	**<0.001**
Sex males, *n* (%)	538	392 (73)	181 (75)	83 (74)	45 (68)	83 (69)	0.486
BMI (Kg/m^2)	529	25.8 ± 3.8	25.9 ± 3.8	26.3 ± 3.9	25.2 ± 4.0	25.7 ± 3.5	0.291
SBP (mmHg)	527	124 ± 21	127 ± 22	124 ± 19	119 ± 23	120 ± 19	**0.004**
DBP (mmHg)	523	72 ± 11	73 ± 12	71 ± 11	71 ± 12	72 ± 12	0.708
Heart rate (bpm)	518	72 ± 16	71 ± 13	72 ± 20	75 ± 20	71 ± 16	0.644
Type of amyloidosis	538						0.188
– ATTR, *n* (%)		359 (67)	154 (64)	83 (74)	40 (61)	82 (68)	
– AL, *n* (%)		179 (33)	86 (36)	29 (26)	26 (39)	38 (32)	
Hypertension, *n* (%)	537	339 (63)	143 (60)	72 (64)	39 (59)	85 (71)	0.195
Dyslipidaemia, *n* (%)	536	213 (40)	101 (42)	46 (41)	17 (26)	49 (41)	0.100
Diabetes, *n* (%)	537	97 (18)	35 (15)	25 (22)	12 (18)	25 (21)	0.274
CAD, *n* (%)	535	105 (20)	31 (13)	31 (28)	11 (17)	32 (27)	**0.002**
COPD, *n* (%)	536	56 (10)	23 (10)	12 (11)	10 (15)	11 (9)	0.586
History of atrial fibrillation, *n* (%)	511	155 (30)	44 (20)	31 (29)	29 (46)	51 (44)	**<0.001**
Previous HF hospitalization, *n* (%)	535	310 (58)	105 (44)	66 (59)	50 (76)	89 (75)	**<0.001**
NYHA class	524						**<0.001**
–I or II *n* (%)		331 (63)	176 (76)	72 (65)	24 (37)	59 (50)	
–III or IV, *n* (%)		193 (37)	55 (24)	38 (35)	40 (63)	60 (50)	
Medical treatment							
Beta-blockers, *n* (%)	501	314 (63)	113 (52)	77 (71)	38 (64)	86 (74)	**<0.001**
ACEi, *n* (%)	501	164 (33)	77 (36)	31 (28)	18 (30)	38 (32)	0.597
ARBs, *n* (%)	501	107 (21)	48 (22)	24 (22)	13 (22)	22 (19)	0.898
ARNI, *n* (%)	501	13 (3)	2 (1)	5 (5)	1 (2)	5 (4)	0.134
Mineralocorticoids, *n* (%)	503	188 (37)	66 (30)	39 (36)	29 (48)	54 (46)	**0.009**
Diuretics, *n* (%)	511	388 (76)	138 (62)	87 (79)	57 (95)	106 (90)	**<0.001**
VKA, *n* (%)	506	77 (15)	15 (7)	12 (19)	17 (29)	33 (28)	**<0.001**
Direct oral anticoagulant, *n* (%)	506	164 (32)	56 (26)	44 (40)	23 (39)	41 (35)	**0.029**
Disease modifying drug[a]	359	92/359 (26)	53 (34)	23 (28)	4(10)	12 (15)	**<0.001**

Values are reported as means ± standard deviations or medians (interquartile ranges).
[a]Disease modifying drugs refer to tafamidis or patisiran in the subgroup of patients with ATTR (percentages refer to patients with ATTR-CA).
ACEi, angiotensin converting enzyme inhibitor; AL, light chain amyloidosis; ARBs, angiotensin receptor blockers; ARNI, angiotensin receptor neprilysin blocker; ATTR, transthyretin amyloidosis; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; HF, heart failure; MR, mitral regurgitation; NYHA, New York Heart Association; PM, pacemaker; SBP, systolic blood pressure; TR, tricuspid regurgitation; VKA, vitamin K antagonist.

Nearly all echocardiographic variables were differently distributed across groups. Particularly, patients without significant MR/TR had better LV diastolic and systolic function, less pronounced left atrial dilatation, better RV longitudinal systolic function, and lower PASP (all *P*-values <0.001). Patients without significant MR/TR had the less altered strain parameters of all four chambers, including LV-GLS, LA-PALS, RA-PALS, RV-GLS, and RV free-wall longitudinal strain. Patients with isolated TR and combined MR/TR presented features of the most advanced disease.

