Journal of the American Heart Association

ORIGINAL RESEARCH

Effect of Tricuspid Regurgitation on the Reported Quality of Life and Subsequent Outcomes in Patients With Atrial Fibrillation

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BACKGROUND: Atrial fibrillation and heart failure (HF) possess mutual risk factors and share a common pathophysiological pathway. Tricuspid regurgitation (TR) is a known predictor of adverse events in patients with HF. However, its implications on patients with atrial fibrillation in its early stage remain unknown.

METHODS AND RESULTS: Data of 2211 patients without previous HF diagnosis were extracted from a prospective, multicenter registry of newly diagnosed patients with atrial fibrillation. TR was categorized as absent, mild, moderate, and severe based on the American Society of Echocardiography recommendations. The primary outcome was time to first hospitalization for HF after enrollment. The Atrial Fibrillation Effects on Quality-of-Life scores were compared. Overall, 1107 patients (50.1%) had TR (42.3%, 7.2%, and 0.6% for mild, moderate, and severe, respectively). During follow-up (median 730 [interquartile range, 366–731] days), 44 patients (2.0%) experienced HF hospitalization, and the incidence increased with severity of TR ($P<0.001$). TR was an associated predictor of the primary outcome (hazard ratio [HR]: 2.51, $P=0.050$; HR: 6.19, $P=0.008$; for moderate and severe TR versus no TR). Changes in AFEQT overall score were negatively related to TR severity (8.7±17.5 versus 8.5±17.0 versus 3.1±17.5 versus 1.4±11.8, absent versus mild versus moderate versus severe TR, respectively), although it was not an independent predictor after adjustments.

CONCLUSIONS: TR severity at atrial fibrillation diagnosis was an associated predictor of subsequent hospitalization for HF, which may warrant the need for a more intensive follow-up and HF-related management.

Key Words: atrial fibrillation ■ heart failure ■ quality of life ■ tricuspid regurgitation

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See Editorial by Mohanty and Natale

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia worldwide and is associated with substantial rates of morbidity and mortality and impaired quality of life (QOL).[1–3] AF and heart failure (HF) are closely associated disorders that worsen life expectancy. The prevalence of AF increases with age and is associated with a higher incidence of HF.[4] Therefore, the interaction between HF and AF and prevention of HF in patients with AF are important issues that need to be elucidated.[5]

In the diagnostic algorithm for HF with preserved ejection fraction, the tricuspid regurgitation (TR) pressure gradient was used as the major diagnostic parameter.[6] TR has been used to predict pulmonary artery systolic pressure and as a responsive metric of worsening HF and even as a prognostic predictor in patients with HF.[7,8] Moreover, TR tended to be present in patients with AF because of annular dilatation, even in the absence of left-sided heart disease.[9] Although prior

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CLINICAL PERSPECTIVE

What Is New?
- This study elucidated that tricuspid regurgitation at the time of atrial fibrillation diagnosis was an associated predictor of subsequent heart failure events, even when the patients with atrial fibrillation did not have a prior history of heart failure.

What Are the Clinical Implications?
- In patients with moderate or severe tricuspid regurgitation, it is important to consider the progression of heart failure.
- Our findings may facilitate the identification of patients with atrial fibrillation with a high risk of subsequent heart failure admission.

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Nonstandard Abbreviations and Acronyms

AFEQT	atrial fibrillation effect on quality-of-life measure
TR	tricuspid regurgitation

observations have demonstrated a strong association between AF and consequent tricuspid valve remodeling,[9] the clinical implications of TR in newly diagnosed patients with AF remain unknown. Accordingly, this study aimed to investigate the influence of TR on the QOL and subsequent admission for HF in newly diagnosed patients with AF without a history of HF.

METHODS

The data and materials used to conduct this research are available to researchers, on request to the corresponding author, for scientific projects aimed at identifying a novel clinical finding that may further improve patient outcome. Attempts to covalidate country-specific observations, risk stratification schemes, and outcomes are also welcome. The procedure does need to follow the Act on the Protection of Personal Information Law (as of May 2017) and the Ethical Guidelines for Medical and Health Research involving Human Subjects (as of March 2015) in Japan.

Study Design and Data Sources

The rationale and design of the Keio Inter-Hospital Cardiovascular Studies-Atrial Fibrillation (KiCS-AF) registry have been described previously.[10,11] In brief, the KiCS-AF registry was designed to prospectively collect clinical information and outcome data from consecutive patients newly diagnosed with AF or referred to the 11 participating tertiary care hospitals in the Kanto area of Japan (Saitama, Tochigi, Chiba, Kanagawa, and Tokyo Prefectures). To obtain a robust assessment of the treatment provided and patient outcomes, baseline data, and outcomes were collected from the medical records by the onsite clinical research coordinator (CRC) at each hospital. The CRCs were trained by the primary investigator (S. K.) and project coordinator (I. U.). The data were entered into an electronic data-capturing software system, which included a data query engine and system validations for data quality. This issue was addressed by the unique feature of the KiCS-AF registry that allowed the assigned CRCs at each site to obtain patient information from the institutional outpatient diagnostic coding system (Diagnosis Procedure Combination) and the ability to link this patient information for auditing enrollment. All of the KiCS-AF institutions agreed to release the administrative information to the assigned CRC and/or investigator for patients whose primary diagnosis was coded as "AF." The institutional review board at each participating hospital approved the study protocol, and all participants provided oral or written informed consent.

Study Population and Definition of Terms

In our study, 3318 newly diagnosed or referred patients with AF were enrolled between 2012 and 2018. Of these, 3078 patients underwent >1 year of follow-up. Patients with unknown HF history (n=39) and those with a history of HF-related admission (n=503) were excluded because TR itself may contribute to an increase in the HF admission rate in these patients.[12,13] Similarly, patients with unknown TR grades (n=325) were excluded. Thus, the remaining 2211 newly diagnosed or referred patients with AF without a prior history of HF and known TR grade at baseline were analyzed in this study (Figure 1). The presence of HF was determined from the medical chart and referral form, and the diagnosis of HF was based on the Japanese guidelines for the diagnosis of acute and chronic HF.[14] Data on TR were obtained from the echo report at enrollment. Patients were divided into 4 groups according to the severity of TR: severe TR group (n=13), moderate TR group (n=159), mild TR group (n=935), and no TR group (n=1104). Although grading of TR was an integrated approach in the participating hospitals, TR was mainly graded qualitatively by using jet area, especially in none or mild TR. The severity of TR was graded according to the recommendations of the American Society of Echocardiography.[15] The following definitions were used in our study: non-paroxysmal AF was defined as AF sustained for ≥7 days (including persistent AF, longstanding AF, and permanent AF) or lasting for <7 days, but necessitating electrical cardioversion. Catheter ablation was defined as AF ablation or ablation of recurrent atrial arrhythmia.
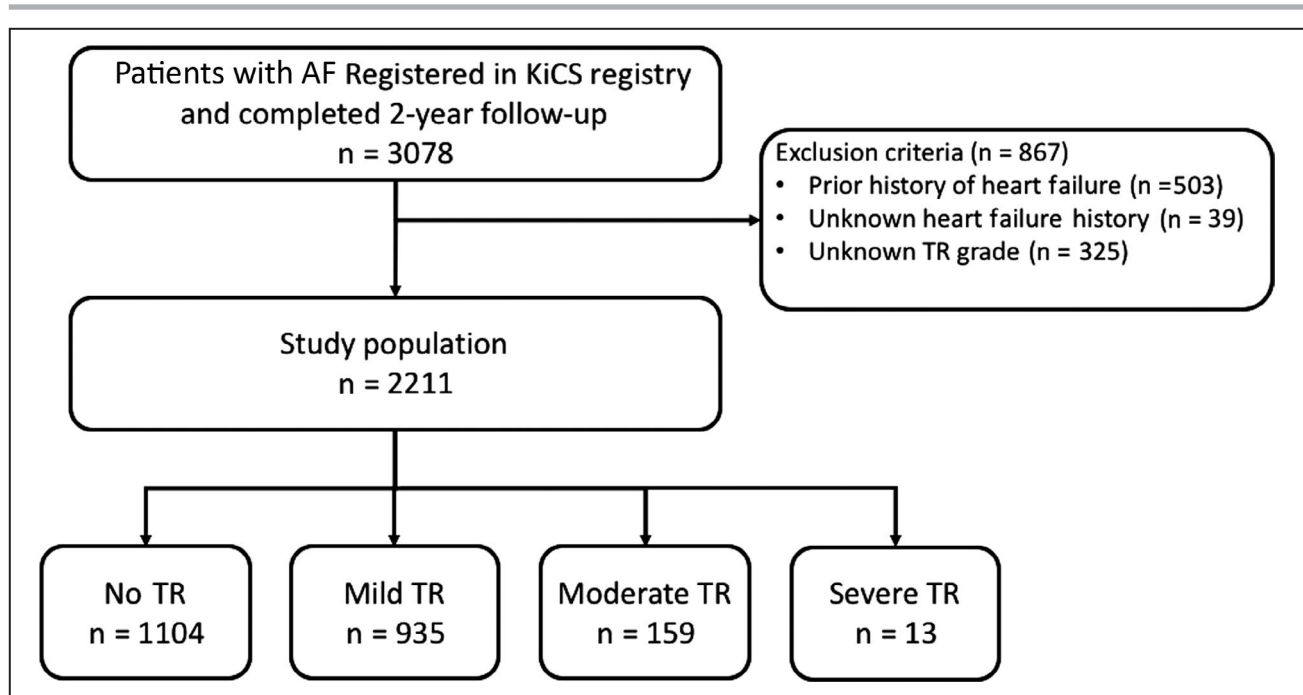
Figure 1. Flow diagram of the study.
AF indicates atrial fibrillation, KiCS, Keio Inter-Hospital Cardiovascular Studies; and TR, tricuspid regurgitation.

