

# Prognostic implications of functional tricuspid regurgitation in asymptomatic degenerative mitral regurgitation

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## Abstract

**Aims** Functional tricuspid regurgitation (FTR) associated with degenerative mitral regurgitation (DMR) accentuates the severity of heart failure and is a marker of poor prognosis. Little is known about FTR associated with asymptomatic DMR.

**Methods and results** The study included 1249 asymptomatic patients with moderate or severe DMR from the Mitral Regurgitation International Database-Quantitative (MIDA-Q) registry (mean age 64 ± 15 years, 25% female). Despite the asymptomatic status, absent/trivial FTR was noted in only 42%, mild in 34.5%, moderate in 11%, and severe FTR in 12.5%. Patients with higher FTR grades were older and more often female and had higher EuroScore II, larger left atrial volumes, and more atrial fibrillation (all  $P < 0.05$ ). Patients with moderate or severe FTR had comparable 5-year survival (64 ± 4% and 65 ± 4%) and lower than patients with no/trivial FTR (96 ± 1%,  $P < 0.001$ ). After adjustment for key prognostic factors, including age, left ventricular dilatation and dysfunction, DMR severity, left atrial dilatation, and pulmonary hypertension, ≥moderate FTR remained a strong predictor of mortality (HR = 2.08 [1.17–3.72],  $P = 0.013$ ). Sensitivity analysis showed stable impact of ≥moderate FTR among patients with/without pulmonary hypertension, in women and men and for any other subset. For patients who underwent mitral valve surgery, post-operative survival rates were similar between those with no/trivial FTR and those with ≥moderate or severe FTR ( $P = 0.76$ ), suggesting that surgery could reduce the excess mortality related to preoperative FTR.

**Conclusions** Among asymptomatic patients with significant DMR, ≥moderate FTR is frequent and independently associated with higher mortality, independently of traditional guideline-based risk factors. These findings suggest that ≥moderate FTR should lead to consideration of early mitral surgery to improve outcomes.

**Keywords** Degenerative mitral regurgitation; Functional tricuspid regurgitation; Outcome; Survival; Surgery

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## Introduction

Degenerative mitral regurgitation (DMR) is the major cause of organic MR in Western communities and, despite the

effectiveness of mitral valve repair, often remains undertreated with important impact on excess mortality associated with the condition.<sup>1</sup> Functional tricuspid regurgitation (FTR) is frequently detected in the context of significant DMR<sup>2</sup> and, if

clinically significant (moderate or severe), is independently associated with severe symptoms and the occurrence of heart failure complicating DMR.<sup>3</sup> Thus, in the context of those symptomatic patients, prompt surgical intervention combining mitral and tricuspid valve repair is highly recommended (class I) by European guidelines.<sup>4</sup>

However, in asymptomatic patients with significant DMR, many issues remain undefined. These patients have few clear triggers for mitral surgery, yielding DMR frequently remaining untreated. In these patients, FTR prevalence and independent impact on survival after diagnosis remain uncertain. Current European guidelines consider surgery for asymptomatic patients based on factors such as atrial fibrillation (AF), left ventricular size and function, left atrial volume index (LAVI), and systolic pulmonary artery pressure (sPAP).<sup>4</sup> Although excess mortality has been demonstrated with FTR associated to mostly symptomatic DMR,<sup>3</sup> the role of FTR in asymptomatic patients with significant DMR remains undefined. Furthermore, guidelines do not consider FTR presence as a class I or class II trigger for mitral valve surgery in asymptomatic, clinically significant DMR.

To analyse the incremental prognostic impact of FTR on the survival after asymptomatic DMR diagnosis, considerable statistical power is required and is linked to the requirement of a very large DMR cohort. The MIDA-Q multicenter international registry (Mitral Regurgitation International DATABASE-Quantitative) gathers the largest ever DMR cohort due to mitral valve prolapse<sup>5</sup> and offers the opportunity to resolve the FTR in asymptomatic DMR conundrum. Thus, in this unique registry, we analysed the prevalence of the various FTR grades of severity and aimed to investigate the relationship between FTR severity and outcomes for patients with significant asymptomatic DMR.