MR aetiologies were equally distributed among subgroups. There was a trend towards more frequent primary TR in patients with isolated TR and more frequent secondary TR among patients with combined MR/TR.

Association between MR and/or TR and clinical outcomes

Over a median follow-up of 1.7 years (IQR 0.7–3.5), a primary composite outcome event occurred in 255 patients (47%); 187 patients (35%) died (*n* = 94, 53% with AL-CA; *n* = 93, 26% with ATTR-CA) and a first episode of worsening HF occurred in 170 patients (32%) (*n* = 68, 38% with AL-CA and 102, 28% with ATTR-CA).

Table 2 Laboratory and echocardiographic findings of the study population stratified by MR/TR categories

	No assessed	All ($n = 538$)	No significant MR/TR ($n = 240$)	Isolated MR ($n = 112$)	Isolated TR ($n = 66$)	Combined MR/TR ($n = 120$)	*P* value
Laboratory findings							
Haemoglobin (g/dL)	501	12.7 ± 1.8	13.1 ± 1.7	12.7 ± 1.9	12.5 ± 1.7	12.2 ± 1.8	**0.001**
eGFR (mL/min)	490	55.2 ± 25.4	62.0 ± 27.9	52.0 ± 23.2	53.9 ± 26.5	47.2 ± 18.6	**<0.001**
Serum sodium (mEq/L)	486	139.2 ± 3.3	139.8 ± 3.4	139.3 ± 3.4	138.5 ± 3.1	138.7 ± 3.1	0.099
Serum potassium (mEq/L)	486	4.1 ± 0.6	4.2 ± 0.5	4.1 ± 0.6	3.9 ± 0.7	4.1 ± 0.5	0.073
Aspartate transaminase (μ/L)	513	27.5 ± 14.6	26.5 ± 14.0	28.9 ± 18.8	28.3 ± 12.2	27.5 ± 12.7	0.625
Alanine aminotransferase (μ/L)	509	25.9 ± 20.1	24.6 ± 16.7	25.9 ± 18.9	26.6 ± 17.9	27.3 ± 25.9	0.732
Gamma-glutamyl transpeptidase (μ/L)	504	47 (26–103)	35 (22–89)	39 (21–69)	87(33–142)	70 (37–139)	**<0.001**
NT-proBNP (ng/L)	480	3178 (1354–8116)	1846 (730–3519)	2715 (1381–7711)	6484 (2927–10 840)	7533 (3201–12521)	**<0.001**
hs-TnT (ng/L)	446	44 (24–80)	33 (18–55)	45 (29–86)	47 (13–96)	71 (41–119)	**<0.001**
Echocardiographic findings							
LVEF (%)	534	51.9 ± 11.0	55.3 ± 9.5	51.6 ± 11.2	50.5 ± 11.3	46.7 ± 11.0	**<0.001**
IVS (mm)	506	16.6 ± 3.5	16.2 ± 3.5	16.5 ± 3.6	17.5 ± 3.6	17.1 ± 3.3	**0.015**
LVPW (mm)	499	14.6 ± 2.7	14.4 ± 7.4	14.2 ± 3.1	15.4 ± 2.8	14.8 ± 2.7	0.493
LVESV (mL)	505	47.0 ± 24.2	43.3 ± 19.6	50.1 ± 27.1	40.5 ± 17.7	54.6 ± 29.5	**<0.001**
LVMI (g)	495	188 ± 89	175 ± 74	189 ± 90	193 ± 98	207 ± 103	**0.016**
LV-GLS (%)	516	−11.8±−4.5	−13.0±−4.6	−12.9±−4.4	−11.1±−4.4	−9.8±−3.7	**<0.001**
E/e′	510	18.7 ± 8.1	16.9 ± 7.9	18.4 ± 8.4	21.5 ± 7.8	21.9 ± 7.5	**<0.001**
LAVI (mL/m^2)	511	44.2 ± 14.0	39.9 ± 12.7	43.6 ± 12.1	46.0 ± 13.9	51.0 ± 14.9	**<0.001**
LA PALS	266	9.6 ± 5.3	11.9 ± 6.2	10.5 ± 5.5	6.9 ± 2.3	7.2 ± 3.1	**<0.001**
Moderate to severe AS	538	34 (6)	13 (5)	8 (7)	4 (6)	9 (8)	0.860
RA PALS (%)	259	10.4 ± 7.3	13.4 ± 7.7	12.7 ± 7.7	6.3 ± 5.8	7.3 ± 4.8	**<0.001**
RV GLS (%)	355	−12.5 ± 7.7	−15.3 ± 7.4	−14.3 ± 7.3	−9.2 ± 6.5	−10.4 ± 7.6	**<0.001**
RV free-wall LS (%)	358	−11.7 ± 8.0	−14.6 ± 7.80	−14.9 ± 6.7	−8.30 ± 7.5	−9.18 ± 7.9	**<0.001**
TAPSE (mm)	527	16.9 ± 4.8	18.7 ± 4.8	17.7 ± 4.4	14.3 ± 4.1	14.3 ± 3.7	**<0.001**
PASP (mmHg)	534	40.8 ± 10.5	36.7 ± 8.7	40.5 ± 9.8	43.6 ± 11.9	46.5 ± 10.0	**<0.001**
Mechanism of moderate-severe MR	231						0.970
Primary				38 (34)		40 (34%)	
Secondary				55 (49%)		60 (50%)	
Both				19 (17%)		19 (16%)	

