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ORIGINAL RESEARCH

Burden of Tricuspid Regurgitation in Patients Diagnosed in the Community Setting

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ABSTRACT

OBJECTIVES This study sought to analyze patients with tricuspid regurgitation (TR) diagnosed in the community setting (Olmsted County) by Doppler echocardiography to define the prevalence, characteristics, and implications of clinically significant (greater or equal to moderate) TR.

BACKGROUND The prevalence, cause distribution, and significance of TR are mostly unknown.

METHODS All adult residents of Olmsted County, Minnesota, who underwent clinically indicated Doppler echocardiography between 1990 and 2000 were evaluated for presence of greater or equal to moderate TR. The characteristics and outcome of TR carriers was then analyzed.

RESULTS During the study period, 417 community residents were diagnosed with greater or equal to moderate TR corresponding to an U.S. age- and sex-adjusted prevalence of 0.55% with 95% confidence interval (0.50 to 0.60). TR adjusted prevalence was higher in women ($p < 0.01$) and strongly linked to age ($p < 0.0001$). Isolated TR (without significant comorbidities, structural left valve disease, pulmonary hypertension, or overt cardiac cause) represented 8.1% of patients with greater or equal to moderate TR. Isolated TR adjusted for age, sex, ejection fraction, atrial fibrillation, and Charlson comorbidity index independently predicted higher mortality (adjusted risk ratio: 1.68; 95% confidence interval: 1.04 to 2.60; $p = 0.03$) for qualitative definition. Mortality in patients with greater or equal to moderate isolated TR was higher than in the matched cases with trivial TR ($p = 0.0014$; matching for age, sex, atrial fibrillation, ejection fraction, comorbidity index). Only 2.6% of patients ever had tricuspid valve surgery during follow-up.

CONCLUSIONS Clinically significant (greater or equal to moderate) TR is common in community residents diagnosed by Doppler echocardiography and increases with age. Isolated TR is associated with excess mortality, thus TR represents an important public health problem. (J Am Coll Cardiol Img 2019;12:433-42) © 2019 by the American College of Cardiology Foundation.

Knowledge of valve disease epidemiology has been poor but recent data have brought some light on prevalence of left-sided diseases showing their link to aging and impact on outcome (1-3). Very little is known about the prevalence of tricuspid regurgitation (TR) because previous studies have focused on hospitalized (4,5) patients or surgical series (6-8), but the minimal number of patients operated compared with left-sided surgery (2,3) suggest very low prevalence. TR, compared with aortic stenosis and mitral regurgitation is due to a variety of causes/contexts, but the most

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CI = confidence interval

HR = hazard ratio

LV = left ventricle

NYHA = New York Heart Association

PHTN = pulmonary hypertension

RA = right atrium

RV = right ventricle

TR = tricuspid regurgitation

commonly described is TR in association with pulmonary hypertension (PHTN) (6). Whether TR in the community is mostly associated with PHTN or appears in a variety of contexts is unclear and description of these causes is unknown. Outcome of TR has been studied in referral centers (4,5) but may have been skewed and overestimated due to referral bias.

Olmsted County provides a unique opportunity to study TR because it has a single echo laboratory, centralizing diagnoses, large samples of patients with single-valve heart disorders, and health care providers linked through the Mayo Clinic's unique database. This database allows information about all clinical cases of valve disease diagnosed in Olmsted County to be obtained through a medical records linkage system that encompasses care delivered to residents of Rochester and Olmsted County by the Mayo Clinic and other providers in the community (1,9). Furthermore, facilities and expertise for the diagnosis and treatment of valve diseases are readily available, so that performance versus nonperformance of repair or replacement cannot be ascribed to access limitations. Thus, our aim was to assess the prevalence, distribution patterns, rate of surgery, and consequences of noteworthy (greater or equal to moderate) TR in community residents diagnosed by Doppler echocardiography.

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METHODS

DESIGN. The study was designed with 2 aims.

First, to estimate the prevalence of all-cause TR among community residents diagnosed by Doppler echocardiography in Olmsted County. Only residents who were alive in December 2000, were analyzed (n = 16,380).

