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CLINICAL RESEARCH

Functional tricuspid regurgitation of degenerative mitral valve disease: a crucial determinant of survival

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Aims To assess functional tricuspid regurgitation (FTR) determinants, consequences, and independent impact on outcome in degenerative mitral regurgitation (DMR).

Methods and results All patients diagnosed with isolated DMR 2003–2011, with structurally normal tricuspid leaflets, prospective FTR grading and systolic pulmonary artery pressure (sPAP) estimation by Doppler echocardiography at diagnosis were identified and long-term outcome analysed. The 5083 DMR eligible patients [63 ± 16 years, 47% female, ejection fraction (EF) 63 ± 7%, and sPAP 35 ± 13 mmHg] presented with FTR graded trivial in 45%, mild in 37%, moderate in 15%, and severe in 3%. While pulmonary hypertension (PHTN-sPAP ≥ 50 mmHg) was the most powerful FTR severity determinant, other strong FTR determinants were older age, female sex, lower left ventricle EF, DMR, and particularly atrial fibrillation (AFib) (all $P \leq 0.002$). Functional tricuspid regurgitation moderate/severe was independently linked to more severe clinical presentation, more oedema, lower stroke volume, and impaired renal function ($P \leq 0.01$). Survival (95% confidence interval) throughout follow-up [70% (69–72%) at 10 years] was strongly associated with FTR severity [82% (80–84%) for trivial, 69% (66–71%) for mild, 51% (47–57%) for moderate, and 26% (19–35%) for severe, $P < 0.0001$]. Excess mortality persisted after comprehensive adjustment [adjusted hazard ratio 1.40 (1.18–1.67) for moderate FTR and 2.10 (1.63–2.70) for severe FTR, $P \leq 0.01$]. Excess mortality persisted adjusting for sPAP/right ventricular function ($P < 0.0001$), by matching [adjusted hazard ratios 2.08 (1.50–2.89), $P < 0.0001$] and vs. expected survival [risk ratio 1.79 (1.48–2.16), $P < 0.0001$]. Within 5-year of diagnosis valve surgery was performed in 73% (70–75%) and 15% (13–17%) of severe and moderate DMR and in only 26% (19–34%) and 6% (4–8%) of severe and moderate FTR. Valvular surgery improved outcome without alleviating completely higher mortality associated with FTR ($P < 0.0001$).

Conclusion In this large DMR cohort, FTR was frequent and causally, not only linked to PHTN but also to other factors, particularly AFib. Higher FTR severity is associated at diagnosis with more severe clinical presentation. Long term, FTR is independently of all confounders, associated with considerably worse mortality. Functional tricuspid regurgitation moderate and even severe is profoundly undertreated. Thus careful assessment, consideration for tricuspid surgery, and testing of new transcatheter therapy is warranted.

Keywords Mitral regurgitation • Tricuspid regurgitation • Surgery • Prognosis • Survival

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Introduction

Functional tricuspid regurgitation (FTR), a malcoaptation of structurally normal tricuspid leaflets,[1] is common,[2] and is most often caused by left-sided valve disease,[3] dominated by degenerative mitral regurgitation (DMR).[4] The classic view is that FTR is secondary to pulmonary hypertension (PHTN) due to the left-sided valve disease and thus is most likely to improve after mitral surgery,[5] with a particular emphasis on the pre-eminence of treating the mitral valve disease.[6,7] This concept of the 'unimportance' of tricuspid regurgitation (TR) was re-emphasized by reported good outcome following complete valvulectomy of the tricuspid valve.[8]

While TR was more recently suggested to negatively affect outcome,[9] doubts regarding this outcome association persists because of the heterogeneity of contexts in which TR occurs.[3] Indeed, it remains uncertain whether poor outcomes are caused by FTR itself or by the FTR causal disease, or by secondary PHTN[10] or by comorbid conditions.[11] The difficulty in demonstrating FTR independent outcome impact is exemplified by recent negative outcome studies.[12,13] Therefore, surgical treatment of TR, particularly of FTR, is extremely rarely performed, in <10 000 patients yearly among the estimated 1.6 million carriers in the USA.[3]

Enrolling in specific clinical contexts, recent cohorts of FTR isolated or complicating heart failure, by gathering detailed baseline information, demonstrated that indeed FTR independently determines poor outcome[14–16] and may be a valuable target for therapy. Conversely in patients with DMR, information on FTR outcome under medical treatment is sparse, potentially biased, and generally inconclusive,[17] and does not allow to specify whether FTR, in and by itself, in the DMR context, warrants attention or treatment. Most reports regard FTR outcome/management with DMR surgery, which remains highly controversial.[7,18–20] While guidelines recommend surgical FTR treatment simultaneously to DMR as the only Class I indication in the category,[21,22] many uncertainties persist in regard to FTR in this context. Resolving whether FTR associated with DMR independently impacts outcome is crucial with trends towards early DMR surgery,[21–23] while FTR surgical treatment remains quite underused.[3] In turn, these new data would help support whether emerging tricuspid transcatheter therapies warrant clinical trials of FTR treatment in patients with DMR.[24]

To resolve this conundrum, a large, powerful cohort of isolated DMR of all grades, with comprehensive clinical/echocardiographic characterization, FTR grading, and assessment of pulmonary pressures at diagnosis, carefully defined cardiac/general comorbid conditions and long-term mortality collection, is warranted. Accordingly, we gathered such a unique cohort to analyse FTR independent contributors, consequences, and impact on outcome and examined the hypothesis that FTR severe but also moderate is, independently of all comorbidities or collinearities, associated with reduced survival in patients with DMR.

Methods

Patients identified as eligible were those: (i) aged ≥18 years, (ii) with isolated degenerative mitral valve disease defined mitral valve prolapse or flail leaflet diagnosed by first echocardiography at the Mayo Clinic between 2003 and 2011 irrespective of mitral regurgitation (MR) grade, and (iii) with comprehensive clinical/echocardiographic characterization, including FTR grading (trivial to severe) and systolic pulmonary artery pressure (sPAP) measurement, at diagnosis. Exclusion criteria were absence of research authorization (per MN law), presence of pacemaker/defibrillator, organic TR, ≥moderate aortic valve disease, mitral stenosis, rheumatic or functional MR, any previous valve surgery, and any other myocardial/pericardial/congenital heart disease (patent foramen ovale, coronary artery disease not excluded). As low-risk study, written consent requirement was waived by Mayo Institutional Review Board, which gave its approval.

Echocardiographic evaluation

Echocardiography performed in routine clinical practice, under direct supervision of a staff cardiologist, followed standardized protocol for all views/windows. At diagnosis, comprehensive measurements and grading using standardized phrases were stored immediately in an image and data repository in a prospective and standardized approach. Those were extracted without alteration or re-interpretation for the study. Degenerative mitral valve disease was diagnosed by the presence of mitral valve prolapse or flail leaflet[25] and DMR severity assessed by integrative grading with quantitative assessment as often as possible.[26] Functional TR was diagnosed by comprehensive tricuspid valve examination excluding structural abnormalities and graded using standardized phrases according to American Society of Echocardiography guidelines as absent, trivial, mild, moderate, and severe.[27] Systolic pulmonary artery pressure was calculated using continuous-wave Doppler FTR velocity and right atrial pressure estimated using inferior vena cava imaging. Per guidelines, PHTN was defined as sPAP ≥50 mmHg.[28] Left atrial volume, left ventricle (LV) and right ventricle size/function, forward cardiac output/index, and stroke volume index were systematically defined according to American Society of Echocardiography guidelines.[29] Right ventricular (RV) function was mainly integratively graded as normal, mildly, moderately, and severely decreased by the responsible physician.

