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ORIGINAL RESEARCH

# Atrial Functional Tricuspid Regurgitation

## Importance of Atrial Fibrillation and Right Atrial Remodeling and Prognostic Significance

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ABSTRACT

**BACKGROUND** Little is known about the determinants and outcomes of significant atrial functional tricuspid regurgitation (AFTR).

**OBJECTIVES** The authors aimed to identify risk factors for significant TR in relation to atrial fibrillation-flutter (AF-AFL) and assess its prognostic implications.

**METHODS** The authors retrospectively studied patients with mild TR with follow-up echocardiography examinations. Significant TR was defined as greater than or equal to moderate TR. AFTR was defined as TR, attributed to right atrial (RA) remodeling or isolated tricuspid annular dilatation, without other primary or secondary etiology, except for AF-AFL. The Mantel-Byar test was used to compare clinical outcomes by progression of AFTR.

**RESULTS** Of 833 patients with mild TR, 291 (34.9%) had AF-AFL. During the median 4.6 years, significant TR developed in 35 patients, including 33 AFTRs. Significant AFTR occurred in patients with AF-AFL more predominantly than in those patients without AF-AFL (10.3% vs 0.6%; $P < 0.001$). In Cox analysis, AF-AFL was a strong risk factor for AFTR (adjusted HR: 8.33 [95% CI: 2.34-29.69]; $P = 0.001$). Among patients with AF-AFL, those who developed significant AFTR had larger baseline RA areas (23.8 vs 19.4 $cm^2$; $P < 0.001$) and RA area-to-right ventricle end-systolic area ratio (3.0 vs 2.3; $P < 0.001$) than those who did not. These parameters were independent predictors of AFTR progression. The 10-year major adverse cardiovascular event was significantly higher after progression of AFTR than before or without progression (79.8% vs 8.6%; Mantel-Byar $P < 0.001$).

**CONCLUSIONS** In patients with mild TR, significant AFTR developed predominantly in patients with AF-AFL, conferring poor prognosis. RA enlargement, especially with increased RA area-to-right ventricle end-systolic area ratio, was a strong risk factor for progression of AFTR. (J Am Coll Cardiol Img 2023;■:■–■) © 2023 by the American College of Cardiology Foundation.

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**ABBREVIATIONS AND ACRONYMS**

**AF** = atrial fibrillation

**AFL** = atrial flutter

**AFTR** = atrial functional tricuspid regurgitation

**EROA** = effective regurgitant orifice area

**MACE** = major adverse cardiovascular event

**PISA** = proximal isovelocity surface area

**RA** = right atrium

**RV** = right ventricle

**RV-FAC** = right ventricle fractional area change

**TR** = tricuspid regurgitation

**TV** = tricuspid valve

Tricuspid regurgitation (TR) affects up to 80% of the general population,[1] and significant TR, defined as at least moderate TR, confers a poor prognosis.[2-4] Secondary or functional TR is caused by the geometric deformation of tricuspid annulus, usually attributed to the right ventricular (RV) remodeling, and constitutes the predominant mechanism, whereas primary (organic) TR is relatively infrequent.[5] Notably, an emerging population with atrial functional tricuspid regurgitation (AFTR) develops significant TR mainly related to right atrium (RA) remodeling without pulmonary hypertension or left-sided heart disease.[6,7]

Atrial fibrillation (AF) is highly prevalent in patients with AFTR and is considered a major contributor to its development.[8-12] However, it remains unclear whether AF causes AFTR or, conversely, whether AF is triggered by significant TR.[13,14] This is because there is a paucity of longitudinal data on the temporal relationship between AF and AFTR. Furthermore, not all patients with AF who had mild TR progressed to significant AFTR, implying additional risk factors. Specifically, patients with severe AFTR and long-standing AF were characterized by prominent RA enlargement and tricuspid annular dilatation.[8-12] The tricuspid annular area was more highly correlated with RA size than with RV size in AF-related AFTR,[11,12] highlighting the important role of RA remodeling. However, data on the association of baseline right heart parameters of mild TR with the subsequent development of significant AFTR during follow-up are scarce.

We hypothesized that AF or atrial flutter (AFL) predisposes patients to the development of significant AFTR in the absence of other overt primary or secondary TR causes. We also sought to identify echocardiographic predictors for significant AFTR. Finally, we aimed to evaluate the cardiovascular outcomes of AFTR progression.

## METHODS

**STUDY POPULATION.** This study was conducted at a large tertiary university hospital (Seoul National University Hospital, South Korea). We retrospectively collected patients with mild TR identified on echocardiography between 2007 and 2019 (**Figure 1A**). The eligibility criterion was the availability of follow-up echocardiography data at least 1 year after the mild TR identification.

In this study, we classified the types of TR following the recent report:[15] primary TR is defined as TR caused by congenital or acquired abnormalities of tricuspid valve (TV) apparatus; cardiac implantable electronic device-related TR is defined as TR resulting from device-associated complications, such as leaflet impingement, avulsion, and perforation; and secondary or functional TR is defined as TR mainly attributed to RV remodeling by pressure or volume overload (= ventricular functional TR) or RA remodeling, in which isolated TV annular dilatation is the major driver with prevalent AF-AFL (= AFTR).

We excluded patients with the following conditions at baseline that could potentially cause significant primary or secondary TR other than AF-AFL (**Figure 1A**): previous heart-valve intervention or surgery, presence of a cardiovascular implantable electronic device, left-sided valvular diseases > a mild degree, reduced left ventricle ejection fraction (<50%), pulmonary hypertension, congenital heart disease, history of heart transplantation, and severe systemic disease (chronic lung disease, liver cirrhosis, end-stage renal disease, and active cancer). The eligibility for each case was independently adjudicated by 2 cardiologists (S.K., J-B.P.) by reviewing echocardiography and clinical data. Patients who developed new-onset AF-AFL during follow-up were also excluded (**Figure 1A**).

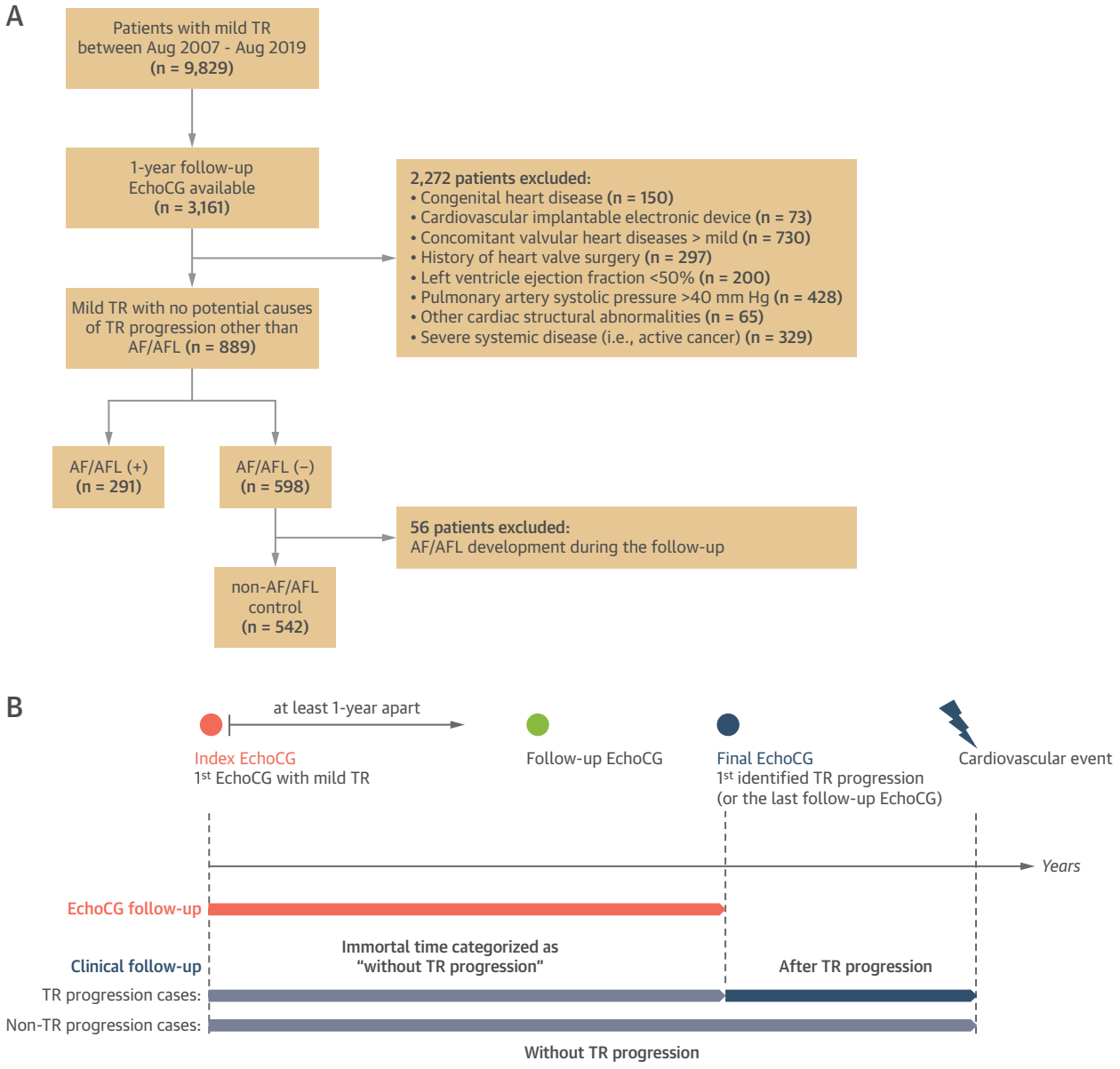
This study complied with the Declaration of Helsinki and was approved by the institutional review board (approval number: H-1911-118-1080). The anonymized nature of the database waived the requirement for written informed consent.