Second, we assessed distribution patterns of TR. Included for the distribution analysis were all Olmsted County residents that had echo exams done from 1990 to 2000, were >18 years of age, unless they had previously denied research authorization in accordance with Minnesota law or if they were incarcerated in the federal medical center, irrespective of survival (n = 21,020). Recent reports have shown that the clinical impact of TR depends on the particular clinical context. Whereas organic TR (10), TR associated with mitral disease (11), and isolated TR (4) had significant influence on survival, TR associated with poor left ventricular (LV) systolic function (12) did not. Based on these data, it is clear that classification just to primary versus secondary TR is not fully reflective of the patient's status. Thus, to assess distribution patterns we performed step-by-step clinical context classification of all patients with equal or greater than moderate TR by qualitative assessment, with particular emphasis on particular clinical context. Congenital TR was defined at the first step (any congenital heart disease resulting in TR including atrial septal defect, irrespective of operational status, LV function, left valvular function, or pulmonary pressure), and organic-associated TR at the second step (TR not due to congenital disease and associated with structural tricuspid disease, irrespective of operational status, LV function, left valvular function, or pulmonary pressure). After excluding all patients with primary involvement of the valve (either congenital or organic) we were left with all patients with secondary (functional) TR. We then defined patients with functional TR associated with left-sided valvular disease at the third step (TR neither congenital nor organic and occurring in patient with left-sided valve prostheses, repair, any degree of mitral stenosis, or any other native organic valve disease of at least moderate degree) and functional TR associated with LV systolic dysfunction at the fourth step (TR neither congenital, organic, nor left valvular occurring in patients with LV dysfunction with ejection fraction <50%). The remaining patients were then classified as isolated TR (without any of the previously defined causes) if they had systolic pulmonary pressure <50 mm Hg, or functional TR associated with PHTN if they had systolic pulmonary pressure ≥50 mm Hg irrespective of whether it was post-capillary (e.g., diastolic dysfunction), pre-capillary (e.g., pulmonary vascular or parenchymal), or of unspecified cause (4). The subgroup with isolated TR included only patients with functional TR and no organic (including pacemaker wires impinging on the leaflets) or congenital involvement of the leaflets, with TR resulting from primary or secondary (due to RA or RV) annular dilatation (**Figure 1**).

Third, we examined the outcome from first detection of TR in all residents performing echocardiography between 1990 and 2000, irrespective of survival until December 2000 (n = 21,020) to determine the effect of the presence of greater or equal to moderate TR on outcome (survival, heart failure hospitalizations, new onset of AF). To avoid outcome interference of background cardiac conditions, that obscure the specific significance of TR, we assessed outcome for each clinical context.

Finally, after clinical context classification of TR, we performed retrospective computerized matching of cases (defined as those with greater or equal

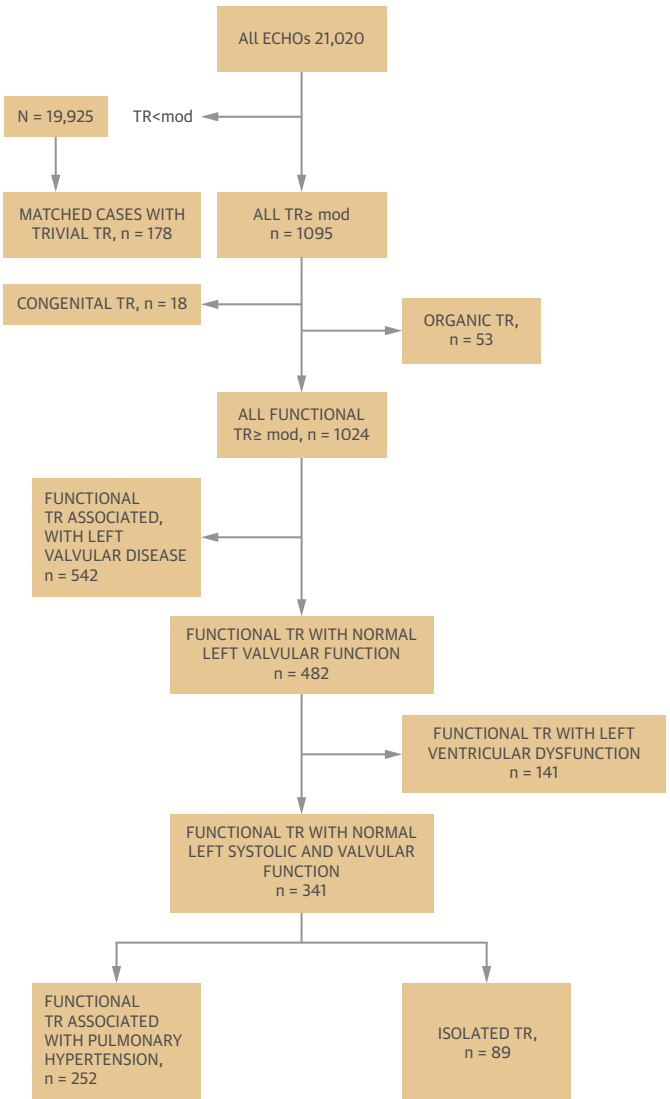
to moderate isolated TR) and cases with trivial TR (cases with normal ejection fraction, systolic pulmonary pressure <50 mm Hg, no left valvular disease, and trivial TR) for core predefined criteria (age, sex, baseline rhythm, LV ejection fraction, systolic pulmonary artery pressure). We then performed a case-control matched survival analysis. For matching of cases (greater or equal to moderate isolated TR) to cases with trivial TR a computerized matching approach was used. Patients with trivial TR were randomly selected from the desired bin of all patients with trivial TR, with similar eligibility criteria (ejection fraction >50%, systolic pulmonary pressure <50 mm Hg, no left valvular disease, and trivial TR) in the computerized Mayo Clinic echo database, achieving groups of patients with trivial and greater or equal to moderate isolated TR comparable in terms of other independent determinants of outcome. The predefined baseline computerized matching parameters were age (within 5 years), exact sex, ejection fraction (within 5%), baseline rhythm, comorbidity index (within 0.2), and systolic TR peak velocity (within 0.2 m/s). Thus, all patients had isolated functional TR fulfilling the same eligibility criteria and were differentiated only by severity of TR (greater or equal to moderate vs. trivial).