Clinical evaluation

Patients' history, symptoms (dyspnoea, oedema, chest pain), and major comorbidities (summated as Charlson index) were recorded at diagnosis by patients' personal physicians in charge in routine practice and electronically retrieved from medical files without alteration by natural language processing. Pacemaker/defibrillator procedures were collected/dated. Vital signs were measured at echocardiography. Atrial fibrillation (AFib) before/at diagnosis relied on electrocardiogram (ECG) or clinical notes for history of proven AFib. Glomerular filtration rate (GFR) was estimated with the Cockroft–Gault formula.

Follow-up data

Outcomes of interest were survival, overall, under medical management, and post-operative, censoring patients who underwent mitral and/or tricuspid surgery at time of surgery. Death occurrence and dates were recovered using Accurint®, a proprietary resource gathering multiple national sources including Social Security Death Index to define occurrence and date of death, interrogated at the end of 2015. To ensure accurate mortality counts, patients considered alive based on Accurint® were censored on 31 December 2014. Surgical procedures were collected and dated using the Mayo Clinic surgical registry and clinical notes for patients operated outside Mayo Clinic. Precision of the type of surgery was specified: isolated mitral or tricuspid surgery (repair/replacement), combined mitral and tricuspid surgery, and mitral surgery followed by tricuspid surgery.

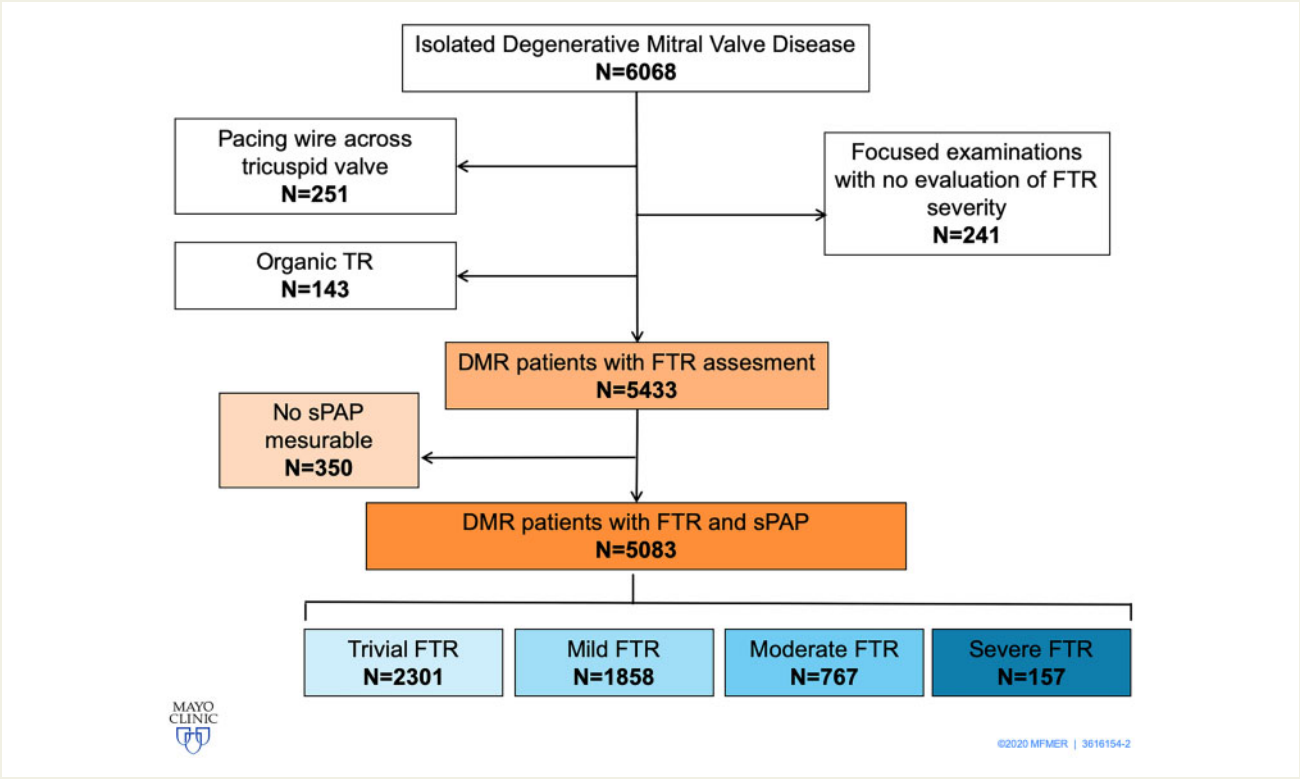


Figure 1 Study population flow chart. The total number of patients with degenerative mitral valve disease diagnosed between 2003 and 2011 is represented in the upper box (after exclusion such as other mitral and aortic valvular diseases, pericardial disease, previous valve surgery). Patients with organic tricuspid regurgitation, those in whom functional tricuspid regurgitation could not be evaluated and with no systolic pulmonary artery pressure measurement were then excluded. The remaining patients with degenerative mitral regurgitation and complete functional tricuspid regurgitation and systolic pulmonary artery pressure evaluation numbered 5083.

Statistical analysis

Continuous data expressed as mean ± standard deviation or median (interquartile range) were compared using the ANOVA or Wilcoxon test. Qualitative data expressed as percentages were compared using the χ^2 tests. Determinants of moderate/severe FTR were assessed by logistic regression and selected based on pathophysiologic links to DMR or TR: age, gender, systolic LV function [ejection fraction (EF)], AFib, MR severity, and PHTN. Because RV dysfunction may be determinant or consequence of FTR, it was not used in the primary model but in a secondary model as adjustment for other determinants of FTR. Overall fitting of models was summarized through *C*-statistic. Odds ratios (ORs) of moderate or severe FTR (vs. trivial FTR) were reported unadjusted and in multivariable analysis. To analyse consequences of mild, moderate, or severe FTR vs. trivial, logistic regression used dependent variables (FTR consequences) identified based on clinical/biological plausible link (dyspnoea, peripheral oedema, forward stroke volume, and cardiac output/index) with reduced GFR tested because of known relationship with venous congestion. Survival was displayed using the Kaplan–Meier method and compared using the log-rank test. Under medical management, the patients at risk were those alive and not censored (for surgery or end of follow-up). Survival estimates were reported with 95% confidence intervals. Independent association of FTR with long-term mortality used several analyses: first, we conducted on the entire population two types of Cox proportional hazard models (to avoid major collinearity issues) adjusting for left-sided variables (age, sex, EF, MR grade, AFib, and comorbidity index) and for right-sided variables (sPAP and RV dysfunction), with excess mortality expressed as hazard ratio vs. trivial FTR (with 95% confidence interval). Second, to attenuate age differences between groups, we matched patients with severe FTR to those with lower FTR grades for age and sex, followed by cox proportional hazard adjustment for persistent differences. Third, each FTR grade subset survival was compared to expected survival of general MN population of same age and sex with excess mortality expressed as risk ratio to expected survival. *P*-value <0.05 was considered significant.

Results

Baseline characteristics and determinants of functional tricuspid regurgitation

Among 6068 patients diagnosed at Mayo Clinic, Rochester, MN, USA, between 2003 and 2011 with isolated degenerative mitral valve disease, 251 were excluded due to pacing wire, 143 due to organic TR, 241 due to focused examinations with no FTR severity evaluation, and 350 with incomplete sPAP estimation (*Figure 1*). The final cohort of 5083 DMR patients with FTR and sPAP characterized at diagnosis, included FTR graded trivial in 45% ($N = 2301$), mild in 37% ($N = 1858$), moderate in 15% ($N = 767$), and severe in 3% ($N = 157$).

