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ORIGINAL RESEARCH

Prognostic Implications of a Novel Algorithm to Grade Secondary Tricuspid Regurgitation

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ABSTRACT

OBJECTIVES A novel tricuspid regurgitation (TR) grading system, using vena contracta (VC) width and effective regurgitant orifice area (EROA), was proposed and validated based on its prognostic usefulness.

BACKGROUND The clinical need of a new grading system for TR has recently been emphasized to depict the whole spectrum of TR severity, particularly beyond severe TR (massive or torrential).

METHODS TR severity was characterized in 1,129 patients with moderate or severe secondary TR (STR). Recently proposed cutoff values of VC width were more effective in differentiating the prognosis of patients with moderate STR, whereas EROA cutoff values performed better in characterizing the risk of patients with more severe STR. Therefore, these 2 parameters were combined into a novel grading system to define moderate (VC <7 mm), severe (VC ≥7 mm and EROA <80 mm^2), and torrential (VC ≥7 mm and EROA ≥80 mm^2) STR.

RESULTS A total of 143 patients (13%) showed moderate STR, whereas 536 patients (47%) had severe STR, and 450 (40%) had torrential STR. Patients with torrential STR had larger right ventricular (RV) dimensions, lower RV systolic function, and were more likely to receive diuretics. The cumulative 10-year survival rate was 53% for moderate, 45% for severe, and 35% for torrential STR ($p = 0.007$). After adjusting for potential confounders, torrential STR retained an association with worse prognosis compared with other STR grades (hazard ratio: 1.245; 95% confidence interval: 1.023 to 1.516; $p = 0.029$).

CONCLUSIONS A novel STR grading system was able to capture the whole range of STR severity and identified patients with torrential STR who were characterized by a worse prognosis. (J Am Coll Cardiol Img 2021;14:1085-95) © 2021 by the American College of Cardiology Foundation.

Tricuspid regurgitation (TR) is a common valvular heart disease, and based on its underlying mechanism, it can be classified as primary or secondary. Primary TR is caused by anatomic abnormalities of the tricuspid valve apparatus, whereas secondary TR (STR) is caused by tricuspid annular (TA) dilation or leaflet tethering due to right ventricular (RV) remodeling and is the

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ABBREVIATIONS AND ACRONYMS

EROA = effective regurgitant orifice area

HR = hazard ratio

PISA = proximal isovelocity surface area

RA = right atrium

RV = right ventricle

STR = secondary tricuspid regurgitation

TA = tricuspid annulus

TAPSE = tricuspid annular plane systolic excursion

TR = tricuspid regurgitation

VC = vena contracta

most frequent form of TR (1). Recently, both the increasing awareness of the negative prognostic impact of STR (2,3) and the possibility of also treating patients at high surgical risk with transcatheter valvular interventions (4) have increased the interest in better understanding the pathophysiology of STR and in improving its grading. At present, assessment of STR severity represents a clinical challenge and the currently recommended grading algorithm, which is based on echocardiographic parameters, is known to have several limitations (5).

Most of the measures used for STR grading are applied with cutoff values simply derived from studies on mitral regurgitation (5), which have never been or poorly validated in the setting of STR. Furthermore, the results of studies in patients who have undergone tricuspid valve interventions suggest that these cutoff values tend to capture only a limited range of regurgitation severity. For instance, patients enrolled in the SCOUT (Percutaneous Tricuspid Valve Annuloplasty System for Symptomatic Chronic Functional Tricuspid Regurgitation) trial presented with a grade of STR far beyond the conventional cutoff value to define severe TR (6). Based on these considerations, the concept of massive and torrential STR has been introduced to better characterize STR severity (5,7,8). New cutoff values for the most commonly used echocardiographic parameters to define STR severity, such as effective regurgitant orifice area (EROA) and vena contracta (VC) width, have been proposed. These parameters extend currently recommended ranges of STR (5,7,8), but their clinical usefulness has not been extensively demonstrated. Accordingly, the aim of the present study was to investigate the prognostic usefulness of the new cutoff values proposed for VC width and EROA in a large cohort of patients with STR. Furthermore, considering that a multiparametric approach is mostly suggested when assessing valvular heart disease severity, and in view of the advantages and disadvantages of different echocardiographic measures (5,9), EROA and VC width were combined to develop a flowchart to effectively characterize STR grades.

METHODS

PATIENT POPULATION. Patients diagnosed with at least moderate STR at the Leiden University Medical Center (Leiden, the Netherlands) between 1995 and 2016 were included in the study. Patients with primary TR (due to valve prolapse, endocarditis, rheumatic heart disease, or tumor), congenital heart disease, and who underwent tricuspid valve interventions after the diagnosis of significant STR were excluded. In addition, patients with incomplete echocardiographic data to quantify STR severity were excluded. All patients were evaluated with transthoracic echocardiography. STR severity was initially classified according to current guidelines (9) and afterward reclassified according to the new criteria proposed for VC width and EROA (5,7,8). Based on the ability of these new cutoff values to differentiate patient prognosis, VC width and EROA were integrated into a novel classification system for STR.

Clinical data were collected from the departmental Cardiology Information System (EPD-vision, Leiden University Medical Center) and analyzed retrospectively. This retrospective analysis was approved by the institutional review board of the Leiden University Medical Center, and the need for patient written informed consent was waived.