The primary outcome was time to first hospitalization for HF after enrollment. In addition, time to the event of stroke, major bleeding, and all-cause death after enrollment were assessed as secondary outcomes. Stroke was defined as a new, sudden loss of neurological function with residual symptoms lasting at least 24 hours after onset that was not attributable to a non-vascular cause. Major bleeding was defined by the International Society of Thrombosis and Hemostasis criteria.[16] All events were adjudicated by the end point adjudication committee, which included 3 individual cardiologists, by reviewing health records and querying the CRCs responsible for each site.

Assessment of Patients' Quality of Life

At baseline and at the 1-year follow-up visit, patients were required to complete a detailed questionnaire based on the internationally validated AF effect on QOL measure (Atrial Fibrillation Effects on Quality-of-Life [AFEQT]; http://www.afeqt.org) for assessment of their QOL and their perception of treatment. The development and validation of AFEQT have been previously described.[17] The AFEQT, which is used to measure AF-specific health status, was developed through serial iterations with patients, factor-level analysis, and psychometric testing. Evaluation of the AFEQT is based on a 20-item survey, with each item measured on a 7-point Likert scale, that evaluates 4 domains of patient health status, namely, symptoms, daily activities, treatment-related concerns, and treatment satisfaction. The scores across the 20 items were summed to provide the overall summary score, as follows:

$$AFEQT\ score = 100 - (sum\ of\ severity\ for\ all\ questions\ answered$$
$$- number\ of\ questions\ answered) \times 100$$
$$/(total\ number\ of\ questions\ answered \times 6)$$

The AFEQT score can range between "0" and "100," with "100" being the best possible health status [no impairment] and "0" representing the worst health status possible. A validated culturally and linguistically translated version of the AFEQT for Japan was used.

Statistical Analysis

Complete baseline and 1-year follow-up data for the 4 groups were stratified and analyzed overall. Data were described as frequencies and percentages for categorical variables and mean±SD for continuous variables. Comparisons among the severe TR, moderate TR, mild TR, and no TR groups were performed using a Chi-squared test or Fisher exact test for categorical variables, as appropriate for the data distribution, and an ANOVA for continuous variables. Binominal logistic regression analysis was performed to determine the predictors of significant TR. We defined moderate and severe TR as significant TR, and the remaining types as non-significant TR.

Cumulative event rates were estimated using the Kaplan–Meier method. Then, we performed a Cox proportional hazards regression analysis to evaluate associations between the severity of TR and the primary outcome and other outcomes of interest; these models were adjusted for clinically relevant variables, which are described in the figure legends. We performed an additional multivariable analysis adjusted for the causal and

clinically relevant factors of pulmonary hypertension (left ventricular ejection fraction [LVEF]), left sided valvular heart disease, congenital heart disease, chronic obstructive pulmonary disease, left atrial diameter). The rates of missing data were <2% for all candidate variables, except for LVEF (3.9%) and serum creatinine level (5.0%). To account for the missing data, we additionally performed a multivariable analysis using the cohort in which a single mean imputation was used for the LVEF and serum creatinine level. The left side valvular heart disease included aortic regurgitation, aortic stenosis, mitral regurgitation, and mitral stenosis of more than moderate severity. Additionally, to rigorously adjust for patients who were underdiagnosed for HF, we constructed another model that additionally adjusted for serum brain natriuretic peptide level. Furthermore, since left atrial dilatation is known to be a diagnostic criterion for HF with preserved ejection fraction,[6] we performed a sensitivity analysis according to the left atrial diameter (eg, left atrial diameter <45 mm or ≥ 45 mm). We also performed a sensitivity analysis according to the performance of the catheter ablation procedure for AF after enrollment and heart rate at enrollment <77 bpm, or ≥77 bpm (which was the median heart rate at enrollment).

The AFEQT scores at baseline and at the 1-year follow-up were calculated and compared among the 4 groups. In addition, to evaluate the effect of catheter ablation on the patients' QOL, we performed a sensitivity analysis based on the performance of catheter ablation for AF after enrollment. To examine the association between the groups and the baseline AFEQT score, a multivariable linear regression model was constructed for the AFEQT scores in the symptom and daily activity domains. The rates of missing AFEQT data were 0.5% (n=10/2211) at baseline and 12.1% (n=238/1973) at 1 year. To ensure that we examined a representative cohort of patients, we examined the differences in baseline characteristics between patients with and without available AFEQT data. We also examined the differences in baseline characteristics between the patients for whom TR data were and were not available.

In addition, we performed a subgroup analysis stratified by catheter ablation performance after enrollment. We assessed the presence of an interaction between TR severity and left atrial diameter, heart rate at rest, and performance of catheter ablation after enrollment. All P values were 2-sided, with values <0.05 defined as significant. Statistical analyses were performed using IBM SPSS software (version 25, IBM, Armonk, NY, USA).

RESULTS

Patient Characteristics

Among the 2211 patients included in our analysis, severe TR, moderate TR, mild TR, and no TR were observed in 13 (0.6%), 159 (7.2%), 935 (42.3%), and 1104 (49.9%) patients, respectively. Relevant clinical patient characteristics are summarized in Table 1. The characteristics of the patients without TR grade data at baseline (n=325) were also largely comparable with those in the analytic cohort, although patients with missing data were likely to have paroxysmal AF (Table S1). Age, sex, the rate of paroxysmal AF, CHADS2 score, CHA_2DS_2-VASc score, serum brain natriuretic peptide level, and left atrial size were significantly different among the groups (P<0.05). With regard to the therapeutic strategy, the rhythm control strategy tended to be chosen in the no TR group (P<0.05). Elevated E/e' (≥14) was more commonly observed in proportion to TR severity. Logistic regression analysis showed that female sex, non-paroxysmal AF, age, left atrial diameter, and serum hemoglobin level were independently associated with the presence of significant TR (Table S2).

Relationship Between TR and HF Admission

During the follow-up period (median, 730 days [interquartile range, 366–731 days]), 44 patients (2.0%) experienced HF hospitalization. The rate of hospitalization increased proportionally with the severity of TR (1.0%, 2.2%, 5.7% and 23.1% for the absent, mild, moderate and severe groups respectively, P<0.001; Figure. 2). After adjustment for known confounders and variables related to pulmonary hypertension, patients with moderate or severe TR were more likely to be hospitalized for HF during the follow-up (Tables 2 and 3). However, TR severity was not associated with other events, such as stroke, major bleeding, and all-cause death (Table 2). Even in the model including brain natriuretic peptide as an adjusted variable, TR remained an associated predictor of HF admission (Table S3). In patients with subsequent HF, LVEF <40% was more commonly observed compared with patients without HF admission (9.3% versus 1.2%, P<0.001; Table S4). However, more patients with HF tended to take β-blockers than patients without HF (77.3% versus 48.8%, P<0.001), and have increased heart rate of >110 beats per minute at baseline (15.9% versus 4.3%, P<0.001). After enrollment, significantly more patients with HF needed pacemaker implantation (4.5% versus 0.5%, P=0.001). In patients admitted with HF, 9 patients (2 paroxysmal AF; 7 non-paroxysmal AF) received catheter ablation procedure after enrollment. Out of these, 3 patients underwent catheter ablation after an HF event. In the subgroup analysis stratified by catheter ablation after enrollment, severe TR was still associated with HF admission (hazard ratio=6.67, P=0.007) only in patients