Table 1 Clinical characteristics of study population, overall and by functional tricuspid regurgitation groups

	Overall (*n* = 5083)	Trivial TR (*n* = 2301)	Mild TR (*n* = 1858)	Moderate TR (*n* = 767)	Severe TR (*n* = 157)	*P*-value
Clinical characteristics						
Age (years)	63 ± 16	57 ± 16	66 ± 14	74 ± 11	78 ± 12	<0.0001
Female gender, *n* (%)	2391 (47)	1028 (45)	876 (47)	402 (52)	85 (54)	0.004
BMI (kg/m^2)	25 ± 5	25 ± 5	25 ± 4	25 ± 5	25 ± 6	0.2
Heart rate (b.p.m.)	68 ± 14	67 ± 13	68 ± 14	71 ± 15	76 ± 18	<0.0001
Dyspnoea, *n* (%)	1848 (36)	690 (30)	691 (37)	371 (48)	96 (61)	<0.0001
Oedema, *n* (%)	673 (13)	200 (9)	227 (12)	169 (22)	77 (49)	<0.0001
Chest pain, *n* (%)	841 (17)	408 (18)	302 (16)	116 (15)	15 (10)	0.03
Atrial fibrillation, *n* (%)	728 (14)	110 (5)	249 (13)	261 (34)	108 (69)	<0.0001
Hypertension, *n* (%)	1942 (38)	716 (31)	768 (41)	375 (49)	83 (53)	<0.0001
Diabetes, *n* (%)	354 (7)	115 (5)	138 (7)	79 (10)	22 (14)	<0.0001
CAD, *n* (%)	1277 (25)	433 (19)	514 (28)	273 (36)	57 (36)	<0.0001
COPD, *n* (%)	307 (6)	92 (4)	113 (6)	82 (11)	20 (13)	<0.0001
Cancer, *n* (%)	998 (20)	384 (17)	407 (22)	174 (23)	33 (21)	<0.0001
Charlson index	1.0 ± 1.2	0.8 ± 1.0	1.0 ± 1.2	1.4 ± 1.3	1.8 ± 1.4	<0.0001
GFR (mL/min/1.73 m^2)	74 ± 30	83 ± 30	72 ± 28	58 ± 24	47 ± 21	<0.0001
Echocardiographic characteristics						
LV-EDD (mm)	51 ± 7	51 ± 6	52 ± 7	51 ± 7	49 ± 8	<0.0001
Indexed LV-EDD (mm/m^2)	28 ± 4	27 ± 3	28 ± 4	28 ± 4	27 ± 4	<0.0001
LV-ESD (mm)	32 ± 6	32 ± 5	33 ± 6	32 ± 6	32 ± 7	0.2
Indexed LV-ESD (mm/m^2)	18 ± 3	17 ± 3	18 ± 3	18 ± 3	18 ± 4	<0.0001
LV-EF (%)	63 ± 7	63 ± 7	63 ± 8	62 ± 8	61 ± 10	0.0002
CI (L/min/m^2)	2.99 ± 0.65	3.04 ± 0.66	2.97 ± 0.62	2.95 ± 0.71	2.64 ± 0.63	<0.0001
SV index (mL/m^2)	45 ± 10	47 ± 9	46 ± 10	43 ± 11	37 ± 9	<0.0001
LAVI (mL/m^2)	44 ± 23	37 ± 17	45 ± 22	55 ± 27	72 ± 34	<0.0001
Normal RV size, *n* (%)	2610 (78)	1368 (91)	951 (80)	279 (54)	12 (9)	<0.0001
Mildly enlarged	570 (17)	125 (8)	205 (17)	176 (34)	64 (46)	<0.0001
≥Mod enlargement	177 (5)	17 (1)	39 (3)	59 (11)	62 (45)	<0.0001
Normal RV function, *n* (%)	4550 (91)	2204 (97)	1683 (92)	600 (81)	63 (42)	<0.0001
Mildly decreased	239 (5)	36 (2)	88 (5)	73 (10)	42 (28)	<0.0001
≥Mod decreased	191 (4)	23 (1)	53 (3)	71 (9)	44 (30)	<0.0001
Systolic PAP (mmHg)	35 ± 13	29 ± 7	35 ± 11	47 ± 17	60 ± 19	<0.0001
sPAP ≥50mmHg (%)	11	2	9	32	68	<0.0001
No/trivial MR, *n* (%)	1009 (20)	715 (31)	238 (13)	51 (7)	5 (3)	<0.0001
Mild MR, *n* (%)	1528 (30)	700 (30)	599 (32)	205 (27)	24 (15)	<0.0001
Moderate MR, *n* (%)	1130 (22)	388 (17)	454 (24)	239 (31)	49 (31)	<0.0001
Severe MR, *n* (%)	1416 (28)	498 (22)	567 (31)	272 (35)	79 (50)	<0.0001
ERO (mm^2)	20 (0–40)	10 (0–34)	23 (11–43)	26 (15–46)	30 (19–49)	<0.0001
RVol (mL)	35 (0–66)	19 (0–56)	40 (18–70)	45 (27–75)	52 (35–76)	<0.0001
Flail leaflet, *n* (%)	526 (12)	198 (9)	251 (14)	146 (19)	31 (20)	<0.0001
Bileaflet MVP, *n* (%)	1964 (39)	927 (40)	724 (39)	262 (34)	51 (32)	0.04
Posterior MVP, *n* (%)	2232 (44)	968 (42)	868 (47)	349 (46)	47 (30)	<0.0001

BMI, body mass index; CAD, history of coronary artery disease; COPD, chronic obstructive pulmonary disease; CI, cardiac index; EDD, end-diastolic diameter; LV-EF, left ventricle ejection fraction; ERO, effective regurgitant orifice; ESD, end-systolic diameter; LAVI, left atrial volume indexed; MR, mitral regurgitation; MVP, mitral valve prolapse; PAP, pulmonary artery pressure; RVol, regurgitant volume; SV, stroke volume.

Baseline characteristics are displayed in *Table 1*. Overall, age was 63 ± 16 years, 47% female, LV-EF 63 ± 7%, and sPAP 35 ± 13 mmHg (11% with PHTN). Clinically, 36% had dyspnoea, 13% oedema, and 14% AFib. By integrative grading, DMR was trivial in 20%, mild in 30%, moderate in 22%, and severe in 28%, with median effective regurgitant orifice 20 (0–40) mm^2. On average, LV dilatation was mild and RV function was normal. Haemodynamically, forward cardiac output/index and renal function were normal.

Stratified by FTR grade subsets, almost all variables were statistically different due to the cohort considerable size. Clinically relevant

Table 2 Univariate and multivariable analysis of functional tricuspid regurgitation determinants

Determinants of FTR	Univariate analysis OR (95% CI) for moderate or severe FTR	*P*-value	Multivariable analysis[a] OR (95% CI) for moderate or severe FTR	*P*-value
Age (for 10 years)	2.14 (2.00–2.29)	<0.0001	1.73 (1.61–1.86)	<0.0001
Female	1.32 (1.14–1.52)	<0.0001	1.94 (1.62–2.32)	<0.0001
AFib	7.03 (5.93–8.34)	<0.0001	4.41 (3.60–5.41)	<0.0001
LV-EF (for 5%)	0.93 (0.89–0.97)	0.002	0.98 (0.92–1.03)	0.4
MR ≥moderate	2.10 (1.82–2.43)	<0.0001	1.45 (1.21–1.73)	<0.0001
PHTN	11.07 (9.15–13.39)	<0.0001	6.52 (5.24–8.11)	<0.0001

AFib, atrial fibrillation; 95% CI, confidence interval; FTR, functional tricuspid regurgitation; LV-EF, left ventricle ejection fraction; MR, mitral regurgitation; OR, odds ratio; PHTN, pulmonary hypertension.
[a]Adjusted for age, gender, AFib, EF, MR ≥moderate, and PHTN.

differences showed patients with higher FTR grade older, more female, more often symptomatic with higher comorbidities, more frequent medical therapy (Supplementary material online, *Table S1*), and worse renal function (all $P < 0.0001$). Echocardiographically, patients with more severe FTR had lower LV-EF, reduced forward cardiac output/index and stroke volume/index, larger left atrium, and more severe MR (all $P \leq 0.0002$). With higher FTR grade, severely impaired RV function and PHTN were substantially more frequent. Characteristics of patients matched to severe FTR subset are presented in the Supplementary material online, *Table S2*, with excellent balance for gender ($P = 0.7$) and attenuation of age differences (71 ± 11 in trivial FTR, 78 ± 6 in mild-moderate FTR, and 78 ± 13 years in severe FTR). Similarly to the main cohort, patients with severe FTR in the matched cohort had more symptoms, larger left atrium, lower LV-EF, lower RV function, and impaired forward cardiac output/index and renal function ($P \leq 0.001$).