Continued

Table 2 Continued

	No assessed	All ($n = 538$)	No significant MR/TR ($n = 240$)	Isolated MR ($n = 112$)	Isolated TR ($n = 66$)	Combined MR/TR ($n = 120$)	*P* value
Mechanism of moderate-severe TR	182						0.092
Primary					27 (43%)	35 (29%)	
Secondary					22 (35%)	61 (51%)	
Both					14 (22%)	23 (19%)	

Values are reported as means ± standard deviations or medians (interquartile ranges).
eGFR, estimated glomerular filtration rate; hs-TnT, high sensitivity troponin T; IVS interventricular septum; LA, left atrium; LAVI, left atrium volume index; LS, longitudinal strain; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LV-GLS, left ventricular global longitudinal strain; LVMI, left ventricular mass index; LVPW, left ventricular posterior wall; MR, mitral regurgitation; NT-proBNP, *n*-terminal pro-brain natriuretic peptide; PALS, peak atrial longitudinal strain; PASP, pulmonary artery systolic pressure; RA, right atrium; RV, right ventricular; TAPSE, tricuspid annular plane excursion; TR, tricuspid regurgitation.

The association of MR and TR degree with outcome is shown in Supplementary data online, *Table S1*. The risk of events progressively increased with the degree of MR and TR.

Moderate to severe MR as compared to no significant MR was associated with a higher risk of all-cause death or worsening HF [unadjusted HR 1.65 (1.28–2.13), adjusted HR (HRadj) 1.40 (1.02–1.91)]. Moderate to severe TR was associated with a higher independent risk of the primary composite endpoint as compared to no significant TR [unadjusted HR 2.22 (1.72–2.87); HRadj 2.01 (1.48–2.73)] (*Figure 3*). After adjusting for NT-proBNP and troponin values, TR [HRadj 1.89 (1.36–2.63)] but not MR [HRadj 1.13 (0.76–1.66)] was associated with an increased risk of the primary endpoint.

As compared to patients without significant MR/TR, the cumulative incidence of all-cause death or worsening HF was higher in patients with isolated MR, isolated TR, and combined MR/TR (31 vs. 46 vs. 71 vs. 69%, respectively, $P < 0.001$, *Table 3*, *Figure 4*). The incident rate/100 patient/years was similarly higher in isolated TR and combined MR/TR [35.7 (26.8–47.5) and 38.4 (31.0–47.7)] as compared to isolated MR or no significant MR/TR [24.6 (18.7–32.4) and 15.2 (12.1–19.0), respectively]. Isolated TR [HR_{adj} 2.75 (1.78–4.24)] and combined MR/TR [HR_{adj} 2.31 (1.44–3.70)], but not isolated MR [HR_{adj} 1.48 (0.93–2.37)], were independently associated with an increased risk of the primary outcome as compared to no significant MR/TR, with isolated TR patients having the highest risk. Similar results were observed after adjustment for NT-proBNP and troponin levels (see Supplementary data online, *Table S2*).

No significant interactions with the subtype of CA were observed for isolated TR (*P*-interaction 0.1836), while a significantly higher risk of the composite endpoint was found in patients with combined MR/TR and AL-CA [HR 4.56 (2.80–7.43)] compared to ATTR-CA [HR 2.17 (1.43–3.30)] (*P*-interaction 0.0248) (see Supplementary data online, *Table S3*). Other independent predictors of the primary composite outcome are reported in Supplementary data online, *Table S4*.