## Methods

We used data from the MIDA-Q registry, which included patients with isolated DMR due to mitral valve prolapse. The methodology has been previously reported.<sup>5</sup> Briefly, consecutive adult patients with a diagnosis of mitral valve prolapse were eligible for inclusion. We excluded patients (i) who declined research authorization; (ii) without quantification of MR; (iii) with functional or rheumatic MR, primary TR,  $\geq$ moderate aortic valve disease or mitral stenosis, congenital heart disease, history of heart failure, active endocarditis, or dilated/hypertrophic/restrictive cardiomyopathies; or (iv) with a history of valvular surgery. The present analysis was based on asymptomatic patients (defined as those without self-reported symptoms and/or without symptoms during exercise tests when performed) with significant (moderate-to-severe or severe) DMR with data on FTR severity. The study was approved by the institutional review board of each

centre and conducted in accordance with institutional guidelines, national legal requirements, and the revised Declaration of Helsinki. MR and TR were graded according to current recommendations using a multiparametric integrative approach.<sup>4,6</sup>

The median follow-up was 5.3 [3.5–8.1] years. The primary endpoint was all-cause mortality during follow-up for the entire cohort. The secondary endpoint was post-operative mortality among patients who underwent mitral valve surgery.

The study population was divided into four groups according to FTR severity. Categorical variables are reported as percentages and counts, and continuous variables are expressed as the mean value  $\pm$  1 standard deviation or median (IQR). Crude survival distributions were estimated according to the Kaplan–Meier method and compared using two-sided log-rank tests. Multivariable analyses of all-cause mortality were performed using Cox proportional hazards models. Statistical significance was  $P < 0.05$ . All tests were two-tailed.

## Results

The cohort of 1249 asymptomatic patients with significant DMR included 525 with no or trivial FTR, 432 with mild FTR, 135 with moderate FTR, and 157 with severe FTR. The baseline characteristics of the study population according to FTR severity are reported in *Table 1*. Patients with higher FTR grades were typically older and more often female, had a higher EuroSCORE II and had more AF (all  $P < 0.05$ ). In terms of echocardiographic parameters, higher FTR grades were associated with higher indexed LV end-diastolic and end-systolic diameters (LVESDi), a higher LAVI, higher sPAP and a lower LV ejection fraction (EF) (all  $P < 0.05$ ; *Table 1*).

During follow-up, 237 (19.0%) deaths were recorded. Five-year estimated survival for patients with no/trivial FTR was  $96 \pm 1\%$ ,  $87 \pm 2\%$ , for mild FTR,  $64 \pm 4\%$  for moderate FTR, and  $65 \pm 4\%$  for severe FTR (overall *log rank*  $P < 0.001$ ) (*Figure 1*). Comparable survival rates were observed for moderate and severe FTR (*log rank*  $P = 0.89$ ). The results were similar for women and men and for patients with or without pulmonary hypertension (sPAP  $< 50$  mmHg or  $\geq 50$  mmHg) (all  $P < 0.001$ ; *Figure 2*).

After comprehensive adjustment for age, sex, EuroSCORE II, AF, effective regurgitant orifice area (EROA), LVESDi, LVEF and LAVI, and  $\geq$ moderate FTR was associated with substantially higher mortality compared to no/trivial FTR (HR = 2.54 [1.50–4.30],  $P = 0.011$ ), whereas mild FTR showed no significant association ( $P = 0.23$ ). These findings remained unchanged even after further adjustment for pulmonary pressures (HR = 2.08 [1.17–3.72],  $P = 0.013$  and  $P = 0.32$ , respectively) (*Table 2*). After adjustment, survival was comparable for patients with moderate or severe FTR ( $P = 0.25$ ). The