Clinical and echocardiographic determinants of higher FTR grade are presented in *Table 2*. Univariably, older age, female sex, low LV-EF, and moderate/severe MR were associated with more severe FTR and remained independent predictors of FTR severity in multivariable analysis ($P < 0.0001$ for all), except low LV-EF. In addition to these variables, AFib was strongly and independently associated with FTR severity, overall ($P < 0.0001$; *Table 2*) and in all subgroups (Supplementary material online, *Table S3*). Pulmonary hypertension was the strongest predictor of FTR severity with largest χ^2 and OR 11.07 (9.15–13.38), $P < 0.0001$ univariably, after adjustment for all other FTR determinants [OR 6.52 (5.24–8.11), $P < 0.0001$] and the model *C*-statistics was high (0.85 for moderate FTR and 0.92 for severe FTR). Pulmonary hypertension remained the main predictor of severe FTR in all subgroups with high ORs (all $P < 0.0001$, Supplementary material online, *Table S4*). Addition of RV dysfunction as independent FTR severity predictor was significant ($P < 0.0001$) but did not affect the multivariable model (Supplementary material online, *Table S5*) or *C*-statistics (0.85 for moderate FTR and 0.93 for severe FTR).

Clinical consequences of functional tricuspid regurgitation

Degenerative MR presentation was remarkably different across FTR grades, including mild, (vs. trivial FTR) with growing clinical impairments: more dyspnoea, more oedema, reduced forward stroke volume/index, and lower GFR with more severe FTR (*Table 3*). With adjustment, the link between mild TR and clinical consequences became notably weaker. For moderate or severe FTR, adjustment in the left-sided model for baseline characteristics including age, sex, comorbidity index, EF, DMR grade, and AFib, the link between FTR grade and potential FTR clinical consequences remained highly significant (*Table 3*, middle column). Adjustment in right-sided model for sPAP and RV dysfunction showed that moderate and particularly severe FTR grade (vs. trivial FTR) remained consistently associated with worse clinical presentation, except in regard to the presence of dyspnoea (*Table 3*, right column), which may be more consequential to DMR. Hence, irrespective of baseline characteristics, FTR moderate and particularly severe is associated with profound clinical consequences.

Outcome after diagnosis

During a total follow-up of 6.8 ± 3.1 years, 1191 patients died, 1043 under medical management, and 148 after mitral or tricuspid surgery.

Overall survival

Overall survival was 95% (91–93%) at 1 year, 85% (84–86%) at 5 years, and 70% (69–72%) at 10 years. Five-year overall survival was considerably different: 92% (91–93%) for trivial FTR, 84% (82–86%) for mild FTR, 72% (65–75%) for moderate FTR, and 46% (38–54%) for severe FTR. At 10 years, survival was 82% (80–84%), 69% (66–71%), 51% (47–57%), and 26% (19–35%), respectively (*Figure 2A*).

Hazard ratios for mortality vs. trivial FTR were 1.89 (1.63–2.17) for mild FTR, 3.41 (2.91–3.99) for moderate FTR, and 8.16 (6.56–10.15) for severe FTR, all *P*-value ≤0.0001 (*Table 4*). Association of adjusting variables to mortality are presented in Supplementary material online, *Table S6*. All FTR grades were associated with worse outcome after comprehensive adjustment for age, gender, LV-EF, MR grade, AFib, and Charlson index (all $P \leq 0.0001$). Adjustment for sPAP and RV dysfunction grade (normal/mild/moderate/severe) did not affect the prognostic impact of higher FTR grade on mortality (*Table 4*).

Subgroup analysis stratified by PHTN and RV dysfunction showed higher FTR grades associated with higher mortality in all subsets (*Figure 3*). Noticeably, while mortality tended to be higher with

Table 3 Clinical consequences of functional tricuspid regurgitation in degenerative mitral regurgitation

FTR consequences		Univariate		Adjusted for age, gender, comorbidity index, LV-EF, MR grade, and AFib		Adjusted for sPAP and RV dysfunction	
Observed	**FTR degree**	**RR (95% CI) of consequence[a]**	***P*-value**	**RR (95% CI) of consequence[a]**	***P*-value**	**RR (95% CI) of consequence[a]**	***P*-value**
Dyspnoea							
No. cases: 690	Trivial FTR	Reference		Reference		Reference	
No. cases: 691	Mild FTR	1.38 (1.21–1.57)	<0.0001	1.21 (1.06–1.39)	0.006	1.03 (0.90–1.18)	0.7
No. cases: 371	Moderate FTR	2.19 (1.85–2.59)	<0.0001	1.61 (1.33–1.95)	<0.0001	1.00 (0.82–1.22)	1
No. cases: 96	Severe FTR	3.67 (2.64–5.13)	<0.0001	2.03 (1.41–2.93)	0.0002	0.88 (0.59–1.33)	0.5
Oedema							
No. cases: 200	Trivial FTR	Reference		Reference		Reference	
No. cases: 227	Mild FTR	1.46 (1.20–1.79)	0.0002	1.05 (0.84–1.30)	0.7	1.12 (0.90–1.38)	0.3
No. cases: 169	Moderate	2.97 (2.37–3.71)	<0.0001	1.39 (1.07–1.81)	0.01	1.42 (1.09–1.85)	0.01
No. cases: 77	Severe FTR	10.11 (7.16–14.28)	<0.0001	3.36 (2.24–5.03)	<0.0001	2.95 (1.94–4.49)	<0.0001
Low SV-I (<35 mL/m^2)							
No. cases: 106	Trivial FTR	Reference		Reference		Reference	
No. cases: 146	Mild FTR	1.71 (1.32–2.23)	<0.0001	1.44 (1.08–1.92)	0.01	1.36 (1.03–1.78)	0.03
No. cases: 114	Moderate	3.88 (2.91–5.16)	<0.0001	2.15 (1.50–3.08)	<0.0001	2.17 (1.55–3.02)	<0.0001
No. cases: 42	Severe FTR	9.91 (6.38–15.40)	<0.0001	3.33 (1.95–5.70)	<0.0001	3.38 (1.98–5.77)	<0.0001
Low CI <2.2 (L/min/m^2)							
No. cases: 128	Trivial FTR	Reference		Reference		Reference	
No. cases: 130	Mild FTR	1.28 (0.99–1.64)	0.06	1.15 (0.88–1.50)	0.3	1.13 (0.87–1.47)	0.4
No. cases: 77	Moderate	1.91 (1.42–2.56)	<0.0001	1.52 (1.07–2.14)	0.02	1.30 (0.92–1.83)	0.1
No. cases: 33	Severe FTR	4.58 (2.99–7.00)	<0.0001	2.91 (1.76–4.83)	<0.0001	2.04 (1.21–3.44)	0.008
GFR <60 (mL/min/m^2)							
No. cases: 430	Trivial FTR	Reference		Reference		Reference	
No. cases: 622	Mild FTR	2.18 (1.88–2.52)	<0.0001	1.10 (0.91–1.32)	0.3	1.97 (1.70–2.30)	<0.0001
No. cases: 439	Moderate	5.80 (4.83–6.96)	<0.0001	1.57 (1.23–2.01)	0.0003	4.58 (3.72–5.63)	<0.0001
No. cases: 112	Severe FTR	13.08 (8.70–19.65)	<0.0001	3.40 (1.95–5.95)	<0.0001	8.28 (5.26–13.05)	<0.0001

95% CI, confidence interval; CI, cardiac index; LV-EF, left ventricle ejection fraction; FTR, functional tricuspid regurgitation; GFR, glomerular filtration rate; RR, risk ratio; RV, right ventricle; SV-I, stroke volume indexed.
[a]Versus trivial FTR.