Table 1. **Baseline Characteristics**

	Missing value, % (n)	No TR (n=1104)	Mild TR (n=935)	Moderate TR (n=159)	Severe TR (n=13)	P value
Age, y	0.0 (0)	64.2±11.6	68.7±10.3	73.8±8.5	76.1±7.9	<0.001
Female sex, % (n)	0.0 (0)	21.3 (235)	37.9 (354)	44.7 (71)	76.9 (10)	<0.001
Type of AF	1.49 (33)					
First detected, % (n)		6.6 (72)	5.9 (55)	4.6 (7)	0.0 (0)	
Paroxysmal AF, % (n)		61.8 (672)	48.4 (448)	31.4 (48)	30.8 (4)	
Non-paroxysmal AF, % (n)		31.6 (343)	45.6 (422)	64.1 (98)	69.2 (9)	<0.001
CHADS2 score	0.05 (1)	1.1±1.0	1.2±1.1	1.3±1.0	2.0±1.3	<0.001
CHA_2DS_2-VASc score	0.05 (1)	1.9±1.5	2.3±1.5	2.8±1.3	3.9±1.5	<0.001
Heart rate at rest, beats per minute	1.67 (37)	76.8±16.2	79.0±17.6	82.3±18.8	88.3±22.8	<0.001
Creatinine, mg/dL	5.02 (111)	0.9±0.5	0.9±0.8	1.0±1.3	0.9±0.3	0.376
Brain natriuretic peptide, pg/mL	27.4 (605)	95.1±121.9	136.0±145.1	204.0±134.6	403.9±302.0	<0.001
Left atrium size, cm	1.58 (35)	4.0±0.7	4.1±0.8	4.4±0.7	4.7±1.0	<0.001
LVEF, %	3.93 (87)	59.1±5.4	59.2±5.4	59.2±6.5	55.2±13.7	0.093
LVEF≥40	3.93 (87)	98.7 (1037)	98.8 (897)	98.0 (149)	84.6 (11)	<0.001
E/e'	22.3 (492)	9.6±4.4	10.5±4.2	12.6±5.7	13.9±4.1	<0.001
E/e' ≥ 14, % (n)	22.3 (492)	11.1 (99)	16.7 (119)	35.1 (39)	62.5 (5)	<0.001
Comorbidities						
Prior mitral valve surgery, % (n)	0.0 (0)	0.1 (1)	0.5 (5)	0.0 (0)	0.0 (0)	0.241
Left side VHD, % (n)	0.0 (0)	5.3 (58)	9.2 (86)	36.5 (58)	46.2 (6)	<0.001
Aortic stenosis ≥ moderate, % (n)	0.05 (1)	0.3 (3)	0.4 (4)	0.6 (1)	0.0 (0)	0.867
Aortic regurgitation ≥ moderate, % (n)	0.0 (0)	2.1 (23)	2.8 (26)	6.9 (11)	7.7 (1)	0.004
Mitral stenosis ≥ moderate, % (n)	0.05 (1)	0.0 (0)	0.2 (2)	1.3 (2)	0.0 (0)	0.006
Mitral regurgitation ≥ moderate, % (n)	0.0 (0)	3.1 (34)	6.3 (59)	31.4 (50)	46.2 (6)	<0.001
Congenital heart disease, % (n)	0.05 (1)	1.0 (11)	2.6 (24)	5.7 (9)	0.0 (0)	<0.001
Hypertension, % (n)	0.0 (0)	54.9 (606)	56.3 (526)	56.6 (90)	61.5 (8)	0.888
Diabetes, % (n)	0.05 (1)	17.3 (191)	12.5 (117)	9.4 (15)	15.4 (2)	0.005
COPD, % (n)	0.05 (1)	2.3 (25)	2.1 (20)	2.5 (4)	0.0 (0)	0.941
Thyroid disease, % (n)	0.05 (1)	1.9 (21)	2.5 (23)	1.9 (3)	0.0 (0)	0.777
Pacemaker implantation,% (n)	0.0 (0)	0.3 (3)	0.5 (5)	0.6 (1)	0.0 (0)	0.772
Therapeutic strategy						
Rhythm control strategy, % (n)	0.14 (3)	63.6 (702)	62.6 (584)	38.4 (61)	15.4 (2)	<0.001
Diuretics use, % (n)	0.0 (0)	8.2 (90)	9.2 (86)	18.9 (30)	53.8 (7)	<0.001
Antiarrhythmic drug use, % (n)	0.0 (0)	26.9 (297)	19.7 (184)	12.6 (20)	0.0 (0)	<0.001
Prior ablation history, % (n)	0.0 (0)	7.8 (86)	6.8 (64)	1.9 (3)	0.0 (0)	0.036
Ablation within 1-y after enrollment	0.05 (1)	45.0 (496)	46.7 (437)	23.3 (37)	0.0 (0)	<0.001

Values are expressed as the mean±SD or % (n). AF indicates atrial fibrillation; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; TR, tricuspid regurgitation; and VHD, valvular heart disease.

who did not undergo catheter ablation (Table S5). In the subgroup analysis stratified by left atrial enlargement (eg, left atrial diameter <45 mm or ≥45 mm), TR was associated with HF admission in patients with left atrial diameter <45 mm (hazard ratio [HR], 4.30; P=0.040 for moderate TR versus no TR and hazard ratio, 26.89; P<0.001 for severe TR versus no TR) (Table S6). In the subgroup analysis stratified by heart rate at rest, the incidence of HF events occurred in proportion to TR severity. Only severe TR was significantly associated with subsequent HF admission in the increased heart rate group (Table S7 and S8).

In terms of subsequent hospitalization for HF, no interaction was observed between TR severity and left atrial diameter, heart rate at rest, and performance of catheter ablation within 1 year after enrollment (P for interaction=0.170, 0.651, 0.140, respectively).

Quality of Life at Baseline and After 1-Year Follow-Up

Patients with greater TR tended to have dyspnea (8.1% versus 12.0% versus 15.1% versus 23.1%, for the no, mild, moderate, and severe TR groups, respectively,
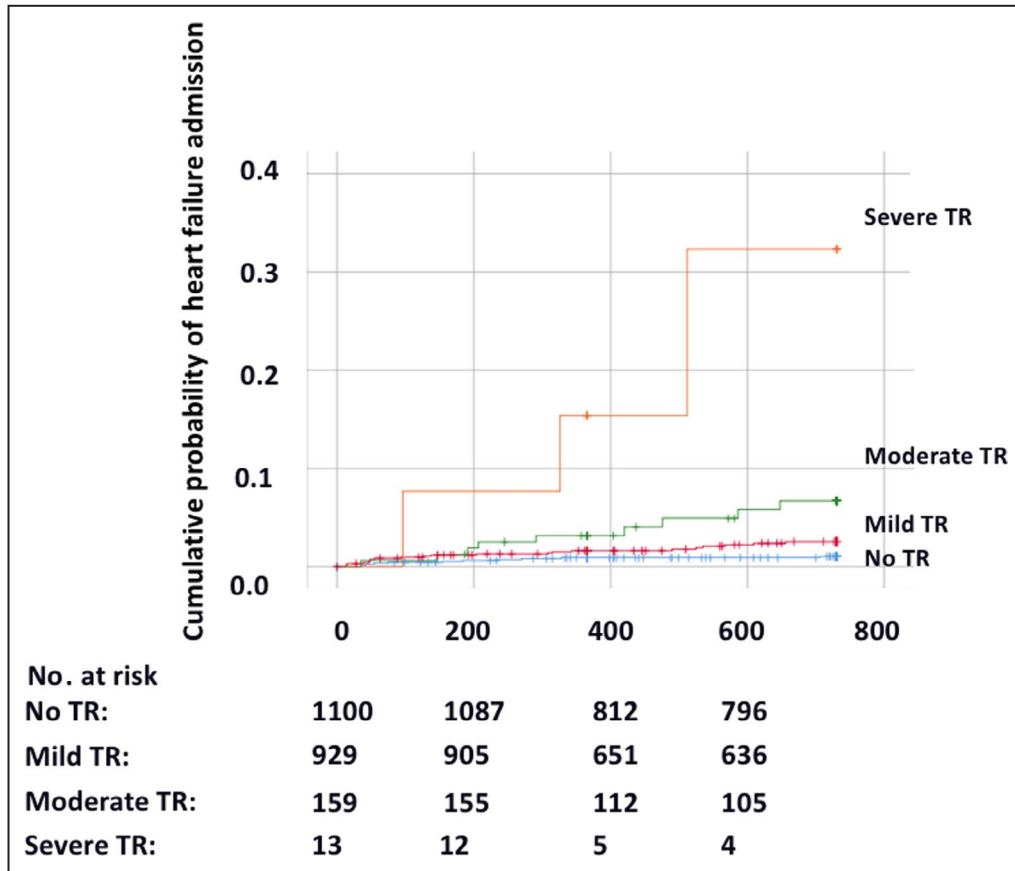
Figure 2. Kaplan−Meier curves showing heart failure admission by tricuspid regurgitation grade.
Kaplan–Meier curves for heart failure admission rates over the 2 years after enrollment. Heart failure admission increased significantly according to the tricuspid regurgitation grade. TR indicates tricuspid regurgitation.

P=0.002), whereas they tended to be asymptomatic (42.3% versus 40.9% versus 55.3% versus 61.5%, for the no, mild, moderate, and severe TR groups, respectively, P=0.003). The characteristics of the patients without AFEQT data at the 1-year follow-up were largely comparable with those in the analytic cohort (Table S9). The baseline AFEQT overall summary score, subscale scores for symptoms and daily activities, and changes during the 1-year follow-up period across the TR severity groups are summarized in Figure 3. At baseline, there were no significant differences among the groups in the AFEQT overall summary score and the scores for the symptoms and daily activities domains. However, the change in the AFEQT overall score was significantly lower in proportion to TR severity (Figure 3). As for the sensitivity analysis, when patients were stratified by the performance of catheter ablation procedures during the follow-up period, there were no significant intergroup differences in the overall and domain AFEQT scores during the 1-year follow-up period (Figure S1).
The severity of TR was significantly associated with a lower baseline AFEQT score for symptom domains in the univariate analysis; it was not associated with the

overall summary score and the daily activity domain score. However, after adjusting for differences in the patients' backgrounds, the trends were not obvious (Table S10).

DISCUSSION

The interaction between AF and HF is an important issue, and it is necessary to elucidate their relationship. TR was shown to be associated with higher mortality in patients with coexisting HF.[14] In our study, TR had a negative effect, even in patients with newly diagnosed AF without previous HF. Patients with higher grade of TR showed a higher rate of dyspnea at baseline, whereas the TR grade was not associated with the AFEQT score both at baseline and during the 1-year follow-up. Moreover, TR was an associated predictor of admission for HF after adjusting for significant clinical variables.

