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ORIGINAL RESEARCH

Epiphenomenon or Prognostically Relevant Interventional Target? A Novel Proportionality Framework for Severe Tricuspid Regurgitation

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BACKGROUND: Tricuspid regurgitation (TR) frequently develops in patients with long-standing pulmonary hypertension, and both pathologies are associated with increased morbidity and mortality. This study aimed to improve prognostic assessment in patients with severe TR undergoing transcatheter tricuspid valve intervention (TTVI) by relating the extent of TR to pulmonary artery pressures.

METHODS AND RESULTS: In this multicenter study, we included 533 patients undergoing TTVI for moderate-to-severe or severe TR. The proportionality framework was based on the ratio of tricuspid valve effective regurgitant orifice area to mean pulmonary artery pressure. An optimal threshold for tricuspid valve effective regurgitant orifice area/mean pulmonary artery pressure ratio was derived on 353 patients with regard to 2-year all-cause mortality and externally validated on 180 patients. Patients with a tricuspid valve effective regurgitant orifice area/mean pulmonary artery pressure ratio ≤1.25 mm^2/mm Hg (defining proportionate TR) featured significantly lower 2-year survival rates after TTVI than patients with disproportionate TR (56.6% versus 69.6%; P=0.005). In contrast with patients with disproportionate TR (n=398), patients with proportionate TR (n=135) showed more pronounced mPAP levels (37.9±9.06 mm Hg versus 27.9±8.17 mm Hg; $P<2.2\times10^{-16}$) and more severely impaired right ventricular function (tricuspid annular plane systolic excursion: 16.0±4.11 versus 17.0±4.64 mm; P=0.012). Moreover, tricuspid valve effective regurgitant orifice area was smaller in patients with proportionate TR when compared with disproportionate TR (0.350±0.105 cm^2 versus 0.770±0.432 cm^2; $P<2.2\times10^{-16}$). Importantly, proportionate TR remained a significant predictor for 2-year mortality after adjusting for demographic and clinical variables (hazard ratio, 1.7; P=0.006).

CONCLUSIONS: The proposed proportionality framework promises to improve future risk stratification and clinical decision-making by identifying patients who benefit the most from TTVI (disproportionate TR). As a next step, randomized controlled studies with a conservative treatment arm are needed to quantify the net benefit of TTVI in patients with proportionate TR.

Key Words: pulmonary hypertension ■ transcatheter tricuspid valve intervention ■ tricuspid regurgitation

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CLINICAL PERSPECTIVE

What Is New?

- Cohort studies have demonstrated that transcatheter tricuspid valve interventions elicit survival-prolonging effects in patients with severe tricuspid regurgitation (TR).
- However, a 1-size-fits-all approach is not necessarily applicable to a heterogeneous patient population as encountered in patients with severe TR, and future patient selection therefore demands refined mechanistic models for prognostic assessment.

What Are the Clinical Implications?

- This study proposes a proportionality framework for severe TR by relating the tricuspid valve insufficiency to the afterload burden imposed from the pulmonary circulation.
- Derived on 353 patients and externally validated on 180 patients with severe TR, a tricuspid valve effective regurgitant orifice area/mean pulmonary artery pressure ratio ≤1.25 mm^2/mm Hg (defining proportionate TR) was associated with lower 2-year survival rates after transcatheter tricuspid valve intervention.
- The proposed proportionality framework could therefore improve future risk stratification and clinical decision-making by addressing the crucial question: Is this case of TR a prognostically relevant interventional target, or does it merely represent an indicator of worse prognosis in patients with pulmonary hypertension?

Nonstandard Abbreviations and Acronyms

COAPT	Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation
MITRA-FR	Percutaneous Repair With the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation
mPAP	mean pulmonary artery pressure
PH	pulmonary hypertension
sPAP	systolic pulmonary artery pressure
TAPSE	tricuspid annular plane systolic excursion
TR	tricuspid regurgitation
TTVI	transcatheter tricuspid valve intervention
TV EROA	tricuspid valve effective regurgitant orifice area

Long-standing tricuspid regurgitation (TR) translates into poor survival,[1] and mortality increases with rising stages of TR severity.[2] However, TR has long been a forgotten valve disease of benign reputation, leading to the consequence that >90% of patients with clinically relevant TR are not offered any treatment beyond conservative management.[3] Functional TR, which accounts for >80% of cases,[4] was traditionally believed to improve upon resolution of the underlying cause, such as severe aortic stenosis or mitral regurgitation, but a growing body of evidence demonstrates that TR persists in a substantial number of cases, for example, after transcatheter aortic valve replacement.[5,6] The once triggered and later self-sustaining vicious circle of volume overload and increased wall stress of the right ventricle, detrimental remodeling including tricuspid annulus dilatation and papillary muscle displacement, and further worsening of TR, could be interrupted by transcatheter tricuspid valve intervention (TTVI).[7]

In the absence of randomized controlled trials, 2 propensity score–matched analyses comparing TTVI with standard medical treatment in inoperable or surgical high-risk patients with severe TR provide the best level of evidence to date that TTVI is associated with better survival rates.[8,9] However, a 1-size-fits-all approach is not necessarily applicable to heterogeneous patient populations as encountered in patients with severe TR, and it may even place some patients at risk for futile or even harmful interventions. A stratification system that considers the heterogeneity in etiology, cardiac status, and comorbidities is therefore necessary to properly evaluate the expected benefit of TTVI.

Akin to the conceptual framework by Grayburn et al,[10] who distinguish proportionate and disproportionate functional mitral regurgitation to explain distinct outcomes following interventions directed at the mitral valve, Fortuni et al[11] proposed to adapt this concept to conservatively managed patients with moderate or severe TR by relating the extent of valvular insufficiency to the degree of tricuspid annulus dilatation. However, it should be debated which pathology best serves to distinguish proportionate from disproportionate TR. The prognostic significance of pulmonary hypertension (PH) for survival after TTVI is well established.[12–14] To place severity of TR into the context of potentially elevated pulmonary artery pressures therefore provides at least 3 advantages:

1. It relates TR severity to a pathology that is causally upstream of the interventional target.
2. PH is unlikely to resolve upon restoration of tricuspid valve integrity.
3. Persistent extra-tricuspid valve cardiac damage such as PH represents an important determinant of prognosis following TTVI.

The present study hypothesizes that relating the extent of tricuspid valve insufficiency to the hemodynamic burden imposed from the pulmonary circulation could further refine the classification of patients with proportionate and disproportionate severe TR. Thus, our proportionality model aims to help gain an understanding whether the tricuspid valve insufficiency is a direct consequence of PH or if there exist additional pathologies that cause a disproportionally large tricuspid valve effective regurgitant orifice area (TV EROA; see Figure 1 for a graphical illustration of the proposed proportionality framework). Per definition, the extent of valvular insufficiency in patients with disproportionate severe TR would exceed that expected on the degree of pulmonary artery pressures. According to our hypothesis, patients with disproportionate severe TR are the ones that benefit the most from TTVI. If proven, stratification according to the hereby proposed proportionality concept of tricuspid valve insufficiency could improve prognostication of survival following TTVI and possibly guide patient selection in the future.

METHODS

The data underlying this article will be shared upon reasonable request to the corresponding author. All requests for raw and analyzed data and related materials, excluding programming code, will be reviewed by the Ethics Committee at Ruhr University Bochum, Germany. Any data and materials that can be shared will be released via a Material Transfer Agreement.