PHTN and RV dysfunction in patients with trivial TR, higher degrees of FTR were associated with excess mortality even in those worse subsets ($P < 0.0001$).

To confirm those results, analysis in the matched cohort showed persistent excess mortality remaining considerable for severe FTR vs. trivial FTR, with univariate hazard ratio 3.98 (3.07–5.17), $P < 0.0001$ and adjusted hazard ratios of 2.08 (1.50–2.89), $P < 0.0001$ within left-sided model and 1.80 (1.29–2.51), $P = 0.0006$ within right-sided model.

To further confirm excess mortality associated with higher FTR degrees, we compared survival in each FTR subset to their specific expected survival in the general population of similar age and sex. This analysis showed no excess mortality in patients with trivial FTR [risk ratio 1.03 (0.92–1.15), $P = 0.60$], barely noticeable excess mortality in mild FTR [risk ratio 1.10 (1.00–1.21), $P = 0.04$] becoming substantial with moderate FTR [risk ratio 1.30 (1.16–1.45), $P < 0.0001$], and considerable with severe FTR [risk ratio 1.79 (1.48–2.16), $P < 0.0001$]. Excess mortality associated with moderate FTR was confirmed in patients without [risk ratio 1.26 (1.07–1.48), $P < 0.01$] and with [risk ratio 1.34 (1.15–1.57), $P < 0.001$] moderate/severe DMR. Similarly, patients with severe FTR incurred excess mortality without [risk ratio 1.41 (1.0–2.01), $P = 0.05$] and with [risk ratio 2.0 (1.6–2.5), $P < 0.0001$] moderate/severe DMR.

Survival under medical management

Under medical management, survival was 94% (94–95%) at 1 year, 83% (81–83%) at 5 years and 68% (66–70%) at 10 years. Ten-year survival was 80% (78–82%) for trivial FTR, 65% (62–68%) for mild FTR, 47% (42–52%) for moderate FTR, and 19% (12–29%) for severe FTR (*Figure 2B*).

Excess mortality was considerably higher with FTR severity, univariate hazard ratios 9.14 (7.21–11.58), $P < 0.0001$ for severe FTR, 3.62 (3.06–4.29), $P < 0.0001$ for moderate FTR, and 1.97 (1.69–2.29), $P < 0.0001$ for mild FTR vs. trivial FTR. Similarly, adjustments did not affect the powerful and independent association between FTR severity and mortality (*Table 4*, central part).

Excess mortality under medical management remained highly significant for severe FTR group vs. trivial FTR matched for age and sex, with univariate hazard ratio for mortality 3.91 (2.94–5.20), $P < 0.0001$, left-sided model adjusted hazard ratio 2.31 (1.62–3.30),

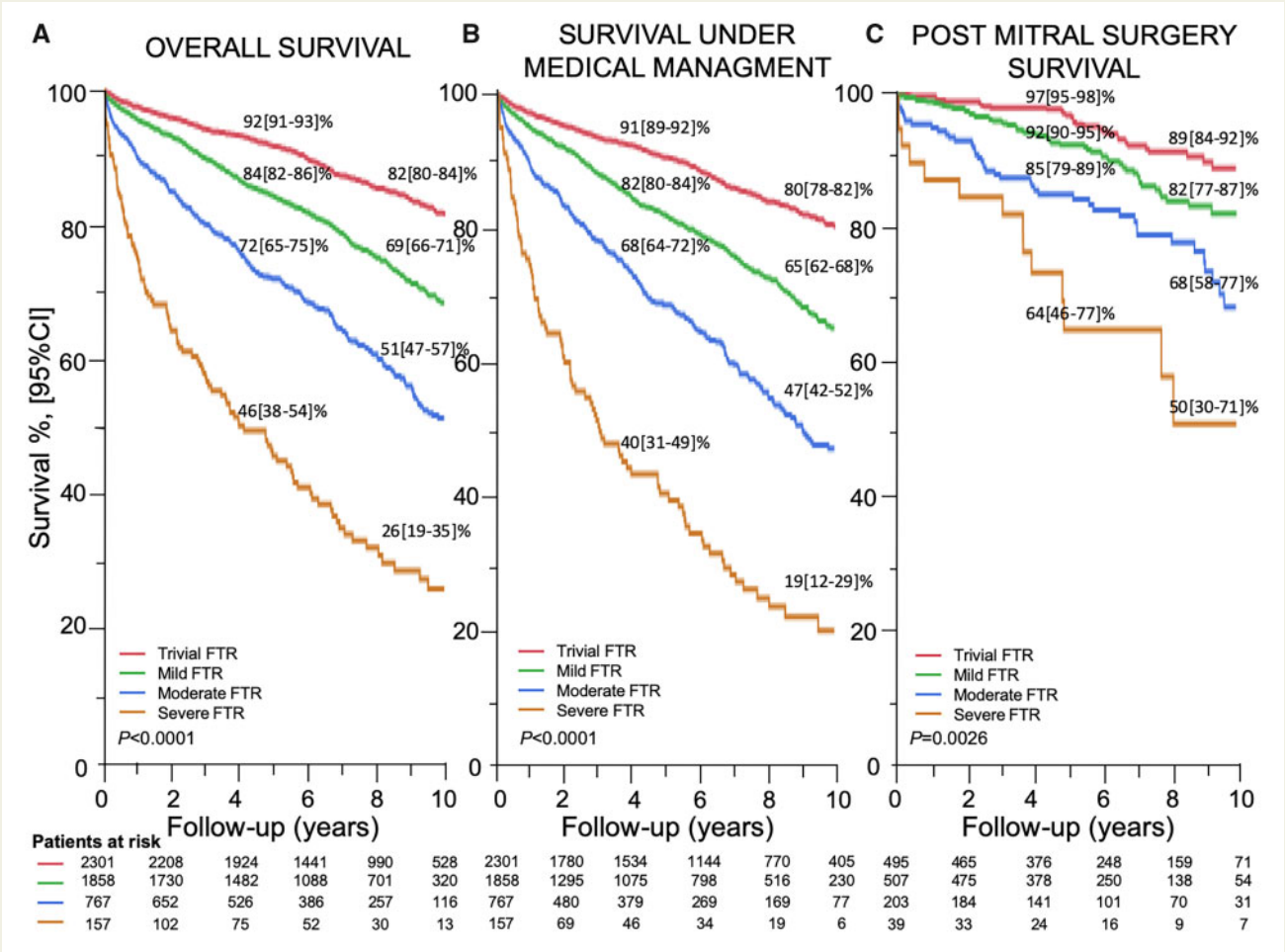


Figure 2 Survival stratified by functional tricuspid regurgitation grade. The figures display Kaplan–Meier curves for the various functional tricuspid regurgitation grades (trivial to severe) followed (*A*) overall, (*B*) under medical management, and (*C*) post-mitral valve surgery. Note the marked separation between curves maintained throughout the entire follow-up period and the considerable mortality associated with severe functional tricuspid regurgitation, even after surgery. CI, confidence interval.

$P < 0.0001$ and right-sided model adjusted hazard ratio 1.56 (1.09–2.23), $P = 0.0006$.

