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Ratio between Vena Contracta Width and Tricuspid Annular Diameter: Prognostic Value in Secondary Tricuspid Regurgitation

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Background: Conventional approaches for the assessment of secondary tricuspid regurgitation (STR) severity do not correct for right heart dimensions. The authors hypothesized that STR severity can be proportional or disproportional to the dilation of the tricuspid annulus (TA) and investigated the prognostic impact of this novel definition.

Methods: A total of 334 patients with moderate to severe STR and preserved left ventricular systolic function were included. The ratio between vena contracta (VC) width and tricuspid annular diameter was calculated. The cutoff value for VC/TA ratio associated with increased risk for all-cause death was identified using spline-curve analysis.

Results: The cutoff value of VC/TA ratio associated with a mortality excess was 0.24, and 165 patients (49%) had VC/TA ratios ≥ 0.24. Compared with those with VC/TA ratios < 0.24, patients with VC/TA ratios ≥ 0.24 had a higher prevalence of moderate to severe mitral regurgitation, had higher pulmonary pressures, and were more frequently treated with diuretics. During a median follow-up period of 62 months (interquartile range, 28–101 months), 128 patients (38%) died. The cumulative 5-year survival rate was significantly worse in patients with VC/TA ratios ≥ 0.24 (55% vs 71%, P = .001). VC/TA ratio ≥ 0.24 was independently associated with poor outcomes on multivariate analysis (hazard ratio, 1.567; 95% CI, 1.044–2.352; P = .030) together with coronary artery disease, renal impairment, right ventricular systolic function (evaluated using either tricuspid annular plane systolic excursion or right ventricular free wall strain), and pulmonary pressures.

Conclusions: VC/TA ratio ≥ 0.24 is independently associated with poor prognosis in patients with STR. This parameter may be considered as a marker of disproportionate STR and could improve risk stratification and clinical decision-making. (J Am Soc Echocardiogr 2021;34:944-54.)

Keywords: Tricuspid regurgitation, Tricuspid annulus, Right ventricle, Prognosis

Secondary tricuspid regurgitation (STR) is a common disease, affecting 1.6 million patients in the United States.[1] Recently, both awareness of the negative prognostic impact of STR[2] and the possibility to treat patients at high surgical risk with transcatheter procedures[3] have increased interest in better understanding the pathophysiology of STR and defining a clinically meaningful grading system.[4]

The pathophysiology of STR involves several mechanisms, which can be divided into two main categories: (1) dilatation of the tricuspid annulus (TA) secondary to right ventricular (RV) and/or right atrial (RA) enlargement and (2) tethering of the subvalvular apparatus, including leaflets, chordae, and/or papillary muscles.[5,6] To define STR severity, current American[7] and European[8] guidelines

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This work was funded by an unrestricted research grant from Edwards Lifesciences (IISUSTHV2018017).

The Department of Cardiology of the Leiden University Medical Center has received research grants from Abbott Vascular, Bioventrix, Medtronic, Biotronik, Boston Scientific, GE Healthcare, and Edwards Lifesciences. Dr. Bax has received speaking fees from Abbott Vascular. Dr. Marsan has received speaking fees from Abbott Vascular and GE Healthcare. Dr. Delgado has received speaking fees from Abbott Vascular, Medtronic, Merck Sharpe & Dohme, Edwards Lifesciences, and GE Healthcare.

John Gorcsan III, MD, FASE, served as guest editor for this report.

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0894-7317

https://doi.org/10.1016/j.echo.2021.03.015

Abbreviations

EDV = End-diastolic volume

EROA = Effective regurgitant orifice area

HR = Hazard ratio

LV = Left ventricular

PASP = Pulmonary artery systolic pressure

RA = Right atrial

RV = Right ventricular

STR = Secondary tricuspid regurgitation

TA = Tricuspid annulus

TR = Tricuspid regurgitation

TV = Tricuspid valve

VC = Vena contracta

recommend the use of transthoracic echocardiography with a combination of multiple qualitative and quantitative parameters. Most of these echocardiographic parameters and their cutoff values are derived from the grading system for mitral regurgitation and directly applied to the right heart.[9] However, for secondary mitral regurgitation, a new conceptual framework has recently been proposed,[10-13] taking into account the effective regurgitant orifice area (EROA) in relation to left ventricular (LV) size. On the basis of this approach, secondary mitral regurgitation may be "proportionate" to LV dimension, when entirely explained by global LV dilatation, or "disproportionate" when regurgitation severity exceeds that expected on the basis of the degree of LV dilatation and is probably related to additional alterations of the valvular and subvalvular apparatus.[12] This new classification attempts to better differentiate patients with increased mortality risk who might benefit from intervention on the mitral valve (disproportionate secondary mitral regurgitation) from those in whom intervention might not lead to improved outcomes (proportionate secondary mitral regurgitation).[12,13] This concept might also be applied to the right heart to improve current assessment of STR severity and obtain a definition of clinically relevant STR. Although a correlation between right heart remodeling (reflected by the tricuspid annular dilatation) and occurrence of STR has been shown,[14,15] no studies so far have evaluated the prognostic value of STR severity corrected for the degree of tricuspid annular dilatation. Therefore, the aim of the present study was to assess the prognostic value of STR severity corrected for annular dimension in patients with significant STR.

METHODS

Study Population

Patients diagnosed with moderate or severe STR at Leiden University Medical Center (Leiden, the Netherlands) between June 1995 and September 2016 were identified. Patients with primary tricuspid regurgitation (TR; valve prolapse, endocarditis, rheumatic heart disease, or tumor), congenital heart disease, or impaired LV systolic function (i.e., LV ejection fraction < 55%) and those who underwent tricuspid valve (TV) repair or replacement after significant STR diagnosis were excluded. Patients with reduced LV systolic function were specifically excluded to avoid its potential confounding effects on patient outcome. In addition, patients with incomplete data to assess STR severity or RV dimensions were excluded.