Study Population

This is a post hoc, multicentric analysis of prospectively and systematically collected data from 702 patients undergoing TTVI for severe TR from 2016 to 2021. The key inclusion criterion was moderate-to-severe or severe TR[15] with high symptomatic burden despite optimal medical treatment. Patients were further deemed inoperable because of prohibitive perioperative risk as assessed by the local heart team. Planned and conducted in conformity with the Declaration of Helsinki, the study was approved by the local ethics committee of each center,

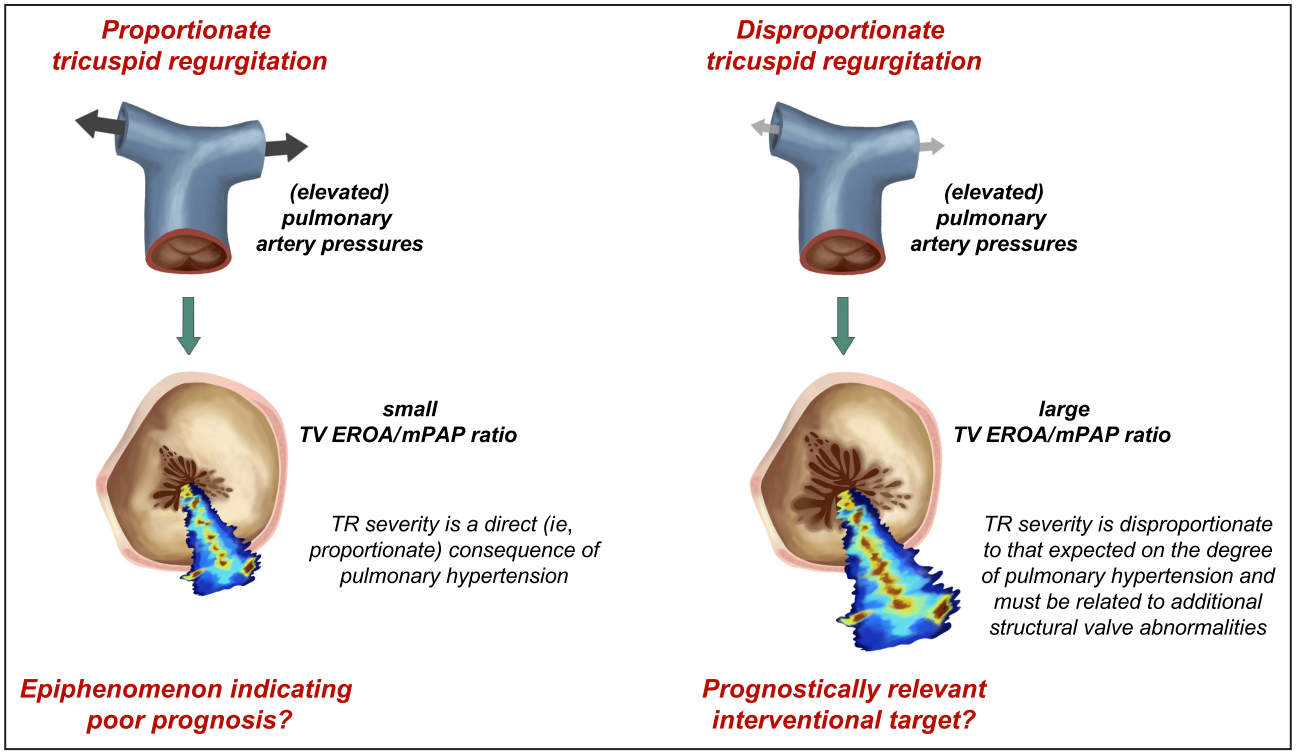

Figure 1. Graphical hypothesis of the proposed proportionality framework for severe TR adjusted to pulmonary artery pressure levels.
The proposed proportionality framework puts TR severity into context with pulmonary artery pressure levels, which are unlikely to be ameliorated upon TTVI. The expected benefit of transcatheter repair would accordingly be limited in patients with proportionate TR, because PH as the disease-triggering pathology persists and further challenges the potentially impaired right ventricle. Taken together, the proportionality framework could thus improve future risk stratification and clinical decision-making by addressing the crucial question: Is this case of TR a prognostically relevant interventional target, or does it merely represent an indicator of worse prognosis in patients with PH? mPAP indicates mean pulmonary artery pressure; TR, tricuspid regurgitation; and TV EROA, tricuspid valve effective regurgitant orifice area.

and all patients provided written informed consent. Patients with incomplete data to calculate the TV EROA to mean pulmonary artery pressure (mPAP) ratio (ie, missing TV EROA or mPAP levels) were specifically excluded. For the discovery analysis, patient data from 3 independent institutions were collected (Heart and Diabetes Center North Rhine-Westphalia in Bad Oeynhausen, Heart Center at University of Cologne Hospital, and Ludwig Maximilians University Hospital of Munich), hereinafter referred to as the derivation cohort. Moreover, an external validation cohort of equally treated patients was provided by 2 independent institutions (Heart Center at University of Leipzig and Department of Cardiology at Bern University Hospital).

Echocardiographic Analysis

All echocardiographic studies were performed by experienced institutional cardiologists during clinical routine. PH was routinely evaluated by preprocedural transthoracic echocardiography. Echocardiographic systolic pulmonary artery pressure (sPAP) levels were calculated by adding peak systolic pressure gradients between the right ventricle and right atrium (estimated from the continuous wave Doppler profile of the TR jet) to right atrial pressure levels. Right atrial pressure, in turn, was estimated by the diameter and collapsibility of the inferior vena cava as described in contemporary guidelines.[16,17] Right ventricular systolic function was estimated on the basis of tricuspid annular plane systolic excursion (TAPSE) measurements and on right ventricular fractional area change calculations. TR vena contracta width was measured from a right ventricle–focused apical 4-chamber view as the narrowest portion of the regurgitant flow that occurs at or immediately downstream of the regurgitant orifice. TV EROA and TR volume were calculated using the flow convergence method (also known as the proximal isovelocity surface area method).[18]

Invasive PH Assessment

Right heart catheterization represents the gold standard to assess pulmonary artery pressure levels.[19] A 7 French Swan-Ganz catheter was routinely used for preprocedural right heart catheterization via femoral access. sPAP and diastolic pulmonary artery pressure levels were directly recorded. mPAP levels were calculated as mPAP=diastolic pulmonary artery pressure+1/3×(sPAP−diastolic pulmonary artery pressure). Mean postcapillary wedge pressure was calculated over the entire cardiac cycle. Cardiac output was determined using the indirect Fick method. Pulmonary vascular resistance was defined as (mPAP−mean postcapillary wedge pressure)/cardiac output. Acknowledging that mean postcapillary wedge pressure and mPAP levels are sensitive to left-sided loading conditions, it was standardized practice at the participating sites to recompensate patients before right heart catheterization and to avoid hemodynamic measurements in the presence of volume overload. Right heart catheterization–derived mPAP levels were the primary source to calculate the TV EROA/mPAP ratio.