**DATA COLLECTION AND VARIABLE DEFINITIONS.** Clinical data were collected at the time of mild TR identification. AF-AFL was defined as documentation of AF-AFL rhythm on electrocardiography or 24-hour Holter tests. AF-AFL type was categorized as paroxysmal or sustained (persistent or permanent) AF-AFL. More information on variable definitions is described in Supplemental Methods.

**ECHOCARDIOGRAPHY.** Index echocardiography was defined as the first echocardiography that identified mild TR (**Figure 1B**). Final echocardiography was defined as a study that identified TR progression to greater than or equal to moderate for the first time or the most recent study if TR progression did not occur.

More details of echocardiography measurement are described in Supplemental Methods. In patients with AF-AFL, all echocardiographic measurements were averaged over 3 to 5 beats. Echocardiographic assessments of the right-sided heart were performed by

**FIGURE 1** **Illustration of Patient Selection and the Method of Dealing With Immortal Time Bias**




**(A)** The patient selection flowchart. **(B)** The definition of index/final echocardiography, endpoints, and duration of follow-up is shown. The Mantel-Byar test was used to compare MACEs or deaths between the period after progression of TR **(dark blue bar)** and the period before or without progression of TR **(gray bar)**. AF = atrial fibrillation; AFL = atrial flutter; EchoCG = echocardiography; MACE = major adverse cardiovascular event; TR = tricuspid regurgitation.

2 experienced sonographers following the guidelines.[16] RV end-diastolic area, end-systolic area, and RV-fractional area change (FAC) were measured from the RV-focused apical 4-chamber view, and care was taken to exclude trabeculations. RA area was measured by tracing the endocardium from the apical 4-chamber view at end-systole, and the inferior-superior vena cava confluences and RA appendages were excluded. We also calculated the RA area to RV end-systolic area ratio.[17] RA volume was calculated using the single area-length method. TV annulus diameters were measured as the distance between lateral and septal inner edges at end-diastole and end-systole from the RV-focused apical view.

A multiparametric approach including qualitative, semiquantitative, and quantitative parameters was used for the assessment of TR severity.[18] Vena contracta width was measured from the RV-focused apical view. The proximal isovelocity surface area (PISA) radius was measured at mid-systole, using the first aliasing. Effective regurgitant orifice area (EROA) was calculated with the PISA radius and TR peak velocity, and regurgitant volume was calculated as EROA multiplied by the TR time-velocity integral.[18] Moderate TR was defined as a moderate regurgitant jet with PISA radius 0.6 to 0.9 cm, EROA 0.20 to 0.39 $cm^2$, or regurgitant volume 30 to 44 mL. Severe TR was defined as the large regurgitant jet with either PISA radius >0.9 cm, EROA ≥0.40 $cm^2$, or regurgitant volume ≥45 mL.

**OUTCOME ASSESSMENT.** The primary outcome was progression to significant TR, defined as moderate or greater TR on the final echocardiography. The etiology of TR progression was adjudicated independently by 2 cardiologists (S.K., J-B.P.) based on serial echocardiography and clinical information, and significant AFTR was further analyzed as the outcome. The outcome was compared among patients with and without AF-AFL, and the time interval between index and final echocardiography was used as the follow-up duration (**Figure 1B**).

The risks of major adverse cardiovascular events (MACEs) and all-cause mortality were compared according to significant progression of AFTR. MACE was defined as a composite of cardiovascular death, heart failure, and surgery for TR. Cardiovascular death included death from sudden cardiac arrest, heart failure, myocardial infarction, or major vascular diseases. Heart failure was defined as inpatient admission caused by heart failure aggravation, with evidence of left ventricle or RV dysfunction. Mortality and causes of death were ascertained from official death certificates provided by Statistics Korea.

**STATISTICAL ANALYSIS.** Continuous variables were presented as medians (IQRs), and categorical variables were presented as frequencies (percentages). The differences between the groups were compared using the Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables. The difference between index and final echocardiography was compared using the paired-sample Wilcoxon test. The cumulative incidence of AFTR progression by AF-AFL was presented using Kaplan-Meier estimates and compared by the log-rank test. Univariable Cox analyses were performed to evaluate the risk factors for AFTR progression and presented as HRs with 95% CIs. Variables with $P < 0.05$ in univariable analyses were selected for multivariable Cox models, with a maximum of 1 covariate per 10 events. When there was a significant correlation between variables, only 1 of them was included to avoid multicollinearity. Cox proportional hazards assumption was tested using Schoenfeld residuals. Simon and Makuch nonparametric method was used to display the cumulative survival from MACEs and all-cause mortality by AFTR progression, which were compared using the Mantel-Byar test.[19,20] The details of this method are described in **Figure 1B** and Supplemental Methods. The time-dependent Cox analysis was performed to investigate the association of significant AFTR with MACEs and deaths, in which the development of AFTR was included as a time-dependent covariate. A 2-tailed $P < 0.05$ was considered statistically significant. All statistical analyses were performed using R.

## RESULTS

**PATIENTS' CHARACTERISTICS ACCORDING TO AF-AFL.** Of 833 patients with mild TR at baseline, 291 (34.9%) had AF-AFL (**Table 1**). Among patients with AF-AFL, 19 (6.5%) had AFL, and 43 (14.8%) had paroxysmal AF-AFL. Patients with AF-AFL were older (69 vs 65 years; $P < 0.001$) and more frequently men than those without AF-AFL (56.0% vs 33.0%; $P < 0.001$). Patients with AF-AFL had more diabetes mellitus and impaired renal function, whereas coronary artery disease was more prevalent in patients without AF-AFL (8.9% vs 25.5%; $P < 0.001$). Dyspnea and palpitation were the most prevalent symptoms in patients with AF-AFL, whereas chest pain was more frequent in patients without AF-AFL. The most common indication for echocardiography was the evaluation for known or suspected cardiovascular diseases.

For medication use, patients with AF-AFL more frequently received diuretic agents than those without AF-AFL. The proportion of patients receiving nondihydropyridines calcium channel blocker, beta-blocker, digoxin, and antiarrhythmics was higher in patients with AF-AFL than in those without (all $P < 0.05$); 119 (40.9%) patients with AF-AFL received anticoagulation therapy.