Relationship Between TR and HF

In our study, TR was an associated predictor of hospitalization for HF after enrollment. To date, the clinical

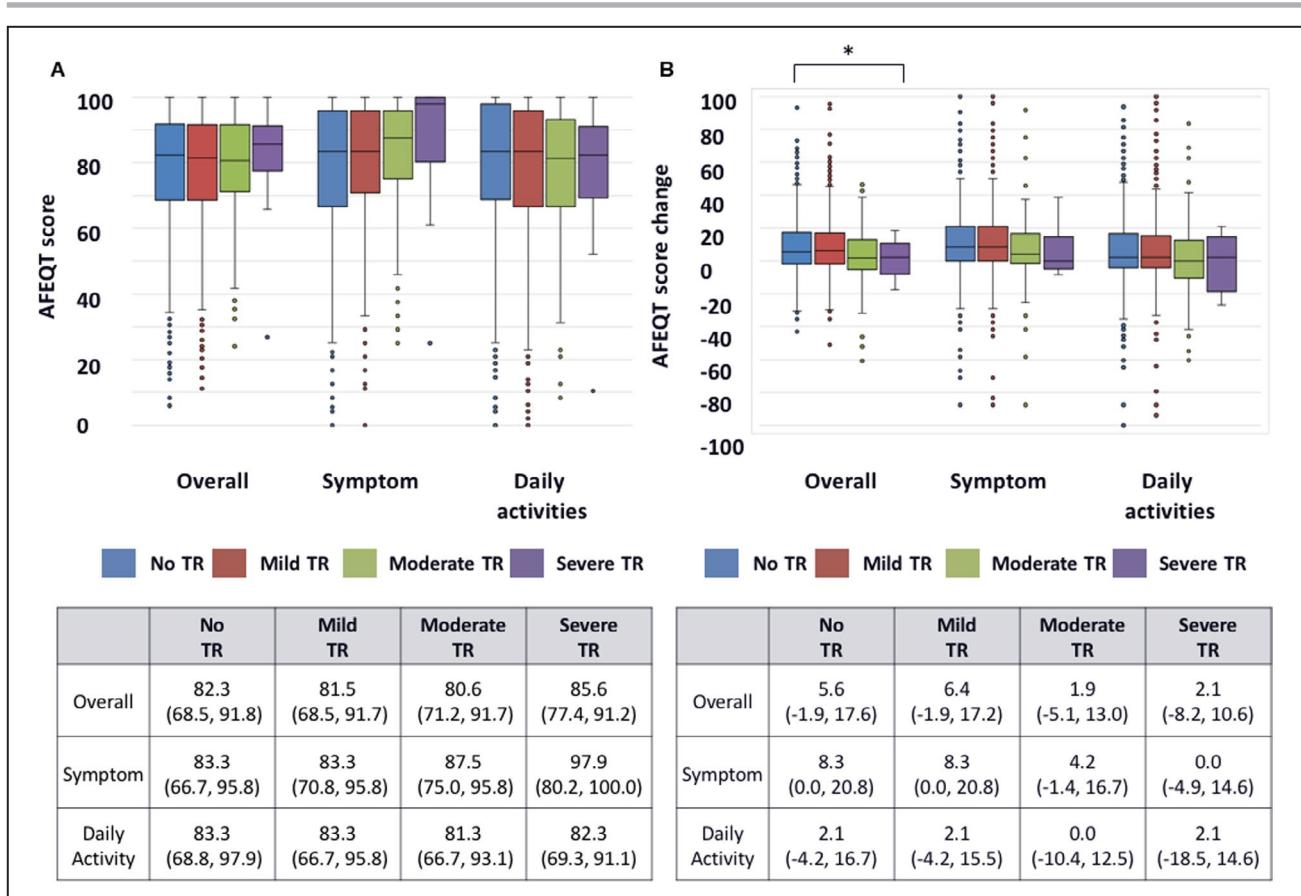**Table 2. Multivariable Analysis for the Influence of TR on Adverse Outcomes**

Outcome	No TR	Mild TR HR (95% CI)	P value	Moderate TR HR (95% CI)	P value	Severe TR HR (95% CI)	P value
HF hospitalization							
Unadjusted	Reference	2.31 (1.11–4.79)	0.025	5.82 (2.41–14.04)	<0.001	28.20 (7.85–101.38)	<0.001
Adjusted by model 1	Reference	1.52 (0.72–3.19)	0.269	2.51 (1.00–6.28)	0.050	6.19 (1.61–23.76)	0.008
Adjusted by model 2	Reference	1.92 (0.91–4.04)	0.087	3.88 (1.49–10.10)	0.005	10.78 (2.70–43.02)	0.001
Composite outcome							
Unadjusted	Reference	1.92 (1.30–2.85)	0.001	3.34 (1.94–5.76)	<0.001	7.89 (2.44–25.52)	0.001
Adjusted	Reference	1.39 (0.80–2.43)	0.241	1.58 (0.71–3.52)	0.261	1.47 (0.30–7.20)	0.634
All-cause death							
Unadjusted	Reference	1.30 (0.61–2.77)	0.494	1.62 (0.46–5.67)	0.454	N/A (N/A–N/A)	N/A
Adjusted	Reference	0.92 (0.43–1.96)	0.821	0.71 (0.20–2.55)	0.596	N/A (N/A–N/A)	N/A
Stroke							
Unadjusted	Reference	1.55 (0.58–4.15)	0.387	1.99 (0.41–9.57)	0.392	N/A (N/A–N/A)	N/A
Adjusted	Reference	1.28 (0.47–3.47)	0.634	1.30 (0.26–6.53)	0.746	N/A (N/A–N/A)	N/A
Major bleeding							
Unadjusted	Reference	2.45 (1.29–4.65)	0.006	2.52 (0.91–7.01)	0.076	N/A (N/A–N/A)	N/A
Adjusted	Reference	1.86 (0.78–4.41)	0.161	1.67 (0.42–6.63)	0.464	N/A (N/A–N/A)	N/A

HF indicates heart failure; HR, hazard ratio; and TR, tricuspid regurgitation. The multivariable model 1 was adjusted by clinically relevant variables (age, left ventricular ejection fraction, left-sided valvular heart disease, CHA$_2$DS$_2$-VASc score). The model 2 was adjusted by pulmonary hypertension related variables (left ventricular ejection fraction, left sided valvular heart disease, congenital heart disease, chronic obstructive pulmonary disease, left atrial diameter). Composite outcomes were adjusted for age, diabetes status, aortic stenosis, aortic regurgitation, mitral regurgitation, hypertension, coronary artery disease, left ventricular ejection fraction, and creatinine, brain natriuretic peptide, aspartate transaminase, and hemoglobin levels. Death was adjusted for age and diabetes status. Stroke events were adjusted for age. Major bleeding was adjusted for age, diabetes status, brain natriuretic peptide level, and aspirin use.

Table 3. Multivariable Analysis for the Influence of TR on Adverse Outcomes Admission With Imputed Data

Outcome	No TR	Mild TR HR (95% CI)	P value	Moderate TR HR (95% CI)	P value	Severe TR HR (95% CI)	P value
HF hospitalization							
Unadjusted	Reference	2.31 (1.11–4.79)	0.025	5.82 (2.41–14.04)	<0.001	28.20 (7.85–101.38)	<0.001
Adjusted by model 1	Reference	1.63 (0.78–3.39)	0.194	2.57 (1.03–6.43)	0.043	6.46 (1.67–24.95)	0.007
Adjusted by model 2	Reference	2.06 (0.99–4.32)	0.055	3.91 (1.50–10.16)	0.005	11.3 (2.82–45.20)	0.001
Composite outcome							
Unadjusted	Reference	1.92 (1.30–2.85)	0.001	3.34 (1.94–5.76)	<0.001	7.89 (2.44–25.52)	0.001
Adjusted	Reference	1.31 (0.76–2.24)	0.330	1.46 (0.66–3.20)	0.349	1.34 (0.27–6.56)	0.722
All-cause death							
Unadjusted	Reference	1.30 (0.61–2.77)	0.494	1.62 (0.46–5.67)	0.454	N/A (N/A–N/A)	N/A
Adjusted	Reference	0.92 (0.43–1.96)	0.821	0.71 (0.20–2.55)	0.596	N/A (N/A–N/A)	N/A
Stroke							
Unadjusted	Reference	1.55 (0.58–4.15)	0.387	1.99 (0.41–9.57)	0.392	N/A (N/A–N/A)	N/A
Adjusted	Reference	1.28 (0.47–3.47)	0.634	1.30 (0.26–6.53)	0.746	N/A (N/A–N/A)	N/A
Major bleeding							
Unadjusted	Reference	2.45 (1.29–4.65)	0.006	2.52 (0.91–7.01)	0.076	N/A (N/A–N/A)	N/A
Adjusted	Reference	1.86 (0.78–4.41)	0.161	1.67 (0.42–6.63)	0.464	N/A (N/A–N/A)	N/A

HF indicates heart failure; HR, hazard ratio; and TR, tricuspid regurgitation. To account for missing data, we performed single mean imputation for left ventricular ejection fraction and serum creatinine level. The multivariable model 1 was adjusted by clinically relevant variables (age, left ventricular ejection fraction, left-sided valvular heart disease, CHA$_2$DS$_2$-VASc score). The model 2 was adjusted by pulmonary hypertension related variables (left ventricular ejection fraction, left sided valvular heart disease, congenital heart disease, chronic obstructive pulmonary disease, left atrial diameter). Composite outcomes were adjusted for age, diabetes status, aortic stenosis, aortic regurgitation, mitral regurgitation, hypertension, coronary artery disease, left ventricular ejection fraction, and creatinine, brain natriuretic peptide, aspartate transaminase, and hemoglobin levels. Death was adjusted for age and diabetes status. Stroke events were adjusted for age. Major bleeding was adjusted for age, diabetes status, brain natriuretic peptide level, and aspirin use.