All-cause death occurred more frequently in patients with combined MR/TR, isolated TR, and isolated MR as compared to no significant MR/TR (54 vs. 53 vs. 33 vs. 21%, $P < 0.001$) (*Table 3*, Supplementary data online, *Figure S1*). After adjustment, isolated TR and combined MR/TR were independently associated with an increased risk of all-cause mortality [HRadj 2.30 (1.36–3.90); HRadj 2.63 (1.53–4.51)], whereas the association was not significant for isolated MR [HRadj 1.62 (0.92–2.86)]. Worsening HF occurred more frequently in patients with combined MR/TR, isolated TR, and isolated MR as compared to no significant MR/TR (47, 50, 29 vs. 20%, $P < 0.001$) (*Table 3*, Supplementary data online, *Figure S1*). Isolated TR and combined MR/TR were independently associated with an increased risk of worsening HF [HR_{adj} 2.13 (1.21–3.73); HR_{adj} 2.01 (1.14–3.56)]. No significant interactions with CA forms were found for the two secondary endpoints (all *P*-interaction >0.05) (see Supplementary data online, *Table S3*). Furthermore, results were consistent after the exclusion of patients with moderate-to-severe aortic stenosis (see Supplementary data online, *Table S5*).

Discussion

The main findings of the present study were the following: (i) in a large cohort of patients with CA, the prevalence of isolated MR, isolated TR and combined MR/TR were of 20.8, 12.3, and 22.3% respectively, with a similar distribution across CA subtypes (AL vs. ATTR-CA); (ii) atrial functional MR and secondary TR due to RV overload were the most common causes of AV valvular regurgitation; (iii) patients with isolated and/or combined MR/TR had a more advanced cardiac disease compared to those without significant MR/TR; (iv) TR (isolated or combined) carried the most advanced features and the worst prognosis (*Graphical Abstract*).