Artificial Intelligence–Enabled mPAP Prediction

The methodology for mPAP prediction by employing an extreme gradient boosting algorithm using standard echocardiographic parameters as data input has been extensively described elsewhere.[14] Echocardiographic parameters serving as input variables included left ventricular ejection fraction, left ventricular end-systolic diameter, left atrial area, sPAP, basal right ventricular diameter, TAPSE, TR vena contracta width, right atrial area, and inferior vena cava diameter. Artificial intelligence–derived mPAP values are hereinafter referred to as $mPAP_{predicted}$.

Etiology of TR

The etiology of TR was defined as recently proposed by Praz et al.[4] This classification scheme recognizes secondary forms (considering functional atrial and ventricular TR as separate entities), primary forms, and cardiac implantable electronic device–related forms.

Procedural Success Definition

Procedural success was defined as a device successfully implanted and delivery system retrieved, with TR reduction ≥I/V°[20] or a residual TR grade ≤II/V°[9] as assessed on transthoracic echocardiography before discharge (ie, 2–5 days after the procedure).

Definition of Primary Clinical End Point

Because an elderly patient population was studied, postprocedural 2-year all-cause mortality was defined as a clinically meaningful primary outcome measure. Survival data were regularly obtained from the German Civil Registry, lastly in February 2022, or from general practitioners, hospitals, and practice cardiologists for patients from foreign countries.

Statistical Analysis

All statistical analyses were performed using R statistical software (R version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria; see Table S1 for a complete list of employed R packages).

Categorical variables are presented as numbers and frequencies (%), while continuous variables are given as means±SD and 95% CI. Chi-square or Fisher's exact test was used to evaluate the association between categorical variables, and independent-samples Wilcoxon test was used for comparison of continuous variables. A *P* value ≤0.05 was considered to indicate statistical significance.

Considering TR proportionality expressed as TV EROA/mPAP ratio as a continuous variable to predict 2-year survival after TTVI, maximally selected log-rank statistics, an outcome-oriented method, was employed.[21] This method was developed for settings in clinical research, where investigators assume that a certain continuous parameter allows a classification of a population in 2 groups (eg, a risk and a control group), which are determined by a yet-to-specify cut point in the continuous parameter. Moreover, a response variable (eg, survival time) quantifies the hypothetical difference between the groups. In our study, maximally selected log-rank statistics were employed to identify a cutoff value for the TV EROA/mPAP ratio that maximizes the measure of difference between patients with proportionate and disproportionate TR in terms of 2-year survival following TTVI. Importantly, the cutoff value for the TV EROA/mPAP ratio was calculated using the derivation cohort, and it was externally validated on patients from 2 independent institutions.

Survival was illustrated using the Kaplan–Meier method, and a Cox proportional hazards model was used to estimate hazard ratios (HRs). A further univariable Cox regression analysis was employed to shed light on additional contributing factors for 2-year all-cause mortality. Variables with a *P* value ≤0.05 in the univariable analysis were further tested in a multivariable analysis, and a multivariable logistic regression model to predict 2-year all-cause mortality was hereinafter constructed. To evaluate the incremental value of TR proportionality to predict 2-year all-cause mortality in a multivariable model, the Akaike information criterion was calculated as the metric of choice, and regression models with or without TR proportionality as a predictor variable were compared by ANOVA testing. In general, the Akaike information criterion is a metric that deals with a trade-off between goodness of fit (explanatory power of a model) on the one hand and simplicity of a model on the other hand; a low score is typically assigned to models with good predictive power while minimizing the number of predictor variables.[22] To be more specific, the Akaike information criterion evaluates the impact of an input variable to the model's performance by assessing the relative loss of information in a model if that specific input variable would be omitted. It thus answers the question, "Is that specific input variable a significant contributor to the model's performance, or can it be ignored for the sake of simplicity?"

RESULTS

The Study Population Is Constituted by 533 Patients From a Multicentric Registry With Complete Echocardiographic and Hemodynamic Assessment Before TTVI for Severe TR

In total, 702 patients undergoing TTVI for severe TR between 2016 and 2021 were enrolled in this multicentric registry. Because this study aimed to analyze the relationship between tricuspid valve insufficiency and PH, only patients with complete echocardiographic and hemodynamic assessment by right heart catheterization obtained before TTVI were included in this study (hereinafter referred to as study population). Consequently, 169 patients (24.1%) with missing measurements of TV EROA and mPAP levels were excluded (Figure 2A). Importantly, baseline characteristics and survival after TTVI were largely indistinguishable between included and excluded patients (Figure S1, Tables S2 and S3). The mean age of the study population (533 patients) was 78.0±7.55 (95% CI, 77.4–78.7) years, and 46.9% of patients were men. Patients typically presented with dyspnea corresponding to New York Heart Association functional class III (74.7%) or IV (14.6%) and with a mean N-terminal pro-B-type natriuretic peptide level of 4764 (95% CI, 4030–5490) pg/mL. Massive and torrential TR were diagnosed in 178 (33.4%) and 101 (18.9%) patients. A successful TR reduction by at least I° could be achieved in 499 (93.6%) out of 533 cases. Moreover, 385 of 533 patients (72.2%) were diagnosed with PH defined as mPAP levels ≥25 mm Hg. Overall, 153 deaths among 533 enrolled patients were recorded, resulting in a median survival of 3.61 years (Figure 1B). Notably, 50% of deaths occurred within 0.783 years after TTVI (Figure 2C). The study population was further divided into derivation and validation cohorts (Figure 2A), presenting with similar demographic, clinical, echocardiographic, and hemodynamic characteristics (Tables 1 and 2). Importantly, comparison of TV EROA and mPAP levels revealed no statistically significant differences between the derivation and validation cohorts (0.686±0.460 [95% CI, 0.638–0.734] cm^2 versus 0.621±0.319 [95% CI, 0.574–0.668] cm^2 and 30.8±9.50 [95% CI, 29.8–31.8] mm Hg versus 29.5±9.33 [95% CI, 28.1–30.9] mm Hg, respectively). Moreover, no statistically significant differences regarding survival following TTVI were detectable between the derivation and validation cohorts (Figure 2D).