CLINICAL AND ECHOCARDIOGRAPHIC VARIABLES. The time of significant STR diagnosis by transthoracic echocardiography was identified as baseline. Baseline clinical features were collected and included demographics, symptoms of heart failure (i.e., dyspnea and peripheral edema), cardiovascular risk factors, comorbidities, and medications. Glomerular filtration rate was calculated by the Modification of Diet in Renal Disease formula, and severe renal impairment was defined as a glomerular filtration rate ≤30 ml/min/1.73 m^2.

Transthoracic echocardiographic data were acquired with patients at rest using available ultrasound systems (Vivid 7, E9 and E95 systems, GE-Vingmed, Milwaukee, Wisconsin) equipped with 3.5 MHz or M5S transducers, adjusting gain and depth settings. A commercially available software (EchoPAC version 113.0.3, 202 or 203, GE-Vingmed) was used to digitally store all images for off-line analysis. The parasternal, apical, and subcostal views were used to collect M-mode, 2-dimensional, as well as color and continuous- and pulse-wave Doppler data according to current recommendations (9-12).

STR severity was assessed by a multiparametric approach that included qualitative, semi-quantitative, and quantitative parameters measured on 2-dimensional, color, as well as continuous- and pulse-wave Doppler data as recommended by current guidelines (9). The grade of STR was then reclassified using the cutoff values recently proposed for VC width and EROA (5,7,8). For VC width, the following cutoff values were used: ≤6.9 mm defined moderate TR; 7 to 13.9 mm was considered severe TR; 14 to 20.9 mm defined massive TR; and ≥21 mm was considered torrential TR. For EROA, the following cutoff values were used: ≤39.9 mm^2 defined moderate TR; 40 to 59.9 mm^2 was considered severe TR; 60 to 79.9 mm^2 defined massive TR; and ≥80 mm^2 defined torrential TR. VC width was measured where best visualized, either in the apical 4-chamber view or in the RV-focused view, and it was identified as the narrowest portion of the regurgitant flow that occurs at or immediately downstream of the regurgitant orifice (9). EROA was estimated using the flow convergence method (also known as the proximal isovelocity surface area [PISA] method). The baseline of the color scale was shifted in the direction of the regurgitant jet to highlight an aliasing contour (at a certain aliasing velocity [Va]) where flow convergence has a roughly hemispheric shape. The PISA radius (r) was measured from the point of color Doppler aliasing to the VC. The peak velocity (pV) of the regurgitant jet of TR was measured from the continuous Doppler trace across the tricuspid valve. EROA was then calculated as: $(6.28 \cdot r^2 \cdot Va)/pV$ (9). In patients with atrial fibrillation, the average of 3 to 5 beats/min was considered for all (color) Doppler measurements.

RV dimensions and TA diameter were acquired on an RV-focused apical view at end-diastole; >40 mm was used to define TA dilation (13). RV systolic function was quantified based on tricuspid annular plane systolic excursion (TAPSE), and <17 mm was used to identify RV systolic dysfunction (14). RV fractional area change was also calculated, and <35% was used to define RV systolic dysfunction (10). Pulmonary artery systolic pressure was estimated from the tricuspid jet peak velocity applying the simplified Bernoulli equation and adding 3, 8, or 15 mm Hg based on inferior vena cava diameter and collapsibility (10). Mitral regurgitation and aortic stenosis were graded according to current recommendations (9,12), and a grade of moderate or higher was considered significant.

FOLLOW-UP AND ENDPOINT DEFINITION. All-cause mortality was the primary outcome. Survival data were assessed from the departmental Cardiology Information System and the Social Security Death Index and were complete for all patients.

STATISTICAL ANALYSIS. Categorical variables are expressed as absolute frequencies and percentages. Continuous variables are presented as mean ± SD in the case of normal distribution and as median (interquartile range) in the case of non-normal distribution. Adherence to normality was visually assessed by comparing histograms of the sample data to a normal probability curve. To assess the prognostic relevance of the new grading systems based on VC width and EROA (5,7,8), a Kaplan-Meier analysis was performed for both parameters separately, and survival rates between STR grades were compared with Mantel-Cox log-rank tests. Based on the ability of VC width and EROA to stratify patient prognosis, these 2 parameters were integrated into a novel grading system for significant STR. The added predictive value of the sequential combination of VC width and EROA (into the novel grading algorithm) compared with their independent use was verified with calculation of the chi-square change. Moreover, the hazard ratio (HR) change for all-cause mortality according to the values of VC width and EROA was investigated with a spline curve analysis. The concordance between STR grades defined according to the new cutoff values proposed for VC width and EROA (5,7,8) was analyzed using the Phi coefficient. For the Phi coefficient, values between 0 and 0.2 were interpreted as no correlation, 0.2 to 0.3 was considered a weak correlation, 0.3 to 0.4 was a moderate correlation, 0.4 to 0.7 was a strong correlation, and >0.7 was a very strong correlation.

Differences among these newly defined grades of STR (moderate, severe, and/or torrential STR) were analyzed using the 1-way analysis of variance for continuous variables with normal distribution, the Kruskal-Wallis test for non-normally distributed continuous variables, and Pearson's chi-square test for categorical variables. Multiple comparisons were performed with the Bonferroni correction.