The study was approved by our institutional review board.

DOPPLER ECHOCARDIOGRAPHY. All patients had comprehensive 2-dimensional and Doppler echocardiography using multiple windows during the same examination. Patients were instructed to breathe normally and all tricuspid and right ventricular (RV) measurements were averages of inspiratory and expiratory measurements over at least 5 cardiac cycles in sinus rhythm and 8 cycles in atrial fibrillation (AF). Measurements of mitral inflow included the peak early filling (E-wave) and late diastolic filling (A-wave) velocities, the E/A ratio, and deceleration time of early filling velocity. Detection and gradation of TR was visually assessed using an integrative, semi-quantitative approach, including assessment of color Doppler jet area, tricuspid valve morphology, right atrial (RA) and RV size, inferior vena cava size, jet density, and contour color Doppler (none = 0, mild = 1, mild-moderate = 2, moderate = 3, moderate-severe = 4, severe = 5) (13).

RV was considered of normal size if it appeared to be no more than two-thirds the size of the LV in the standard apical 4-chamber view. If the RV was larger than the LV in this view, or if the RV displaced the LV and occupied the apex, it signified that the RV was dilated. Annular diameter was considered dilated when >4 cm in the standard apical 4-chamber view. RV qualitative function assessment was based on multiple views of the RV (short-axis parasternal at basal, mid, and apical levels; lower parasternal RV inflow view; apical 4-chamber view and, if possible, RV long-axis view; and subcostal short-axis and 4-chamber views). Using these multiple views, an integrative qualitative grading was formulated by the physician responsible for the echo study. Hemodynamic assessment measured the TR velocity and

FIGURE 1 Patient Selection Process



The flow chart describes the selection process of classification of all 21,020 adult residents of Olmsted County, Minnesota, who underwent clinically indicated Doppler echocardiography between 1990 and 2000, until the final isolated tricuspid regurgitation (TR) group, consisting of 89 patients. mod = moderate.

TABLE 1 The Prevalence of All-Cause TR in the Community by Age and Sex and Adjusted for the Age and Sex Distribution of the U.S. White Population

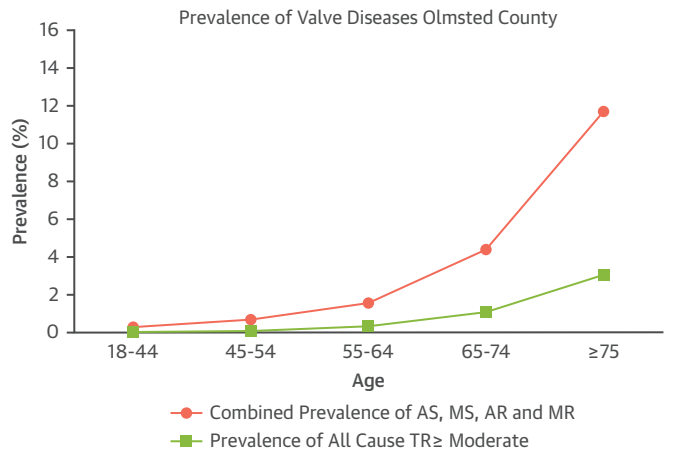
		All-Cause TR Greater or Equal to Moderate						
		Age Group, yrs						
	Number of Cases	18-44 (n = 51)	45-54 (n = 36)	55-64 (n = 58)	65-74 (n = 128)	75+ (n = 408)	Linear Trend p Value	Age Adjusted U.S. Burden
Female	426	0.04 (0.02-0.07)	0.06 (0.02-0.13)	0.36 (0.24-0.53)	1.23 (0.94-1.58)	4.40 (3.89-4.96)	0.0001	0.59 (0.52-0.67)
Male	255	0.05 (0.03-0.08)	0.16 (0.10-0.26)	0.30 (0.19-0.47)	0.93 (0.67-1.27)	3.16 (2.58-3.84)	0.0001	0.47 (0.39-0.55)
Overall	681	0.05 (0.03-0.07)	0.11 (0.07-0.16)	0.33 (0.24-0.44)	1.09 (0.89-1.33)	3.96 (3.56-4.39)	0.0001	0.55 (0.50-0.60)

Values are % (95% confidence interval) unless otherwise indicated.
TR = tricuspid regurgitation.

estimated RA pressure using the inferior vena cava to calculate the systolic pulmonary artery pressure. The systolic pulmonary pressure was estimated based on the peak systolic tricuspid velocity so the pressure gradient between the RV and RA at systole was calculated by applying the Bernoulli equation. We then added the gradient to the estimated RA pressure (14).