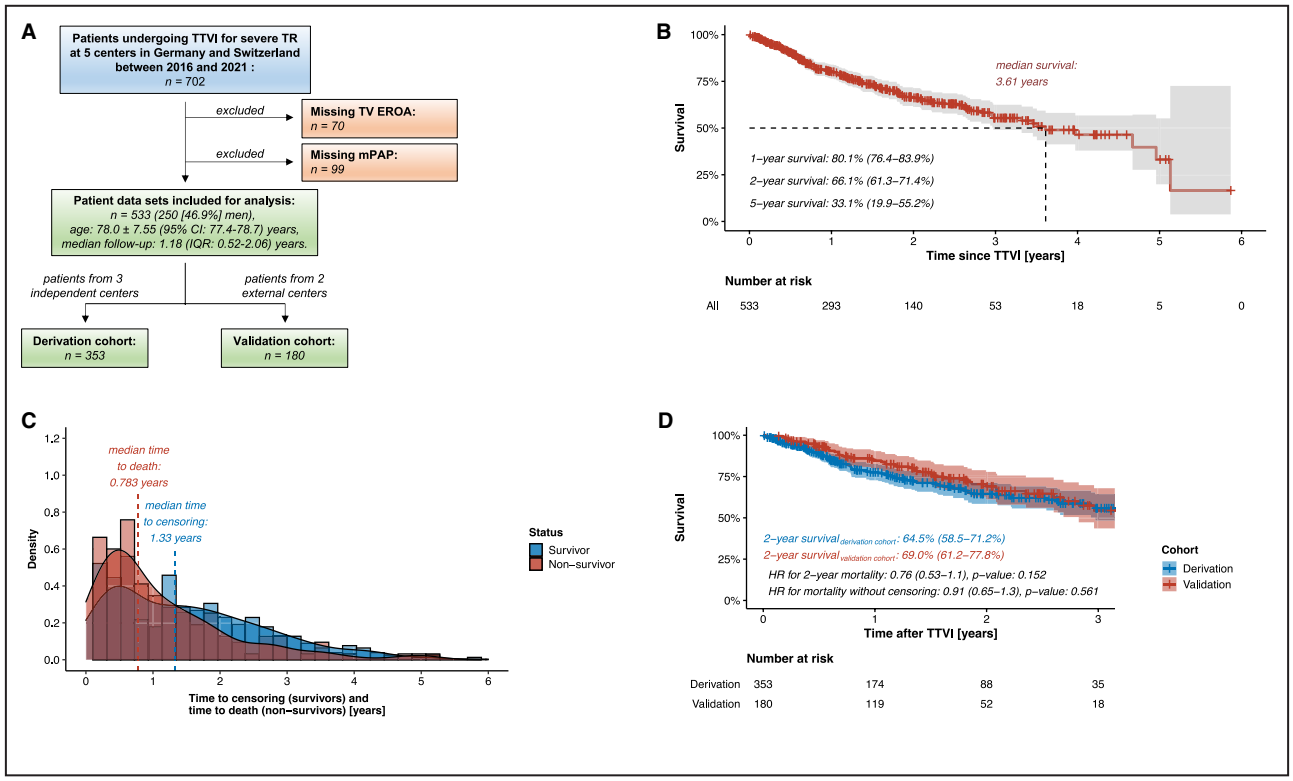

Figure 2. General information about the study population from recruitment to follow-up.
A, Flowchart for patient recruitment and definition of derivation and validation cohorts. **B**, Kaplan–Meier survival plot for the entire study population. **C**, Density plot showing time to censoring (survivors) and time to death (nonsurvivors) in consecutively enrolled patients. **D**, Kaplan–Meier survival plot comparing survival rates between patients from derivation and validation cohorts. HR indicates hazard ratio; IQR, interquartile range; mPAP, mean pulmonary artery pressure; TTVI, transcatheter tricuspid valve intervention; and TV EROA, tricuspid valve effective regurgitant orifice area.

TV EROA/mPAP Ratio as a Marker for TR Proportionality Stratifies Patients Into Low-Risk and High-Risk Cohorts for All-Cause Mortality After TTVI

Applying maximally selected log-rank statistics to dichotomize the derivation cohort according to TV EROA/mPAP levels resulted in an ideal threshold of 1.25 mm^2/mm Hg with respect to 2-year all-cause mortality. Proportionate TR is hence defined by low TV EROA/mPAP levels (≤1.25 mm^2/mm Hg), while disproportionate TR is defined by high TV EROA/mPAP levels (>1.25 mm^2/mm Hg; Figure 3A). Kaplan–Meier analysis revealed that patients with proportionate TR feature a significantly reduced survival after TTVI in comparison with patients with disproportionate TR (2-year survival: 56.9% [95% CI, 46.1–70.3] versus 67.4% [95% CI, 60.3–75.2]; HR for 2-year mortality: 1.6 [95% CI, 1.0–2.4]; P=0.047; Figure 3B). Notably, PH defined as mPAP levels ≥25 mm Hg was diagnosed in 89 of 92 patients with proportionate TR, resulting in a significantly higher prevalence than in patients with disproportionate TR (96.7% versus 65.5%; P=1.1×10^{-8}; Table 3). Lowering the mPAP threshold to 20 mm Hg to diagnose PH resulted in a PH prevalence of 100% in patients with proportionate TR (Table 3). Concomitant with elevated pulmonary artery pressures and higher pulmonary vascular resistance levels, patients with proportionate TR were also characterized by reduced right ventricular function expressed as TAPSE (15.8±3.95 [95% CI, 15.0–16.6] mm versus 17.5±4.52 [95% CI, 16.9–18.0] mm; P=0.002) and right ventricular fractional area change (36.5±11.4% [95% CI, 33.9–39.1] versus 40.7±10.8% [95% CI, 39.3–42.2]; P=0.001; Table 4). On the other hand, patients with disproportionate TR displayed dilated right ventricular diameters and enlarged right atrial areas compared with patients with proportionate TR (48.5±8.47 [95% CI, 47.5–49.6] mm versus 45.7±7.42 [95% CI, 44.2–47.2] mm; P=0.006; and 38.2±12.1 [95% CI, 36.7–39.7] cm^2 versus 32.0±9.41 [95% CI, 30.1–34.0] cm^2, P=4.1×10^{-5}, respectively). Moreover, patients with disproportionate TR featured significantly higher indices for TR severity such as TV EROA (0.809±0.474 [95% CI, 0.751–0.867] cm^2 versus 0.336±0.107 [95% CI, 0.314–0.358] cm^2; P<2.2×10^{-16}), TR volume (60.7±33.6 [95% CI, 56.3–65.1] mL versus 34.4±14.2 [95% CI, 31.3–37.5] mL; P<2.2×10^{-16}), and TR vena contracta width (12.9±4.67

Table 1. Demographic and Clinical Characteristics of the Study Population

	All (n=533)	Derivation cohort (n=353)	Validation cohort (n=180)	*P* value
Age, y, mean±SD (95% CI)	78.0±7.55	78.2±8.23	77.7±6.02	0.034
	(77.4–78.7)	(77.3–79.1)	(76.8–78.6)	
Sex, male, n (%)	250 (46.9)	159 (45.0)	91 (50.6)	0.265
BMI, kg/m^2, mean±SD (95% CI)	26.2±4.83	26.1±5.00	26.3±4.49	0.342
	(25.8–26.6)	(25.6–26.7)	(25.7–27.0)	
Arterial hypertension, n (%)	464 (87.1)	310 (87.8)	154 (85.6)	0.549
Diabetes, n (%)	144 (27.0)	88 (24.9)	56 (31.1)	0.157
NYHA class ≤II, n (%)	57 (10.7)	24 (6.80)	33 (18.3)	8.6×10^{-5}
NYHA class III, n (%)	398 (74.7)	276 (78.2)	122 (67.8)	0.012
NYHA class IV, n (%)	78 (14.6)	53 (15.0)	25 (13.9)	0.827
EuroScore II (%)	7.36±7.25	6.60±6.54	8.83±8.28	0.004
	(6.74–7.98)	(5.91–7.29)	(7.61–10.0)	
eGFR, mL/min, mean±SD (95% CI)	51.8±21.5	48.5±21.0	58.3±21.2	2.0×10^{-8}
	(50.0–53.7)	(46.3–50.7)	(55.2–61.4)	
NT-proBNP, pg/mL, mean±SD (95% CI)	4764±8457	4803±8217	4689±8921	0.599
	(4030–5490)	(3930–5680)	(3370–6010)	
CAD, n (%)	229 (43.0)	167 (47.3)	62 (34.4)	0.006
COPD, n (%)	97 (18.2)	54 (15.3)	43 (23.9)	0.021
Atrial fibrillation, n (%)	479 (89.9)	317 (89.8)	162 (90.0)	1.0
Pacemaker, n (%)	153 (28.7)	98 (27.8)	55 (30.6)	0.567
Pulmonary hypertension defined as mPAP≥25 mm Hg, n (%)	385 (72.2)	260 (73.7)	125 (69.4)	0.355
Pulmonary hypertension defined as mPAP≥20 mm Hg, n (%)	473 (88.7)	316 (89.5)	157 (87.2)	0.517

Categorical variables are presented as numbers and frequencies (%), while continuous variables are given as means±SD and 95% CI. BMI indicates body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; mPAP, mean pulmonary artery pressure (as assessed by right heart catheterization); NT-proBNP, N-terminal pro-B-type natriuretic peptide; and NYHA, New York Heart Association.