Kaplan-Meier curves were used to estimate the 10-year survival rates, and differences between newly defined groups (moderate, severe, and/or torrential STR) were tested with the Mantel-Cox log-rank test. A multivariable Cox proportional hazard regression analysis was used to assess the clinical and echocardiographic features associated with all-cause mortality. Potential confounders with a significant p value at univariate analysis were included in the multivariable Cox regression analysis. The proportional hazards assumption was confirmed using statistics and graphs on the basis of the Schoenfeld residuals. Values of $p < 0.05$ were considered statistically significant. The intraobserver and interobserver agreements for VC width and EROA were investigated on a sample of 15 randomly selected subjects using intraclass correlation coefficients. An 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 with SPSS for Windows, version 25 (IBM Corp., Armonk, New York) and in R environment 4.0.1 (R

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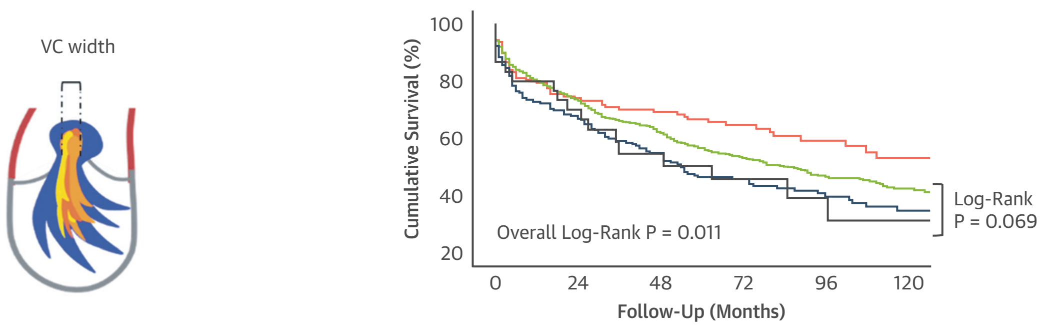
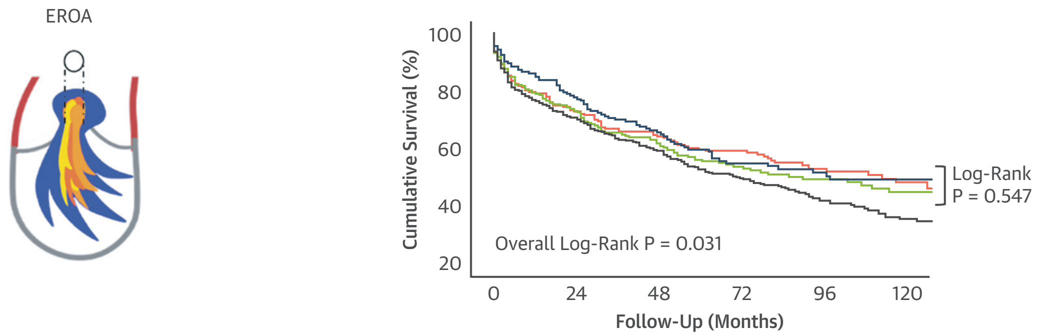
FIGURE 1 Prognostic Relevance of VC Width and EROA to Grade STR



	0	24	48	72	96	120
Moderate STR VC ≤6.9 mm	143	101	83	58	35	21
Severe STR VC 7 - 13.9 mm	747	545	421	263	151	85
Massive STR VC 14 - 20.9 mm	209	140	103	63	40	21
Torrential STR VC ≥21 mm	30	21	13	9	5	2



	0	24	48	72	96	120
Moderate STR EROA ≤39.9 mm^2	253	178	139	96	51	30
Severe STR EROA 40 - 59.9 mm^2	254	181	138	81	53	32
Massive STR EROA 60 - 79.9 mm^2	169	131	101	62	40	20
Torrential STR EROA ≥80 mm^2	453	317	242	154	87	47

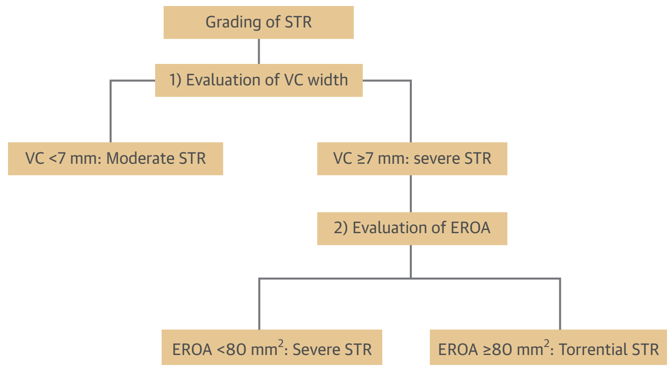
The survival rates of patients with severe to torrential secondary tricuspid regurgitation (STR) defined according to vena contracta (VC) width did not differ but were significantly worse compared with patients with moderate STR **(upper panel)**. In contrast, the survival rates of patients with moderate to massive STR defined according to effective regurgitant orifice area (EROA) **(lower panel)** did not differ but were significantly better compared with torrential STR.

Foundation for Statistical Computing, Vienna, Austria) using the Stats, Survival, rms, and Greg packages.