**Table 1** Baseline characteristics according to tricuspid regurgitation severity.

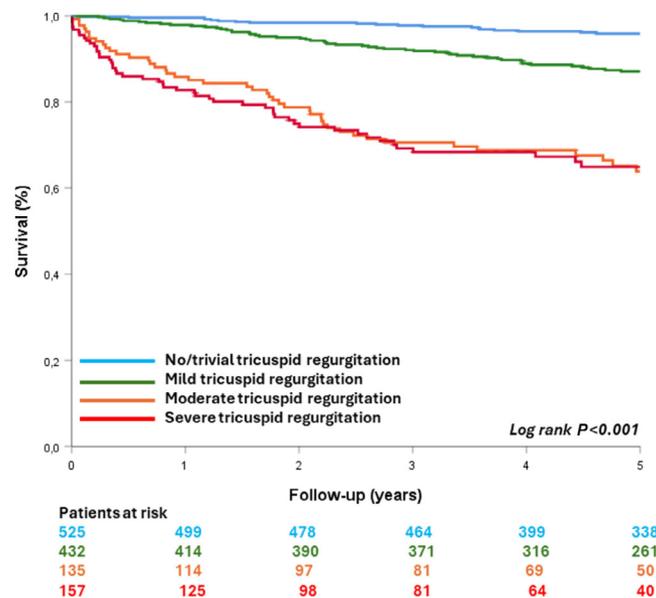
Characteristics	No or trivial FTR <i>n</i> = 525	Mild FTR <i>n</i> = 432	Moderate FTR <i>n</i> = 135	Severe FTR <i>N</i> = 157	<i>P</i> value
<b>Clinical characteristics</b>					
Age, years	58 ± 13	64 ± 13†	75 ± 13†	72 ± 16†	<0.001
Female gender (%), <i>n</i>	19.6 (103)	24.1 (104)*	36.3 (49)†	35.0 (55)†	<0.001
Body surface area (m <sup>2</sup> )	1.96 ± 0.22	1.91 ± 0.20*	1.85 ± 0.20†	1.84 ± 0.22†	<0.001
Body mass index, kg/m <sup>2</sup>	25.4 ± 3.4	25.3 ± 3.7	25.8 ± 6.2	25.4 ± 5.1	0.72
Diabetes mellitus (%), <i>n</i>	3.0 (16)	5.3 (23)	13.3 (18)†	14.0 (22)†	<0.001
Coronary artery disease (%), <i>n</i>	17.5 (92)	21.8 (94)†	12.6 (17)†	3.8 (6)†	<0.001
EuroSCORE II, %	0.7 ± 0.2	0.8 ± 0.3*	2.4 ± 2.5†	2.2 ± 1.7†	<0.001
Atrial fibrillation (%), <i>n</i>	7.2 (38)	13.4 (58)*	31.1 (42)†	29.9 (47)	
<b>Biological characteristics</b>					
Creatinine level (mg/dL)	0.87 ± 0.19	0.94 ± 0.23	1.37 ± 0.85†	1.54 ± 0.82†	<0.001
eGFR (mL/mn)	105 ± 31	92 ± 29	59 ± 32†	49 ± 28†	<0.001
NT-pro BNP (pg/mL)	147 ± 143	225 ± 203*	463 ± 216†	492 ± 281†	<0.001
<b>Echocardiographic characteristics</b>					
LV end-diastolic diameter, mm	58 ± 6	58 ± 6	54 ± 6†	55 ± 8†	<0.001
Indexed LV end-diastolic diameter, mm/m <sup>2</sup>	30 ± 4	31 ± 4*	29 ± 4	30 ± 5	0.003
LV end-systolic diameter, mm	35 ± 6	36 ± 6	34 ± 6	35 ± 8	0.09
Indexed LV end-systolic diameter, mm/m <sup>2</sup>	18 ± 3	18 ± 4	19 ± 3*	19 ± 5*	0.015
LV ejection fraction, %	66 ± 6	65 ± 8	58 ± 8†	59 ± 7†	<0.001
LA volume index, mL/m <sup>2</sup>	58 ± 21	63 ± 28*	66 ± 27*	67 ± 30*	0.001
EROA, mm <sup>2</sup>	48 ± 15	50 ± 17	43 ± 17*	54 ± 19†	<0.001
PA systolic pressure, mmHg	32 ± 9	38 ± 11†	45 ± 16†	53 ± 18†	<0.001

Note: Continuous variables are expressed as mean ± 1 standard deviation and categorical variables are expressed as percentages and numbers. NT pro BNP values were only available for 113 patients, creatinine levels for 397 patients and eGFR for 359 patients.