[95% CI, 12.3–13.4] mm versus 9.02±3.57 [95% CI, 8.27–9.77] mm; $P=3.9\times10^{-15}$).

External Validation Confirms the Prognostic Value of TV EROA/mPAP Ratio Regarding 2-Year Mortality After TTVI

The proposed proportionality model was hereinafter applied to patient data from 2 external centers including 180 patients undergoing TTVI for severe TR. Upon classifying TR as proportionate (TV EROA/mPAP ≤1.25 mm^2/mm Hg) or disproportionate (TV EROA/mPAP >1.25 mm^2/mm Hg; Figure 3C), Kaplan–Meier analysis confirmed that patients with proportionate TR show a significantly lower survival after TTVI compared with patients with disproportionate TR (2-year survival: 56.2% [95% CI, 40.9–77.2] versus 73.1% [95% CI, 64.5–82.9], HR for 2-year mortality: 1.9 [95% CI, 1.0–3.6], $P=0.048$; Figure 3D). Moreover, it was tested whether predicted mPAP levels based on a previously established extreme gradient boosting algorithm using 9 input parameters from routine echocardiography could also serve for risk stratification. Overall, only 3 of 1620 data points had missing values for those 9 input variables (Figure S2A), and those 3 missing data points were exclusively found for measurements of inferior vena cava diameter (1.67% of values missing; Figure S2B). After imputing missing values, initially observed and later imputed values for inferior vena cava diameter displayed a similar distribution (25.4±6.20 [95% CI, 24.5–26.3] mm versus 28.3±1.18 [95% CI, 25.4–31.2] mm; $P=0.155$; Figure S2C and S2D). The predicted mPAP level showed a significant correlation with the invasive measurements (Pearson correlation coefficient R, 0.51; $P=1.9\times10^{-13}$; Figure 3E), and Kaplan–Meier analysis ultimately confirmed that TV EROA/mPAP$_{predicted}$ levels ≤1.25 mm^2/mm Hg translate into increased mortality after TTVI (HR for 2-year mortality, 2.2 [95% CI, 1.1–4.4], $P=0.025$; Figure 3F).

Proportionality of TR Remains a Significant Predictor for 2-Year All-Cause Mortality After Adjusting for Clinical, Laboratory, and Hemodynamic Variables

Univariable and multivariable Cox proportional hazards regression analyses were additionally performed to test whether proportionality of TR remains significantly

Table 2. Echocardiographic and Hemodynamic Characteristics of the Study Population

	All (n=533)	Derivation cohort (n=353)	Validation cohort (n=180)	*P* value
LVEF, %, mean±SD (95% CI)	53.4±11.5	53.7±10.8	53.0±12.7	0.930
	(52.4–54.5)	(52.5–54.9)	(51.2–54.9)	
LVESD, mm, mean±SD (95% CI)	39.7±14.2	45.0±14.6	31.4±8.38	$<2.2\times10^{-16}$
	(38.4–41.0)	(43.3–46.7)	(30.2–32.7)	
LVEDD, mm, mean±SD (95% CI)	47.8±8.07	47.8±7.74	47.7±9.92	0.760
	(47.0–48.6)	(46.9–48.6)	(45.0–50.4)	
LA area, cm^2, mean±SD (95% CI)	31.3±9.62	30.5±9.39	32.5±9.89	0.023
	(30.4–32.2)	(29.4–31.6)	(31.0–33.9)	
$sPAP_{echo}$, mm Hg, mean±SD (95% CI)	40.4±14.7	41.0±14.5	39.3±15.1	0.087
	(39.2–41.7)	(39.5–42.5)	(37.1–41.5)	
TAPSE, mm, mean±SD (95% CI)	16.7±4.53	17.0±4.44	16.1±4.66	0.070
	(16.3–17.1)	(16.6–17.5)	(15.4–16.8)	
RV FAC, %, mean±SD (95% CI)	38.5±11.3	39.7±11.1	32.0±10.4	5.6×10^{-6}
	(37.3–39.7)	(38.4–40.9)	(29.2–34.8)	
Basal RV diameter, mm, mean±SD (95% CI)	47.3±8.15	47.8±8.29	46.5±7.83	0.165
	(46.6–48.0)	(46.9–48.7)	(45.3–47.6)	
TV EROA, mm^2, mean±SD (95% CI)	66.4±41.9	68.6±46.0	62.1±31.9	0.407
	(62.8–70.0)	(63.8–73.4)	(57.4–66.8)	
TR volume, mL, mean±SD (95% CI)	51.2±27.5	53.5±31.8	47.2±17.6	0.246
	(48.7–53.6)	(49.9–57.1)	(44.6–49.8)	
TR vena contracta width, mm, mean±SD (95% CI)	11.1±4.29	11.9±4.72	9.74±2.86	3.6×10^{-6}
	(10.8–11.5)	(11.4–12.4)	(9.32–10.2)	
TR≤III/V°, n (%)	254 (47.7)	166 (47.0)	88 (48.9)	0.752
TR=IV/V°, n (%)	178 (33.4)	110 (31.2)	68 (37.8)	0.151
TR=V/V°, n (%)	101 (18.9)	77 (21.8)	24 (13.3)	0.025
RA area, cm^2, mean±SD (95% CI)	37.3±11.4	36.5±11.8	38.6±10.6	0.024
	(36.3–38.2)	(35.3–37.8)	(37.1–40.2)	
Inferior vena cava diameter, mm, mean±SD (95% CI)	26.0±6.47	26.3±6.59	25.4±6.20	0.061
	(25.4–26.6)	(25.6–27.0)	(24.5–26.3)	
Cardiac output, L/min, mean±SD (95% CI)	4.16±1.63	4.52±1.81	3.54±1.02	5.7×10^{-10}
	(4.02–4.31)	(4.31–4.72)	(3.39–3.69)	
Cardiac index, mean±SD (95% CI), L/min per m^2	2.24±0.836	2.44±0.929	1.88±0.460	4.2×10^{-13}
	(2.16–2.31)	(2.34–2.55)	(1.81–1.95)	
PVR, WU, mean±SD (95% CI)	3.04±1.97	2.93±1.81	3.38±2.37	0.144
	(2.85–3.24)	(2.72–3.14)	(2.91–3.85)	
$sPAP_{invasive}$, mm Hg, mean±SD (95% CI)	47.1±15.0	47.7±15.0	45.9±14.9	0.140
	(45.8–48.4)	(46.2–49.3)	(43.7–48.1)	
dPAP, mm Hg, mean±SD (95% CI)	19.5±7.63	19.9±7.93	18.6±6.96	0.104
	(18.8–20.1)	(19.1–20.8)	(17.6–19.7)	
mPAP, mm Hg, mean±SD (95% CI)	30.4±9.46	30.8±9.50	29.5±9.33	0.123
	(29.6–31.2)	(29.8–31.8)	(28.1–30.9)	
mPCWP, mm Hg, mean±SD (95% CI)	19.5±7.39	19.5±7.48	19.2±7.10	0.851
	(18.7–20.2)	(18.7–20.4)	(17.8–20.6)	