All patients underwent standard transthoracic echocardiography, and clinical and demographic data at the time of significant STR diagnosis (baseline) were collected from the departmental cardiology information system (EPD-VisionVR; Leiden University Medical Center) and analyzed retrospectively. The institutional review board of Leiden University Medical Center approved this retrospective analysis of clinically acquired data and waived the need to obtain written informed consent from patients.

Clinical and Echocardiographic Variables

Baseline demographic, clinical, and laboratory variables were collected. Clinical characteristics included symptoms of left- and right-sided heart failure (dyspnea and peripheral edema, respectively), cardiovascular risk factors, main comorbidities, previous cardiac surgery, and medications. Glomerular filtration rate was calculated using the Modification of Diet in Renal Disease formula, and renal impairment was defined as glomerular filtration rate < 60 mL/min/1.73 m^2 and according to medical records.[16]

Transthoracic echocardiographic data were acquired with patients at rest using available ultrasound systems (Vivid 7 and E9; GE Vingmed Ultrasound, Horten, Norway) equipped with 3.5-MHz or M5S transducers. All images were digitally stored for offline analysis using commercially available software (EchoPAC versions 113.0.3 and 202; GE Vingmed Ultrasound). M-mode, bidimensional and color, and continuous- and pulsed-wave Doppler data were acquired from parasternal, apical, and subcostal views according to current guidelines.[7,8,17-20] The original, digitized echocardiographic data were reassessed and reanalyzed taking into account the criteria of current guidelines.[7,8,17-20] Therefore, the present study does not simply concern tabulation of descriptive data included in the clinical reports. Aortic stenosis and mitral regurgitation were graded according to current guidelines,[7,8,19,20] and grade moderate or greater was defined as significant. RV dimensions, including tricuspid annular diameter, end-diastolic RV basal and midventricular diameters, end-diastolic RV base-to-apex length, and RV end-systolic and end-diastolic areas, were acquired and assessed in an RV-focused apical four-chamber view.[18] Tricuspid annular diameter was measured from an RV-focused apical four-chamber view as the largest diameter between opposing TV leaflet insertion (or hinge) points during diastole (mostly at end-diastole).[19-21] RV systolic function was quantified on the basis of tricuspid annular plane systolic excursion measured on M-mode recordings of the lateral TA in an apical four-chamber view and also on the basis of RV fractional area change, defined as (end-diastolic area − end-systolic area)/end-diastolic area × 100.[18] The RV-focused apical view was used to derive longitudinal strain values of the right ventricle using commercially available software (EchoPAC versions 113.0.3 and 202). The RV endocardial border was traced at an end-systolic frame, and the software automatically identified a region of interest and divided the right ventricle into three septal and three free wall segments. The region of interest was manually adjusted to include the RV wall thickness and to ensure correct tracking throughout the cardiac cycle. RV global longitudinal strain was calculated as the average of all six segments and RV free wall strain as the average of the three RV free wall segments.[22] Longitudinal strain measures the shortening of the myocardial fibers and is conventionally presented as negative values. However, in this study, absolute values of RV global longitudinal strain and free wall strain are presented. TR grade was assessed using a multiparametric approach including qualitative, semiquantitative, and quantitative parameters, as recommended in the guidelines.[7,8,19,20] Vena contracta (VC) width was measured from an RV-focused apical four-chamber view as the narrowest portion of the regurgitant flow that occurs at or immediately downstream of the regurgitant orifice.[19,20,23] EROA and regurgitant volume were calculated using the flow convergence method (also known as the proximal isovelocity surface area

HIGHLIGHTS

- VC/TA ratio can be used to correct TR severity for right heart size.
- VC/TA ratio ≥0.24 is independently associated with worse prognosis in STR.
- VC/TA ratio may improve risk stratification in STR with standard echocardiography.

method).[19,20] TV tenting height and area were measured from an RV-focused apical four-chamber view at mid-systole as the distance between the TA and TV leaflet coaptation point and as the area between the TA and TV leaflet body, respectively.[19,20] Pulmonary artery systolic pressure (PASP) was estimated from the tricuspid regurgitant jet peak velocity applying the modified Bernoulli equation and adding 3, 8, or 15 mm Hg according to inferior vena cava diameter and collapsibility.[18] In patients with atrial fibrillation, for all (color) Doppler measurements, the average of three to five beats was considered.

In the recently proposed classification of proportionate and disproportionate secondary mitral regurgitation, Grayburn *et al.*[12] used the ratio of EROA to LV end-diastolic volume (EDV) for the evaluation of secondary mitral regurgitation severity with respect to LV dilatation. The complex geometry of the right ventricle, however, does not allow a reliable measure of RV volumes using standard echocardiography, and in routine clinical practice, as well as in current guidelines, the RV-focused apical view is used to derive RV and tricuspid annular dimensions.[18] Therefore, two linear measures potentially derived from the sample plane of the same view, VC width (a parameter recommended in the guidelines to grade TR[7,8,19,20]) and tricuspid annular diameter (a parameter reflecting RV and RA remodeling[2,5,6] and currently recommended to set the indication for TV repair in patients with significant TR[8]), were chosen to define the ratio (Figure 1). In line with this assumption, in the present cohort, tricuspid annular diameter showed an excellent correlation with RV basal diameter (correlation coefficient = 0.856, $P < .001$) and a strong correlation with RA area (correlation coefficient = 0.666, $P < .001$), indicating an important relation between tricuspid annular diameter and both RA and RV size.

Follow-Up and Primary Outcome Definition

The primary end point was all-cause mortality. All patients were followed up for the occurrence of the primary end point. Survival data were retrieved from the departmental cardiology information system and the Social Security Death Index and were collected for all patients.

Statistical Analysis

Continuous variables are presented as mean ± SD in the case of Gaussian distribution and as median and interquartile range if not normally distributed. Normality was visually assessed by comparing the histograms of the sample data with a normal probability curve. Categorical variables are presented as absolute frequencies and percentages. Multivariate linear regression analyses were performed to characterize the independent associates of VC width and tricuspid annular diameter. Potential confounders with significant P values ($P < .05$) on univariate analysis were selected and included in the multivariate models. B coefficient and 95% CIs were calculated.