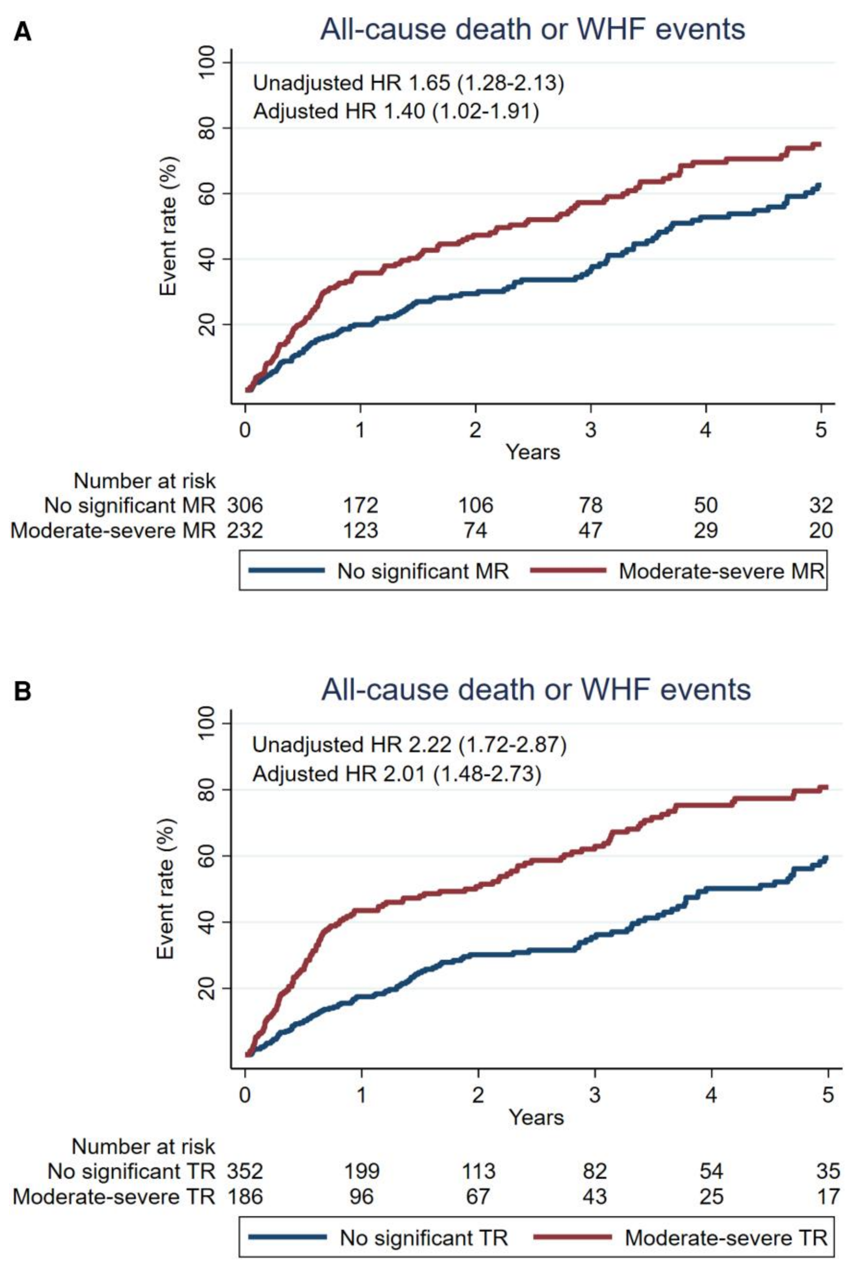


Figure 3 Kaplan–Meier curve for the composite endpoint of all cause of death or worsening HF stratified by *A*) MR degree (moderate to severe MR vs. no significant MR) *B*) TR degree (moderate to severe TR vs. no significant TR). HR, hazard ratio; MR, mitral regurgitation; TR, tricuspid regurgitation.

Prevalence of MR and TR in CA patients

Several studies reported the prevalence of MR and/or TR in patients with HF across different LVEF categories.[11,12,28] However, data on MR/TR epidemiology in the specific HF subset of CA are limited.[17,21,32] This study showed a higher proportions of patients with moderate to severe MR/TR than in the study by Chacko et al., who reported 11.9, 0.9, and 0.1%, of patients as having moderate, moderate/severe, and severe MR, and 12.5, 2.5, and 2.3% as having moderate, moderate/severe, and severe TR, respectively. A possible explanation might be related to the different study populations. Chacko et al. included 877 patients with ATTR-CA attending the National Amyloidosis Centre (NAC), Royal Free Hospital, London, in the United Kingdom between 2000 and 2020, whereas the present study included both patients with ATTR-CA and AL-CA. Furthermore, the proportion of patients with variant (v-) ATTR-CA form was significantly lower (4%) than in Chacko et al. (36%). The clinical spectrum of v-ATTR varies widely from an exclusively/predominantly neurological involvement to a predominantly cardiac presentation; thus, a less overt cardiac phenotype might be expected. Of note, Chacko et al. also used a slightly different grading of MR and TR, introducing a sub-classification of the intermediate grade ('moderate') into three grades ('mild to moderate', 'moderate', and 'moderate to severe').[17] In a different cohort of patients with both ATTR- and AL-CA from the University Hospital of Toulouse, the distribution of TR was consistent with the results of

Table 3 No. of events, incidence rate/100 pts/years, unadjusted, and adjusted HR for clinical outcomes stratified by MR/TR categories

Outcomes		All (538)	No significant MR/TR (n = 240)	Isolated MR (n = 112)	Isolated TR (n = 66)	Combined MR/TR (n = 120)
All-cause mortality or worsening HF	Num. Events, incident rate/100 pts/y	255, 24.4 (21.6–27.6)	74, 15.2 (12.1–19.0)	51, 24.6 (18.7–32.4)	47, 35.7 (26.8–47.5)	83, 38.4 (31.0–47.7)
	Crude HR (95% CI), *P*-value	—	Ref	1.68 (1.17–2.41), 0.005	2.37 (1.64–3.42), <0.001	2.56 (1.87–3.50), <0.001
	Adjusted HR (95% CI), *P*-value*	—	Ref	1.48 (0.93–2.37), 0.099	2.75 (1.78–4.24), <0.001	2.31 (1.44–3.70), <0.001
All-cause mortality	Num. events, incident rate/100 pts/y	187, 15.4 (13.4–17.8)	50, 9.0 (6.8–11.9)	37, 15.3 (11.1–21.1)	35, 21.3 (15.3–29.6)	65, 26.0 (20.4–33.2)
	Crude HR (95% CI), *P*-value	—	Ref	1.76 (1.15–2.70), 0.010	2.35 (1.52–3.62), <0.001	2.91 (2.01–4.22), <0.001
	Adjusted HR (95% CI), *P*-value*	—	Ref	1.62 (0.92–2.86), 0.096	2.30 (1.36–3.90), 0.002	2.63 (1.53–4.51), <0.001
Worsening HF	Num. Events, incident rate/100 pts/y	170, 16.3 (14.0–18.9)	49, 10.0 (7.6–13.3)	32, 15.4 (10.9–21.8)	33, 25.0 (17.8–35.2)	56, 25.9 (20.0–33.7)
	Crude HR (95% CI), *P*-value	—	Ref	1.57 (1.00–2.46), 0.050	2.55 (1.64–3.97), <0.001	2.59 (1.77–3.81), <0.001
	Adjusted HR (95% CI), *P*-value*	—	Ref	1.21 (0.68–2.17), 0.518	2.13 (1.21–3.73), 0.009	2.01 (1.14–3.56), 0.016