Continuous variables are given as means±SD and 95% CI. dPAP indicates diastolic pulmonary artery pressure (as assessed by right heart catheterization); LA, left atrial; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; mPAP, mean pulmonary artery pressure (as assessed by right heart catheterization); mPCWP, mean postcapillary wedge pressure (as assessed by right heart catheterization); PVR, pulmonary vascular resistance; RA, right atrial; RV, right ventricular; RV FAC, right ventricular fractional area change; $sPAP_{echo}$, systolic pulmonary artery pressure (as assessed by echocardiography); $sPAP_{invasive}$, systolic pulmonary artery pressure (as assessed by right heart catheterization); TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TV EROA, tricuspid valve effective regurgitant orifice area.

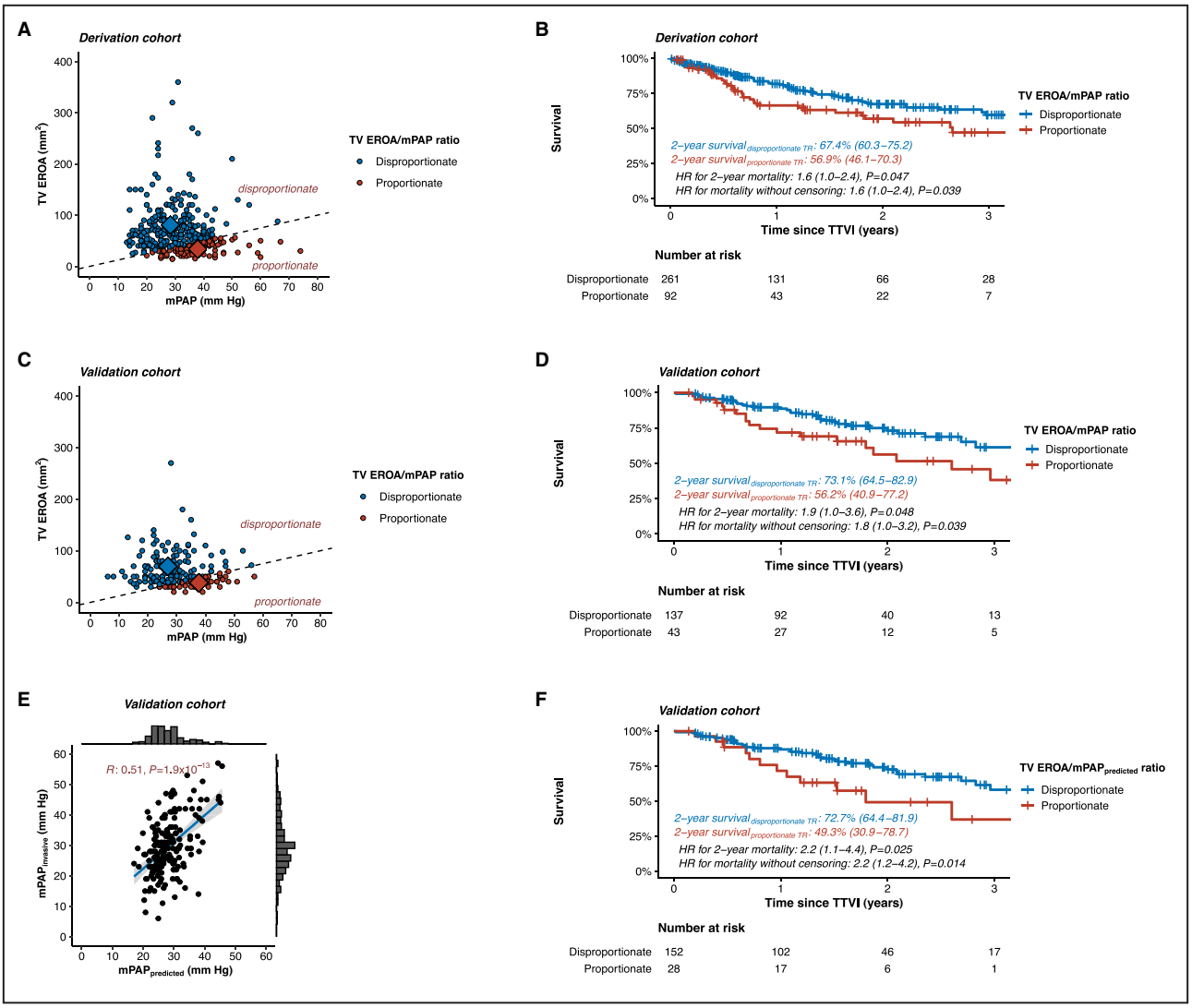

Figure 3. A TV EROA/mPAP ratio ≤1.25 mm²/mm Hg, defining proportionate TR, translates into lower survival rates in patients with severe TR undergoing TTVI.

A, Scatter plot showing the distribution of patients with proportionate and disproportionate TR (derivation cohort). Notably, no correlation between TV EROA and mPAP levels could be detected (correlation coefficient by Pearson [*R*]: −0.0764; *P*=0.152). **B**, Kaplan–Meier survival plot comparing survival rates between patients with proportionate and disproportionate TR (derivation cohort). **C**, Scatter plot showing the distribution of patients with proportionate and disproportionate TR (validation cohort). **D**, Kaplan–Meier survival plot comparing survival rates between patients with proportionate and disproportionate TR (validation cohort). **E**, Correlation plot (*R*=correlation coefficient by Pearson) displaying invasively measured and predicted mPAP levels among patients from the validation cohort. Blue line: linear regression line. Gray area: 95% CI. **F**, Kaplan–Meier survival plot comparing survival rates between patients with proportionate and disproportionate TR based on predicted mPAP levels (validation cohort). HR indicates hazard ratio; mPAP, mean pulmonary artery pressure; TR, tricuspid regurgitation; TTVI, transcatheter tricuspid valve intervention; and TV EROA, tricuspid valve effective regurgitant orifice area.

associated with 2-year all-cause mortality after adjusting for clinical, laboratory, and hemodynamic variables (Table 5). Over a period of maximum 2 years, 130 deaths among 533 patients were registered. Multivariable analysis confirmed that classification of proportionate TR remained significantly associated with 2-year all-cause mortality (HR, 1.9 [95% CI, 1.1–3.1]; *P*=0.014), emphasizing the prognostic relevance of the proposed proportionality framework for severe TR independent from pulmonary artery pressure levels and TR severity expressed as TV EROA at initial presentation. Constructing a logistic regression model that includes all independent predictors for 2-year all-cause mortality (diagnosis of atrial fibrillation, New York Heart Association class at initial presentation, right ventricular function expressed as TAPSE, residual TR severity after TTVI, and classification of proportionate TR) revealed that the addition of TR proportionality

Table 3. Demographic and Clinical Characteristics in Accordance With TV EROA/mPAP Ratio (Derivation Cohort)