To assess the hazard ratio (HR) change for all-cause mortality across a range of VC/TA ratios, a spline-curve analysis was performed, and the population was divided according to the cutoff value of VC/TA ratio associated with excess mortality. Differences between groups were analyzed using the unpaired Student's t test for normally distributed continuous variables, the Mann-Whitney U test, for continuous variables not normally distributed, and the Pearson χ^2 test for categorical variables. To further characterize the echocardiographic and clinical characteristics associated with an increased VC/TA ratio (according to the cutoff value identified in the spline-curve analysis), a multivariate logistic regression analysis was conducted. Potential confounders with significant P values ($P < .05$) in the univariate analysis were included in the multivariate model. Odds ratios and 95% CIs were calculated.

Kaplan-Meier curves were used to estimate the 1- and 5-year cumulative survival rates, and differences between groups were analyzed using the Mantel-Cox log-rank test. A multivariate Cox

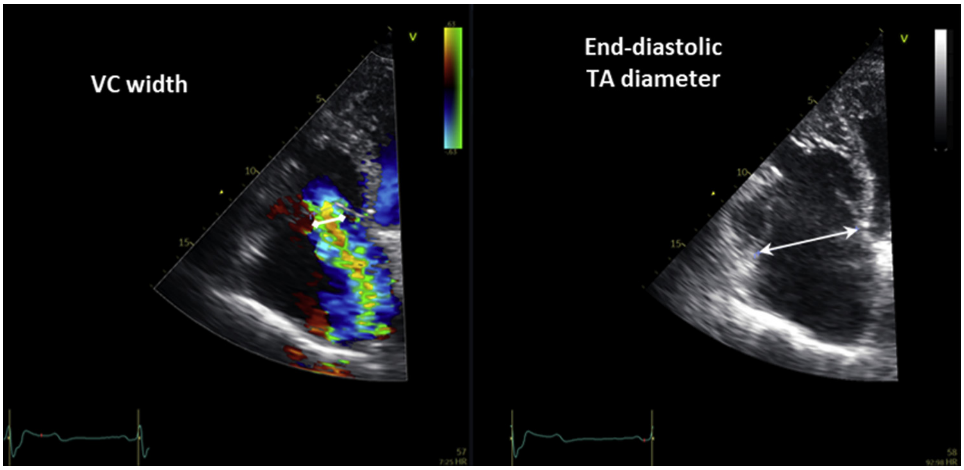

Figure 1 VC/TA ratio to identify disproportionate and proportionate STR. Proportionate and disproportionate STR may be defined on the basis of the ratio between two linear standard echocardiographic measurements: the numerator represents the grade of STR (VC width), while the denominator reflects right heart remodeling (tricuspid annular diameter). This approach makes it possible to mathematically relate STR grade to the dilatation of the TA.