Regarding echocardiographic parameters, patients with AF-AFL had lower left ventricle ejection fraction, greater left atrium and RA size (RA area: 19.8 vs 13.2 $cm^2$; $P < 0.001$; RA volume: 55.5 vs 29.6 mL; $P < 0.001$), larger RV end-systolic area, and lower RV-FAC than those without AF-AFL (**Table 2**). RA-RV end-systolic area ratio was also significantly higher in patients with AF-AFL (2.4 vs 1.8; $P < 0.001$). Tricuspid annular diameters measured at end-diastole and

end-systole and vena contracta width were higher in patients with AF-AFL (all $P < 0.001$).

**AF-AFL AS A RISK FACTOR FOR SIGNIFICANT AFTR.** During the 4.6 years (IQR: 2.6-7.3 years) of echocardiographic follow-up, 35 patients developed significant TR (29 moderate and 6 severe). Of these cases, new-onset severe mitral regurgitation was identified in 2 patients, and 33 were identified as having AFTR. The cumulative incidence of AFTR progression was markedly higher in patients with AF-AFL than in those without (30 of 291 patients with AF-AFL [10.3%] vs 3 of 542 patients without AF-AFL [0.6%]; $P < 0.001$) (**Figure 2**). The clinical course of these 35 patients is summarized in Supplemental Table 1. For patients with AF-AFL who developed significant AFTR (n = 30), the median duration from the initial diagnosis of AF-AFL to development of significant AFTR was 13 years (IQR: 5-16 years). In the entire cohort, the annualized rate of AFTR progression was 7.9 (95% CI: 5.4-11.1) cases per 1,000 person-years. The progression rate of AFTR was significantly higher in patients with AF-AFL than in those without (21.1 [95% CI: 14.3-30.2] cases per 1,000 person-year vs 1.1 [95% CI: 0.2-3.2] cases per 1,000 person-years; $P < 0.001$).

When stratified by AF and AFL, there was no significant difference in the rate of progression of AFTR between the 2 groups (Supplemental Figure 1A). The progression rate of AFTR appeared higher in patients with sustained AF-AFL compared with those with paroxysmal AF-AFL, although statistically marginal ($P = 0.083$) (Supplemental Figure 1B).

**RISK FACTORS OF SIGNIFICANT AFTR PROGRESSION IN THE ENTIRE PATIENTS.** Univariable Cox analysis showed that AF-AFL was associated with a markedly higher risk of development of significant AFTR in all patients (HR: 20.58 [95% CI: 6.28-67.50]; $P < 0.001$) (Supplemental Table 2). The increased age, left atrium dimension, area and volume, RA area and volume, RA-RV end-systolic area ratio, tricuspid annular diameters, and vena contracta width were also significant risk factors for progression of AFTR.

In the multivariable Cox model (Model 1, **Table 3**), AF-AFL remained an independent risk factor for significant AFTR progression (adjusted HR: 8.33 [95% CI: 2.34-29.69]; $P = 0.001$), as did the increase in age (adjusted HR: 1.08 [95% CI: 1.03-1.13]; $P = 0.003$) and RA area (per 1 $cm^2$ increase, adjusted HR: 1.08 [95% CI: 1.03-1.13]; $P = 0.002$). Notably, the RA-RV end-systolic area ratio was a significant predictor of

**TABLE 1 Baseline Characteristics of Study Patients According to the Presence of AF-AFL**

| | AF-AFL at Baseline (n = 291) | No AF-AFL at Baseline (n = 542) | *P* Value |
|---|---|---|---|
| Age, y | 69 (63-75) | 65 (57–72) | <0.001 |
| Male | 163 (56.0) | 179 (33.0) | <0.001 |
| Body mass index, kg/$m^2$ | 24.0 (22.0-26.1) | 23.5 (21.1-25.6) | 0.043 |
| Systolic blood pressure, mm Hg | 127 (115-138) | 126 (116-140) | 0.458 |
| Diastolic blood pressure, mm Hg | 76 (70-84) | 74 (68-80) | 0.024 |
| Heart rate, beats/min | 78 (65-91) | 65 (59-73) | <0.001 |
| Hypertension | 147 (50.5) | 264 (48.7) | 0.671 |
| Diabetes | 54 (18.6) | 70 (12.9) | 0.038 |
| Coronary artery disease | 26 (8.9) | 138 (25.5) | <0.001 |
| Stroke | 47 (16.2) | 42 (7.7) | <0.001 |
| AFL | 19 (6.5) | – | – |
| Subtype of AF-AFL | | | |
| Paroxysmal AF | 38 (13.1) | – | – |
| Sustained AF | 234 (80.4) | – | – |
| Paroxysmal AFL | 5 (1.7) | – | – |
| Sustained AFL | 14 (4.8) | – | – |
| Previous AF-AFL ablation | 3 (1.0) | – | – |
| Symptoms | | | |
| Chest pain | 23 (7.9) | 97 (17.9) | <0.001 |
| Dyspnea | 70 (24.1) | 62 (11.4) | <0.001 |
| Palpitation | 46 (15.8) | 30 (5.5) | <0.001 |
| Edema | 16 (5.5) | 10 (1.8) | 0.007 |
| Syncope | 11 (3.8) | 18 (3.3) | 0.884 |
| Reasons for echocardiography | | | <0.001 |
| Evaluation for known or suspected CVD[a] | 242 (83.2) | 300 (55.4) | – |
| Routine health check-ups | 9 (3.1) | 139 (25.6) | – |
| Preoperative evaluation before noncardiac surgery | 11 (3.8) | 45 (8.3) | – |
| Evaluation of stroke etiology | 14 (4.8) | 30 (5.5) | – |
| Other medical evaluations | 15 (5.2) | 28 (5.2) | – |
| Laboratory examination | | | |
| Hemoglobin, g/L | 13.9 (12.6-15.4) | 13.1 (12.2-14.1) | <0.001 |
| Platelet, $10^3/\mu L$ | 204 (167-238) | 222 (192-258) | <0.001 |
| Glucose, mg/dL | 104 (94-124) | 97 (89-111) | <0.001 |
| eGFR, mL/min/1.73 $m^2$ | 68.6 (56.0-80.5) | 77.3 (64.5-89.9) | <0.001 |
| Albumin, g/dL | 4.2 (3.9-4.4) | 4.3 (4.0-4.4) | 0.012 |
| Bilirubin, mg/dL | 0.9 (0.7-1.2) | 0.7 (0.6-0.9) | <0.001 |
| Medications | | | |
| Loop diuretics | 19 (6.5) | 7 (1.3) | <0.001 |
| Thiazides diuretics | 51 (17.5) | 60 (11.1) | 0.012 |
| MR antagonists | 29 (10.0) | 12 (2.2) | <0.001 |
| RAS blockers | 104 (35.7) | 159 (29.3) | 0.069 |
| Dihydropyridines CCBs | 51 (17.5) | 97 (17.9) | 0.969 |
| Nondihydropyridines CCBs | 37 (12.7) | 21 (3.9) | <0.001 |
| Beta-blockers | 92 (31.6) | 118 (21.8) | 0.002 |
| Digoxin | 65 (22.3) | 3 (0.6) | <0.001 |
| Antiarrhythmic drugs[b] | 34 (11.7) | 4 (0.7) | <0.001 |
| Oral anticoagulation | 119 (40.9) | 3 (0.6) | <0.001 |

Values are n (%) or median (IQR), unless otherwise indicated. [a]Symptoms caused by CVD (ie, dyspnea, chest pain, and palpitation) or suspected CVD. [b]Class I and III antiarrhythmic drugs

AF = atrial fibrillation; AFL = atrial flutter; CCB = calcium-channel blocker; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; MR = mineralocorticoid receptor; RAS = renin-angiotensin system.