RESULTS

DEFINITION OF A NOVEL GRADING ALGORITHM FOR SIGNIFICANT STR. A total of 1,129 patients diagnosed with significant STR (79% moderate and 21% severe STR according to standard grading) were included in the analysis (median age: 72 years [range 63 to 79 years]; 50% men) (Supplemental Figure 1S). When considering VC width novel cutoff values, survival rates of the patients with severe, massive, and torrential STR were similar (log-rank $p = 0.069$) but significantly different from moderate STR (log-rank: $p = 0.017$) (Figure 1). Conversely, when considering novel EROA cutoff values, survival rates of patients with moderate, severe. and massive STR were similar (log rank $p = 0.547$), but they differed from those of the patients with torrential STR (log-rank $p = 0.005$) (Figure 1). VC width was thus more effective in differentiating the better survival of patients with moderate STR, whereas EROA performed better in characterizing the higher risk of patients with torrential STR. Furthermore, according to the Phi coefficient, VC width and EROA showed a strong correlation in identifying moderate STR but weak or no correlation in identifying severe or more STR (Supplemental Table 1S). Based on these considerations, a new algorithm to grade STR was developed combining VC width and EROA (Figure 2). A VC width <7 mm identified patients at lowest risk and defined moderate STR, whereas patients with a VC width ≥7 mm were further categorized according to EROA into severe (VC ≥7 mm and EROA <80 mm²) and torrential STR (VC width ≥7 mm and EROA ≥80 mm²). The novel algorithm reclassified 143 cases (13%) as moderate, 536 (47%) as severe, and 450 (40%) as torrential STR (**Figure 3**). The spline curve analyses supported the step-wise integration of VC width and EROA into the novel algorithm because the risk for all-cause mortality increased until it reached a peak, followed by a plateau for VC width, whereas it increased continuously without any plateau phase for higher values of EROA (Supplemental Figure 2S). Moreover, the sole use of VC width with the cutoff value of 7 mm could discriminate the better prognosis of patients with moderate TR compared with more severe TR (chi-square of the model including VC width: 5.618; $p = 0.018$), but the addition of EROA (with the cutoff value of 80 mm²) to the Cox model determined a significant improvement in predictivity (chi-square of the model including VC width and EROA: 10.315; $p = 0.006$; chi-square change compared with the model including only VC width: 4.518; $p = 0.034$). This once again supported the sequential integration of VC width and EROA as specified in our algorithm (**Figure 2**).

FIGURE 2 A Novel Algorithm to Grade Significant STR



The figure illustrates a novel algorithm to grade STR by combining VC width and EROA. Abbreviations as in **Figure 1**.

PATIENT POPULATION. **Clinical characteristics.** **Table 1** illustrates the clinical characteristics of the overall population and according to the newly defined STR grades. Overall, approximately one-half of the patients had known atrial fibrillation and presented with dyspnea. Approximately one-quarter presented with peripheral edema, and 57% were using diuretics. In per-group analysis, patients with moderate STR showed a lower prevalence of cardiovascular risk factors and had similar comorbidities compared with patients with severe or torrential STR. The prevalence of symptoms (dyspnea or peripheral edema) did not significantly differ among the various STR grades. Nonetheless, the patients with torrential STR were more likely to receive diuretic agents compared with those with milder STR.

Echocardiographic characteristics. In accordance with previous studies (15,16), both VC width and EROA showed an excellent intra- and interobserver agreement (Supplemental Table 2S).

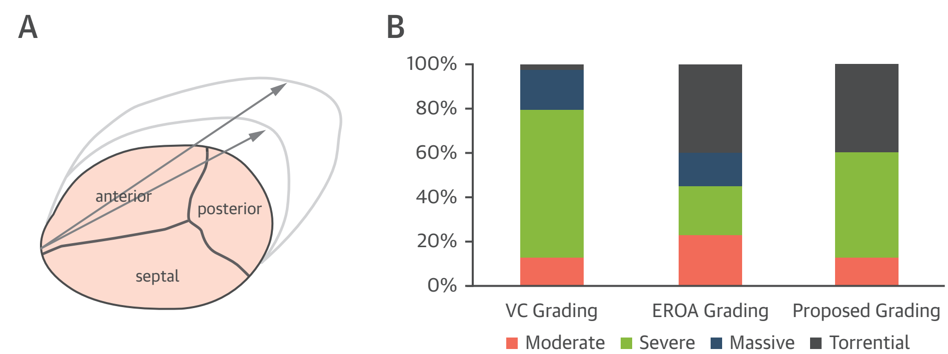
Table 2 summarizes the echocardiographic features of the overall population according to the newly defined STR severity. Overall, left ventricular systolic function was moderately impaired (mean left ventricular ejection fraction: 44 ± 16%), and approximately one-quarter of the patients presented with concomitant mitral regurgitation or aortic stenosis of at least a moderate grade. Importantly, 66% of the patients presented with RV systolic dysfunction according to TAPSE and 51% based on fractional area change, and more than one-half of the patients had a dilated TA.

In per-group analysis, patients with torrential STR had more impaired left ventricular ejection fraction, larger left atrial volumes, larger RV dimensions, a higher prevalence of RV systolic dysfunction according to TAPSE, larger TA diameters, and a higher prevalence of pacemaker or implantable cardioverter-defibrillator leads compared with patients with milder forms of STR.

PROGNOSTIC IMPACT OF THE NOVEL TR GRADING SYSTEM. During a median follow-up of 52 months (interquartile range: 18 to 88 months), 572 (51%) patients died. The cumulative 1-, 5- and 10-year survival rates were 79%, 56%, and 42%, respectively.

The Kaplan-Meier analysis showed significantly lower survival rates in patients with more advanced STR (log-rank chi-square: 10.790; $p = 0.005$) (**Central Illustration**). The cumulative 10-year survival rates were significantly different among the groups—53% for moderate STR, 45% for severe STR, and 35% for torrential STR ($p = 0.007$). Univariable Cox regression analysis showed that age, known coronary artery disease, diabetes, chronic obstructive pulmonary disease, severe renal impairment, left ventricular ejection fraction, concomitant significant mitral regurgitation or aortic stenosis, RV and RA dimensions, RV systolic dysfunction (both evaluated with TAPSE or fractional area change), pulmonary artery pressures, TA dilation, the presence of a

FIGURE 3 **The Need to Combine VC Width and EROA Into a New Comprehensive Grading System for STR**