Figure 3. **Atrial Fibrillation Effects on Quality-of-Life score at baseline and score changes after 1 year of treatment.**
A, Atrial Fibrillation Effects on Quality-of-Life score at baseline. **B**, Atrial Fibrillation Effects on Quality-of-Life score change after 1 year of treatment. The thick line in the middle is the median. Asterisk indicates a statistically significant difference ($P<0.05$) among the groups. The top and bottom box lines show the first and third quartiles. The whiskers show the maximum and minimum values, with the exceptions of outliers (circles) which are at least 1.5 box length from the median. Data are presented as median (interquartile range). AFEQT indicates Atrial Fibrillation Effects on Quality-of-Life; and TR, tricuspid regurgitation.

influence of TR has been evaluated mainly in patients with HF and is reportedly influenced by LVEF and pulmonary hypertension, depending on the study[8,18]; the prognostic impact of TR in patients without HF or left ventricular dysfunction has been scarcely investigated. Although AF is a leading cause of TR,[9] the association between the clinical end point and AF-induced TR without HF remains largely unknown. According to our study's findings, we speculate that TR may be a sensitive surrogate marker of HF in patients with AF or that TR itself can serve as a causal factor of HF admission through volume overload in the right ventricle. As a surrogate marker, TR is known to be associated with the severity of left-sided HF, pulmonary hypertension, and right ventricular function deterioration in patients with HF with preserved EF.[19,20] In our study, we could not show an independent association between severe TR and subsequent HF events in the multivariable model adjusted for brain natriuretic peptide, nor in patients with left atrial diameter ≥45 mm. This may indicate that TR works as a surrogate marker of early phase

left-sided HF without progressive atrial remodeling and advanced HF. In right-sided HF, TR may cause HF through TR-induced volume overload in the right ventricle, leading to right ventricular dysfunction and interventricular interaction.

Association Between TR and QOL

As for patients' QOL, significant TR in patients with post-mitral valve surgery and HF with reduced LVEF is reported to be associated with impaired symptoms.[13,21] Although the relationship between right-sided HF symptoms such as edema and TR in patients with HFrEF has been reported,[13] no study has evaluated this relationship using a quantitative QOL measurement tool. Moreover, the QOL of patients with AF with regard to TR has not been reported. In our study, there were no significant differences in baseline AFEQT scores among the different TR grades; however, patients with TR still showed a higher rate of dyspnea. Patients with severe TR and preserved LVEF were

reported to have lower peak VO$_2$ and higher pulmonary capillary wedge pressure during exercise, which might explain the higher rate of dyspnea in our cohort.[21] On the other hand, the higher rate of persistent AF and asymptomatic patients in the significant TR group might account for the higher AFEQT score. A previous study reported that TR severity did not change or worsen during rate control therapy in patients with AF and TR, although it improved heart rate and HF symptoms. The result was compatible with our findings showing a non-significant impact of TR on patients' QOL.[22] The higher rate of catheter ablation in the non-TR group would explain the improved QOL in the non-TR group compared with the significant TR group since catheter ablation can improve patients' QOL better than conservative treatment.[17] From the sensitivity analysis according to catheter ablation performance, there were no significant differences among the groups, suggesting the higher rate of catheter ablation explains the improved AFEQT score change in the non-TR group compared with the significant TR group.

Treatment of TR in Patients With AF

Conservative treatment is recommended in the current guidelines for severe isolated secondary TR without severe ventricular dysfunction or pulmonary hypertension.[23] Recently, rhythm control strategies, including catheter ablation, have been proposed to promote reverse atrial remodeling and decrease TR severity.[24,25] In our subgroup analysis stratified by catheter ablation, TR was not associated with HF admission in patients who underwent catheter ablation after enrollment. Although patients who underwent catheter ablation tended to be younger and had fewer coexisting diseases, it is possible that a sinus restoration strategy could induce reverse remodeling of the right atrium and lessen TR severity, leading to less subsequent HF admission. Certainly, catheter ablation could reduce the occurrence of subsequent HF admission, irrespective of TR, according to the CASTLE-AF Trial.[26] Further detailed studies are needed to determine the influence of sinus restoration and TR improvement on the occurrence of subsequent HF events.

Study Limitations

Our study's limitations should be acknowledged for a thorough understanding of the results. First, non-randomized observational research has inherent limitations, although it is the best approach to describe the current treatment patterns and outcomes of care. There are likely to be unmeasured confounders, such as depression or frailty, that may explain some of the observed differences in QOL between the TR and non-TR groups. Second, the method of grading TR might differ among the hospitals, and we could not assess

quantitative data about the severity of TR and right ventricular dysfunction, such as the TR pressure gradient, pulmonary artery systolic pressure, right atrial diameter, tricuspid annulus diameter, and right ventricular diameter. Although pulmonary hypertension and right ventricular dysfunction were reported to be associated with the influence of TR,[12,27,28] we could not obtain the relevant data in this study. Moreover, although we adjusted for the confounding factor related to pulmonary hypertension, we could not adjust for the confounding effects of idiopathic pulmonary hypertension. Third, we did not have data on the detailed information of HF events including the rhythm at admission and could not separate HF admissions between left-sided and right-sided HF. Fourth, in the assessments of TR's pathogenicity, reduced LVEF had a substantial influence. However, our registry included only a small number of patients with LVEF <40% (1.4% [n=30 /2124]), and we could not perform subgroup analysis for the degree of LVEF. Fifth, although TR improvement during the follow-up period is of concern, we did not have information about the change of TR. Sixth, the rhythm information at follow-up was obtained from medical record within 3 months from the date of annual follow-up. Therefore, the rhythm at the time of the HF event and the exact recurrence rate of AF following catheter ablation were unknown. Finally, since our registry enrolled only patients in Japan who were treated in large tertiary care referral centers, the possibility of an effect of selection bias on our measured outcomes cannot be denied.

CONCLUSIONS

TR severity at AF diagnosis was an associated predictor of subsequent hospitalization for HF, which warrants the need for a more intensive follow-up and management aiming towards prevention of HF progression.

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Supplemental Material

Tables S1–S10
Figure S1

REFERENCES

1. Santhanakrishnan R, Wang NA, Larson MG, Magnani JW, McManus DD, Lubitz SA, Ellinor PT, Cheng S, Vasan RS, Lee DS, et al. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. *Circulation*. 2016;133:484–492. doi: 10.1161/CIRCULATIONAHA.115.018614

2. Marijon E, Le Heuzey J-Y, Connolly S, Yang S, Pogue J, Brueckmann M, Eikelboom J, Themeles E, Ezekowitz M, Wallentin L, et al. Causes of death and influencing factors in patients with atrial fibrillation: a competing-risk analysis from the randomized evaluation of long-term anticoagulant therapy study. *Circulation*. 2013;128:2192–2201. doi: 10.1161/CIRCULATIONAHA.112.000491

3. Gomez-Outes A, Lagunar-Ruiz J, Terleira-Fernandez AI, Calvo-Rojas G, Suarez-Gea ML, Vargas-Castrillon E. Causes of death in anticoagulated patients with atrial fibrillation. *J Am Coll Cardiol*. 2016;68:2508–2521. doi: 10.1016/j.jacc.2016.09.944

4. Pandey A, Kim S, Moore C, Thomas L, Gersh B, Allen LA, Kowey PR, Mahaffey KW, Hylek E, Peterson ED, et al. Predictors and prognostic implications of incident heart failure in patients with prevalent atrial fibrillation. *JACC Heart Fail*. 2017;5:44–52. doi: 10.1016/j.jchf.2016.09.016

5. Al-Khatib SM, Benjamin EJ, Albert CM, Alonso A, Chauhan C, Chen P-S, Curtis AB, Desvigne-Nickens P, Ho JE, Lam CSP, et al. Advancing research on the complex interrelations between atrial fibrillation and heart failure: a report from a US national heart, lung, and blood institute virtual workshop. *Circulation*. 2020;141:1915–1926. doi: 10.1161/CIRCULATIONAHA.119.045204

6. Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CSP, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J*. 2019;40:3297–3317. doi: 10.1093/eurheartj/ehz641

7. Zile MR, Bennett TD, St. John Sutton M, Cho YK, Adamson PB, Aaron MF, Aranda JM, Abraham WT, Smart FW, Stevenson LW, et al. Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights obtained from continuous monitoring of intracardiac pressures. *Circulation*. 2008;118:1433–1441. doi: 10.1161/CIRCULATIONAHA.108.783910

8. Santas E, Chorro FJ, Miñana G, Méndez J, Muñoz J, Escribano D, García-Blas S, Valero E, Bodí V, Núñez E, et al. Tricuspid regurgitation and mortality risk across left ventricular systolic function in acute heart failure. *Circ J*. 2015;79:1526–1533. doi: 10.1253/circj.CJ-15-0129

9. Ortiz-Leon XA, Posada-Martinez EL, Trejo-Paredes MC, Ivey-Miranda JB, Pereira J, Crandall I, DaSilva P, Bouman E, Brooks A, Gerardi C, et al. Understanding tricuspid valve remodelling in atrial fibrillation using three-dimensional echocardiography. *Eur Heart J Cardiovasc Imaging*. 2020;21:747–755. doi: 10.1093/ehjci/jeaa058