Operative outcomes

During follow-up, 1244 patients underwent mitral valve surgery for DMR (1121 repairs—90% and 123 replacements—10%) and 114 had tricuspid valve surgery (100 repairs—88% and 14 replacements—12%) of which 100 were performed concomitantly to mitral surgery. Baseline differences between operated and unoperated patients, significant due to the considerable cohort size, were clinically negligible with slightly younger age (62.4 ± 14 vs. 63.8 ± 17 years), more frequent dyspnoea (47% vs. 33%), AFib (12% vs. 8%), and slightly higher sPAP (37 ± 14 vs. 34 ± 13 mmHg) in operated patients, while RV size and function were similar. Mitral surgery performance at 5-year was 24% (23–25%) overall, 73% (70–75%) with severe DMR, and 15% (13–17%) with moderate DMR. Tricuspid surgery performance at 5-year was 2% (2–3%) overall, 26% (19–34%) with severe FTR, and 6% (4–8%) with moderate FTR. Among patients with severe DMR and moderate/severe FTR undergoing DMR surgery, 30% underwent concomitant FTR surgery. Degenerative MR and FTR surgery performance excluding trivial/mild FTR and no/trivial/mild DMR are presented in Supplementary material online, *Table S7*. Moderate/severe FTR with mild DMR patients showed infrequent use of valve surgery despite comparable comorbidities ($P = 0.2$, Supplementary material online, *Table S8*).

After mitral surgery, survival was 92% (90–94%) at 5 years and 81% (78–84%) at 10 years. Ten-year post-operative survival was 89% (84–92%) for trivial FTR, 82% (77–87%) for mild FTR, 68% (58–77%) for moderate FTR, and 50% (30–71%) for severe FTR (*Figure 2C*). In univariable analysis, higher FTR grade (vs. trivial) was associated with increasing excess mortality [hazard ratios 1.77 (1.14–2.73), $P = 0.01$ for mild FTR, 3.35 (2.12–5.30), $P < 0.0001$ for moderate FTR, and 7.40 (4.01–13.67), $P < 0.0001$ for severe FTR]. Multivariable analysis attenuated FTR impact on survival but severe FTR remained associated with notable excess mortality vs. trivial FTR with any type of adjustment (*Table 4*, right part). In patients who underwent tricuspid surgery simultaneous to mitral valve surgery, pre-operative FTR

Table 4 Univariate and multivariable hazard ratio of mortality

	FTR grade	Overall mortality		Mortality under medical treatment		Post-mitral surgery mortality	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Univariate	Mild FTR[a]	1.89 (1.63–2.17)	<0.0001	1.97 (1.69–2.29)	<0.0001	1.77 (1.14–2.73)	0.01
	Moderate FTR[a]	3.41 (2.91–3.99)	<0.0001	3.62 (3.06–4.29)	<0.0001	3.35 (2.12–5.30)	<0.0001
	Severe FTR[a]	8.16 (6.56–10.15)	<0.0001	9.14 (7.21–11.58)	<0.0001	7.40 (4.01–13.67)	<0.0001
Adjusted on age, gender, LV-EF, MR grade, AFib, and comorbidity index	Mild FTR[a]	1.21 (1.04–1.40)	0.01	1.24 (1.06–1.46)	0.006	1.06 (0.68–1.67)	0.8
	Moderate FTR[a]	1.40 (1.18–1.67)	<0.0001	1.39 (1.15–1.67)	0.0006	1.45 (0.88–2.39)	0.14
	Severe FTR[a]	2.10 (1.63–2.70)	<0.0001	2.13 (1.62–2.79)	<0.0001	2.16 (1.04–4.50)	0.04
Adjusted on sPAP and RV dysfunction	Mild FTR[a]	1.58 (1.36–1.83)	<0.0001	1.64 (1.40–1.92)	<0.0001	1.49 (0.95–2.33)	0.08
	Moderate FTR[a]	2.09 (1.75–2.49)	<0.0001	2.10 (1.74–2.54)	<0.0001	2.11 (1.28–3.50)	0.004
	Severe FTR[a]	3.19 (2.47–4.12)	<0.0001	3.39 (2.59–4.44)	<0.0001	2.90 (1.35–6.21)	0.006

AFib, atrial fibrillation; HR, hazard ratio; LV-EF, left ventricle ejection fraction; MR, mitral regurgitation; sPAP, systolic pulmonary artery pressure; RV, right ventricle.
[a]Versus trivial FTR.

severity lost all association to post-operative survival ($P = 0.76$) while in those without tricuspid correction, FTR severity remained strongly associated with post-operative survival ($P < 0.0001$). Post-mitral surgery survival curves (*Figure 2C*) suggest improved survival, confirmed by time-dependent analysis [adjusted hazard ratios 0.39 (0.31–0.48), $P < 0.0001$] showing also persistent deleterious effect of moderate FTR (adjusted hazard ratio 1.66 (1.44–1.93)] and severe FTR [adjusted hazard ratio 2.15 (1.73–2.69) vs. trivial FTR, both $P < 0.0001$]. Due to the small number of tricuspid surgery performed, its impact on survival cannot be analysed.

Discussion

The present study, by gathering a considerable cohort of single isolated DMR of full range severity, quite unique by its extensive clinical and Doppler Echocardiographic characterization, allowing to define specifically FTR (by excluding organic FTR) and to define its grade at diagnosis, provides an exceptional power and opportunity to analyse for the first time within the entire span of DMR severity and baseline characteristics, FTR prevalence, independent determinants, consequences, and outcome impact.

The main result is that in the context of degenerative mitral valve disease, FTR increasing grade is associated with more severe and quite considerable excess mortality by any type of analysis, univariable or multivariable, with matching or by comparison to expected survival. Long-term mortality is not the only FTR consequence, as moderate/severe FTR is associated with worse clinical presentation at diagnosis with more severe right-sided heart failure, low forward cardiac output, and reduced renal function despite full use of medical therapy. This poor presentation and marked excess mortality, particularly noticeable under medical management but also present post-cardiac surgery underscores the importance of detecting and managing appropriately FTR associated with DMR. Indeed, FTR moderate or severe is frequent in this context, affecting almost one patient in five. While FTR is most powerfully determined by PHTN, there are several other factors contributing to its occurrence particularly AFib. Surgical treatment of the tricuspid valve is considerably underused for moderate or even severe FTR even in the eminently surgical context of severe DMR (*Take home figure*). In light of present results from this large and comprehensive cohort, careful detection and management of FTR in clinical practice of DMR is crucial. The considerable independent outcome impact of FTR, not only severe but also moderate, warrants actively considering FTR treatment. Tricuspid surgery is the only approved treatment for FTR to date, although its effectiveness remains unproven, and may be considered whether DMR justifies surgical indication or not. Conducting clinical trials of new, less invasive therapies is imperative and may ultimately reduce the pervasive underuse of FTR treatment, if proven effective.

Tricuspid regurgitation complicating degenerative mitral regurgitation

Although TR associated with DMR is the only form benefitting from a Class I indication for surgery,[21,22] surprisingly, little is known about its prevalence and cause/mechanisms. It is generally considered that tricuspid valve prolapse may occur with mitral prolapse and cause TR.[30] But for FTR with structurally normal tricuspid valve, the most frequent form of TR,[3] common 'knowledge' is that it is secondary to PHTN due to the mitral disease, emphasizing its 'secondary' nature.[10] This simplistic view of excess pressure exclusively yielding FTR is currently reconsidered. Indeed, while the tricuspid valve is structurally normal in FTR, functional deformations of valve tenting and annular enlargement have been linked to FTR occurrence.[31] These observations do not hinder the importance of PHTN as FTR cause, for which it is the strongest determinant in our study; however, it emphasizes the adjunct importance of other factors such as older age, female gender, and DMR severity.[14] However, FTR most important determinant besides PHTN is AFib, probably through its link to marked right atrial enlargement with tricuspid annular enlargement, suggested by mounting evidence.[31,32] In the DMR context, similarly to isolated TR[15] or heart failure,[14] AFib considerably contributes to FTR occurrence and severity. Hence, it is essential in patients with DMR, to