(A) Progressive dilation of the tricuspid annulus that occurs more on its antero-posterior diameter than the septo-lateral diameter. The tricuspid regurgitant orifice may follow the same directions of the TA dilation, and this may explain the high level of agreement between VC width and EROA in identifying moderate STR (Supplemental Table S1) and **(B)** the higher detection rate of EROA for torrential STR. Abbreviations as in **Figure 1**.

pacemaker or implantable cardioverter-defibrillator lead, and torrential STR (HR for torrential STR vs. other STR grades: 1.271; 95% confidence interval: 1.078 to 1.499; $p = 0.004$) were associated with an increased risk of all-cause mortality. After adjusting for the previously mentioned potential confounders, torrential STR was independently associated with a 25% increased risk of all-cause mortality compared with the other STR grades (**Table 3**), together with age, diabetes, chronic obstructive pulmonary disease, severe renal impairment, left ventricular ejection fraction, concomitant significant aortic stenosis or mitral regurgitation, RV end-diastolic area, RV systolic dysfunction (evaluated with TAPSE but not with fractional area change), and pulmonary artery systolic pressure. In contrast, severe STR as defined by the current recommendations (9) did not show a significant association with the primary outcome.

DISCUSSION

The main findings of this study can be summarized as follows: although VC width performed well in stratifying the prognosis of patients with moderate versus severe STR, EROA effectively differentiated the risk of patients with torrential STR from those with moderate and severe STR. Based on these findings, VC width and EROA were combined into a novel algorithm to classify significant STR into 3 clinically meaningful categories: moderate, severe, and torrential. Importantly, a high percentage of patients (40%) presented with torrential STR at the time of diagnosis, and this condition was independently associated with worse prognosis.

A NOVEL ALGORITHM TO GRADE STR. Echocardiography is currently the imaging modality of choice to assess TR severity and to define its etiology. Current guidelines recommend a multiparametric approach that includes qualitative, semi-quantitative, and quantitative evaluations (9), but grading of TR nevertheless remains challenging (7,8). Qualitative and semi-quantitative parameters are highly subjective and therefore dependent on physician experience and prone to underestimation. For the quantitative parameters such as EROA and VC width, both American (9) and European (11) guidelines suggest the use of specific cutoff values to identify mild (VC width <3 mm and EROA <20 mm^2), moderate (VC width 3 to 6.9 mm and EROA 20 to 39 mm^2), and severe TR (VC width ≥7 mm and EROA ≥40 mm^2). Recently, it was reported that most patients enrolled in trials for tricuspid valve interventions far exceeded the lower threshold of severe TR (6,17), which suggested that current cutoff values did not comprehensively reflect the true spectrum of TR severity. For example, in the SCOUT trial, the mean value of EROA decreased from 85 ± 22 mm^2 to 63 ± 29 mm^2 after tricuspid valve percutaneous annuloplasty. This change was accompanied by a significant increase in RV stroke volume with improvements in quality of life measures (6). Nevertheless, the standard TR grading (9,11) failed to detect any improvement in TR grade after the procedure because EROA, as mentioned previously, remained far above the lower limit of severe TR (i.e., ≥40 mm^2).

To overcome these limitations, new cutoff values for the echocardiographic quantitative parameters were proposed to identify 2 additional categories of

TABLE 1 Clinical Characteristics of the Study Population and According to STR Grade

		New Grading System	VC Width ≥7 mm		
	Overall Population (N = 1,129)	Moderate STR (VC 3-6.9 mm) (n = 143)	Severe STR (EROA <80 mm^2) (n = 536)	Torrential STR (EROA ≥80 mm^2) (n = 450)	p Value
Demographic characteristics					
Age (yrs)	72 (63–79)	72 (65–78)	73 (64–79)	71 (61–78)	0.137
% male	568 (50)	65 (46)	267 (50)	236 (52)	0.329
BMI ≥30 kg/m^2	123 (14)	9 (8)	61 (15)	53 (15)	0.160
Medical history					
CAD	450 (40)	43 (31)*	219 (41)	188 (42)	0.047
Hypertension	839 (81)	95 (74)	403 (81)	341 (82)	0.137
Hypercholesterolemia	501 (48)	48 (38)*	258 (52)	195 (47)	0.012
DM	204 (20)	20 (16)	109 (22)	75 (18)	0.176
AF	527 (49)	61 (45)	238 (47)	228 (54)	0.043
COPD	154 (15)	27 (20)	74 (15)	53 (13)	0.102
eGFR ≤30 ml/min/1.73 m^2 (%)	97 (9)	8 (6)	49 (10)	40 (9)	0.450
Symptoms and medications					
Dyspnea	598 (55)	69 (51)*	277 (53)	252 (57)	0.219
Peripheral edema	244 (23)	28 (21)	111 (21)	105 (24)	0.470
Diuretic use	624 (57)	53 (39)*†	288 (55)†	283 (65)	<0.001

Values are median (interquartile range) or n (%). Percentages are calculated based on data availability. *$p < 0.05$ vs. severe secondary tricuspid regurgitation (STR). †$p < 0.05$ vs. torrential STR.

AF = atrial fibrillation; BMI = body mass index; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; EROA = effective regurgitant orifice area; VC = vena contracta.