10. Ikemura N, Kohsaka S, Kimura T, Ueda I, Katsumata Y, Nishiyama T, Aizawa Y, Tanimoto K, Momiyama Y, Akaishi M, et al. Assessment of sex differences in the initial symptom burden, applied treatment strategy, and quality of life in Japanese patients with atrial fibrillation. *JAMA Netw Open*. 2019;2:e191145. doi: 10.1001/jamanetworkopen.2019.1145

11. Ikemura N, Spertus JA, Kimura T, Mahaffey K, Piccini JP, Inohara T, Ueda I, Tanimoto K, Suzuki M, Nakamura I, et al. Cohort profile: patient characteristics and quality-of-life measurements for newly-referred patients with atrial fibrillation-Keio interhospital cardiovascular studies-atrial fibrillation (KICS-AF). *BMJ Open*. 2019;9:e032746. doi: 10.1136/bmjopen-2019-032746

12. Mutlak D, Lessick J, Khalil S, Yalonetsky S, Agmon Y, Aronson D. Tricuspid regurgitation in acute heart failure: is there any incremental risk? *Eur Heart J Cardiovasc Imaging*. 2018;19:993–1001. doi: 10.1093/ehjci/jex343

13. Benfari G, Antoine C, Miller WL, Thapa P, Topilsky Y, Rossi A, Michelena HI, Pislaru S, Enriquez-Sarano M. Excess mortality associated with functional tricuspid regurgitation complicating heart failure with reduced ejection fraction. *Circulation*. 2019;140:196–206. doi: 10.1161/CIRCULATIONAHA.118.038946

14. Tsutsui H, Isobe M, Ito H, Ito H, Okumura K, Ono M, Kitakaze M, Kinugawa K, Kihara Y, Goto Y, et al. JCS 2017/JHFS 2017 guideline on diagnosis and treatment of acute and chronic heart failure - digest version. *Circ J*. 2019;83:2084–2184. doi: 10.1253/circj.CJ-19-0342

15. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr*. 2003;16:777–802. doi: 10.1016/S0894-7317(03)00335-3

16. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. *J Thromb Haemost*. 2015;13:2119–2126. doi: 10.1111/jth.13140

17. Spertus J, Dorian P, Bubien R, Lewis S, Godejohn D, Reynolds MR, Lakkireddy DR, Wimmer AP, Bhandari A, Burk C. Development and validation of the atrial fibrillation effect on quality-of-life (AFEQT) questionnaire in patients with atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2011;4:15–25. doi: 10.1161/CIRCEP.110.958033

18. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. *J Am Coll Cardiol*. 2004;43:405–409. doi: 10.1016/j.jacc.2003.09.036

19. Mascherbauer J, Kammerlander AA, Zotter-Tufaro C, Aschauer S, Duca F, Dalos D, Winkler S, Schneider M, Bergler-Klein J, Bonderman D. Presence of isolated tricuspid regurgitation should prompt the suspicion of heart failure with preserved ejection fraction. *PLoS One*. 2017;12:e0171542. doi: 10.1371/journal.pone.0171542

20. Obokata M, Reddy YNV, Melenovsky V, Pislaru S, Borlaug BA. Deterioration in right ventricular structure and function over time in patients with heart failure and preserved ejection fraction. *Eur Heart J*. 2019;40:689–697. doi: 10.1093/eurheartj/ehy809

21. Andersen MJ, Nishimura RA, Borlaug BA. The hemodynamic basis of exercise intolerance in tricuspid regurgitation. *Circ Heart Fail*. 2014;7:911–917. doi: 10.1161/CIRCHEARTFAILURE.114.001575

22. Kusaka K, Takahashi T, Kotajima N, Sekiguchi K, Fukumura Y, Murakami M, Kanda T. Congestive heart failure induced by the combination of atrial fibrillation and tricuspid regurgitation. *J Int Med Res*. 2003;31:475–480. doi: 10.1177/147323000303100602

23. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38:2739–2791. doi: 10.1093/eurheartj/ehx391

24. Itakura K, Hidaka T, Nakano Y, Utsunomiya H, Kinoshita M, Susawa H, Harada Y, Izumi K, Kihara Y. Successful catheter ablation of persistent atrial fibrillation is associated with improvement in functional tricuspid regurgitation and right heart reverse remodeling. *Heart Vessels*. 2020;35:842–851. doi: 10.1007/s00380-019-01546-3

25. Fender EA, Zack CJ, Nishimura RA. Isolated tricuspid regurgitation: outcomes and therapeutic interventions. *Heart*. 2018;104:798–806. doi: 10.1136/heartjnl-2017-311586

26. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J, et al. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med*. 2018;378:417–427. doi: 10.1056/NEJMoa1707855

27. Mohammed SF, Hussain I, AbouEzzeddine OF, Takahama H, Kwon SH, Forfia P, Roger VL, Redfield MM. Right ventricular function in heart failure with preserved ejection fraction: a community-based study. *Circulation*. 2014;130:2310–2320. doi: 10.1161/CIRCULATIONAHA.113.008461

28. Topilsky Y, Nkomo VT, Vatury O, Michelena HI, Letourneau T, Suri RM, Pislaru S, Park S, Mahoney DW, Biner S, et al. Clinical outcome of isolated tricuspid regurgitation. *JACC Cardiovasc Imaging*. 2014;7:1185–1194. doi: 10.1016/j.jcmg.2014.07.018

Supplemental Material

Table S1. Comparison between TR-grade missing and non-missing group.

	missing (n =325)	non-missing (n = 2211)	P value
Age, years	67.4±12.3	66.9±11.2	0.502
Female sex, % (n)	29.8 (97)	30.3 (670)	0.867
Type of AF			
first detected, % (n)	9.1 (29)	6.2 (134)	
paroxysmal, % (n)	60.6 (194)	53.8 (1172)	
non-paroxysmal, % (n)	30.3 (97)	40.0 (872)	0.002
CHADS2 score	1.2±1.1	1.1±1.1	0.335
CHA_2DS_2-VASc score	2.3±1.6	2.2±1.5	0.135
Heart rate at rest, bpm	75.6±16.4	78.2±17.1	0.013
Creatinine, mg/dL	0.9±0.4	0.9±0.7	0.403
Brain natriuretic peptide, pg/mL	103.1±112.4	121.9±139.8	0.068
Left atrium size, cm	4.7	4.1±0.7	0.370
Left ventricular ejection fraction, %	45.0	59.1±5.6	0.012
E/e'	N/A	10.2±4.5	N/A
Comorbidities			
prior mitral valve surgery, % (n)	0.6 (2)	0.3 (6)	0.302
significant MR, % (n)	0.0 (0)	6.7 (149)	0.788
left side VHD, % (n)	0.0 (0)	9.4 (208)	0.747
Hypertension, % (n)	56.9 (185)	55.6 (1230)	0.661
Diabetes mellitus, % (n)	16.3 (53)	14.7 (325)	0.449
COPD, % (n)	1.8 (6)	2.2 (49)	0.668
Thyroid disease, % (n)	1.2 (4)	2.1 (47)	0.286
Pacemaker Implantation,% (n)	0.9 (3)	0.4 (9)	0.206

Values are expressed as the mean ± standard deviation or % (n).

AF = atrial fibrillation, MR = mitral regurgitation, VHD = valvular heart disease, COPD = chronic

obstructive pulmonary disease.

Table S2. Logistic regression analysis for the predictor of significant TR.

	Univariate		Multivariable	
	OR (95% CI)	P value	OR (95% CI)	P value
Female sex	2.19 (1.60 - 3.00)	<0.001	1.58 (1.08 – 2.33)	0.020
Mitral valve surgery	N/A	0.999		
Hypertension	1.06 (0.78 - 1.45)	0.711		
Diabetes	0.62 (0.37 - 1.03)	0.065		
COPD	1.05 (0.38 - 2.97)	0.920		
Thyroid disease	0.80 (0.25 - 2.62)	0.718		
Pacemaker implantation	1.49 (0.19 - 11.94)	0.710		
Non-paroxysmal AF (vs. paroxysmal AF)	3.01 (2.14 – 4.25)	<0.001	2.77 (1.87 – 4.12)	<0.001
Age (per 1year increase)	1.08 (1.06 - 1.10)	<0.001	1.06 (1.04 – 1.09)	<0.001
CAD	1.69 (1.03 - 2.78)	0.037		
LVEF (per 1% increase)	0.99 (0.97 – 1.02)	0.625		
Left atrial diameter (per 1cm increase)	1.96 (1.59 - 2.42)	<0.001	1.53 (1.19 – 1.97)	0.001
Hb (per 1g/dl increase)	0.76 (0.70 - 0.84)	<0.001	0.85 (0.76 – 0.96)	0.006
Creatinine (per 1 mg/dl increase)	1.13 (0.97 – 1.32)	0.130		

OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; CAD, coronary artery disease; LVEF, left ventricular ejection fraction.

Table S3. Multivariable analysis for the influence of TR on heart failure admission including brain natriuretic peptide as an adjusted variable.