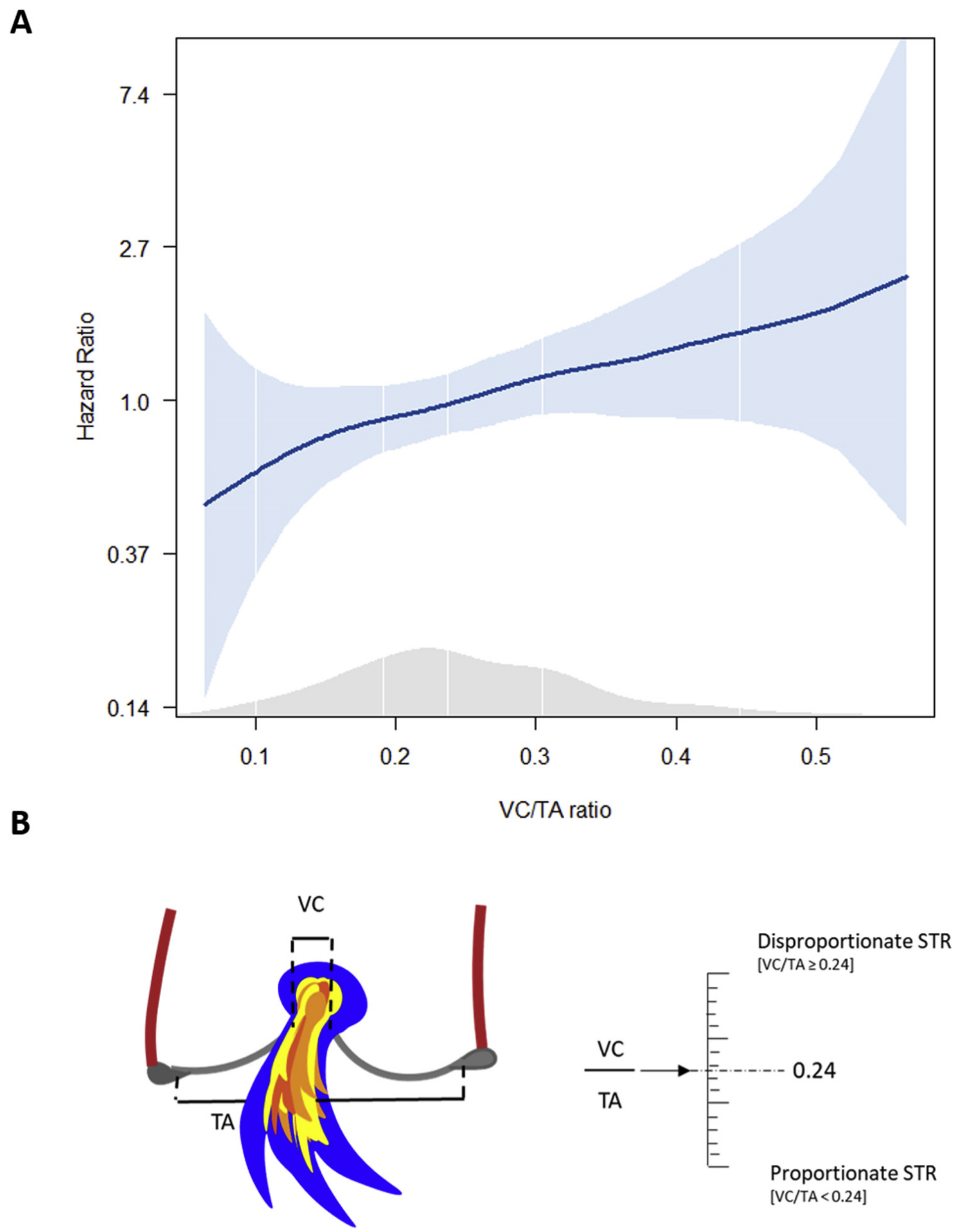

Figure 2 Relation between VC/TA ratio and all-cause mortality. The *blue curve* displayed in **(A)** shows the changes in the HR for all-cause mortality across different values of VC/TA ratio. The *gray density plot* shows the distribution of the population according to VC/TA ratio. **(B)** Cutoff value of 0.24 for VC/TA ratio, which was chosen to identify disproportionate and proportionate STR.

proportional-hazards regression analysis was performed to assess the clinical and echocardiographic factors that were independently associated with all-cause mortality. Possible confounders with significant *P* values ($P < .05$) in the univariate analysis were included in the multivariate regression analysis. HRs and 95% CIs were calculated. Two-sided *P* values $< .05$ were considered to indicate statistical significance.

Intra- and interobserver agreement for VC width, tricuspid annular diameter, and VC/TA ratio were investigated in a sample of 15 randomly selected subjects using intraclass correlation coefficients. Excellent agreement was defined by an intraclass correlation coefficient > 0.75, whereas strong agreement was defined by a value between 0.60 and 0.74. All data were analyzed using SPSS for Windows version 25 (IBM, Armonk, NY) and in R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria) using the Stats, Survival, rms, and Greg packages.

RESULTS

Patient Population

Overall, 334 patients met the inclusion criteria and were included in the study (Supplemental Figure 1); mean age was 70 ± 12 years, 40% were men, 79% had moderate STR, and 21% had severe STR according to conventional grading.[7,8,19,20] For VC/TA ratio, after a small plateau phase, the HR for all-cause mortality crossed the neutral effect

Table 1 Clinical characteristics of the study population and comparison between patients with VC/TA ratios < 0.24 and those with VC/TA ratios ≥ 0.24

Variable	Overall (*N* = 334)	VC/TA ratio < 0.24 (*n* = 169)	VC/TA ratio ≥ 0.24 (*n* = 165)	*P*
Age, y	70 ± 12	69 ± 12	71 ± 12	.066
Gender, male	133 (40)	76 (45)	57 (35)	.052
HR, beats/min	76 ± 19	75 ± 18	78 ± 20	.081
BMI, kg/m^2	25.60 ± 4.42	25.49 ± 4.62	25.72 ± 4.19	.689
Hypertension	228 (77)	116 (76)	112 (78)	.681
Hypercholesterolemia	125 (43)	72 (48)	53 (37)	.066
DM	50 (17)	23 (15)	27 (19)	.406
CAD	95 (29)	49 (30)	46 (28)	.768
COPD	45 (15)	19 (12)	26 (18)	.176
Renal impairment	98 (30)	51 (31)	47 (30)	.820
AF	142 (47)	67 (43)	75 (51)	.162
CIED	83 (25)	42 (25)	41 (25)	.975
Previous cardiac surgery*	99 (32)	46 (29)	53 (34)	.333
Dyspnea	157 (49)	71 (44)	86 (54)	.065
Peripheral edema				.177
Mild	37 (12)	15 (9)	22 (14)	
Moderate to severe	23 (7)	9 (6)	14 (9)	
Diuretic use	144 (45)	61 (38)	83 (53)	.007

AF, Atrial fibrillation; *BMI*, body mass index; *CAD*, coronary artery disease; *CIED*, cardiac implantable electronic device; *COPD*, chronic obstructive pulmonary disease; *DM*, diabetes mellitus; *HR*, heart rate.
Data are expressed as mean ± SD or number (percentage). Percentages were calculated on the basis of data availability.
*Including previous coronary artery bypass surgery or any valvular surgery.

(HR, 1.00) at 0.24 and steadily increased with greater values (Figure 2). According to this cutoff value, 165 patients (49%) of the study population had VC/TA ratios ≥ 0.24.

Clinical Characteristics

The clinical characteristics of the overall population and according to VC/TA ratio with the identified cutoff value of 0.24 are presented in Table 1. Approximately half of the patients were known to have atrial fibrillation. A total of 157 patients (49%) presented with dyspnea; furthermore, peripheral edema was observed in 60 patients (18%), and 144 patients (45%) were prescribed diuretics at the time of diagnosis of significant STR.

In per group analysis, patients with VC/TA ratios ≥ 0.24 and those with VC/TA ratios < 0.24 had similar demographic characteristics, prevalence of cardiovascular risk factors, and comorbidities. Patients with VC/TA ratios ≥ 0.24 were more likely to be treated with diuretics compared with their counterparts.

Echocardiographic Variables

VC width, tricuspid annular diameter, and VC/TA ratio showed excellent intra- and interobserver agreement (Supplemental Table 1). The multivariate linear regression analysis showed independent association between tricuspid annular diameter and the following parameters: RV basal diameter, RA area, VC width, and TV leaflet tenting area (Supplemental Table 2). As shown in Supplemental Table 3, TV leaflet tenting area showed also an independent association with VC width.

The echocardiographic characteristics of the overall population and according to VC/TA ratio with the identified cutoff value of 0.24 are presented in Table 2. Overall, 25% of the patients had concomitant significant aortic stenosis, and 18% had concomitant significant mitral regurgitation.