TR grade (i.e., massive and torrential) (5,7,8). Initial studies tried to investigate the independent use of these new cutoff values for VC width (18,19) or EROA (20) to grade TR and to predict the prognosis of patients with primary or STR. However, no study so far has focused on STR (but included mixed etiology of TR), which has a different management and prognosis than primary TR. Furthermore, although the use of a multiparametric approach was recommended, most previous studies tested only individual parameters of TR severity (either EROA or VC width), and none of them tried to integrate these 2 parameters into an algorithm to classify TR severity based on their ability to discriminate patient prognosis. The present study included the largest cohort so far of patients with significant STR and showed that the new cutoff values for EROA and VC width had high concordance in defining moderate STR but weak or no correlation in identifying more than severe STR. Moreover, EROA showed a higher detection rate for torrential STR compared with VC width (**Figure 3B**). A possible explanation of the differences in performance of these indexes might relate to geometric changes of the regurgitant orifice of STR with an increase in severity. STR imposes a condition of chronic volume overload on the RV, which induces further remodeling (21) and progressive dilation of the TA (**Figure 3A**) (22). With worsening of STR, the TA dilates more in the antero-posterior than in the septo-lateral dimension, and the size of the regurgitant orifice might increase following the same directions (23). These geometric changes in relation to the roughly elliptical shape of the tricuspid regurgitant orifice could explain the failure of VC width and the usefulness of EROA (calculated with the PISA method) to differentiate torrential from severe STR.

PROGNOSTIC IMPLICATIONS OF THE NOVEL STR GRADING SYSTEM. Several studies have shown the association between STR severity and mortality risk (2,3,24,25). Recently, Bartko et al. (26) demonstrated that the mortality risk in patients with TR increased continuously with the increase of quantitative parameters of TR severity such as EROA (HR per 1 mm^2 increase: 1.01; $p < 0.001$) and VC width (HR per 1 mm increase: 1.11; $p < 0.001$). Nevertheless, the current grading system does not take into account an increase of VC width or EROA above the cutoff values for severe TR, and therefore, may be limited in risk stratifying very advanced STR. The conventional 3 TR categories (i.e., mild, moderate, and severe) allow only identification of the lower end of the spectrum of TR severity and significantly lack power in further prognosticating TR that exceeds the lower limit of severe. In view of the inadequacy of current TR grading, the introduction of 2 new TR categories

TABLE 2 Echocardiographic Characteristics of the Study Population and According to STR Grade

		New Grading System			
			VC Width ≥7 mm		
	Overall Population (N = 1,129)	Moderate STR (VC 3-6.9 mm) (n = 143)	Severe STR (EROA <80 mm²) (n = 536)	Torrential STR (EROA ≥80 mm²) (n = 450)	p Value
Left heart					
LV EDV (ml)	111 (80–166)	112 (75–172)	105 (77–155)*	118 (84–188)	0.001
LV EF (%)	44 ± 16	46 ± 16	45 ± 16*	42 ± 15	0.002
LA maximum volume (ml) (ml/m²)	93 (59–128)	63 (43–99)*†	87 (57–123)	102 (75–140)	<0.001
Significant MR (%)	291 (26)	32 (23)	138 (26)	121 (27)	0.570
Significant AS (%)	253 (23)	41 (30)	123 (24)	89 (21)	0.118
Right heart					
RV basal diameter (mm)	45 ± 8	45 ± 8*	44 ± 8*	47 ± 8	<0.001
RV mid diameter (mm)	35 ± 9	33 ± 8*	34 ± 8*	38 ± 9	<0.001
RV base-to-apex length (mm)	72 ± 12	72 ± 12	70 ± 12*	74 ± 12	<0.001
RV EDA (cm²)	24 (19–30)	22 (16–28)*	22 (18–28)*	27 (21–33)	<0.001
FAC (%)	34 ± 13	36 ± 14	35 ± 13	33 ± 13	0.038
FAC <35% (%)	574 (51)	65 (46)	266 (50)	243 (54)	0.178
TAPSE (mm)	15 ± 5	17 ± 5*†	15 ± 5	15 ± 5	<0.001
TAPSE <17 mm (%)	744 (66)	66 (47)*†	360 (67)	318 (71)	<0.001
PASP (mm Hg)	44 ± 16	42 ± 15†	47 ± 16*	42 ± 15	<0.001
Tricuspid valve					
Annular diameter (mm)	42 ± 8	37 ± 7*†	41 ± 7*	45 ± 8	<0.001
Annulus >40 mm	630 (56)	48 (34)*†	269 (50)*	313 (70)	<0.001
Vena contracta (mm)	10 (8–13)	5 (4–6)*†	9 (8–11)*	13 (11–16)	<0.001
EROA (mm²)	67 (43–104)	22 (14–38)*†	50 (39–64)*	115 (95–157)	<0.001
PM/ICD lead (%)	410 (37)	32 (23)*	165 (31)*	213 (48)	<0.001

Values are median (interquartile range), mean ± SD, or n (%). Percentages are calculated based on data availability. *$p < 0.05$ vs. torrential STR. †$p < 0.05$ vs. severe STR.