	TV EROA/mPAP ratio		
	Disproportionate (n=261)	Proportionate (n=92)	*P* value
Age, y, mean±SD (95% CI)	78.3±8.15	78.0±8.49	0.928
	(77.3–79.3)	(76.2–79.8)	
Sex, male, n (%)	121 (46.4)	38 (41.3)	0.474
BMI, kg/m^2, mean±SD (95% CI)	26.4±5.02	25.5±4.91	0.082
	(25.8–27.0)	(24.4–26.5)	
Arterial hypertension, n (%)	222 (85.1)	88 (95.7)	0.013
Diabetes, n (%)	61 (23.4)	27 (29.3)	0.318
NYHA class ≤II, n (%)	17 (6.51)	7 (7.61)	0.906
NYHA class III, n (%)	210 (80.5)	66 (71.7)	0.111
NYHA class IV, n (%)	34 (13.0)	19 (20.7)	0.112
EuroScore II (%)	6.09±5.65	8.04±8.46	0.090
	(5.40–6.79)	(6.27–9.81)	
eGFR, mL/min, mean±SD (95% CI)	50.1±21.4	44.2±19.2	0.011
	(47.5–52.7)	(40.3–48.2)	
NT-proBNP, pg/mL, mean±SD (95% CI)	4089±6740	6785±11 166	7.8×10^{-6}
	(3250–4930)	(4450–9120)	
CAD, n (%)	120 (46.0)	47 (51.1)	0.470
COPD, n (%)	36 (13.8)	18 (19.6)	0.249
Atrial fibrillation, n (%)	237 (90.8)	80 (87.0)	0.396
Pacemaker, n (%)	78 (29.9)	20 (21.7)	0.172
Pulmonary hypertension defined as mPAP ≥25 mm Hg, n (%)	171 (65.5)	89 (96.7)	1.1×10^{-8}
Pulmonary hypertension defined as mPAP ≥20 mm Hg, n (%)	224 (85.8)	92 (100)	3.0×10^{-4}

Categorical variables are presented as numbers and frequencies (%), while continuous variables are given as means±SD and 95% CI. BMI indicates body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; mPAP, mean pulmonary artery pressure (as assessed by right heart catheterization); NT-proBNP, N-terminal pro-B-type natriuretic peptide; and NYHA, New York Heart Association.

significantly improved the model's predictive performance as assessed by comparison of the Akaike information criterion (*P*=0.001). In total, patients with disproportionate TR featured significantly better 2-year survival rates after TTVI than patients with proportionate TR (69.6% [95% CI, 64.0–75.6] versus 56.6% [95% CI, 47.5–67.5]; *P*=0.005; Figure 4, Tables S4 and S5).

Failure to Achieve a Significant Reduction in TR Severity Is Associated With Increased Mortality

While patients with disproportionate TR had more extensive TR at initial presentation (Table S5, Figure 5A), equal proportions of successful TR reduction by at least I° were observed among patients with either disproportionate (93.5%) or proportionate TR (94.1%; Table 6, Figure 5B). Failure to ameliorate TR severity according to the aforementioned definition (ie, neither TR reduction to ≤II/V° nor any TR reduction by at least I°) translated into a 2.2-fold increase in 2-year mortality (Figure 5C). Notably, the rate of patients with residual TR ≤II/V° was significantly higher in patients with proportionate TR than in patients with disproportionate TR (89.6% versus 76.6%; *P*=0.002; Table 6, Figure 5A). Would survival differences still be evident if only patients with a small residual TR are compared? As a subset analysis, only patients with residual TR ≤II/V° were compared, finally confirming that patients with disproportionate TR have a significantly better 2-year survival outcome after TTVI than patients with proportionate TR (*P*=0.001; Figure 5D).

Cardiac Implantable Electronic Device-Related Forms of TR Are Predominantly Classified as Disproportionate TR

Most patients were diagnosed with a secondary form of TR, either ventricular (59.3%) or atrial (30.6%), and only a few patients were diagnosed with cardiac implantable electronic device–related TR (5.44%) and primary TR (4.69%; Table 7). Notably, secondary forms of TR were equally prevalent in patients with disproportionate and proportionate TR, but cardiac implantable electronic device–related forms of TR were more often observed in patients with disproportionate TR than in

Table 4. Comparison of Echocardiographic and Hemodynamic Characteristics in Accordance With TV EROA/mPAP Ratio (Derivation Cohort)

	TV EROA/mPAP ratio		
	Disproportionate (n=261)	Proportionate (n=92)	*P* value
LVEF, %, mean±SD (95% CI)	54.1±10.6	52.4±11.0	0.245
	(52.7–55.5)	(50.0–54.9)	
LVESD, mm, mean±SD (95% CI)	45.2±14.4	44.4±15.1	0.734
	(43.2–47.2)	(41.1–47.8)	
LVEDD, mm, mean±SD (95% CI)	47.9±7.55	47.4±8.29	0.467
	(47.0–48.9)	(45.6–49.1)	
LA area, cm^2, mean±SD (95% CI)	30.9±10.1	29.6±7.31	0.362
	(29.5–32.3)	(28.0–31.2)	
$sPAP_{echo}$, mm Hg, mean±SD (95% CI)	37.6±12.5	50.6±15.5	3.9×10^{-12}
	(36.1–39.1)	(47.4–53.8)	
TAPSE, mm, mean±SD (95% CI)	17.5±4.52	15.8±3.95	0.002
	(16.9–18.0)	(15.0–16.6)	
RV FAC, %, mean±SD (95% CI)	40.7±10.8	36.5±11.4	0.001
	(39.3–42.2)	(33.9–39.1)	
Basal RV diameter, mm, mean±SD (95% CI)	48.5±8.47	45.7±7.42	0.006
	(47.5–49.6)	(44.2–47.2)	
TV EROA, mm^2, mean±SD (95% CI)	80.9±47.4	33.6±10.7	$<2.2\times10^{-16}$
	(75.1–86.7)	(31.4–35.8)	
TR volume, mL, mean±SD (95% CI)	60.7±33.6	34.4±14.2	$<2.2\times10^{-16}$
	(56.3–65.1)	(31.3–37.5)	
TR vena contracta width, mm, mean±SD (95% CI)	12.9±4.67	9.02±3.57	3.9×10^{-15}
	(12.3–13.4)	(8.27–9.77)	
TR≤III/V°, n (%)	97 (37.2)	69 (75.0)	8.8×10^{-10}
TR=IV/V°, n (%)	89 (34.1)	21 (22.8)	0.061
TR=V/V°, n (%)	75 (28.7)	2 (2.2)	2.5×10^{-7}
RA area, cm^2, mean±SD (95% CI)	38.2±12.1	32.0±9.41	4.1×10^{-5}
	(36.7–39.7)	(30.1–34.0)	
Inferior vena cava diameter, mm, mean±SD (95% CI)	26.9±6.82	24.6±5.55	0.010
	(26.0–27.7)	(23.4–25.8)	
Cardiac output, L/min, mean±SD (95% CI)	4.40±1.62	4.85±2.22	0.186
	(4.18–4.61)	(4.36–5.34)	
Cardiac index, L/min per m^2, mean±SD (95% CI)	2.35±0.834	2.69±1.12	0.018
	(2.25–2.46)	(2.44–2.94)	
PVR, WU, mean±SD (95% CI)	2.74±1.53	3.44±2.36	0.052
	(2.54–2.95)	(2.91–3.97)	
$sPAP_{invasive}$, mm Hg, mean±SD (95% CI)	43.9±12.7	58.8±15.8	4.4×10^{-15}
	(42.4–45.5)	(55.5–62.2)	
dPAP, mm Hg, mean±SD (95% CI)	18.2±7.00	25.0±8.33	1.5×10^{-11}
	(17.3–19.1)	(23.2–26.8)	
mPAP, mm Hg, mean±SD (95% CI)	28.3±8.10	37.9±6.42	2.3×10^{-16}
	(27.4–29.3)	(35.9–39.9)	
mPCWP, mm Hg, mean±SD (95% CI)	17.8±9.65	24.3±8.07	7.8×10^{-12}
	(16.9–18.6)	(22.5–26.0)	