STATISTICAL ANALYSIS. Descriptive results were expressed as mean ± SD for continuous variables and as percentages for categorical variables. Group comparisons used analysis of variance or chi-square test, as appropriate. For the prevalence analyses, we calculated the ratio of participants affected to those examined to estimate age- and sex-specific frequencies of all-cause TR in the sampled population. Age-specific TR rates were compared between groups with *z*-scores; we tested for trends across age groups with the Cochran-Armitage test. Confidence intervals (95%) were calculated with Poisson standard errors. After echocardiographic diagnosis, survival was estimated by the Kaplan-Meier method and linearized yearly rates. Comparisons of survival between participants with isolated TR and cases with trivial TR were done with the 2-sample log-rank test and were adjusted for age, sex, LV ejection fraction, AF, Charlson comorbidity index, and body mass index with the Cox proportional hazards model. The p values <0.05 were considered significant. All authors participated in designing the study, collecting and analyzing data, and drafting and revising the manuscript.

FIGURE 2 Prevalence of TR and Combined Prevalence of All Left Valvular Heart by Age

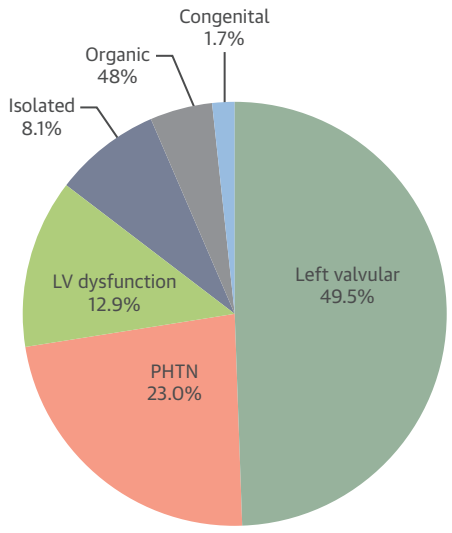


The graph shows the prevalence of tricuspid regurgitation (TR) **(green line)** compared with the combined prevalence of all left valvular heart disease including greater or equal to aortic stenosis (AS), aortic regurgitation (AR), mitral stenosis (MS), and mitral regurgitation (MR) **(pink line)** by age. Note the significant increase in the prevalence of TR with age. All-cause TR is frequent, approximately one-fourth of all left-sided valve disease, similar to the prevalence of aortic stenosis.

RESULTS

PREVALENCE OF CLINICALLY SIGNIFICANT TR IN COMMUNITY RESIDENTS DIAGNOSED BY DOPPLER ECHOCARDIOGRAPHY. Among 16,380 residents alive on December 31, 2000, who underwent Doppler echocardiography during the study period in the only echocardiographic laboratory available in the county, the prevalence of all-cause TR, irrespective of cause and mechanisms, is presented in Table 1 by age, sex, and adjusted for the age and sex distribution of the U.S. white population, and in Figure 2, compared with the prevalence of total left valvular heart disease (combined prevalence of greater or equal to moderate aortic stenosis and regurgitation, mitral stenosis and regurgitation). A significant increase in the prevalence of TR was seen with age in both men and women (Table 1). All-cause TR was more commonly diagnosed in women than in men after adjustment for age ($p < 0.01$). All-cause TR was frequent (0.55% with 95% confidence interval [CI]: 0.50 to 0.60),

FIGURE 3 Distribution Patterns of TR in the Community



Congenital includes any congenital heart disease resulting in tricuspid regurgitation (TR) including atrial septal defect or patients after surgical repair. Organic includes TR not due to congenital disease and associated with structural tricuspid disease. Left valvular includes TR that is neither congenital nor organic and occurring in patient with left-sided valve prostheses, repair, any degree of mitral stenosis, or any other native organic valve disease of at least moderate degree. Systolic dysfunction includes TR associated with left ventricular (LV) systolic dysfunction (ejection fraction <50%) that is neither congenital, nor organic, nor left-valvular. Isolated includes TR occurring without any of the previously defined causes and without pulmonary hypertension (PHTN) (systolic pulmonary pressure <50 mm Hg). PHTN TR includes functional TR associated with pulmonary hypertension (systolic pulmonary pressure ≥50 mm Hg), occurring without any of the previously defined causes.

approximately one-fourth of all left-sided valve disease, similar to the prevalence of aortic stenosis.