Abbreviations: eGFR, glomerular filtration rate; EROA, effective regurgitant orifice; FTR, functional tricuspid regurgitation; LA, left atrial; LV, left ventricular; PA, pulmonary artery.

\**P* < 0.05 versus no or trivial TR group.

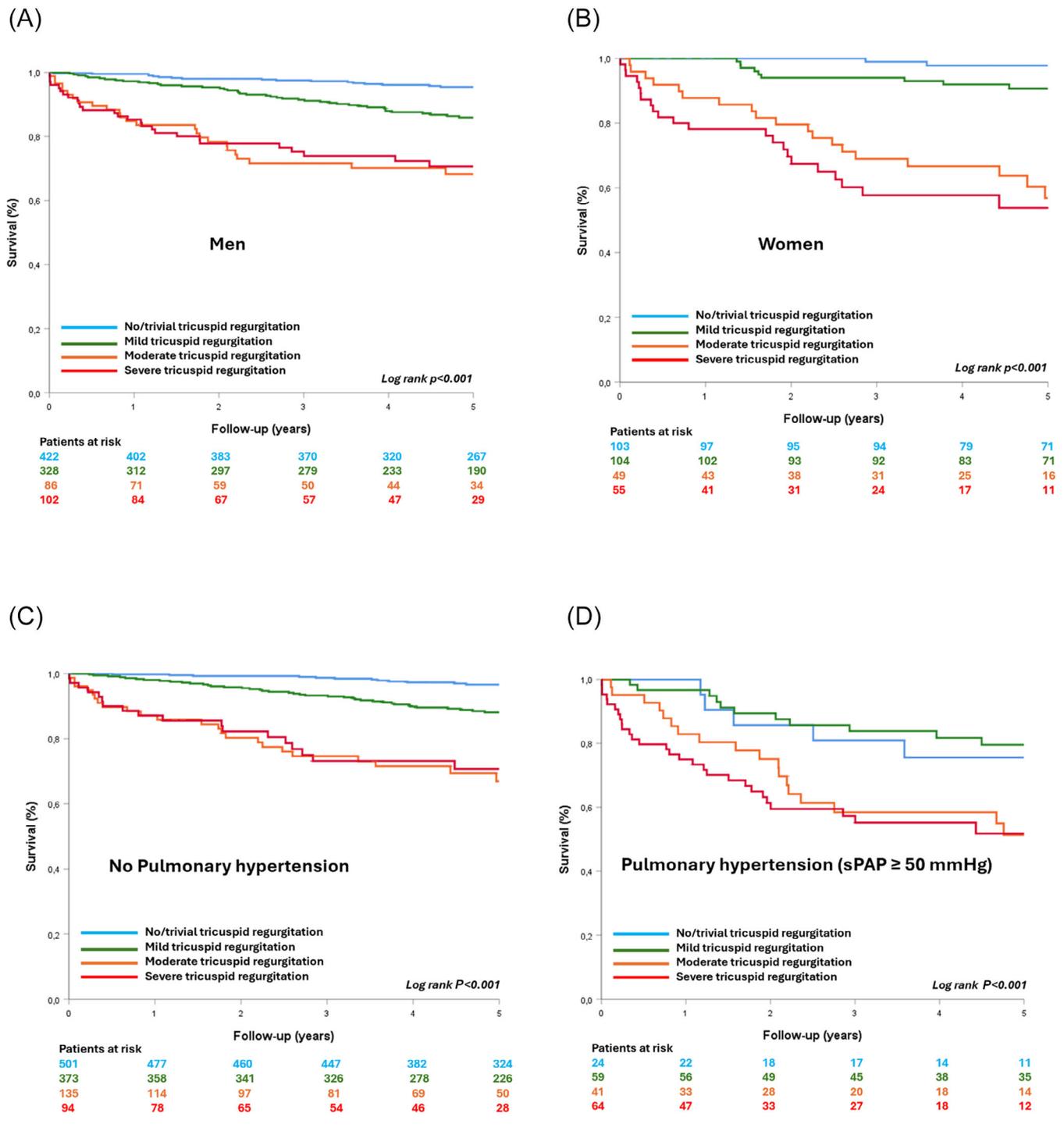
†*P* < 0.001 versus no or trivial TR group.