**TABLE 2 Echocardiography Parameters of Study Patients According to the Presence of AF-AFL**

| | AF-AFL at Baseline (n = 291) | No AF-AFL at Baseline (n = 542) | *P* Value |
|---|---|---|---|
| Echocardiographic parameters | | | |
| Left heart structure and function | | | |
| LV end-diastolic diameter, mm | 48.0 (45.0-51.0) | 47.0 (45.0-50.0) | 0.005 |
| LV end-systolic diameter, mm | 30.0 (28.0-33.0) | 29.0 (27.0-31.0) | <0.001 |
| LV end-diastolic volume, mL | 67.2 (55.0-80.4) | 71.3 (60.4-84.8) | 0.001 |
| LV end-diastolic volume index, mL/m$^2$ | 39.0 (33.7-47.0) | 45.1 (38.7-52.5) | <0.001 |
| LV end-systolic volume, mL | 26.2 (20.9-33.3) | 24.9 (20.8-31.5) | 0.343 |
| LV end-systolic volume index, mL/m$^2$ | 15.5 (12.7-19.3) | 16.0 (13.2-19.5) | 0.279 |
| LV ejection fraction, % | 60.3 (55.9-64.9) | 63.8 (60.2-67.2) | <0.001 |
| Septal thickness, mm | 9.0 (8.0-10.0) | 9.0 (8.0-10.0) | 0.002 |
| Posterior wall thickness, mm | 9.0 (8.0-10.0) | 9.0 (8.0-10.0) | 0.002 |
| LV mass index, g/m$^2$ | 90.7 (77.6-107.2) | 88.4 (76.1-103.3) | 0.122 |
| Left atrium dimension, mm | 50.0 (44.0-55.0) | 38.0 (34.0-42.0) | <0.001 |
| Left atrium area, cm$^2$ | 26.4 (20.8-32.0) | 16.7 (14.1-20.5) | <0.001 |
| Left atrium volume, mL | 94.7 (66.4-125.2) | 46.3 (35.1-65.2) | <0.001 |
| Left atrium volume index, mL/m$^2$ | 56.9 (41.3-73.5) | 32.2 (23.7-41.6) | <0.001 |
| E/A ratio | – | 0.85 (0.71-1.17) | – |
| Deceleration time, msec | 162 (139-193) | 207 (176-244) | <0.001 |
| e′-wave, cm/s | 7.6 (6.1-9.1) | 6.0 (5.0-7.7) | <0.001 |
| E/e′ ratio | 10.2 (7.9-13.0) | 10.0 (8.1-12.2) | 0.329 |
| Right heart structure and function | | | |
| RV end-diastolic area, cm$^2$ | 14.9 (11.8-17.5) | 14.2 (11.9-17.0) | 0.151 |
| RV end-diastolic area index, cm$^2$/m$^2$ | 9.0 (7.5-10.4) | 8.9 (7.7-10.5) | 0.602 |
| RV end-systolic area, cm$^2$ | 8.4 (6.5-10.2) | 7.5 (5.9-9.5) | <0.001 |
| RV end-systolic area, index, cm$^2$/m$^2$ | 5.1 (4.1-6.1) | 4.8 (3.9-5.9) | 0.075 |
| RV-FAC, % | 43.0 (38.5-47.5) | 46.1 (41.4-51.6) | <0.001 |
| RA area, cm$^2$ | 19.8 (16.6-23.4) | 13.2 (11.3-15.4) | <0.001 |
| RA area index, cm$^2$/m$^2$ | 11.7 (10.0-13.9) | 8.4 (7.2-9.7) | <0.001 |
| RA/RV end-systolic area ratio | 2.4 (2.0-3.0) | 1.8 (1.5-2.2) | <0.001 |
| RA volume, mL | 55.5 (42.5-69.9) | 29.6 (23.6-38.2) | <0.001 |
| RA volume index, mL/m$^2$ | 32.7 (24.3-42.0) | 19.0 (15.2-23.4) | <0.001 |
| TV annular diameter (end-diastole), mm | 33.2 (30.6-36.2) | 28.6 (26.0-31.4) | <0.001 |
| TV annular diameter (end-systole), mm | 29.9 (27.7-33.4) | 26.1 (23.7-28.8) | <0.001 |
| TR peak velocity, m/s | 2.3 (2.2-2.5) | 2.3 (2.2-2.4) | 0.863 |
| Vena contracta width, cm | 0.34 (0.27-0.40) | 0.28 (0.23-0.34) | <0.001 |

Values are n (%) or median (IQR), unless otherwise indicated.

FAC = fraction area change; LV = left ventricle; RA = right atrium; RV = right ventricle; TR = tricuspid regurgitation; TV = tricuspid valve; other abbreviations as in Table 1.

progression of AFTR (Model 3, per 0.1 increase, adjusted HR: 1.05 [95% CI: 1.03-1.07]; $P < 0.001$). However, left atrium dimension and TV annular diameters were not independent predictors of progression of AFTR (Table 3).

**RISK FACTORS OF AFTR PROGRESSION IN THE SUBGROUP OF PATIENTS WITH AF-AFL.** Table 4 shows the baseline and final echocardiographic measures of right heart in patients with AF-AFL according to development of significant AFTR. The baseline RA area and volume were significantly higher in patients with AF-AFL who developed significant AFTR compared with those who did not (RA area: 23.8 vs 19.4 cm$^2$; $P < 0.001$; RA volume: 64.4 vs 54.7 mL; $P = 0.002$). At baseline, there was no significant RV dilatation in patients who developed significant AFTR compared with those who did not (RV end-diastolic area: 13.9 vs 15.1 cm$^2$; $P = 0.206$). Notably, the baseline RA-RV end-systolic area ratio was significantly higher in patients with AF-AFL who developed significant AFTR compared with those who did not (3.0 vs 2.3; $P < 0.001$).

In the univariable Cox analysis, age, RA area, and volume were again significant risk factors for progression of AFTR in the AF-AFL subgroup (n = 291) (Supplemental Table 2). Notably, lower RV end-systolic area was associated with progression of AFTR ($P = 0.037$), and the increase in RA-RV end-systolic area ratio was associated with a significantly higher risk of progression of AFTR (per 0.1 increase, HR: 1.05 [95% CI: 1.03-1.07]; $P < 0.001$). These associations remained significant in the multivariable models (Table 3).

When patients with AF-AFL were stratified by tertiles of RA-RV end-systolic area ratio, there was a stepwise increase in progression of AFTR from the lowest (≤2.1) to mid (>2.1 and ≤2.8) and highest tertiles (>2.8) (Figure 3A). Examples of cases with different RA-RV end-systolic area ratios are shown in Figures 3B and 3C.

**RIGHT HEART REMODELING BEFORE AND AFTER PROGRESSION OF SIGNIFICANT AFTR IN PATIENTS WITH AF-AFL.** The RA size significantly increased from index to final echocardiography in patients with AF-AFL who developed significant AFTR (n = 30) (RA area: 23.8-28.0 cm$^2$; $P < 0.001$; RA volume: 64.4-103.3 mL; $P < 0.001$) (Table 4), whereas the increase in RA area was not observed and that in RA volume was relatively small in those who did not (RA area: 19.4-18.8 cm$^2$; $P = 0.017$; RA volume: 54.7-69.0 mL; $P < 0.001$). A significant increase in RV size was found in patients with significant AFTR progression (RV end-systolic area: 7.8-9.3 cm$^2$; $P = 0.003$) but not in those without. Estimated RA pressure was also significantly increased only among patients who developed significant AFTR (3.0-8.0 mm Hg; $P = 0.011$).

In patients with AF-AFL who developed significant AFTR, the median of TR EROA, regurgitant volume, and PISA radius in the final echocardiography was 0.47 cm$^2$, 31.8 mL, and 0.70 cm, respectively. In logistic regression analyses, the increases in RA volume and RV end-systolic area from index to final echocardiography were significantly associated with the presence of significant AFTR (Supplemental Tables 3 and 4).