In per group analysis, patients with VC/TA ratios ≥ 0.24 and those with VC/TA ratios < 0.24 had similar LV dimensions and systolic function, RV end-diastolic area, and RV systolic function, whereas RV basal dimeter was larger in patients with VC/TA ratios < 0.24. On the contrary, patients with VC/TA ratios ≥ 0.24 had a higher prevalence of concomitant significant mitral regurgitation, had higher pulmonary artery pressures, and were more likely to present with severe STR (both on the basis of individual parameters of TR severity and conventional grading) compared with their counterparts. Figure 3 illustrates the prevalence of potential determinants of STR[24] in patients with VC/TA ratios ≥ 0.24 and <0.24. Interestingly, although almost all potential determinants of STR were numerically more frequent in patients with VC/TA ratios ≥ 0.24, only PASP ≥ 50 mm Hg and moderate to severe mitral regurgitation were significantly more represented in the group of patients with VC/TA ratio ≥ 0.24. In addition, the univariate logistic regression analysis showed significant associations between VC/TA ratio ≥ 0.24 and the following patient characteristics (Supplemental Table 4): LV EDV, moderate to severe mitral regurgitation, and PASP. After adjusting for potential confounders, LV EDV and PASP retained an independent association with VC/TA ratio ≥ 0.24.

Prognostic Impact of Increased VC/TA Ratio

During a median follow-up period of 62 months (interquartile range, 28–101 months), 128 patients (38%) died. Overall, the cumulative survival rates were 80% at 1 year and 63% at 5 years. The Kaplan-

Table 2 Echocardiographic characteristics of the study population and comparison between patients with VC/TA ratios < 0.24 and those with VC/TA ratios ≥ 0.24

Variable	Overall (*N* = 334)	VC/TA ratio < 0.24 (*n* = 169)	VC/TA ratio ≥ 0.24 (*n* = 165)	*P*
Left heart				
LV EDD, mm	43 ± 8	43 ± 9	43 ± 7	.642
LV ESD, mm	31 ± 8	31 ± 9	31 ± 8	.362
LV EDV, mL	87 (66–114)	91 (69–125)	85 (63–105)	.054
LVEF, %	61 (58–66)	61 (58–66)	61 (58–66)	.672
LA maximum volume, mL	76 (47–115)	70 (46–109)	83 (51–123)	.100
Significant AS	78 (25)	38 (24)	40 (25)	.722
Significant MR	58 (18)	22 (13)	36 (22)	.030
Right heart				
RV basal diameter, mm	44 ± 8	45 ± 8	42 ± 8	<.001
RV mid diameter, mm	35 ± 9	35 ± 9	35 ± 9	.671
RV base-to-apex length, mm	69 ± 10	70 ± 10	68 ± 10	.121
RV EDA, cm^2	23 ± 7	23 ± 7	22 ± 7	.607
RA area, cm^2	27 ± 10	26 ± 10	28 ± 10	.147
RA maximal long-axis distance, mm	61 ± 11	60 ± 11	62 ± 12	.136
Mid-RA minor distance, mm	51 ± 12	50 ± 12	51 ± 11	.480
FAC, %	39 ± 13	38 ± 12	40 ± 13	.895
TAPSE, mm	17 ± 6	17 ± 6	17 ± 6	.439
RV global longitudinal strain, %	15.3 ± 6	15.5 ± 6	15.1 ± 6	.531
RV free wall strain, %	17.8 ± 8	18.3 ± 8	17.2 ± 8	.260
PASP, mm Hg	40 (32–52)	37 (30–48)	42 (34–59)	.002
TV				
Annulus diameter, mm	41 ± 8	42 ± 8	40 ± 8	.084
VC width, mm	10 ± 4	8 ± 2	13 ± 3	<.001
PISA radius, mm	11 ± 4	9 ± 3	13 ± 3	<.001
EROA, mm^2	59 (39–92)	43 (29–60)	85 (56–111)	<.001
RVol, mL/beat	55 (35–91)	40 (24–58)	77 (54–110)	<.001
Leaflet tenting height, mm	7.0 (0–12)	6.5 (0–12)	8.0 (0–13)	.281
Leaflet tenting area, cm^2	1.6 (0–3.2)	1.4 (0–3.1)	1.7 (0–3.3)	.714

AS, Aortic stenosis; *EDA*, end-diastolic area; *EDD*, end-diastolic diameter; *EDV*, end-diastolic volume; *ESD*, end-systolic diameter; *FAC*, fractional area change; *LA*, left atrial; *LVEF*, LV ejection fraction; *MR*, mitral regurgitation; *PISA*, proximal isovelocity surface area; *RVol*, regurgitant volume; *TAPSE*, tricuspid annular plane systolic excursion.
Data are expressed as mean ± SD, median (interquartile range), or number (percentage). Percentages were calculated on the basis of data availability.

Meier analysis showed significantly lower survival rates in patients with VC/TA ratios ≥ 0.24 compared with those with VC/TA ratios < 0.24 (log-rank $\chi^2 = 6.802$, $P = .009$; Figure 4), whereas no significant difference was observed between patients with severe and moderate STR defined according to conventional grading (log-rank $\chi^2 = 0.109$, $P = .742$). The 1- and 5-year cumulative survival rates were significantly worse in patients with VC/TA ratios ≥ 0.24 compared with those with VC/TA ratios < 0.24 (75% vs 86% at 1 year [$P = .002$] and 55% vs 71% at 5 years [$P = .001$], respectively), while they were similar between patients with severe and moderate STR (76% vs 81% at 1 year [$P = .358$] and 60% vs 64% at 5 years [$P = .424$], respectively).