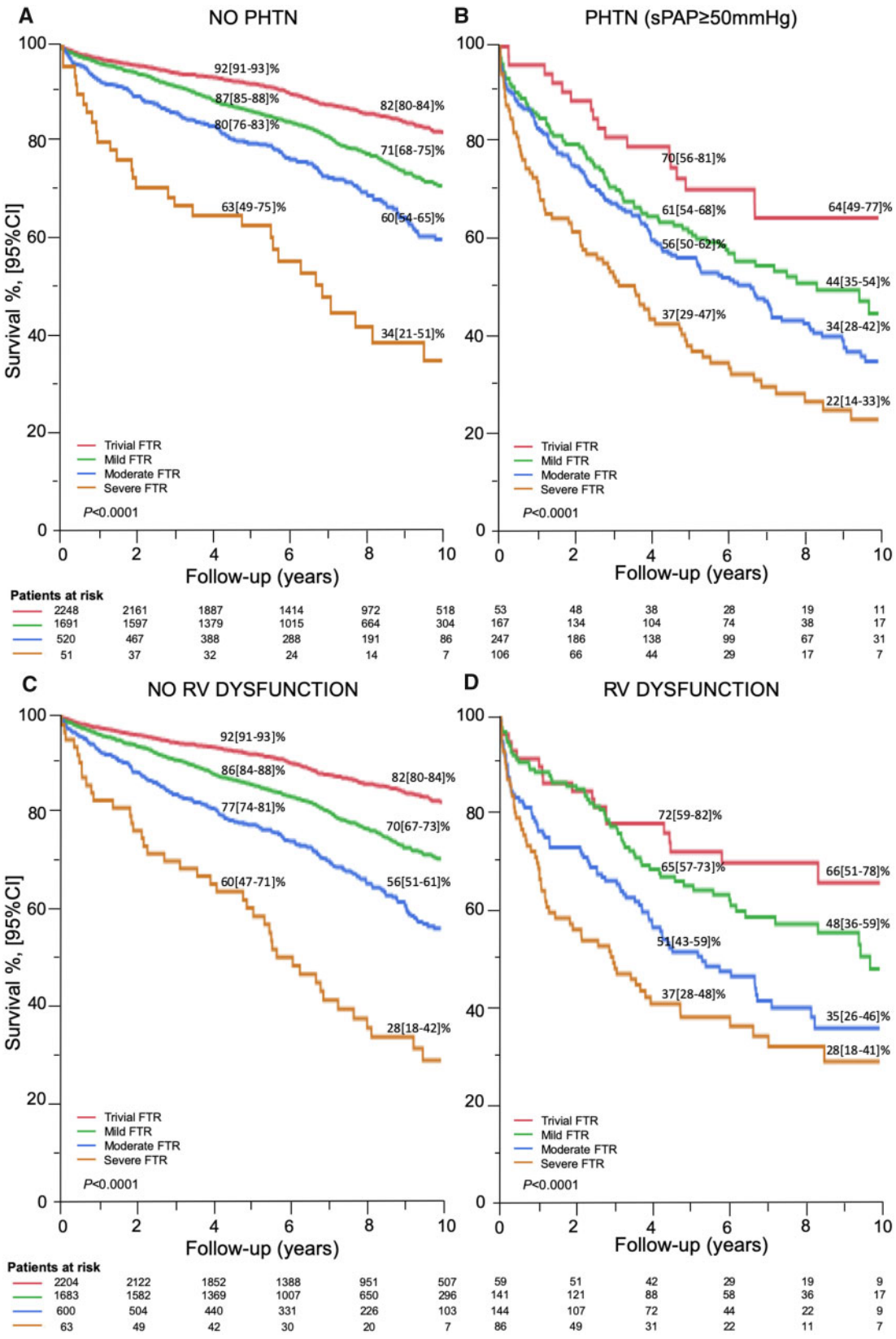
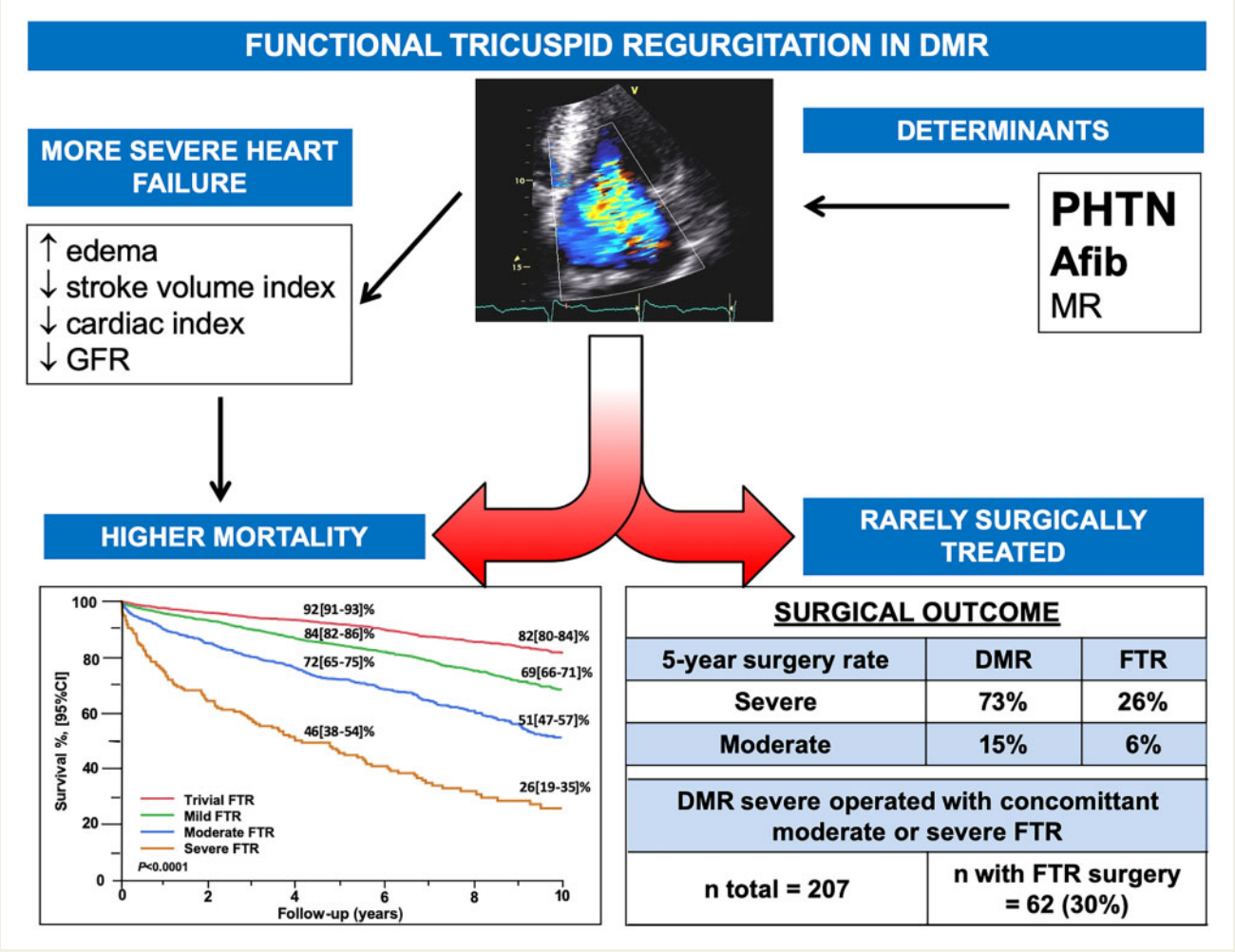


Figure 3 Survival associated with functional tricuspid regurgitation grade stratified by pulmonary hypertension or right ventricular dysfunction. Kaplan–Meier survival curves for the range of functional tricuspid regurgitation grades in patients without (*A*) and with (*B*) pulmonary hypertension ($n = 573$) and without (*C*) and with (*D*) moderate or severe right ventricular dysfunction ($n = 430$). Note that in all subgroups, increasing functional tricuspid regurgitation grade is associated with excess long-term mortality. CI, confidence interval; PHTN, pulmonary hypertension; RV, right ventricle.