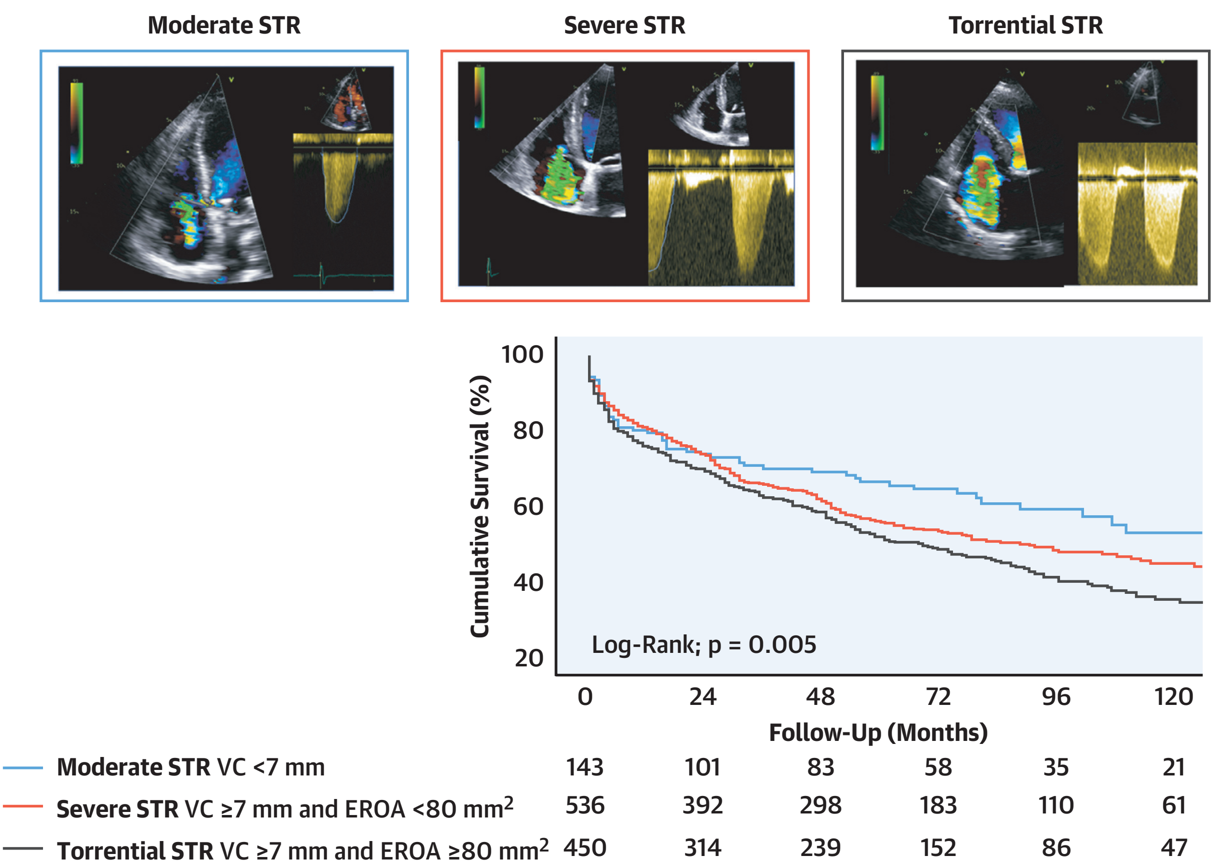
AS = aortic stenosis; EDA = end-diastolic area; EDV = end-diastolic volume; EF = ejection fraction; FAC = fractional area change; ICD = implantable cardioverter-defibrillator; LA = left atrium; LV = left ventricle; MR = mitral regurgitation; PASP = pulmonary artery systolic pressure; PM = pacemaker; RA = right atrium; RV = right ventricle; STR = secondary tricuspid regurgitation; TAPSE = tricuspid annular plane excursion; other abbreviation as in Table 1.

(massive and torrential) were proposed (5,7,8). However, the cutoff values to define these new TR grades were only based on the extension of current values used to define mild, moderate, and severe TR, and their clinical usefulness for prognostication has not been extensively investigated. In the present study, the prognostic value of the new TR categories based on the combination of VC width and EROA was assessed in a large cohort of patients with STR with a long-term follow-up. Although the prognosis of patients with torrential STR was significantly worse compared with the other STR grades, the prognosis of massive STR did not differ from that of patients with severe STR (either defined with VC width or EROA). Accordingly, massive STR was considered a redundant category and was not implemented into the proposed algorithm.

The novel proposed classification of STR (**Figure 2**) integrated VC width and EROA based on their ability to differentiate prognosis (**Figure 1**). This algorithm was designed by including the measure of VC width as first step to distinguish moderate and severe STR and then EROA (with a cutoff value of 80 mm²) was added to allow identification of torrential STR. The detection of torrential STR was of particular importance because, compared with other STR grades, torrential STR was independently associated with 25% increased risk of all-cause mortality. Interestingly, 40% of the patients of this cohort presented with torrential STR at the time of diagnosis, and this condition was characterized by more advanced RV remodeling (i.e., RV dilation and systolic dysfunction) that supported an early referral and close follow-up to avoid the occurrence of adverse and potentially irreversible alterations.

CLINICAL IMPLICATIONS. This novel quantitative classification for STR might overcome several limitations of the current grading system and could be effectively integrated into a more complex comprehensive clinical evaluation or scoring system (27) that is needed when assessing patients with significant STR. First, this algorithm was based on easy and widely available echocardiographic measurements

CENTRAL ILLUSTRATION Kaplan-Meier Curves for Survival in Patients With Moderate, Severe, and Torrential Secondary Tricuspid Regurgitation Defined According to the Proposed Novel Algorithm to Grade Significant Secondary Tricuspid Regurgitation



Fortuni, F. et al. J Am Coll Cardiol Img. 2021;14(6):1085–95.

The Kaplan-Meier curves start to separate after 2 years and show significantly lower 10-year cumulative survival rates in patients with more advanced secondary tricuspid regurgitation (STR) (53% for moderate STR **[blue box and blue line]**, 45% for severe STR **[red box and red line]**, and 35% for torrential STR **[black box and black line]**). EROA = effective regurgitant orifice area; VC = vena contracta.