Univariable Cox regression analysis showed that age, diabetes mellitus, known coronary artery disease, chronic obstructive pulmonary disease, renal impairment, the presence of dyspnea, significant aortic stenosis, RV end-diastolic area, RV systolic function (evaluated with fractional area change, tricuspid annular plane systolic excursion, RV global longitudinal strain, or free wall strain), PASP, VC width, and VC/TA ratio ≥ 0.24 (HR, 1.583; 95% CI, 1.115–2.248; $P = .010$; Table 3) were associated with all-cause mortality. For collinearity reasons, several multivariate Cox regression models were constructed including one parameter of RV systolic function at a time. As shown in Table 4, VC/TA ratio ≥ 0.24 was independently associated with an increased risk for all-cause mortality in all the multivariate models, together with coronary artery disease, renal impairment, RV systolic function (evaluated with tricuspid annular plane systolic excursion or RV free wall strain but not with fractional area change) and pulmonary artery pressures. The presence of atrial fibrillation did not show any significant interaction on the effect of VC/TA ratio ≥ 0.24 on all-cause mortality (P for interaction = .482), indicating a consistent prognostic value of this ratio both in patients with and without atrial fibrillation. When introducing VC width (either as a

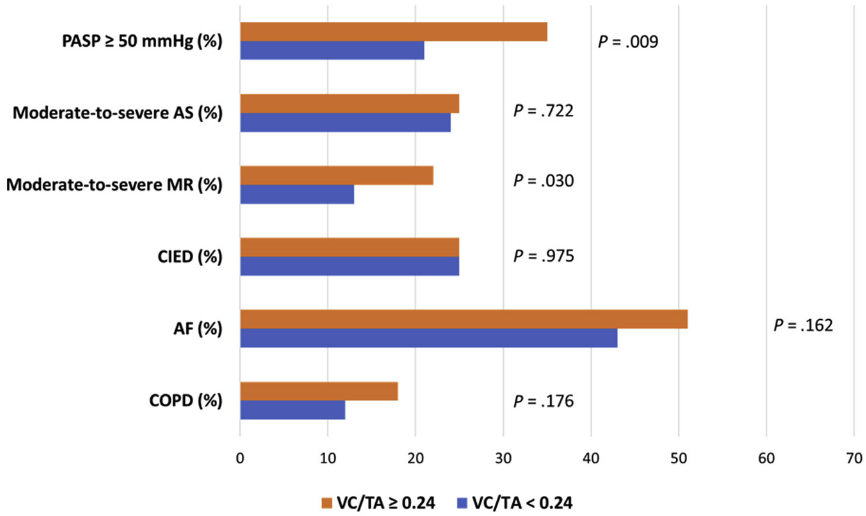

Figure 3 Prevalence of potential determinants of STR in patients with VC/TA ratios ≥ 0.24 versus those with VC/TA ratios < 0.24. The figure illustrates the prevalence of STR determinants in patients with VC/TA ratio ≥ 0.24 *(orange bars)* versus those with VC/TA ratios < 0.24 *(blue bars)*. *AF*, Atrial fibrillation; *AS*, aortic stenosis; *CIED*, cardiac implantable electronic device; *COPD*, chronic obstructive pulmonary disease; *MR*, mitral regurgitation.

continuous or a dichotomous variable using both the cutoff value for severe STR[19,20] and the recently proposed cutoff of 9 mm[25] to identify massive STR) in the Cox regression analysis, instead of VC/TA ratio ≥ 0.24, this parameter did not retain any significant association with the primary end point, suggesting that the evaluation of STR severity in relation to tricuspid annular dimensions provides additional predictive power compared with the isolated evaluation of STR severity (Supplemental Table 5). Moreover, severe STR as defined by individual parameters or according to the conventional multiparametric grading did not show any association with the primary outcome either in this analysis.

DISCUSSION

The present study showed that in patients with significant STR, a VC/TA ratio ≥ 0.24 is independently associated with an excess of

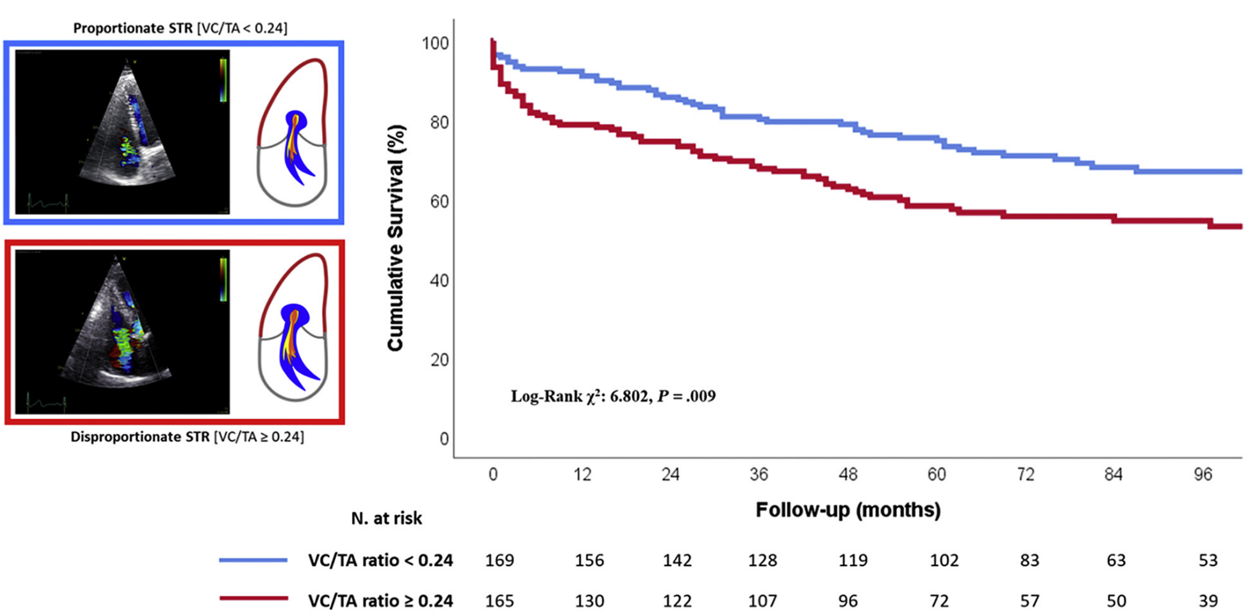

Figure 4 Kaplan-Meier curve for survival in patients with VC/TA ratios ≥ 0.24 versus those with VC/TA ratios < 0.24. The Kaplan-Meier curves show significantly lower 1- and 5-year survival rates for patients with VC/TA ratios ≥ 0.24 *(red line and box)* compared with those with VC/TA ratios < 0.24 (*light blue line and box*; 75% vs 86% at 1 year [$P = .002$] and 55% vs 71% at 5 years [$P = .001$], respectively).