DISTRIBUTION OF TR IN COMMUNITY RESIDENTS DIAGNOSED BY DOPPLER ECHOCARDIOGRAPHY. The distribution pattern of TR among all 1,095 patients with greater or equal to moderate TR (out of 21,020 Olmsted County residents that had echo exams done from 1990 to 2000) is shown in Figure 3. The most common etiology of greater or equal to moderate TR in community residents diagnosed by Doppler echocardiography was functional TR secondary to left valvular disease (n = 542; 49.5%), followed by functional TR associated with PHTN unrelated to any heart disease (n = 252; 23.0%), functional TR related to LV systolic dysfunction (n = 141; 12.9%), functional isolated TR (n = 89; 8.1%), organic TR (n = 53; 4.8%), and congenital causes (n = 18; 1.7%). The clinical and echo characteristics of the different TR subcategories are shown in Table 2.

OUTCOME OF ALL-CAUSE TR IN THE COMMUNITY RESIDENTS DIAGNOSED BY DOPPLER ECHOCARDIOGRAPHY. In the Olmsted County residents, patients that had at least moderate TR, observed survival was 28.5 ± 1.3% at 5 years, 14.1 ± 1.1% at 10 years, 10.2 ± 1.1% at 15 years, significantly lower than in patients with trivial TR ($p < 0.0001$). The risk of death associated with all-cause greater or equal to moderate TR compared with Olmsted County residents with trivial TR adjusted for age, sex, AF, ejection fraction, presence of restrictive physiology, mitral regurgitation grade, and systolic pulmonary pressure was 1.17 (95% CI: 1.02 to 1.22; $p = 0.01$). Yearly mortality, heart failure hospitalization, and new onset of AF by TR clinical context are shown in Figure 4. The poorest survival was seen with functional TR associated with left valvular disease, or associated with LV systolic dysfunction, followed by functional TR associated with PHTN and organic TR, but was ominous even in isolated TR, with no other systemic or cardiac comorbidity. Clinical management after diagnosis was medical in 1,079 (97.6%) and by tricuspid surgery only in 26 patients (2.4%). All patients undergoing surgery had heart failure symptoms that could not be controlled with medications at the time of surgery. They were classified as New York Heart Association (NYHA) functional class II (n = 4, 15%), III (n = 14; 54%), or IV (n = 8; 31%). Three patients died in the peri-operative period (11%; 1 with NYHA III and 2 with NYHA IV). At the last follow-up, 1 patient still had NYHA functional class IV, 9 patients still had NYHA functional class III, 11 patients had NYHA functional class II, and 2 were asymptomatic (median: 3 [interquartile range: 3 to 4] vs. median: 2 [interquartile range: 2 to 3]; $p < 0.001$).

OUTCOME OF ISOLATED TR IN COMMUNITY RESIDENTS DIAGNOSED BY DOPPLER ECHOCARDIOGRAPHY. To avoid outcome interference of background cardiac conditions that obscure the specific significance of TR, we assessed survival of isolated TR. In the Olmsted County residents that had at least moderate isolated TR, observed survival was 51.7 ± 5% at 5 years, 30.5 ± 5% at 10 years, and 25.8 ± 5% at 15 years, and much lower than in patients with no identifiable heart disease in echocardiograms ($p < 0.0001$). The risk of death associated with isolated TR compared with Olmsted County residents with no identifiable heart disease (adjusted for age, sex, LV ejection fraction, AF, Charlson comorbidity

TABLE 2 Clinical and Echo Characteristics of the Different TR Subcategories

	Congenital (n = 18)	Organic (n = 53)	Associated With Left Valvular Disease (n = 542)	Associated With LV Systolic Dysfunction (n = 141)	Associated With PHTN (n = 252)	Isolated (n = 89)
Age, yrs	61 ± 22*†‡§‖	77 ± 13¶	79 ± 11¶	76 ± 12¶	75 ± 12¶	75 ± 15¶
Female	58	52	63§‖¶	40*‡‖	74‡§	72‡§
BMI, kg/m^2	25.6 ± 6	24.1 ± 6	25.6 ± 15	26.2 ± 6	28.8 ± 6	24.7 ± 6
AF	39*†‡§‖	58¶	65¶	63¶	68¶	68¶
Systolic blood pressure, mm Hg	132 ± 16	128 ± 22	129 ± 24	125 ± 21*‖	133 ± 23§	133 ± 24§
Diastolic blood pressure, mm Hg	77 ± 13	71 ± 15	71 ± 14	71 ± 13	71 ± 13	73 ± 13
Charlson comorbidity index	1 (0-3)†‡§	4 (2-5)*‖¶	3 (2-5)*¶	3 (2-5)*¶	3 (2-5)	2 (1-3)†‡§
Ejection fraction, %#	56 ± 13§	50 ± 17*§‖	46 ± 18*§‖	33 ± 10*†‡‖	64 ± 7†‡§	63 ± 6†‡§
Systolic pulmonary pressure, mm Hg#	45 ± 17‡‖	53 ± 14‖	57 ± 14*‖¶	55 ± 16‖	64 ± 15*†‡§	40 ± 6‡§‖
Mitral E wave, m/s#	0.9 ± 0.3	1.00 ± 0.3	1.1 ± 0.4*§‖	0.9 ± 0.4‡	1.0 ± 0.4§	0.9 ± 0.3§
Mitral A wave, m/s#	0.7 ± 0.3	0.8 ± 0.4	0.7 ± 0.3	0.7 ± 0.3‖	0.9 ± 0.3§	0.8 ± 0.2
Deceleration time, ms#	201 ± 60	181 ± 47	172 ± 54‖	173 ± 49	198 ± 62‡	203 ± 41
RV enlargement#	11 (61)	27 (51)	237 (44)	68 (48)	122 (48)	31 (35)
Annular dilatation#	1 (6)	5 (9)	28 (5)	7 (5)	30 (12)	5 (6)
RV dysfunction#	3 (17)	5 (17)	90 (17)	24 (17)	42 (17)	8 (9)
Yearly mortality	5.5 ± 8*†‡§‖	22.2 ± 19¶	29.5 ± 22*¶	28.1 ± 20¶	26.9 ± 21*¶	12.1 ± 12‡‖¶
Yearly HF hospitalization	14.0 ± 8.8†‡§‖	28.7 ± 15*¶	33.8 ± 16.9*‖¶	25.8 ± 13.2‖¶	15.3 ± 10*‡§¶	9.0 ± 7.0†‡‖
Yearly new AF	8.2 ± 6.9‡§	14.4 ± 8.5‡	28.4 ± 14.6*†‖¶	21.6 ± 11.4¶	20.5 ± 11.0‡	12.6 ± 8.3‡