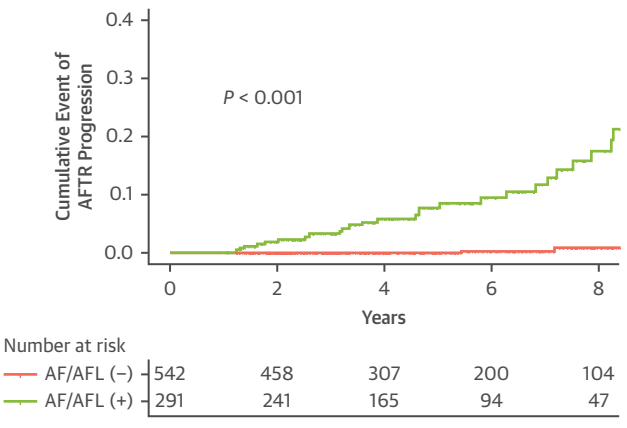
When temporal changes in right heart parameters were assessed in patients with AF-AFL developing significant AFTR, whose serial echocardiographic data were available (n = 10), RA area and volume tended to increase gradually from index to final echocardiography, whereas this pattern was not evident for RV end-systolic area (Supplemental Figure 2).

**CLINICAL OUTCOMES ASSOCIATED WITH SIGNIFICANT AFTR.** During the 8.7 years (IQR: 6.2-10.6 years) of clinical follow-up, 66 patients had MACEs (7.9%), including 36 cardiac deaths, 29 heart failures, and 4 TV surgeries, and 93 patients died (11.2%). Simon and Makuch survival analysis showed that 10-year cumulative MACE-free survival was significantly lower after progression of AFTR (20.2%) than before or without progression of AFTR (91.4%) (Mantel-Byar $P < 0.001$) (Figure 4A). All-cause mortality was also significantly higher after progression of AFTR than before or without progression of AFTR (10-year cumulative survival: 41.7% vs 86.5%, Mantel-Byar $P < 0.001$) (Figure 4B). The result was reproduced in the subgroup of patients with AF-AFL (Supplemental Figure 3).

In the time-dependent Cox analysis, progression of AFTR was associated with a significantly higher risk of 5-year MACE (adjusted HR: 11.16 [95% CI: 3.94-31.65]; $P < 0.001$) and all-cause mortality (adjusted HR: 7.00 [95% CI: 2.12-23.14]; $P = 0.001$) (Table 5).

**INTERACTIONS BETWEEN AF/AFL AND RA SIZE WITH REGARD TO AFTR PROGRESSION AND OUTCOMES.** A subgroup analysis was performed by the tertiles of

**FIGURE 2 Cumulative Event of Significant AFTR Progression in Patients With Mild TR According to AF-AFL**




AFTR = atrial functional tricuspid regurgitation; other abbreviations as in Figure 1.

**TABLE 3 Multivariable Cox Models for Significant Progression of AFTR in All Patients and the Subgroup of Patients With AF-AFL**

| | All Patients (n = 833) | | | Patients With AF-AFL (n = 291) | |
|---|---|---|---|---|---|
| | HR (95% CI) | *P* Value | | HR (95% CI) | *P* Value |
| Model 1 | | | Model A | | |
| Age, y | 1.08 (1.03-1.13) | 0.003 | Age, y | 1.07 (1.02-1.13) | 0.007 |
| AF-AFL | 8.33 (2.34-29.69) | 0.001 | RA area, $cm^2$ | 1.08 (1.03-1.13) | 0.002 |
| RA area, $cm^2$ | 1.08 (1.03-1.13) | 0.002 | | | |
| Model 2 | | | Model B | | |
| Age, y | 1.08 (1.03-1.13) | 0.002 | Age, y | 1.07 (1.02-1.13) | 0.006 |
| AF-AFL | 9.75 (2.77-34.32) | <0.001 | RA volume, per 10 mL increase | 1.15 (1.04-1.27) | 0.009 |
| RA volume, per 10 mL increase | 1.14 (1.03-1.27) | 0.012 | | | |
| Model 3 | | | Model C | | |
| Age, y | 1.08 (1.03-1.14) | 0.002 | Age, y | 1.08 (1.02-1.14) | 0.005 |
| AF-AFL | 9.15 (2.69-31.19) | <0.001 | RA-RV end-systolic area ratio, per 0.1 increase | 1.05 (1.03-1.07) | <0.001 |
| RA-RV end-systolic area ratio, per 0.1 increase | 1.05 (1.03-1.07) | <0.001 | | | |
| Model 4 | | | Model D | | |
| Age, y | 1.08 (1.03-1.13) | 0.002 | Age, y | 1.07 (1.02-1.13) | 0.011 |
| AF-AFL | 12.09 (3.32-44.00) | <0.001 | RA area, $cm^2$ | 1.09 (1.05-1.14) | <0.001 |
| Left atrium dimension, mm | 1.02 (0.97-1.07) | 0.530 | RV end-systolic area, $cm^2$ | 0.79 (0.67-0.93) | 0.005 |
| Model 5 | | | | | |
| Age, y | 1.08 (1.03-1.13) | <0.001 | | | |
| AF-AFL | 14.07 (4.09-48.46) | <0.001 | | | |
| TV annular diameter (end-diastole), mm | 1.00 (0.93-1.08) | 0.904 | | | |

AFTR = atrial functional tricuspid regurgitation; other abbreviations as in Tables 1 and 2.

**TABLE 4** Baseline and Follow-Up Echocardiographic Measures of Right-Heart Remodeling by AFTR Progression in 291 Patients With AF-AFL