CI, confidence interval; HF, heart failure; HR, hazard ratio; MR, mitral regurgitation; TR, tricuspid regurgitation.
*Multivariable Cox model included age, sex, type of CA, NYHA functional class, atrial fibrillation, eGFR, LVEF, LV-GLS, and RV coupling.

this study, with more than a quarter of patients presenting moderate to severe TR.[32]

The prevalence of both isolated and combined MR and TR was investigated as well. Secondary AV valve regurgitation may occur isolated or concomitantly across the entire HF spectrum.[12,28,33–36] Bartko et al. found that 30% of consecutive patients with HF and reduced ejection fraction (HFrEF) suffered from moderate or severe concomitant mitral and tricuspid regurgitation.[35] HF with preserved ejection fraction (HFpEF) was recently found as a strong and important driver of isolated TR.[28] To date there is a paucity of data regarding isolated or combined MR and TR profiles in patients with HFpEF,[28] and no data in patients with CA.

Characteristics of CA patients with MR and TR

Patients with either combined or isolated MR/TR presented worse symptoms, higher levels of both NT-proBNP and hs-TnT, worse liver and renal function, and more advanced disease at echocardiography, compared to those without significant MR/TR. TR, isolated or combined with MR, carried the worst features.

In patients with CA, MR, and TR can simultaneously develop because of parallel amyloid deposition within the valve (primary MR and TR). Also, bi-atrial enlargement/dysfunction may play a major role ('atrial MR' and 'atrial TR').[21] A more pronounced functional impairment, maladaptive cardiac remodelling, and neurohumoral pathway activation were also described among HF patients with combined MR/TR as compared to those without in previous studies regardless of HF aetiology.[28] Involvement of the right chambers may be secondary to the haemodynamic effects of more severe LV ventricular diastolic dysfunction causing pulmonary hypertension, RV overload, and TR.[37] Thus, TR might represent a marker of advanced CA with RV involvement. Novel data regarding the specific aetiologies of MR and TR in a cohort of patients with CA are reported. Atrial functional MR was the most common cause of MR in this population. Also, secondary TR occurred more frequently than primary TR and the most common mechanisms were pulmonary hypertension and RV overload due to left heart disease, followed by atrial functional TR. Different proportions of primary and secondary TR aetiologies were reported in different populations.[34] No data are available in literature on patients with CA as a comparison.

Association between MR and TR and prognosis in CA patients

Moderate to severe MR and moderate to severe TR were previously associated with an adverse prognosis in HF populations.[1,33,34,38–43] Baseline moderate to severe MR and severe TR were found to be independent predictors of mortality in previous cohorts of patients with CA.[17,32] The study extends previous findings. Indeed, additional outcomes related to HF, namely hospitalization for HF or urgent HF visits, were explored. Moreover, population was stratified according to different MR/TR categories, including combined MR/TR. After extensive adjustment for known predictors of prognosis, including laboratory and echocardiographic markers of disease severity, combined MR/TR, but not isolated MR was associated with an increased risk of events. Nevertheless, isolated TR was associated with the worst composite outcome, with ~2.8-fold increased risk of the all-cause death or worsening HF compared to no significant MR/TR. The association of isolated TR and combined MR/TR with outcome was confirmed in both ATTR- and AL-CA. The prognostic significance of AV regurgitation in patients with CA leads to questions regarding the interventional therapeutic options. Doldi et al. showed the feasibility of mitral transcatheter edge-to-edge repair (M-TEER) in patients with atrial functional MR.[44] Among 120 consecutive patients undergoing M-TEER for MR and screened for concomitant CA, CA was diagnosed in 14 patients