Values are mean ± SD, %, median (interquartile range), or n (%). *p < 0.05 compared to isolated TR. †p < 0.05 compared with organic. ‡p < 0.05 compared with valvular. §p < 0.05 compared with left systolic dysfunction. ‖p < 0.05 compared with PHTN. ¶p < 0.05 compared with congenital. #Defined in the methods section.

AF = atrial fibrillation; BMI = body mass index; HF = heart failure; LV = left ventricular; PHTN = pulmonary hypertension; RV = right ventricular; TR = tricuspid regurgitation.

index was 1.68 (95% CI: 1.04 to 2.6; p = 0.03). Mortality in patients with greater or equal to moderate isolated TR was higher than in the matched cases with trivial TR (retrospective computerized matching for age, sex, AF, ejection fraction, systolic pulmonary pressure, comorbidity index) (Figure 5).

ATRIAL FIBRILLATION. The prevalence of AF in all subgroups was very high (range: 39% to 68%). The impact of AF on mortality in univariate analysis (hazard ratio [HR]: 3.1; 95% CI: 3.0 to 3.37; p < 0.0001), and adjusted for greater or equal to moderate TR (HR: 2.4; 95% CI: 2.27 to 2.58; p < 0.0001) was significant. However, presence of greater or equal to moderate TR was still associated with increased mortality even when adjusted for AF alone (HR: 3.5; 95% CI: 3.2 to 3.8; p < 0.0001) or with comprehensive adjustment including AF, age, sex, election fraction, presence of restrictive physiology, mitral regurgitation grade, and systolic pulmonary pressure (HR: 1.17; 95% CI: 1.02 to 1.22; p = 0.01).

DISCUSSION

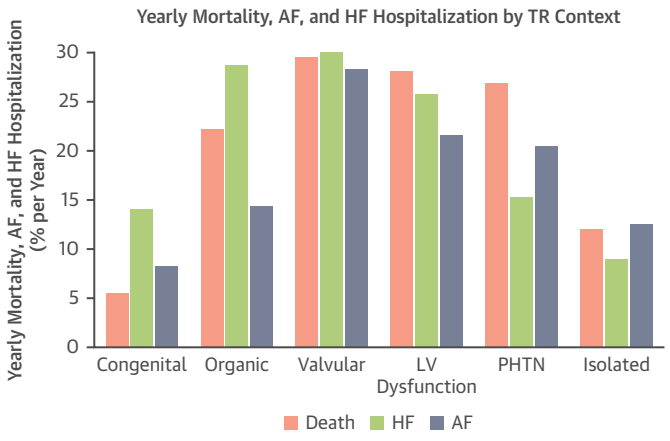
The study was designed with several aims. First, assess the prevalence of TR in community residents diagnosed by Doppler echocardiography. Second, analyze distribution patterns of TR, and third, to assess survival of all-cause, heart failure hospitalizations, new onset of AF, and tricuspid valve surgery in specific clinical contexts of TR, including isolated TR in community residents diagnosed by Doppler echocardiography.

Our prevalence and distribution analyses have shown that TR is frequent (0.55%), approximately one-fourth of all left-sided valve disease in total, and similar to the prevalence of aortic stenosis (1). TR was also found to be heterogeneous in cause, morbidity and survival, but overall with very high mortality even in isolated TR. Lastly, even though TR is associated with ominous outcome and is prevalent, it remains markedly undertreated compared with left valvular disease (2,3), thus clearly needs more attention, with emphasis on better means of treatment.