Table 3 Univariate Cox regression analysis for all-cause mortality

Variable	Univariate analysis	
	HR (95% CI)	*P*
Patient demographics and comorbidities		
Age	1.027 (1.011–1.044)	.001
Male gender	1.028 (0.723–1.461)	.879
BMI	1.020 (0.972–1.070)	.424
AF	0.936 (0.654–1.341)	.720
Hypertension	1.001 (0.646–1.550)	.997
Hypercholesterolemia	1.142 (0.791–1.648)	.480
DM	2.281 (1.505–3.456)	<.001
CAD	2.069 (1.455–2.942)	<.001
COPD	2.160 (1.403–3.325)	<.001
Renal impairment	2.627 (1.839–3.752)	<.001
CIED	1.071 (0.724–1.586)	.731
Previous cardiac surgery	0.879 (0.599–1.291)	.511
Dyspnea	1.696 (1.188–2.421)	.004
Echocardiographic parameters		
LVEF	1.023 (0.998–1.048)	.077
LA volume	1.002 (1.000–1.004)	.088
Significant MR	1.454 (0.950–2.226)	.085
Significant AS	1.597 (1.088–2.346)	.017
RV basal diameter	1.014 (0.991–1.038)	.222
RV EDA	1.039 (1.015–1.062)	.001
FAC	0.976 (0.963–0.988)	<.001
TAPSE	0.933 (0.901–0.966)	<.001
RV GLS	0.947 (0.921–0.974)	<.001
RV free wall strain	0.958 (0.937–0.980)	<.001
RA area	1.012 (0.995–1.029)	.175
PASP	1.034 (1.025–1.043)	<.001
Severe TR*	1.073 (0.705–1.631)	.743
VC width	1.068 (1.021–1.117)	.004
VC width > 7 mm	1.354 (0.875–2.098)	.174
VC width > 9 mm	1.371 (0.965–1.948)	.078
EROA	1.003 (1.000–1.006)	.091
Tricuspid annular diameter	1.011 (0.989–1.035)	.330
VC/TA ratio ≥ 0.24	1.583 (1.115–2.248)	.010

AF, Atrial fibrillation; *AS*, aortic stenosis; *BMI*, body mass index; *CAD*, coronary artery disease; *CIED*, cardiac implantable electronic device; *COPD*, chronic obstructive pulmonary disease; *DM*, diabetes mellitus; *EDA*, end-diastolic area; *FAC*, fractional area change; *GLS*, global longitudinal strain; *LVEF*, LV ejection fraction; *MR*, mitral regurgitation; *TAPSE*, tricuspid annular plane systolic excursion.
*According to standard grading.

mortality and could therefore represent a new tool to improve risk stratification of these patients using standard echocardiography.

Correction of STR Severity for Tricuspid Annular Dimensions: A Novel Conceptual Framework

Recently, a new conceptual framework to classify secondary mitral regurgitation was proposed,[12] and it is based on the correction of secondary mitral regurgitation severity for LV dimensions using the ratio of EROA to LV EDV. This simple ratio makes it possible to define whether secondary mitral regurgitation can be entirely explained by LV dilatation (proportionate secondary mitral regurgitation) or if it exceeds the expected severity on the basis of LV dimensions, probably because of additional alterations of the valvular and subvalvular apparatus and/or LV dyssynchrony (disproportionate secondary mitral regurgitation).[12] Initial studies had shown the prognostic and clinical value of this pathophysiologically based classification. Bartko *et al.*[26] demonstrated that disproportionate secondary mitral regurgitation if left untreated is associated with an almost twofold increase in the risk for all-cause mortality compared with nonsevere secondary mitral regurgitation or proportionate secondary mitral regurgitation. Furthermore, Packer and Grayburn[13] showed the clinical value of this conceptual framework by retrospectively reassessing the results of randomized clinical trials, in which "proportionate" secondary mitral regurgitation tended to respond favorably to treatments aimed at LV reverse remodeling but did not seem to benefit from interventions intended to directly reduce secondary mitral regurgitation.[11,12] Differently, patients with "disproportionate" secondary mitral regurgitation benefited more from interventions directed at the mitral valve[10] or subvalvular apparatus[13] rather than simply targeting the left ventricle.

Similarly to secondary mitral regurgitation, the grade of STR had been associated with the remodeling of the right heart being secondary both to tricuspid annular dilatation[14,15] and to the distortion and tenting of the tricuspid subvalvular apparatus.[5,6] However, as proposed for secondary mitral regurgitation, STR severity could be greater than expected on the basis of a certain degree of tricuspid annular dilatation, because the distortion of leaflets, chordae, and/or papillary muscles may lead to a higher grade of leaflet malcoaptation. The same pathophysiologic concept developed to define disproportionate secondary mitral regurgitation could therefore be applied to the right heart to define disproportionate STR, potentially providing similar prognostic and clinical implications.

To define STR severity, current echocardiographic guidelines recommend the use of an integrative approach of multiple qualitative and quantitative parameters[7,8,19,20] derived mostly from the knowledge of left-sided valvular regurgitation.[9] Furthermore, the need to integrate measures of RV and RA dimensions in the assessment of STR severity has been advocated,[2,5,6] but so far no studies have adjusted STR grade for right heart dimensions (reflected by tricuspid annular size), and the concept of disproportionate STR has never been investigated. However, the geometric and functional characteristics of the right heart present specific challenges when translating this concept from secondary mitral regurgitation to STR. Considering the complex geometry of the right heart,[18] specifically when significant remodeling occurs,[27,28] standard echocardiography does not provide robust measurements of RV volumes. Therefore, in the present study, a ratio between two easily measurable, widely used, and reproducible parameters[18-21,23] both derivable from the same plane was chosen to facilitate the clinical application of this novel classification (Figures 1 and 2). Disproportionate STR could thus be defined using a VC/TA ratio cutoff of ≥0.24, which roughly corresponds to a VC width of one fourth or more of the tricuspid annular diameter.