| | Significant AFTR progression (+) (n = 30) | | | Significant AFTR progression (−) (n = 261) | | | | |
|---|---|---|---|---|---|---|---|---|
| | Index Echocardiography | Final Echocardiography | *P* Value | Index Echocardiography | Final Echocardiography | *P* Value | *P* Value[a] | *P* Value[b] |
| LV end-diastolic volume, mL | 65.3 (55.7-78.7) | 89.9 (73.0-104.0) | <0.001 | 67.2 (54.6-80.6) | 79.5 (66.1-96.0) | <0.001 | 0.827 | 0.126 |
| LV end-diastolic volume index, mL/m$^2$ | 38.6 (35.0-43.5) | 53.1 (43.2-59.0) | <0.001 | 39.3 (33.4-47.6) | 48.1 (41.2-56.3) | <0.001 | 0.808 | 0.185 |
| LV end-systolic volume, mL | 26.4 (22.1-29.9) | 34.0 (24.4-50.8) | 0.001 | 26.1 (20.9-33.6) | 31.6 (24.9-40.2) | <0.001 | 0.927 | 0.342 |
| LV end-systolic volume index, mL/m$^2$ | 15.3 (13.6-16.9) | 19.8 (15.0-28.2) | 0.001 | 15.6 (12.6-19.7) | 19.3 (15.6-24.1) | <0.001 | 0.792 | 0.451 |
| LV ejection fraction | 60.4 (56.0-64.8) | 62.2 (52.0-65.3) | 0.637 | 60.3 (55.9-64.9) | 60.0 (56.1-65.0) | 0.613 | 0.829 | 0.966 |
| RV end-diastolic area, cm$^2$ | 13.9 (11.7-15.0) | 15.4 (12.8-18.6) | 0.031 | 15.1 (11.9-17.6) | 11.0 (9.3-13.5) | <0.001 | 0.206 | <0.001 |
| RV end-diastolic area index, cm$^2$/m$^2$ | 8.6 (6.9-10.4) | 9.0 (8.3-10.6) | 0.059 | 9.1 (7.5-10.4) | 6.7 (5.7-8.0) | <0.001 | 0.375 | <0.001 |
| RV end-systolic area, cm$^2$ | 7.8 (6.5-9.0) | 9.3 (7.4-10.9) | 0.003 | 8.5 (6.6-10.3) | 6.5 (5.4-7.7) | <0.001 | 0.143 | <0.001 |
| RV end-systolic area, index, cm$^2$/m$^2$ | 4.8 (3.9-5.7) | 5.7 (4.7-6.3) | 0.007 | 5.1 (4.1-6.1) | 3.9 (3.4-4.7) | <0.001 | 0.178 | <0.001 |
| RV-FAC, % | 44.4 (41.2-47.4) | 41.2 (37.1-44.7) | 0.066 | 42.4 (38.3-47.5) | 41.2 (34.8-46.4) | 0.006 | 0.136 | 0.736 |
| RA area, cm$^2$ | 23.8 (21.2-27.3) | 28.0 (23.9-35.9) | <0.001 | 19.4 (16.5-23.0) | 18.8 (15.4-22.0) | 0.017 | <0.001 | <0.001 |
| RA area index, cm$^2$/m$^2$ | 14.9 (13.3-16.6) | 17.4 (15.3-21.4) | <0.001 | 11.5 (9.9-13.1) | 11.2 (9.4-12.9) | 0.014 | <0.001 | <0.001 |
| RA/RV end-systolic area ratio | 3.0 (2.5-3.7) | 3.4 (2.7-4.2) | 0.156 | 2.3 (2.0-2.9) | 2.9 (2.3-3.3) | <0.001 | <0.001 | 0.018 |
| RA volume, mL | 64.4 (58.0-84.1) | 103.0 (77.8-131.9) | <0.001 | 54.7 (41.4-68.3) | 69.0 (51.6-88.9) | <0.001 | 0.002 | <0.001 |
| RA volume index, mL/m$^2$ | 42.7 (34.2-49.2) | 61.9 (47.6-79.4) | <0.001 | 32.0 (23.9-39.4) | 40.5 (31.1-50.8) | <0.001 | <0.001 | <0.001 |
| TV annulus diameter (end-diastole), mm | 34.1 (30.7-37.0) | 35.5 (34.3-38.9) | 0.002 | 33.0 (30.6-36.1) | 32.6 (29.3-35.9) | 0.019 | 0.483 | <0.001 |
| TV annulus diameter (end-systole), mm | 31.4 (29.0-33.6) | 33.4 (29.0-36.0) | 0.040 | 29.8 (27.6-33.3) | 28.8 (25.7-31.9) | <0.001 | 0.374 | <0.001 |
| TR peak velocity, m/s | 2.2 (2.1–2.4) | 2.4 (2.2-2.7) | 0.027 | 2.3 (2.2-2.5) | 2.4 (2.2-2.6) | <0.001 | 0.073 | 0.580 |
| Estimated RA pressure, mm Hg | 3.0 (3.0-3.0) | 8.0 (8.0-15.0) | 0.011 | 3.0 (3.0-8.0) | 3.0 (3.0-8.0) | 0.051 | 0.994 | <0.001 |
| Vena contracta width, cm | 0.35 (0.29-0.36) | 0.64 (0.48-0.73) | <0.001 | 0.33 (0.27-0.40) | 0.36 (0.27-0.47) | 0.062 | 0.872 | <0.001 |
| TR EROA, cm$^2$ | – | 0.47 (0.31-0.59) | – | – | – | – | – | – |
| TR RVol, mL | – | 31.8 (22.2-41.0) | – | – | – | – | – | – |
| TR PISA radius, mm | – | 0.70 (0.62-0.83) | – | – | – | – | – | – |

Values are median (IQR). [a]Comparison of index echocardiography examinations between patients who developed significant AFTR and those who did not. [b]Comparison of final echocardiography examinations between patients who developed significant AFTR and those who did not.

EROA = effective regurgitant orifice area; PISA = proximal isovelocity surface area; RVol = regurgitant volume; other abbreviations as in Tables 1 to 3.

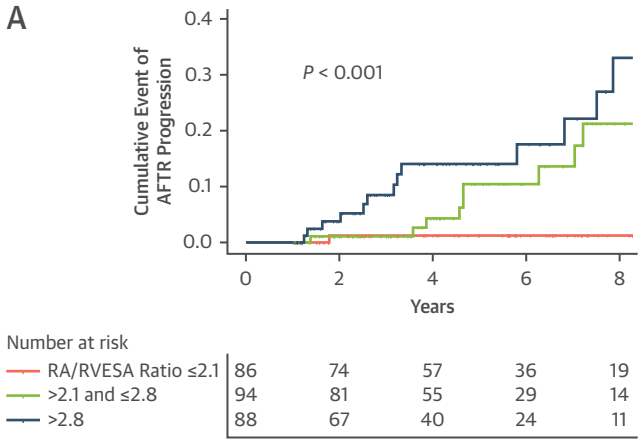
RA area (≤13.2 cm$^2$, >13.2 and ≤17.3 cm$^2$, and >17.3 cm$^2$). The development of significant AFTR predominantly occurred in patients with the highest tertile of RA area, and among this group, these events were exclusively observed in patients with AF-AFL ($P$ = 0.002) (**Central Illustration** and Supplemental Figure 4). However, there was no significant progression of AFTR regardless of AF-AFL in the lowest tertile group. For patients in the highest tertile of RA area, MACE and all-cause mortality rates were significantly higher after progression of AFTR than before or without AFTR progression (10-year cumulative MACE: 83.0% vs 16.6%, Mantel-Byar $P < 0.001$; 10-year cumulative all-cause mortality: 59.4% vs 23.7%, Mantel-Byar $P < 0.001$). Similar findings were found in the subgroup analysis by the tertiles of RA-RV end-systolic area ratio (Supplemental Figure 5).

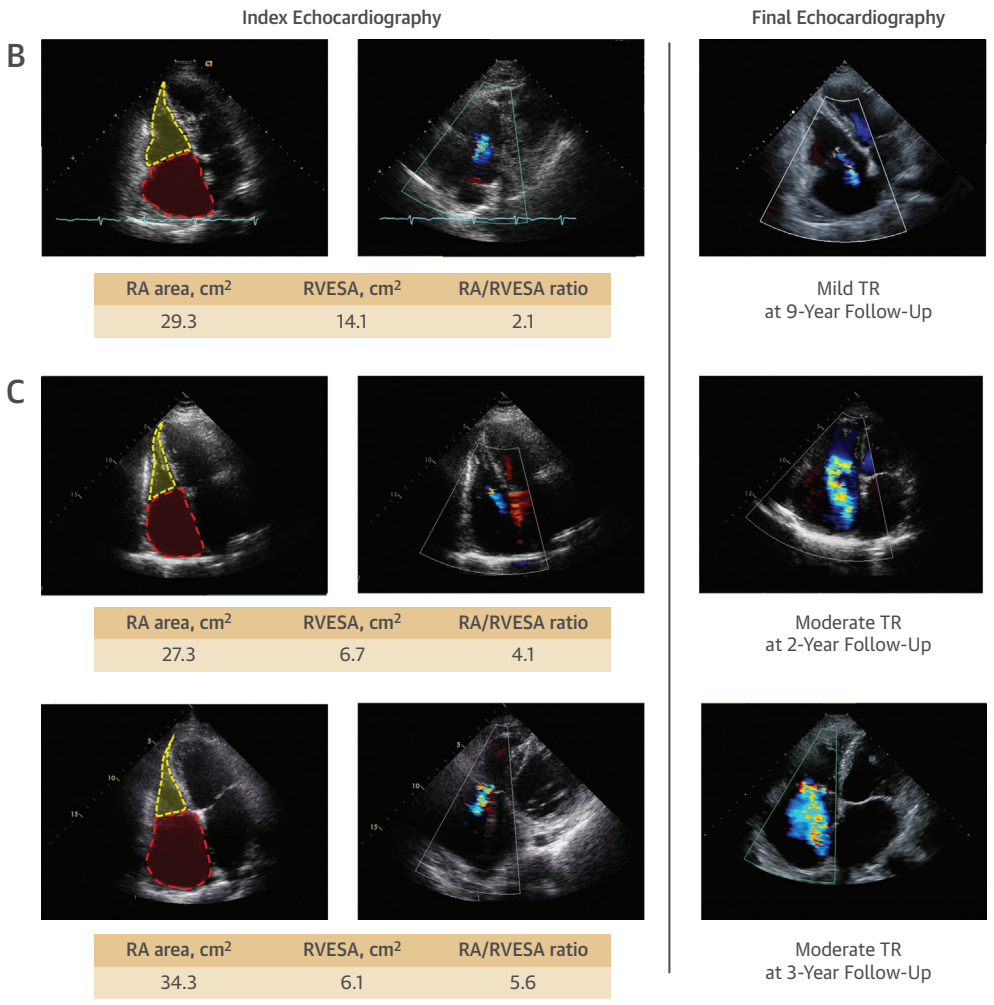
## DISCUSSION

We demonstrated that 4% of patients with mild TR developed significant progression of TR during 4.6 years of follow-up. Significant progression of TR almost exclusively occurred in patients with AF-AFL (32 of 35 cases), of which 30 were AF-AFL-related AFTR cases. In patients with AF-AFL, RA enlargement, especially with a higher RA-RV end-systolic area ratio, was a significant risk factor for progression of AFTR. Patients who developed significant AFTR exhibited markedly higher MACEs and deaths than those who did not (**Central Illustration**).