THE BURDEN AND DISTRIBUTION PATTERNS OF TR IN THE COMMUNITY. Our study provides information on all-cause TR in community residents diagnosed by Doppler echocardiography (i.e., individuals coming to clinical attention). Distribution patterns show that functional TR secondary to left heart disease (systolic, diastolic, or valvular) is the major cause of TR, in agreement with previous surgical- and

hospitalized-based series (6,15,16). We believe that with the aging population, the predominance of functional TR with all its diversity is expected to grow even further. Patterns of distribution of TR show that older age is an independent determinant of all-cause TR, in accord with the notion that the burden of valve disease increases with aging (1). Although most valvular diseases were equally diagnosed in men and women in the population groups (1), all-cause TR was more often diagnosed in women than in men. The mechanisms for such an imbalance are unknown and should be investigated prospectively. Importantly, our study shows not only the trend of increasing prevalence with age but also very high absolute rates of all-cause TR in elderly people. Indeed, 1 in 25 people ages 75 and older have a moderate or severe TR by visual estimation. Furthermore, we show that TR without structural valve disease, PHTN, or overt cardiac cause is not uncommon and consists of around 8% of all-cause TR cases.

FIGURE 4 Linearized Yearly Mortality by TR Clinical Context

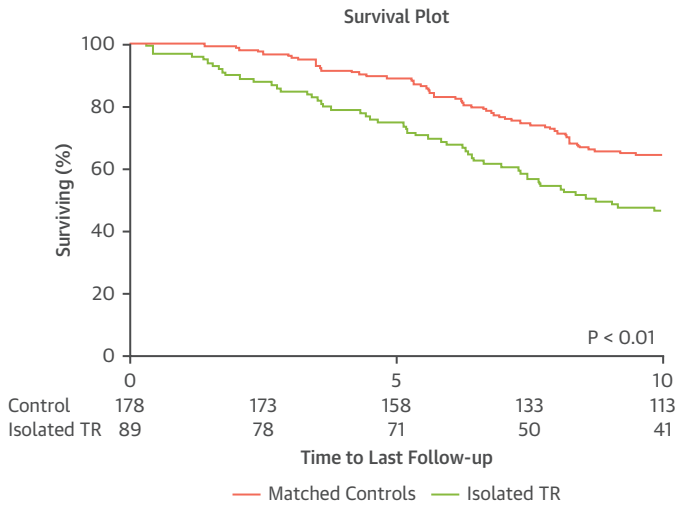


Congenital includes any congenital heart disease resulting in TR including ASD or patients after surgical repair. Organic includes TR not due to congenital disease and associated with structural tricuspid disease. Left valvular includes TR that is neither congenital nor organic and occurring in patient with left-sided valve prostheses, repair, any degree of mitral stenosis, or any other native organic valve disease of at least moderate degree. Systolic dysfunction includes TR associated with LV systolic dysfunction (EF<50%) that is neither congenital, nor organic, nor left-valvular. Isolated includes TR occurring without any of the previously defined causes and without PHTN (systolic pulmonary pressure <50 mm Hg). PHTN TR includes functional TR associated with pulmonary hypertension (systolic pulmonary pressure ≥50 mm Hg), occurring without any of the previously defined causes. AF = atrial fibrillation; HF = heart failure; other abbreviations as in Figure 3.

OUTCOME OF ALL-CAUSE AND ISOLATED TR IN THE COMMUNITY. TR detected in community residents diagnosed by Doppler echocardiography is not a mere imaging peculiarity but is associated with increased mortality. With the projected shift to an older and larger population, the clinical burden of all-cause TR will probably increase substantially in the future. TR is a heterogeneous condition with or without organic valve lesions, PHTN, LV dysfunction, left-sided valvular diseases, or comorbid or causal diseases that have confused previous attempts at defining the specific role of the regurgitation in affecting the outcome (10,11,17). Furthermore, the outcome of TR is still disputed because previous studies have focused mostly on hospitalized patients or surgical series. Thus, reports can be found suggesting that TR affects seriously the outcome (5,11), opposed by others reporting that it is benign (17) or well tolerated for many years (10). Patients with isolated TR are excellent targets to analyze the impact of TR on outcome because it is functional (excluding patients with intrinsic tricuspid valve disease) and excludes patients with likely pulmonary hypertension, LV systolic dysfunction, or other valve or congenital diseases (4,6-8). We analyzed the outcome of isolated TR patients (to minimize heterogeneity of clinical context and the impact of comorbid conditions) and compared it to matched cases with trivial TR but similar inclusion criteria. This process provided patients that were mostly differentiated by the degree of TR and allowed us to demonstrate robustly that clinically significant TR, even when isolated, is associated with excess mortality (4).