	Multivariable model 1		Multivariable model 2	
	HR (95% CI)	P value	HR (95% CI)	P value
No TR	Reference		Reference	
Mild TR	1.32 (0.52 – 3.36)	0.563	1.46 (0.56 – 3.81)	0.446
Moderate TR	3.46 (1.15 – 10.44)	0.028	4.21 (1.37 – 12.95)	0.012
Severe TR	2.82 (0.43 – 18.77)	0.283	3.56 (0.52 – 24.62)	0.198

Multivariable Cox proportional hazard models for the influence of different degrees of TR on heart failure admission at the 2-year follow-up. The multivariable model 1 was adjusted by clinically relevant variables (age, left ventricular ejection fraction, left-sided valvular heart disease, CHA_2DS_2-VASc score) and brain natriuretic peptide level. The model 2 was adjusted by pulmonary hypertension related variables (left ventricular ejection fraction, left sided valvular heart disease, congenital heart disease, chronic obstructive pulmonary disease, left atrial diameter) and brain natriuretic peptide level. HR, hazard ratio; CI, confidence interval; TR, tricuspid regurgitation.

Table S4. the characteristics of patients with and without heart failure.

	non-HF (n=2167)	HF (n=44)	P value
Age, years	66.7 ± 11.2	77.3 ± 9.6	<0.001
AF type			
first detected, % (n)	6.1 (131)	7.0 (3)	
paroxysmal, % (n)	54.2 (1158)	32.6 (14)	
non-paroxysmal, % (n)	39.6 (846)	60.5 (26)	0.016
Left atrium diameter, cm	4.0 ± 0.7	4.5 ± 0.9	<0.001
Ablation within 1year after enrollment, % (n)	44.5 (963)	15.9 (7)	<0.001
AAD use, % (n)	22.9 (497)	9.1 (4)	0.030
LVEF < 40%, % (n)	1.2 (26)	9.3 (4)	< 0.001
tachycardia at rest (≥110 bpm), % (n)	4.3 (91)	15.9 (7)	< 0.001
β blocker use, % (n)	48.8 (1057)	77.3 (34)	<0.001
CAD, % (n)	7.4 (161)	13.6 (6)	0.123
ACS or PCI admission after enrollment, % (n)	1.6 (34)	2.3 (1)	0.711
Bleeding admission after enrollment, % (n)	2.1 (45)	6.8 (3)	0.033
Sick sinus syndrome, % (n)	3.4 (74)	4.5 (2)	0.684
Pacemaker implanted before enrollment, % (n)	0.4 (8)	2.3 (1)	0.050
Pacemaker implantation after enrollment, % (n)	0.5 (11)	4.5 (2)	0.001
Hb, g/dl	14.1±1.6	12.9±2.4	0.002
Total bilirubin	0.8 ± 0.5	0.7 ± 0.3	0.233
AST, IU/L	26.2 ± 14.2	32.8 ± 34.3	0.214
ALT, IU/L	23.8 ± 15.5	27.2 ± 36.2	0.549
Brain natriuretic peptide, pg/mL	117.1 ± 132.3	374.4 ± 251.9	<0.001

HF, heart failure; AF, atrial fibrillation; AAD, antiarrhythmic drug; LVEF, left ventricular ejection fraction; bpm, beats per minute; CAD, coronary artery disease; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table S5. Multivariable analysis for the impact of TR on heart failure admission stratified by catheter ablation after enrollment.

Catheter ablation group	Univariate		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
No TR	Reference		Reference	
Mild TR	1.18 (0.24 – 5.83)	0.843	0.84 (0.16 – 4.42)	0.833
Moderate TR	4.51 (0.47 – 43.39)	0.192	3.95 (0.37 – 42.28)	0.256
Severe TR	N/A	N/A	N/A	N/A
Non-Catheter ablation group	Univariate		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
No TR	Reference		Reference	
Mild TR	2.79 (1.21 - 6.42)	0.016	1.91 (0.82 – 4.47)	0.134
Moderate TR	5.06 (1.90 - 13.48)	0.001	2.71 (0.98 – 7.48)	0.055
Severe TR	20.96 (5.55 - 79.20)	<0.001	6.67 (1.69 – 26.40)	0.007

HR, hazard ratio; CI, confidence interval; TR, tricuspid regurgitation.

Table S6. Multivariable analysis for the impact of TR on heart failure admission stratified by left atrial diameter.

Left atrial diameter < 45 mm	Univariate		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
No TR	Reference		Reference	
Mild TR	4.03 (1.30 – 12.50)	0.016	2.49 (0.78 – 7.89)	0.122
Moderate TR	11.87 (3.19 – 44.20)	<0.001	4.30 (1.07 – 17.27)	0.040
Severe TR	90.58 (16.53 –496.29)	<0.001	26.89 (4.53 – 159.68)	<0.001

Left atrial diameter ≥ 45 mm	Univariate		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
No TR	Reference		Reference	
Mild TR	1.04 (0.38 – 2.88)	0.934	0.82 (0.29 – 2.34)	0.715
Moderate TR	2.09 (0.61 – 7.13)	0.240	1.25 (0.36 – 4.41)	0.727
Severe TR	5.52 (0.68 – 45.03)	0.111	1.39 (0.15 – 13.26)	0.777

HR, hazard ratio; CI, confidence interval; TR, tricuspid regurgitation.

Table S7. the incidence of HF admission stratified by TR severity.

patients with HR ≥ 77 bpm	no TR (n = 515)	mild TR (n = 475)	moderate TR (n = 91)	severe TR (n = 10)	P Value
Heart failure admission, % (n)	1.4 (7)	2.3 (11)	5.5 (5)	30.0 (3)	< 0.001
patients with HR < 77 bpm	no TR (n = 565)	mild TR (n = 450)	moderate TR (n = 65)	severe TR (n = 3)	P Value
Heart failure admission, % (n)	0.7 (4)	2.2 (10)	6.2 (4)	0.0 (0)	0.007

HR, heart rate; bpm, beats per minute; TR, tricuspid regurgitation.

Table S8. **Multivariable analysis for the impact of TR on heart failure admission stratified by heart rate at enrollment.**

patients with heart rate ≥ 77 bpm	Univariate		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
No TR	Reference		Reference	
Mild TR	1.74 (0.68 - 4.50)	0.250	1.05 (0.40 – 2.77)	0.926
Moderate TR	4.13 (1.31 - 13.01)	0.015	1.88 (0.56 – 6.36)	0.311
Severe TR	28.75 (7.37 - 112.14)	<0.001	6.05 (1.34 – 27.30)	0.019
patients with heart rate < 77 bpm	Univariate		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
No TR	Reference			
Mild TR	3.24 (1.02 - 10.32)	0.047	2.25 (0.69 – 7.32)	0.179
Moderate TR	8.90 (2.23 - 35.60)	0.002	3.59 (0.87 – 14.86)	0.078
Severe TR	N/A (N/A – N/A)	N/A	N/A (N/A – N/A)	N/A

HR, hazard ratio; CI, confidence interval; bpm, beats per minute; TR, tricuspid regurgitation.

Table S9. Comparison between AFEQT missing and non-missing group.

	missing (n =238)	non-missing (n = 1973)	P value
Age, years	67.1 ± 13.9	66.9 ± 10.9	0.828
Female sex, % (n)	29.4 (70)	30.4 (600)	0.751
Type of AF			
first detected, % (n)	9.8 (23)	5.7 (111)	
paroxysmal, % (n)	48.9 (115)	54.4 (1057)	
non-paroxysmal, % (n)	41.3 (97)	39.9 (775)	0.031
CHADS2 score	1.1 ± 1.1	1.1 ± 1.0	0.808
CHA_2DS_2-VASc score	2.1 ± 1.6	2.2 ± 1.5	0.854
Heart rate at rest, bpm	78.6 ± 18.1	78.1 ± 17.0	0.673
Creatinine, mg/dL	0.9 ± 0.6	0.9 ± 0.7	0.976
Brain natriuretic peptide, pg/mL	145.1 ± 196.5	119.5 ± 132.4	0.120
Left atrium size, cm	4.0 ± 0.7	4.1 ± 0.7	0.363
Left ventricular ejection fraction, %	58.7 ± 6.8	59.2 ± 5.4	0.343
E/e'	10.8 ± 4.4	10.1 ± 4.5	0.042
E/e' ≥ 14, % (n)	22.9 (40)	14.4 (222)	0.003
Comorbidities			
prior mitral valve surgery, % (n)	0.0 (0)	0.3 (6)	0.394
significant MR, % (n)	9.2 (22)	6.4 (127)	0.103
Hypertension, % (n)	50.0 (119)	56.3 (1111)	0.064
Diabetes mellitus, % (n)	13.9 (33)	14.8 (292)	0.698
COPD, % (n)	3.8 (9)	2.0 (40)	0.080
Thyroid disease, % (n)	2.5 (6)	2.1 (41)	0.647
Pacemaker Implantation,% (n)	0.4 (1)	0.4 (8)	0.973

Values are expressed as the mean ± standard deviation or % (n).

AF = atrial fibrillation, MR = mitral regurgitation, VHD = valvular heart disease, COPD = chronic

obstructive pulmonary disease

Table S10. The linear regression analysis of AFEQT score in daily activity domain and symptom domain at baseline and score change after 1-year of treatment.