Recently, AFTR has been recognized as an important entity in TR, accounting for approximately 10% of significant TRs.[6,9,11] Although patients with AFTR have a high prevalence of AF,[9,11] only a few previous studies have shown that AF is a preceding risk factor for progression of TR.[21,22] However, these studies included a substantial proportion of patients with left-sided valvular diseases ≥ moderate degree[21,22] or depressed left ventricle ejection fraction (ie, <45%).[22] Considering that these conditions can cause significant secondary TR, the longitudinal association between AF and AFTR remains uncertain. Importantly, we exclusively enrolled patients without any conditions that may lead to significant primary or secondary TR at baseline (**Figure 1A**) and found that

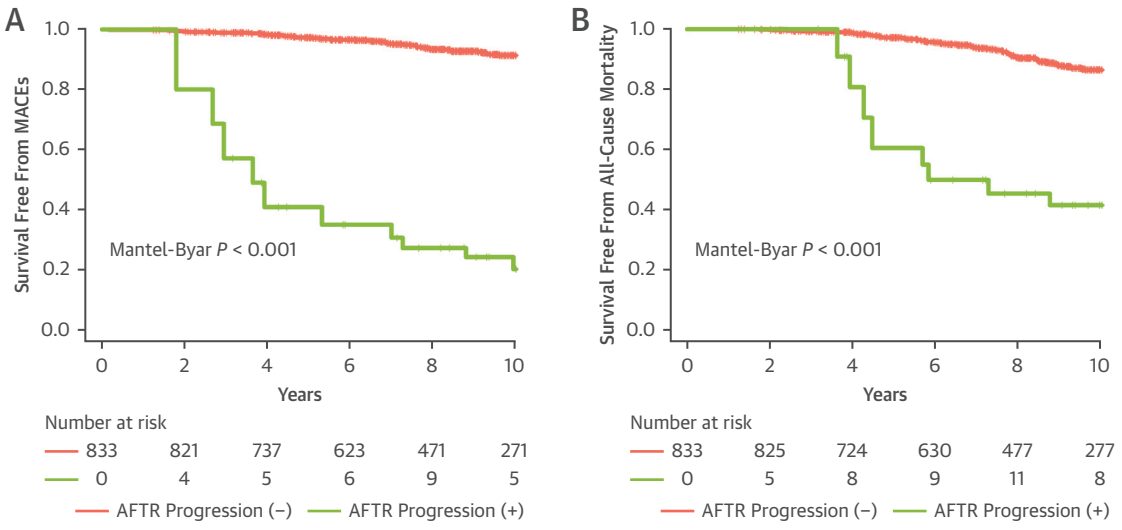
**FIGURE 3** **Risk of AFTR Progression According to the RA-RVESA Ratio in Patients With AF-AFL**




**(A)** Among patients with AF-AFL, the cumulative event of progression of AFTR was significantly higher in those with higher RA-RVESA ratios. **(B)** A patient with RA enlargement but a low RA-RVESA ratio did not develop significant AFTR during a 9-year period. **(C)** However, 2 patients with high RA-RVESA ratios developed significant AFTR within the short-term follow-up. RA = right atrium; RVESA = right ventricle end-systolic area; other abbreviations as in Figures 1 and 2.

**FIGURE 4** Risk of Adverse Outcomes According to Development of Significant AFTR




Simon and Makuch survival curves for MACEs **(A)** and all-cause mortality **(B)** between the period after AFTR progression **(green line)** and the period before or without progression of AFTR **(red line)**. Abbreviations as in Figures 1 and 2.

new-onset moderate or greater TR developed predominantly in patients with AF-AFL (Figure 2). We also verified that, in most significant TR cases, there were no definitive causes of TR other than long-standing AF-AFL (Supplemental Table 1). These results suggest that AF-AFL is an important factor that influences the development of TR from mild to significant.

AFTR caused by AF is characterized by prominent RA enlargement.[8-12] In AF-related AFTR, RA enlargement may develop in the earlier stages, unlike RV dilatation, which occurs later once TR becomes severe.[23] Our findings also support the hypothesis, demonstrating that the baseline RA area was significantly larger in patients with AF-AFL who developed AFTR than in those who did not, although the RV and TV sizes were similar (Table 4). Intriguingly, RA area further increased when significant AFTR developed (Table 4). This supports the concept of "TR begets TR," which indicates a vicious cycle of progressively worsening RA remodeling and TR severity.

The geometry of the right heart and its relationship with TV may also be an important mechanism of progression of AFTR. A recent study showed that patients with severe AFTR had prominent RA enlargement but smaller RV end-systolic volume and a significantly higher RA-RV end-systolic volume ratio than those with ventricular functional TR (2.2 vs 0.9; $P < 0.001$).[17] Notably, the RA-RV end-systolic volume ratio had the strongest correlation with the TV annular orientation angle,[17] suggesting that geometric changes in TV may be dependent on the balance between RA and RV remodeling. We also showed that a higher RA-RV end-systolic area ratio was associated with a higher risk of progression of AFTR, which may be an early indicator of AFTR.