**Figure 1** Kaplan–Meier survival curves stratified by FTR grade.

association between  $\geq$ moderate FTR and risk of death was consistent in different subgroups of patients with no interactions between  $\geq$ moderate FTR and any of the subgroups (all *p* for interaction  $\geq 0.15$ ; Figure 3).

Among the patients who underwent mitral valve surgery during follow-up (*n* = 823 [65.9%]), 806 [98%] mitral valve repair and 17 mitral valve replacement [15 bioprostheses and 2 mechanical], there was no significant difference in

**Figure 2** Kaplan–Meier survival curves stratified by FTR grade according to sex (A,B) and the presence or absence of pulmonary hypertension (C,D). sPAP, systolic pulmonary artery pressure.



post-operative survival between those with no/trivial pre-operative FTR and those with  $\geq$ moderate pre-operative FTR (adjusted HR = 1.14 [0.50–2.61],  $P = 0.76$ ), suggesting that surgery reduces the excess mortality related to associated  $\geq$ moderate pre-operative FTR.

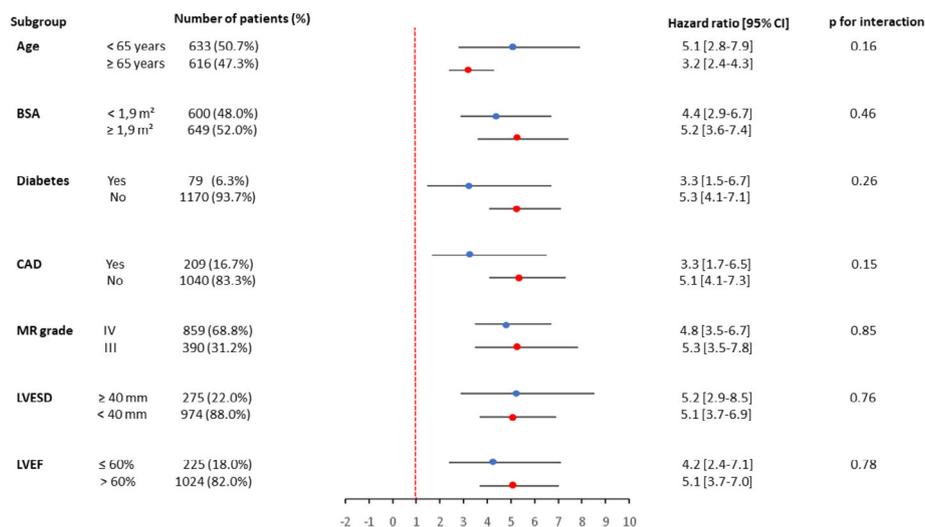
## Discussion

Our study is the first to highlight the significant prognostic impact of moderate or greater FTR for patients with asymptomatic DMR. We found that  $\geq$ moderate FTR is common, affect-

**Table 2** Univariable and multivariable hazard ratio for mortality for moderate tricuspid regurgitation.

Model	Conservative management	
	HR (CI [95%]) for RVD	P value
Univariable		
Mild vs. no/trivial TR	2.47 [1.71–3.59]	<0.001
Moderate and severe vs. no/trivial TR	8.16 [5.68–11.20]	<0.001
Model 1: Adjusted for age, sex, EuroSCORE II		
Mild vs. no/trivial TR	1.43 [0.98–2.09]	0.066
Moderate and severe vs. no/trivial TR	2.37 [1.53–3.64]	<0.001
Model 2: Model 1 + atrial fibrillation, EROA, LVEF, LVESDi, LAVI		
Mild vs. no/trivial TR	1.30 [0.84–2.01]	0.23
Moderate and severe vs. no/trivial TR	2.54 [1.50–4.30]	0.011
Model 3: Model 2 + sPAP		
Mild vs. no/trivial TR	1.26 [0.80–1.98]	0.31
Moderate and severe vs. no/trivial TR	2.08 [1.17–3.72]	0.013

Abbreviations: EROA, effective regurgitant orifice area; LAVI, left atria volume index; LVEF, left ventricular ejection fraction; LVESDi, indexed left ventricular end-systolic diameter; sPAP, systolic pulmonary artery pressure.