Take home figure Functional tricuspid regurgitation determinants, consequences, and outcome in degenerative mitral regurgitation. (Top right) Functional tricuspid regurgitation determinants. (Top left) Functional tricuspid regurgitation consequences on clinical presentation, with increasing oedema, lower stroke volume index, lower forward cardiac output/index, and lower glomerular filtration rate associated with higher functional tricuspid regurgitation grade. (Bottom left) Overall survival stratified by functional tricuspid regurgitation grade underscores excess mortality with higher functional tricuspid regurgitation. (Bottom right) Underuse of functional tricuspid regurgitation surgery compared to degenerative mitral regurgitation surgery for moderate and severe regurgitation. CI, confidence interval; DMR, degenerative mitral regurgitation; FTR, functional tricuspid regurgitation.

thoroughly detect/evaluate FTR with AFib. These multiple determinants are probably linked to hitherto undescribed high prevalence of moderate/severe FTR, affecting almost one of five DMR patients. While FTR and DMR are somewhat correlated, moderate/severe FTR often occurs without severe DMR, impacts outcome, and warrants careful detection and severity grading. This in turn, will allow addressing therapeutic decisions for FTR independently and in conjunction of those for the DMR.

Functional tricuspid regurgitation consequences and outcomes

In the early days of cardiac surgery, TR was considered truly 'secondary', implying negligible impact on outcome and minimal need for therapeutic interventions.[5,6] These concepts translated into very few double or triple valve replacements,[33] often only with extreme rheumatic disease and into performance of tricuspid valvulectomy, reported as well-tolerated.[8] These concepts, while currently reconsidered, remain present, leading to fewer than 10 000 tricuspid surgeries yearly in the USA[34] among the 1.6 million affected by moderate/severe TR.[3] Root causes of uncertainties regarding the outcome impact of TR are its heterogeneity of clinical contexts, each carrying its own prognostic implications, and the collinearity of TR with older age, PHTN[35] and comorbidities, cardiac, and non-cardiac.[3] These confounders are the rationales for focusing in the present study on a single causal context (DMR) with comprehensive characterization in a very large cohort. Short of obtaining these conditions, scarce previous publications on FTR 'complicating' MR remained inconclusive.[17] While more data are available on FTR post-DMR surgery, conclusions remain widely divergent.[7,18–20] These gaps of knowledge underscore the importance of resolving the FTR conundrum, as DMR is frequently referred for surgery in view of its high

reparability[36,37] and excellent outcome after early surgery.[23] Currently hesitant FTR management, also due to generally poor reputation of tricuspid surgery (high mortality[34] and frequent recurrence[38,39]), may become more decisive in the DMR context if FTR is proven to affect outcome, making it a crucial issue to resolve. Our considerable cohort shows that FTR is a critical component of worse clinical presentation at diagnosis although ascertaining relative contributions to dyspnoea of DMR or FTR is difficult. Conversely, FTR undoubtedly is independently linked to worse right-sided heart failure, low forward stroke volume, and reduced GFR. Furthermore, FTR grade at diagnosis is a major independent determinant of long-term survival, with excess mortality, considerable with severe FTR but also sizeable with moderate FTR. This FTR mortality effect, confirmed in all types of analysis, is particularly important as it is shown in our study to be independent of all comorbid conditions, PHTN[35] and of DMR severity.[26] Excess mortality is highest under medical management but persists after cardiac surgery, with profound underuse of FTR treatment,[3] particularly compared to mitral surgery.[4] While guidelines suggest treating severe FTR repair when DMR is repaired, little is done to patients with moderate FTR and overall FTR treatment is profoundly underused, even more than the very effective surgical treatment of DMR.[4] This may relate to classical teachings of FTR 'unimportance' or to doubts about risks/efficacy of tricuspid surgery. Irrespective, with the important demonstration by the present cohort of FTR-linked excess mortality in the context of DMR, it is essential that FTR treatment underuse and effectiveness be actively addressed. Thus, currently developed/attempted TR transcatheter treatment efficacy should be fully tested in appropriate clinical trials.[40] Hence, in the specific context of DMR, FTR moderate/severe is shown by our considerable cohort to have major consequences for presentation and outcome, independent of all characteristics and comorbid conditions and therefore has profound clinical implications.

Clinical implications

The crucial findings of this first observation in the present large cohort that FTR complicating DMR is associated with more severe presentation and excess mortality imply that:

- FTR requires heightened attention: while severe FTR is the best-known target of imaging,[11] the frequency and serious consequences of moderate FTR complicating DMR underscore its diagnostic importance.
- Pulmonary hypertension is the strongest determinant of FTR but other factors, most importantly AFib complicating DMR,[41] contribute and should alert towards clinically significant FTR.[32]
- In the DMR context, clinical decision-making for surgical indications should be strongly influenced by the presence of severe but also moderate FTR, particularly in patients who do not present with surgical indications purely based on DMR.[11]
- The low FTR surgical rate, even with severe FTR, coupled with FTR high mortality represents a clear unmet need for treatment[3] and despite uncertainty regarding therapeutic effectiveness, warrants addressing. To address mitral[4] and tricuspid[3] underuse of treatment, testing of strategies such as repair of moderate regurgitations[26] or as development[24] and testing of transcatheter treatment of TR[40] should be considered.

Limitations and strengths

Inclusion of patients beyond severe DMR may be criticized but this full range grants our study unprecedented power, ability to determine for the first time FTR prevalence in all DMR grades, to demonstrate FTR impact on survival with any adjustment/subgroup, to define the excess risk attached to each FTR grade and particularly to emphasize the importance of moderate FTR in addition to severe FTR and to underscore the variety of FTR determinants besides PHTN. Our cohort in routine practice identified patients retrospectively, but FTR grading and all characteristics were prospectively collected for clinical care, stored immediately, retrieved electronically without alteration and are therefore fully applicable to routine practice.

In a cohort of this magnitude, one cannot exclude missed events. However, the 5-year mitral surgery rate of 72.7 ± 1% for patients with severe DMR, almost identical to the 72.4 ± 1% of the large MIDA registry of DMR[42] is quite reassuring.

Functional TR was consistently graded integratively per guidelines and rarely quantified as customary in routine clinical practice. While quantitative measures are much less frequently obtained in tricuspid than MR, the finding that FTR has considerable prognostic significance, even if moderate, should enhance the attention to FTR quantitation in the future. In that context, tricuspid annulus measurement may prove useful.

Cohort enrolment required sPAP estimation for adjustment of FTR impact on outcome. While estimated sPAP precision has been criticized with severe FTR, determination of PHTN presence remains highly accurate. Moreover, modelling by PHTN instead of sPAP showed that moderate FTR [adjusted hazard ratio 2.39 (2.01–2.84), $P < 0.0001$] and severe FTR [adjusted hazard ratio 3.65 (2.82–4.71), $P < 0.0001$] remained highly predictive of survival. Also, excluded patients without sPAP had 10-year survival similar trivial FTR (85 ± 2%, $P = 0.38$), suggesting that this exclusion did not affect our results.

Our cohort was not submitted to protocolized care imposing specific standards of care but is based on routine clinical practice, allowing demonstration of variability of care approaches, frequent FTR surgery underuse, and high FTR mortality in the DMR context. With the present demonstration of FTR outcome importance, future studies should focus on incremental potential outcome determinants, such as FTR progression/regression or tricuspid annular size as potential contributors to clinical decision-making.

Conclusions

The present study demonstrates, in a large cohort of isolated DMR of all grades, diagnosed in routine practice with FTR graded prospectively at diagnosis, that higher FTR grade is frequent and associated with increasing long-term excess mortality, independently of all baseline characteristics. Moreover, moderate/severe FTR is associated with worse clinical presentation at diagnosis, with more severe right-sided heart failure, low forward cardiac output, and reduced renal function. While FTR is most powerfully determined by PHTN, several other baseline characteristics contribute to its occurrence, particularly AFib. Given those untoward consequences and marked underuse of tricuspid surgical treatment, FTR moderate and severe

associated with DMR at diagnosis should be carefully detected, graded, and considered for tricuspid surgery and for inclusion in clinical trials of new transcatheter therapies.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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