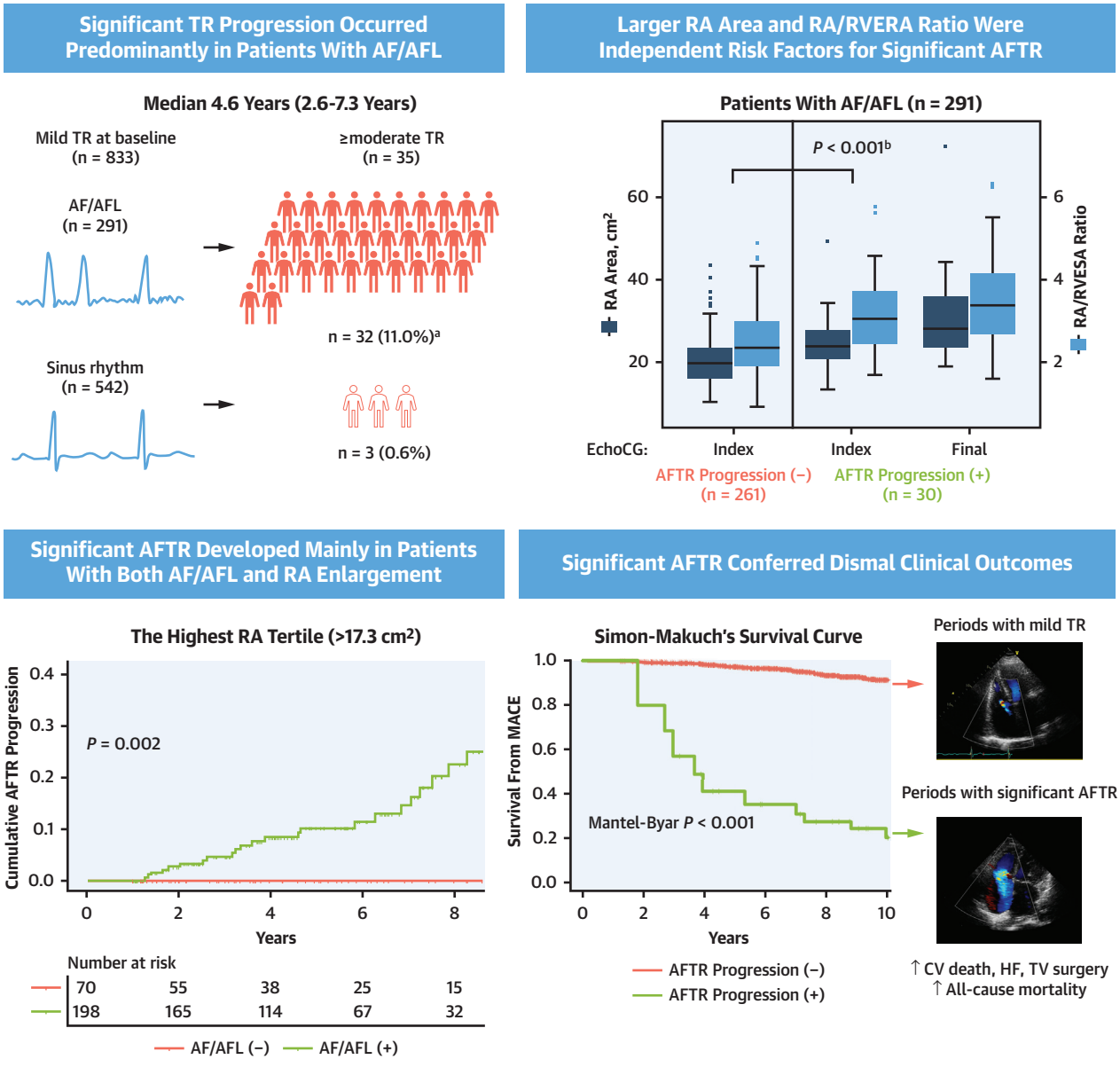
Several studies have indicated that patients with AFTR have significantly worse cardiovascular outcomes,[24-26] which was also confirmed in our study (Figure 4). Despite the poor prognosis, TV surgery has rarely been performed in patients with significant AFTR.[24-26] The benefit of surgery over medical management for patients with significant TR alone is still debatable, and a recent study including 3,276 patients with significant TR but without left-sided valvular dysfunction showed that surgery for TR did not improve survival over conservative treatment.[27] This result may stem from the delay in TR

**TABLE 5** Multivariable Cox Models for 5-Year MACE and Mortality in All Patients

| | 5-Year MACE | | 5-Year All-Cause Mortality | |
|---|---|---|---|---|
| | HR (95% CI) | *P* Value | HR (95% CI) | *P* Value |
| AFTR progression[a] | 11.16 (3.94-31.65) | <0.001 | 7.00 (2.12-23.14) | 0.001 |
| Age, y | 1.10 (1.05-1.16) | <0.001 | 1.11 (1.05-1.16) | <0.001 |
| AF/AFL | 3.42 (1.30-8.98) | 0.013 | 1.60 (0.66-3.85) | 0.294 |
| LV ejection fraction, % | 0.98 (0.94-1.02) | 0.306 | 1.00 (0.95-1.05) | 0.899 |

[a]AFTR progression was analyzed as a time-dependent covariate.
MACE = major adverse cardiovascular event; other abbreviations as in Tables 1 to 3.

**CENTRAL ILLUSTRATION** **Risk Factors and Outcomes of Significant Atrial Functional Tricuspid Regurgitation**




**Kwak S, et al. J Am Coll Cardiol Img. 2023;■(■):■-■.**

Among patients with mild TR, progression to significant TR occurred predominantly in patients with AF-AFL **(upper left).** In patients with AF-AFL, the baseline RA area and RA-RVESA ratio were significantly higher in those who developed significant AFTR than in those who did not, which were further increased from index to final echocardiography **(upper right)**. When stratified by RA area tertiles, significant AFTR predominantly developed in patients with AF-AFL in the highest RA tertile (>17.3 $cm^2$) but rarely occurred in the lowest or middle RA tertiles, regardless of AF-AFL, suggesting the additive role of RA enlargement and AF-AFL **(lower left)**. Simon and Makuch survival curve showed that cumulative MACE was higher after progression of AFTR than before or without progression of AFTR (Mantel-Byar $P < 0.001$) **(lower right)**. [a]Two patients developed new-onset severe mitral regurgitation during follow-up, leaving 30 AFTRs. [b]Both RA area and RA-RVESA ratio. AF = atrial fibrillation; AFL = atrial flutter; AFTR = atrial functional tricuspid regurgitation; CV = cardiovascular; EchoCG = echocardiography; HF = heart failure; MACE = major adverse cardiovascular event; RA = right atrium; RVESA = right ventricle end-systolic area; TR = tricuspid regurgitation; TV = tricuspid valve.

surgery, given that most study patients had already developed signs of heart failure, and more than 25% of patients waited for more than 1 year for surgical referral.[27] Timely surgical intervention based on individualized risks may improve the outcomes of patients with AFTR.

Our findings suggest that patients with mild TR who have concurrent AF-AFL and RA enlargement are at increased risk of significant progression of AFTR and subsequent adverse events, which may help clinicians to risk stratify patients with mild TR. These findings also emphasize the importance of comprehensive echocardiographic assessments of RA remodeling. Future studies are required to determine how frequently patients with mild TR and AF need to be monitored with surveillance echocardiography, which echocardiographic parameters should be quantitatively measured and followed up, and when additional imaging modalities should be considered. Although our study may reassure physicians that current guidelines recommending periodic echocardiographic evaluation every 3 to 5 years for mild left-sided valvular regurgitation is also advisable for patients with mild TR but without AF-AFL, scrutiny of such patients for the development of AF-AFL is important. Furthermore, our findings imply the potential role of antiarrhythmic therapies—including drugs, electrical cardioversion, and ablation—in preventing the progression of AFTR (Supplemental Figure 1B).[6] Further studies are needed to test this possibility and determine the optimal timing of such therapies to maximize their benefits.

**STUDY LIMITATIONS.** First, this study was conducted at a single center and had a retrospective design, and more information on comorbidities, biomarkers, EROA, and regurgitant volume at baseline or myocardial strain was unavailable. We also lack more comprehensive data on loading conditions at echocardiography examinations, which may affect severity of TR. Second, as patients who underwent repeated echocardiography were exclusively enrolled, potential selection bias may have influenced the results. In addition, follow-up echocardiography examinations were not performed at fixed time intervals, and patients without symptoms may have had delayed diagnoses of significant TR. Third, most cases did not have 3-dimensional transesophageal echocardiography images, which enables more precise assessments of TV anatomy disturbances.[11,28] Further prospective studies using this technique are necessary to elucidate the impact of AF-AFL and right heart remodeling on progression of AFTR. Fourth, the number of patients who developed significant AFTR was small. However, this was mainly because we included patients without any risk factors for progression of TR other than AF-AFL at baseline (Figure 1A), which is an important strength compared with previous studies. Finally, as most patients developed moderate TR in our study, further studies are warranted to evaluate RA and RV remodeling in the late stage of AFTR.

## CONCLUSIONS

In patients with mild TR, significant AFTR developed predominantly in those with AF-AFL. RA enlargement was a strong risk factor for progression of AFTR in the presence of AF-AFL. Development of significant AFTR conferred poor cardiovascular outcomes. Closer echocardiographic surveillance may be advisable for patients with mild TR, AF-AFL, and increased RA size.

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## PERSPECTIVES

**COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:** In patients with mild TR, AF-AFL, and RA enlargement are strong risk factors for the progression to significant AFTR, leading to worse cardiovascular outcomes.

**TRANSLATIONAL OUTLOOK:** Future studies are warranted to investigate the mechanism of development of AFTR in relation to RA remodeling. In addition, the optimal timing of intervention and the benefits of AF-AFL rhythm control in patients with significant AFTR need to be examined.

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**KEY WORDS** atrial fibrillation, right atrium, tricuspid regurgitation

**APPENDIX** For an expanded Methods section as well as supplemental references, tables, and figures, please see the online version of this paper.