The impact of AF on mortality was significant showing that it is associated with increased mortality in community residents with TR diagnosed by Doppler echocardiography. Nevertheless, presence of greater or equal to moderate TR was still associated with increased mortality even when adjusted for AF showing that although AF is an associate of advanced disease in patients with TR, it is not the sole factor responsible for the increased mortality in TR. Recently, AF has been suggested to be a major cause of TR. Previous studies (6,18-20) have suggested that most isolated TR is concomitant with chronic AF proposing a link between chronic AF, RA enlargement with resultant functional TR. A more recent 3-dimensional study (21) showed that features of isolated TR associated with AF included RA enlargement, lower systolic pulmonary artery pressure, a larger tricuspid annular area with weaker annular contraction, but a smaller tethering angle despite a similar leaflet coaptation status compared with other

FIGURE 5 Overall Survival Under Medical Management in Patients With Isolated TR Compared With Matched Cases With Trivial TR



The graph shows the overall survival after diagnosis (matched trivial tricuspid regurgitation [TR] patients are represented by the **pink line;** greater or equal to moderate isolated TR patients are represented by the **green line**). The p value was <0.01. Note that there is decrease in survival with greater or equal to moderate isolated TR even when matched for all comorbidities.

types of functional TR. Although we show high prevalence of AF in our isolated TR group, similarly to the previous reports, our data suggest that the prevalence of AF is very high in all types of functional TR and not unique to isolated TR. Based on our previous work (4,20), we believe that AF plays an important role in the pathogenesis of isolated TR, but probably begets TR in all types of TR, and is not unique for isolated TR alone (22).

Finally, our data demonstrate that there is considerable undertreatment of TR. TR is rarely treated by cardiac surgery (2,3), raising the need for improved detection and enhanced research to develop new therapeutic, preferably less invasive solutions directed toward this entity (23-26).

STUDY LIMITATIONS. Echo exams were done and read by many different people. Because echo exams were not saved in an electronic format, we did not reread original echocardiographs and could not assess reader variability for severity of TR. Nevertheless, because the Mayo Clinic echo laboratory is the only provider of echocardiography in Olmsted County, TR grading criteria remained consistent throughout the study period, with the same criteria used for all patients examined, ensuring that all diagnoses are standardized and centralized. The use of Doppler echocardiography and the Bernoulli equation to assess systolic pulmonary pressure in the presence of severe TR and early equalization of RV and RA pressures may result in underestimation of pulmonary pressure. Invasive hemodynamics are rarely performed for TR and confirmation of normal pulmonary artery pressure was not standard clinical practice. TR assessment was semiquantitative. The standard assessment of TR is fraught with problems, but recent advances in noninvasive Doppler echocardiography allow consistent measurement of regurgitant volume and effective regurgitant orifice (27,28) and provide important insights into TR pathophysiology (29). TR is very load dependent, thus it is hard to differentiate patients who are volume overloaded from those who have persistent TR. Furthermore, fluid status may impact on pulmonary pressure, thus may change the classification in some of our patients. Thus, to gain insights specific to outcomes in the different etiologies of TR, prospective analyses, in whom comprehensive assessment of mechanism and quantitative evaluation of TR severity are essential.

CLINICAL IMPLICATIONS. The link of all-cause TR with advancing age emphasizes its growing importance with aging of the population underscoring the importance of its detection and management. Currently, TR is treated primarily with optimal medical therapy or surgery (2,30). Recent advancements in technology allow transcatheter valve-in-valve placement of balloon-expandable valves, transcatheter procedures reducing the regurgitant flow into the vena cava by the implantation of transcatheter valves in these large vessels (24), or percutaneous placation devices (23). These solutions may prove to be effective less invasive options for these high surgical risk patients, especially if nonresponsive to optimal medical therapy.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Very little is known about the prevalence of TR because previous studies have focused on hospitalized patients or surgical series. Whether TR in the community appears in a variety of contexts is unclear and descriptions of these causes and their individual outcomes are unknown. In this study, analysis of prevalence, clinical context, and outcome of adult residents of Olmsted County, Minnesota, who underwent clinically indicated Doppler echocardiography was performed. This community-based analysis permitted us to evaluate outcome of individual causes of TR without referral bias that may have overestimated the poor consequences of TR described in previous reports. We showed that clinically significant TR is common in community and increases with age. TR was also found to be heterogeneous in cause, morbidity, and survival, but overall with very high mortality even in isolated TR, thus represents an important public health problem. Lastly, even though TR was associated with ominous outcome, it was markedly undertreated compared with left valvular disease. We believe that this analysis may improve indications and selection for targeted therapeutics in TR patients.

TRANSLATIONAL OUTLOOK: Currently, TR is treated primarily with optimal medical therapy or surgery. Recent advancements in technology allow transcatheter procedures reducing the regurgitant flow into the RA or vena cava. Although these solutions may prove to be effective less invasive options for these high surgical risk patients, they need to be tested in adequately powered, prospective, randomized, controlled studies before they can be suggested for use in individual TR patient management.

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