**Figure 3** Forrest plot for the risk of all-cause mortality associated with  $\geq$  moderate FTR for different subgroups. BSA, body surface area; CAD, coronary artery disease; CI, confidence interval; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-s diameter; MR, mitral regurgitation.

ing nearly one in four patients, and associated with more than a twofold increase in all-cause mortality, even after adjusting for key prognostic factors such as age, EuroSCORE II, left ventricular size and function, left atrial size, and pulmonary pressure.

FTR is primarily driven by PH, but also AF, which contribute to right atrial enlargement and subsequent tricuspid annular dilation.<sup>3</sup> Essayagh *et al.* previously demonstrated a strong independent association between moderate/severe FTR and mortality in a cohort of patients with DMR of varying severity, mainly symptomatic, without adjustment for symptoms.<sup>3</sup> Our study is the first to specifically focus on asymptomatic patients with significant DMR, a group for whom the optimal timing of surgical intervention remains debated, while

uniquely exploring whether the severity of FTR should influence the decision to perform early mitral valve repair. Interestingly, our findings show that moderate FTR has a pejorative prognostic impact comparable to that of severe FTR for asymptomatic patients with significant MR. These results underscore the need to approach moderate and severe FTR with the same level of concern and to systematically perform a rigorous and systematic comprehensive and integrative echocardiographic assessment of TR.<sup>2,6</sup> Given that  $\geq$ moderate FTR is a powerful independent prognostic indicator and surgery appears to correct the associated excess mortality related to associated pre-operative FTR,  $\geq$ moderate FTR could be considered as a new additive factor in deciding whether to consider early mitral surgical repair for asymp-

omatic severe DMR. Regarding sex differences, the lower proportion of women with asymptomatic DMR may be due to their tendency to present with more symptoms than men.<sup>7</sup> In contrast, the observed increase in the proportion of women with greater FTR severity has been previously reported,<sup>2</sup> but the mechanisms underlying this imbalance remain unclear and warrant prospective investigation. Notably, the prognostic impact of  $\geq$ moderate FTR was comparable between women and men.

Our study was subject to the inherent limitations of observational registries with retrospective follow-up data. However, the echocardiographic data were collected prospectively. Our findings are specifically applicable to DMR due to mitral valve prolapse, and further research is needed to assess their relevance in other subsets of patients with primary MR. Exercise tests were not systematic, but the relatively young patient cohort (mean age 64) likely provided accurate self-reports of symptoms. Data on invasive hemodynamic pressure measurements, medical therapy, and specific types of mitral valve repair were not available in our database. The impact of mitral annular disjunction on FTR associated to DMR remains to be evaluated. Large prospective studies are necessary to confirm our results and to support the inclusion of moderate or severe FTR as a new criterion for early surgical intervention for asymptomatic, low-risk patients with severe DMR.

## Conclusion

Among patients with asymptomatic significant DMR due to mitral valve prolapse, moderate or severe FTR is an additional

independent prognostic factor to traditional risk factors, including PH. As surgery appears to correct the excess mortality related to FTR, the presence of  $\geq$ moderate FTR could warrant earlier referral for mitral valve surgery to improve long-term outcomes.

## Conflict of interest

The Department of Cardiology of the Leiden University Medical Center received research grants from Abbott Vascular, Alnylam, Bayer, Bioentrix, Medtronic, Biotronik, Boston Scientific, GE Healthcare, and Edwards Lifesciences. Dr Bax has received speaking fees from Abbott and Edwards Lifesciences. Dr Ajmone Marsan has received speaking fees from Abbott Vascular, Philips Ultrasound, and GE Healthcare and has served on the Medical Advisory Board of Philips Ultrasound and Trimensio/Pie and as a councillor on the board of the EACVI. Dr Roussel has received consulting fees from Edwards Lifesciences. Dr Le Tourneau received payments/honoraria from Bayer and GE Healthcare. Dr Enriquez-Sarano received consulting fees from Edwards LLC, Cryolife Inc., Chemimage, and HighLife Inc. The remaining authors have nothing to disclose.

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