(i.e., EROA and VC width) and proposed a simplified and standardized approach that might help introduction in the clinical setting, and therefore, refine the assessment and follow-up of these patients. Second, it permitted further characterizing severe STR with the introduction of torrential STR, which is associated with worse prognosis and might benefit from treatment before irreversible RV remodeling occurs. Third, it might allow the detection of an eventual improvement in STR grade after tricuspid valve interventions. For instance, after transcatheter tricuspid valve annuloplasty, EROA might significantly decrease while TR remains severe according to the current classification. The newly proposed algorithm might detect a significant improvement from torrential to severe TR that, based on our data, could be likely related to a better prognosis.

STUDY LIMITATIONS. This was a single-center study that included a large cohort of patients over a time span of 21 years, and its limitations were inherent to its retrospective design. Although standard echocardiography remains the mainstay imaging modality for TR identification and grading in clinical practice, VC width and EROA have known limitations (9,11). The use of more advanced imaging techniques, such as 3-dimensional echocardiography or cardiac magnetic resonance, might allow for a better definition of STR severity. In particular, 3-dimensional echocardiography could help to better characterize the shape of the

TABLE 3 Univariable and Multivariable Cox Proportional Hazard Models for All-Cause Mortality

	Univariate Analysis		Multivariate Analyses			
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Patient demographics and comorbidities						
Age	1.023 (1.015–1.030)	<0.001	1.029 (1.020–1.038)	<0.001	1.028 (1.020–1.037)	<0.001
Male	1.171 (0.994–1.380)	0.060				
BMI ≥30 kg/m²	0.886 (0.674–1.166)	0.389				
CAD	1.600 (1.357–1.886)	<0.001	1.151 (0.949–1.397)	0.153	1.170 (0.965–1.418)	0.111
Hypertension	0.949 (0.766–1.174)	0.627				
Hypercholesterolemia	1.150 (0.971–1.363)	0.104				
DM	1.713 (1.408–2.084)	<0.001	1.373 (1.100–1.713)	0.005	1.362 (1.090–1.702)	0.006
AF	1.070 (0.905–1.264)	0.430				
COPD	1.696 (1.367–2.105)	<0.001	1.328 (1.043–1.690)	0.021	1.336 (1.051–1.700)	0.018
GFR ≤30 ml/min/1.73 m²	2.603 (2.048–3.308)	<0.001	1.862 (1.417–2.446)	<0.001	1.842 (1.404–2.417)	<0.001
Echocardiographic parameters						
LVEF	0.983 (0.978–0.988)	<0.001	0.989 (0.983–0.996)	0.001	0.989 (0.982–0.995)	<0.001
Moderate-to-severe AS	1.449 (1.201–1.747)	<0.001	1.246 (1.011–1.536)	0.039	1.270 (1.031–1.564)	0.025
Moderate-to-severe MR	1.521 (1.272–1.818)	<0.001	1.244 (1.018–1.521)	0.033	1.236 (1.012–1.510)	0.038
RV basal diameter (mm)	1.020 (1.011– 1.030)	<0.001				
RA area (cm²)	1.008 (1.001–1.015)	0.018	0.997 (0.987–1.007)	0.569	0.997(0.987–1.007)	0.570
RV EDA (cm²)	1.007 (1.004–1.011)	<0.001	1.010 (1.005–1.015)	<0.001	1.009 (1.004–1.014)	<0.001
TAPSE <17 mm	1.509 (1.256–1.813)	<0.001	1.256 (1.018–1.550)	0.034		
FAC <35%	1.415 (1.199–1.669)	<0.001			1.061 (0.873–1.290)	0.554
PASP (mm Hg)	1.022 (1.017–1.028)	<0.001	1.017 (1.011–1.023)	<0.001	1.017 (1.011–1.023)	<0.001
TA diameter >40 mm	1.206 (1.020–1.425)	0.028	1.001 (0.809–1.237)	0.996	1.014 (0.820–1.253)	0.900
PM/ICD lead	1.389 (1.176–1.640)	<0.001	1.198 (0.989–1.452)	0.065	1.187 (0.979–1.440)	0.081
Severe STR*	1.144 (0.940–1.393)	0.180				
New STR grading system		0.005				
Moderate vs. torrential	0.648 (0.485–0.865)	0.003				
Severe vs. torrential	0.825 (0.649–0.980)	0.029				
Torrential vs. moderate to severe	1.271 (1.078–1.499)	0.004	1.245 (1.023–1.516)	0.029	1.251 (1.027–1.523)	0.025

*Defined according to current recommendations (9).
CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1 and 2.

regurgitant orifice that might determine an underestimation of TR severity with the PISA method (28). Nevertheless, these imaging techniques could be time-consuming; their use is not widely available in daily clinical practice compared with 2-dimensional echocardiography. Although a correction for low-flow velocities to improve the estimation of TR severity with the PISA method was described in published reports (16,29), this was not applied in the present study, because it was not recommended by current guidelines (9); and the uncorrected EROA showed a clear prognostic value. The usefulness of the proposed grading algorithm in guiding clinical management and predicting prognosis would need to be further validated in other cohorts.

CONCLUSIONS

A novel algorithm based on standard echocardiographic measurements (i.e., VC width and EROA) could improve the classification of STR severity with the introduction of a new category, torrential STR, which was independently associated with worse prognosis.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The current grading system of TR captures only the lower end of TR severity. A novel prognostic relevant grading algorithm based on VC width and EROA can characterize the whole spectrum of TR severity and identify patients with torrential TR who have a worse prognosis.

TRANSLATIONAL OUTLOOK: Future studies could investigate the benefit of transcatheter interventions on patients with TR according to the newly defined TR categories.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.