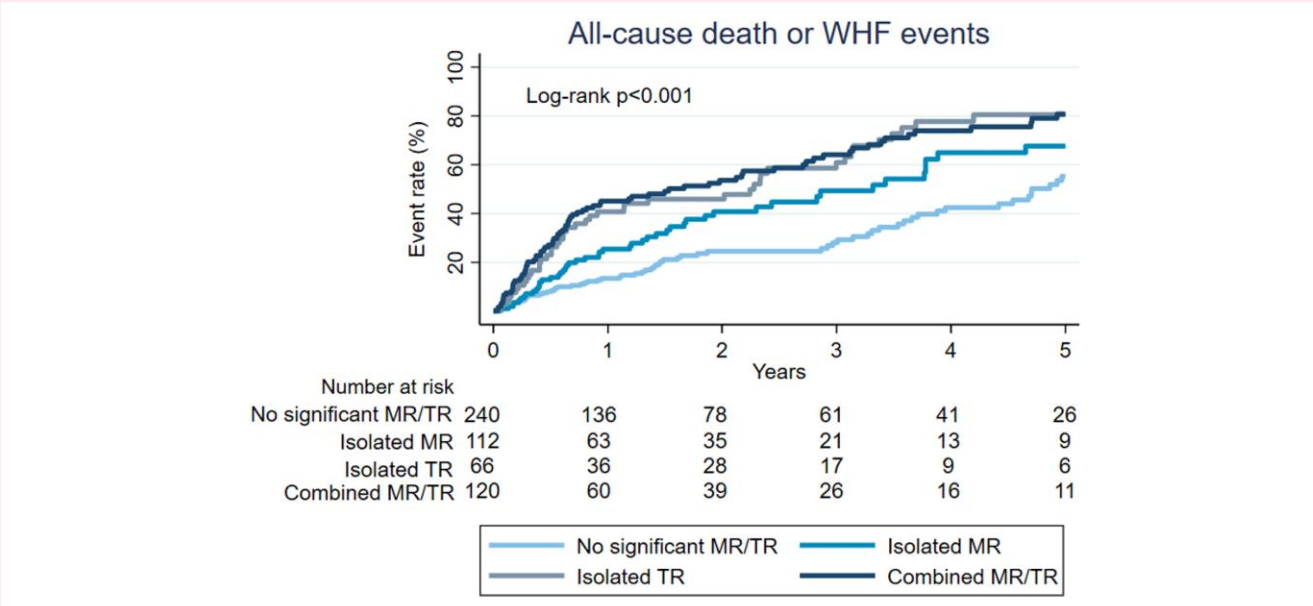


Figure 4 Kaplan–Meier curve for the composite endpoint of all cause of death or worsening HF stratified by MR/TR categories (no significant MR/TR vs. isolated MR vs. isolated TR vs. combined MR/TR). MR, mitral regurgitation; TR, tricuspid regurgitation; WHF, worsening heart failure.

(11.7%).[45] Procedural success and peri-procedural complications of M-TEER were similar in patients with concomitant MR and CA compared with those with MR without CA.[45] In the present cohort only a minority of patients (4%) received surgical or percutaneous correction of MR with procedural success in all cases. However, whether the treatment of MR and/or TR in patients with CA will improve the clinical course of the disease and attenuate the progression of four chambers remodelling remains unexplored and should be investigated in future studies.

Limitations

The main limitation of this study is represented by its retrospective nature. Thus, the role of residual confounding cannot be excluded. Second, the degree of MR and TR was evaluated at a single time-point and, therefore, changes over time, namely, worsening of MR/TR, were not registered. Third, although different study sites were chosen to include a diverse mix of healthcare providers, data reflect patients from three high-volume Italian centres and thus may not be generalizable to all care practices. Fourth, the limited sample size did not allow further analysis in the subgroup of patients with different subtypes of CA (ATTR- vs. AL-CA).

Conclusions

In a large cohort of patients with CA, the prevalence of isolated MR and isolated TR was 21 and 12%, respectively, while combined MR/TR was observed in 22% of patients. The presence of isolated TR or combined MR/TR was associated with a worse prognosis regardless of CA aetiology, LV, RV function, and NT-proBNP, with TR carrying the highest risk.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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