Daily activity domain	Univariate		Multivariable	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
Baseline				
Age (per 1year increase)	-0.232 to -0.073	<0.001	-0.167 to 0.012	0.088
Female sex	-9.731 to -5.886	<0.001	-9.878 to -5.526	<0.001
Paroxysmal AF (vs. Non-paroxysmal)	-6.208 to -2.458	<0.001	-5.246 to -1.122	0.002
COPD	-12.599 to -0.231	0.042	-12.240 to 0.596	0.075
Creatinine (per 1mg/dL increase)	-2.773 to -0.181	0.026	-3.619 to -0.977	0.001
LVEF (per 1% increase)	-0.129 to 0.197	0.685		
Left atrial diameter (per 1cm increase)	0.265 to 2.772	0.018	-0.688 to 2.194	0.306
Tricuspid Regurgitation (per 1 grade increase)	-2.104 to 0.659	0.305		
Mitral Regurgitation (per 1 grade increase)	-1.816 to 1.043	0.596		
Heart rate (per 1bpm increase)	-0.101 to 0.005	0.075		
AFEQT change				
Age (per 1year increase)	-0.350 to -0.172	<0.001	-0.330 to -0.184	<0.001
Female sex	-1.681 to 2.535	0.691		
Paroxysmal AF (vs. Nonparoxysmal)	2.931 to 6.997	<0.001	-0.014 to 3.288	0.052
COPD	-8.036 to 5.728	0.742		
Creatinine (per 1mg/dL increase)	-0.899 to 1.903	0.483		
LVEF (per 1% increase)	-0.171 to 0.190	0.919		
Left atrial diameter (per 1cm increase)	-3.391 to -0.695	0.003	-1.177 to 1.077	0.931
Tricuspid Regurgitation (per 1 grade increase)	-2.960 to 0.044	0.057		
Mitral Regurgitation (per 1 grade increase)	-1.941 to 1.175	0.629		

	Estimate (95%CI)	P value	Estimate (95% CI)	P value
Heart rate (per 1bpm increase)	-0.084 to 0.031	0.372		
Ablation after enrollment	8.791 to 12.566	<0.001	5.606 to 8.758	<0.001
AFEQT daily activities at baseline (per 1point increase)	-0.664 to -0.595	<0.001	-0.656 to -0.585	<0.001

	Univariate		Multivariable	
Symptom domain	Estimate (95%CI)	P value	Estimate (95% CI)	P value
Baseline				
Age (per 1year increase)	0.023 to 0.168	0.010	0.012 to 0.173	0.025
Female sex	-6.603 to -3.062	<0.001	-6.488 to -2.582	<0.001
Paroxysmal AF (vs. Nonparoxysmal)	-11.270 to -7.918	<0.001	-10.237 to -6.344	<0.001
COPD	-2.834 to 8.379	0.332		
Creatinine (per 1mg/dL increase)	-0.960 to 1.430	0.700		
LVEF (per 1% increase)	-0.272 to 0.027	0.109		
Left atrial diameter (per 1cm increase)	3.069 to 5.336	<0.001	0.256 to 2.847	0.019
Tricuspid Regurgitation (per 1 grade increase)	0.222 to 2.749	0.021	-1.377 to 1.620	0.874
Mitral Regurgitation (per 1 grade increase)	0.510 to 3.113	0.006	-1.380 to 1.730	0.825
Heart rate (per 1bpm increase)	0.003 to 0.100	0.037	-0.060 to 0.043	0.747
AFEQT change				
Age (per 1year increase)	-0.301 to -0.131	<0.001	-0.168 to -0.040	0.002
Female sex	-1.196 to 2.833	0.426		
Paroxysmal AF (vs. Nonparoxysmal)	6.132 to 9.992	<0.001	-1.329 to 1.757	0.785
COPD (per 1mg/dL increase)	-7.669 to 5.486	0.745		
Creatinine (per 1mg/dL increase)	-1.625 to 1.068	0.685		
LVEF (per 1% increase)	-0.060 to 0.285	0.201		
Left atrial diameter (per 1cm increase)	-5.755 to -3.197	<0.001	-1.979 to 0.034	0.058
Tricuspid Regurgitation	-2.752 to 0.120	0.073		

(per 1 grade increase)				
Mitral Regurgitation (per 1 grade increase)	-2.831 to 0.145	0.077		
Heart rate (per 1bpm increase)	-0.133 to -0.023	0.006	-0.065 to 0.016	0.231
Ablation after enrollment	7.794 to 11.415	<0.001	2.566 to 5.378	<0.001
AFEQT symptom score at baseline (per 1 point increase)	-0.791 to -0.727	<0.001	-0.771 to -0.700	<0.001

CI = confidence interval, AF = atrial fibrillation, AFEQT = Atrial Fibrillation Effects on Quality of Life, COPD = chronic obstructive pulmonary disease, LVEF = left ventricular ejection fraction, bpm = beat per minute.

Figure S1. **AFEQT score changes after 1 year of treatment stratified by catheter ablation procedure after enrollment.**

	No TR	Mild TR	Moderate TR	Severe TR
Overall	12.0 (2.8, 25.0)	10.3 (1.3, 22.2)	10.2 (0.4, 17.6)	N/A
Symptom	12.5 (0.0, 29.2)	12.5 (0.0, 25.0)	12.5 (0.0, 25.0)	N/A
Daily Activity	6.8 (0.0, 22.9)	6.25 (0.0, 21.9)	8.3 (-2.1, 20.8)	N/A

	No TR	Mild TR	Moderate TR	Severe TR
Overall	1.9 (-5.6, 10.2)	1.9 (-4.6, 11.1)	0.7 (-10.2, 11.1)	2.1 (-8.2, 10.6)
Symptom	4.2 (-4.2, 12.5)	4.2 (-4.2, 16.7)	0.0 (-4.2, 16.0)	0.0 (-4.9, 14.6)
Daily Activity	0.0 (-10.4, 8.3)	0.0 (-7.9, 10.4)	0.0 (-14.5, 10.4)	2.1 (-18.5, 14.6)
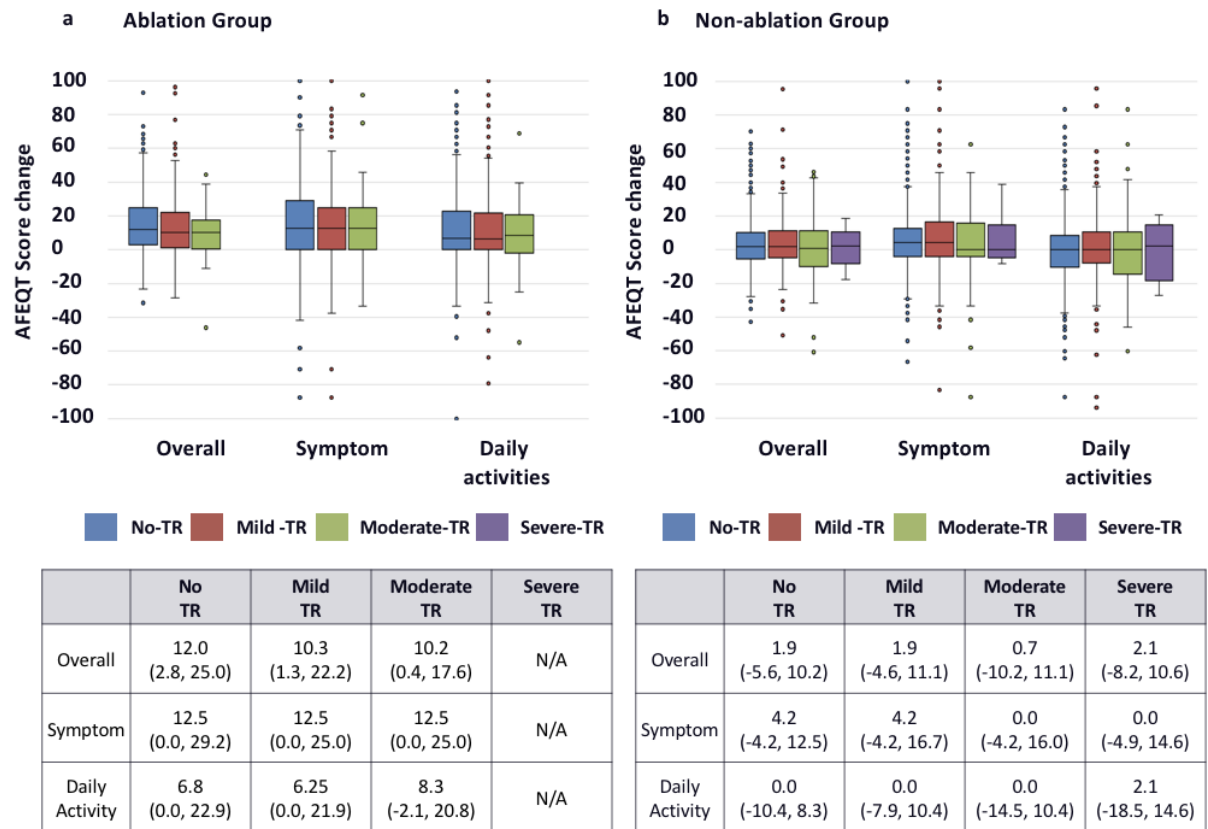
a: AFEQT score change after 1 year of treatment in patients who underwent catheter ablation after enrollment. b: AFEQT score change after 1 year of treatment in patients who did not undergo catheter ablation after enrollment. The thick line in the middle is the median. The top and bottom box lines show the first and third quartiles. The whiskers show the maximum and minimum values, with the exceptions of outliers (circles) which are at least 1.5 box length from the median. Data are presented as median (IQR). TR = tricuspid regurgitation.