Prognostic Significance and Clinical Implications

In the present study, disproportionate STR (VC/TA ratio ≥ 0.24) was associated with a 56% to 75% increase in the risk for all-cause

Table 4 Multivariate Cox proportional-hazard models for all-cause mortality

Variable	Multivariate model 1		Multivariate model 2		Multivariate model 3	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Patient demographics and comorbidities						
Age	1.021 (1.002–1.041)	.032	1.019 (1.000–1.039)	.051	1.018 (0.998–1.039)	.074
DM	1.262 (0.789–2.019)	.331	1.246 (0.770–2.014)	.370	1.350 (0.824–2.212)	.233
CAD	2.045 (1.349–3.102)	.001	2.255 (1.479–3.439)	<.001	2.251 (1.452–3.490)	<.001
COPD	1.240 (0.746–2.062)	.407	1.249 (0.743–2.097)	.401	1.169 (0.690–1.980)	.561
Renal impairment	2.064 (1.346–3.164)	.001	1.848 (1.210–2.823)	.004	1.875 (1.217–2.888)	.004
Dyspnea	1.230 (0.822–1.842)	.314	1.345 (0.897–2.019)	.152	1.222 (0.798–1.872)	.356
Echocardiographic parameters						
Significant AS	1.631 (1.059–2.512)	.026	1.498 (0.971–2.310)	.067	1.257 (0.803–1.967)	.317
RV EDA	1.007 (0.979–1.036)	.634	1.006 (0.977–1.036)	.683	1.008 (0.978–1.039)	.594
TAPSE	0.936 (0.899–0.975)	.001				
FAC			0.985 (0.969–1.001)	.062		
RV free wall strain					0.971 (0.944–0.999)	.039
PASP	1.031 (1.018–1.044)	<.001	1.026 (1.013–1.040)	<.001	1.029 (1.015–1.042)	<.001
VC/TA ratio ≥ 0.24	1.567 (1.044–2.352)	.030	1.564 (1.043–2.345)	<.001	1.749 (1.134–2.698)	.011

AS, Aortic stenosis; *CAD*, coronary artery disease; *COPD*, chronic obstructive pulmonary disease; *DM*, diabetes mellitus; *EDA*, end-diastolic area; *FAC*, fractional area change; *HR*, hazard ratio; TAPSE, tricuspid annular plane systolic excursion.

mortality, and the association with the primary outcome was retained after correcting for potential confounders such as age, comorbidities, previous cardiac surgery, presence of dyspnea, RV dimensions, systolic function, and pulmonary artery pressures. When assessed separately, neither tricuspid annular dimension nor VC width or other individual parameters of TR severity (such as EROA) were independently associated with all-cause mortality. This may underline the clinical relevance of the proposed concept because the definition of disproportionate STR implies the integration of STR severity and tricuspid annular dimensions (which reflects both RA and RV remodeling), providing additional prognostic information that cannot be derived by their independent evaluations.

Importantly, this novel approach also outperformed the STR grading system recommended in the current guidelines,[7,8,19,20] whose limits had already been noticed by looking at the results of the studies on transcatheter TV interventions.[4,9,29] Following the clinical implications derived by the definition of disproportionate or proportionate secondary mitral regurgitation,[12,13] it could be hypothesized that patients with proportionate STR (VC/TA ratio < 0.24) might benefit more from therapies targeting the causes of RA and/or RV remodeling, which in this case are the main determinants of STR, whereas interventions to repair the TV[3] could be more effective for patients with disproportionate STR (VC/TA ratio ≥ 0.24). Moreover, the identification of disproportionate STR could also have implications on the repair technique, which should address not only tricuspid annular dilation but probably also the presence of TV leaflet tethering. Although we showed that disproportionate STR if left untreated is related to worse prognosis compared with proportionate STR, these hypotheses need to be verified in dedicated prospective studies. Interestingly, our results, in accordance with the existing literature,[30] show that pulmonary pressures are important determinants of both STR severity and patient outcomes. Although patients with very high pulmonary pressures (estimated PASP > 60 mm Hg) have been excluded from previous and ongoing clinical trials of transcatheter TV interventions,[29,31] Lurz *et al.*[32] recently demonstrated similar outcomes after transcatheter TV repair in patients with and without pulmonary hypertension (defined as estimated and invasive PASP ≥ 50 mm Hg), encouraging further investigations in this subgroup of patients[33] and potentially also in patients with disproportionate STR and concomitant pulmonary hypertension.

Limitations

The limitations of this single-center study are inherent to its retrospective design. A time span of 21 years was considered for inclusion to acquire the large cohort as presented. Patients with cardiac implantable electronic device were not per se excluded, as the attribution of the device lead as the cause of TR is challenging in a retrospective study and is often just a bystander. The inclusion of patients from a single referral center and the exclusion of patients with impaired LV systolic function (i.e., LV ejection fraction < 55%) or who underwent TV interventions after the diagnosis of significant STR may represent a source of selection bias and may limit the external validity of this new classification, which would need to be verified in further studies as well as the cutoff value to define disproportionate STR. The proposed definition of disproportionate STR could be verified and improved using more accurate three-dimensional echocardiographic or cardiac magnetic resonance parameters of TR severity (i.e., VC area or regurgitant volume) and right heart remodeling (i.e., TV area or RV three-dimensional volumes)[9] compared with VC width and tricuspid annular diameter, which may be an oversimplification of the complex RV and TV anatomy; however, unlike standard echocardiography, these techniques are not widely available and might be time consuming. Finally, the usefulness of this novel approach to guide clinical decision-making needs to be tested in future prospective studies, preferably including also three-dimensional echocardiographic measurements.

CONCLUSION

VC/TA ratio ≥ 0.24 is independently associated with poor outcomes in patients with significant STR. This parameter may be considered a marker of disproportionate STR and could improve risk stratification and clinical decision-making in patients with STR.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.echo.2021.03.015.

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