Continuous variables are given as means±standard deviation and 95% confidence interval. dPAP, diastolic pulmonary artery pressure (as assessed by right heart catheterization); LA area, left atrial area; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; mPAP, mean pulmonary artery pressure (as assessed by right heart catheterization); mPCWP, mean postcapillary wedge pressure (as assessed by right heart catheterization); PVR, pulmonary vascular resistance; RA area, right atrial area; RV, right ventricular; RV FAC, right ventricular fractional area change; $sPAP_{echo}$, systolic pulmonary artery pressure (as assessed by echocardiography); $sPAP_{invasive}$, systolic pulmonary artery pressure (as assessed by right heart catheterization); TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; and TV EROA, tricuspid valve effective regurgitant orifice area.

patients with proportionate TR (6.78% versus 1.48%; *P*=0.033).

DISCUSSION

A Proportionality Framework for Severe TR Relating Tricuspid Valve Insufficiency to the Degree of Pulmonary Artery Pressure Levels Might Aid in Distinguishing Cases of Severe TR as Causative Conditions From Epiphenomena and Thus Improve Prognostic Resolution for Survival After TTVI

To distinguish causative conditions from epiphenomena is pivotal for clinical decision-making, yet physicians commonly encounter a dilemma when treating patients with severe TR. This is because PH is frequently observed in patients with severe TR, and long-standing elevations of right ventricular afterload and subsequent right ventricular dilatation ultimately result in exacerbation of TR through a combination of tricuspid annulus dilatation and papillary muscle displacement. To correct the degree of TR severity expressed as TV EROA for the level of PH might therefore identify patients in whom the extent of valvular insufficiency is disproportionately larger than expected on the basis of the degree of PH and who might therefore show better outcomes after TTVI than patients with proportionate TR. Developed on 533 patients from a multicentric registry, this study hereby establishes the TV EROA/mPAP ratio as a prognostic marker for 2-year survival after TTVI, revealing that patients with disproportionate TR feature a significantly better outcome (2-year survival rates: 69.6% [95% CI, 64.0–75.6] versus 56.6% [95% CI, 47.5–67.5]; *P*=0.005; Figure 6). Thus, the proposed proportionality framework for severe TR might aid in identifying patients with proportionate TR who require different or complementary therapeutic strategies targeting PH. The key advantages of the hereby proposed TR proportionality model are as follows: (1) It provides pathophysiologically and prognostically meaningful information to patients and clinicians; (2) it is easy to calculate; (3) it is widely applicable; and (4) reproducibility has been demonstrated by external validation.

The Valve-Centered Perception "Severe TR Equals High Mortality" Is True for the Natural Course of TR, but TTVI Makes It Possible to Assign a Relatively Good Prognosis to Patients With Disproportionate Severe TR

Before the introduction of TTVI, it was a well-consolidated clinical observation that increasing TR

Table 5. Univariable and Multivariable Cox Regression Analysis With 2-Year Mortality as a Dependent Variable (Entire Study Population)

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, y (increment per 10 y)	0.97 (0.78–1.2)	0.810		
Sex, male	1.1 (0.77–1.5)	0.650		
BMI (increment per 1 kg/m^2)	0.98 (0.94–1.0)	0.220		
Arterial hypertension	0.97 (0.59–1.6)	0.890		
Diabetes	1.1 (0.76–1.6)	0.600		
CAD	1.2 (0.89–1.8)	0.210		
COPD	1.3 (0.87–2.0)	0.190		
Atrial fibrillation	0.62 (0.39–0.99)	0.043	0.58 (0.36–0.92)	0.022
eGFR (increment per 10 mL/min)	0.9 (0.83–0.98)	0.017	0.97 (0.89–1.1)	0.559
NYHA class (increment per class)	1.6 (1.2–2.3)	0.005	1.5 (1.1–2.2)	0.014
NT-proBNP (increment per 2000 pg/mL)	1.0 (1.0–1.1)	0.006	1.0 (0.99–1.1)	0.283
LVEF (increment per 10%)	0.88 (0.76–1.0)	0.080		
mPAP (increment per 10 mm Hg)	1.4 (1.2–1.6)	3.1×10^{-5}	1.2 (0.97–1.4)	0.108
sPAP (increment per 10 mm Hg)	1.1 (0.95–1.2)	0.260		
TAPSE (increment per 1 mm)	0.93 (0.89–0.96)	1.1×10^{-4}	0.96 (0.92–0.99)	0.022
TAPSE/sPAP ratio (increment per 1 mm/mm Hg)	0.56 (0.25–1.2)	0.150		
TV EROA (increment per 1 cm^2)	1.5 (1.1–2.1)	0.021	1.5 (0.96–2.3)	0.072
Preprocedural TR grade (increment per 1 grade)	1.3 (1.0–1.6)	0.029	1.1 (0.81–1.4)	0.657
Postprocedural TR grade (increment per 1 grade)	1.4 (1.1–1.6)	0.001	1.3 (1.0–1.6)	0.049
Classification of proportionate TR	1.7 (1.2–2.4)	0.005	1.9 (1.1–3.1)	0.014

BMI indicates body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; sPAP, systolic pulmonary artery pressure (as assessed by echocardiography); TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; and TV EROA, tricuspid valve effective regurgitant orifice area.

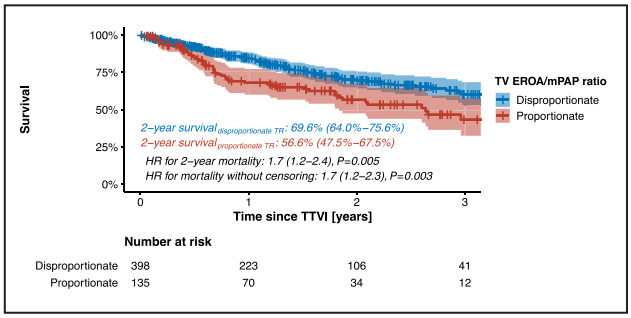

Figure 4. Kaplan–Meier survival plot comparing survival rates between patients with proportionate and disproportionate TR (entire study population).
HR indicates hazard ratio; mPAP, mean pulmonary artery pressure; TR, tricuspid regurgitation; TTVI, transcatheter tricuspid valve intervention; and TV EROA, tricuspid valve effective regurgitant orifice area.

severity is associated with worse survival,[1] and the presence of severe TR per se indicated increased mortality across different etiologies and independent of cardiac function, pulmonary artery pressure levels, and atrial fibrillation.[23] However, being a predictor for mortality does not necessarily imply a prognostically relevant interventional target.[24,25] Risk stratification for patients with, for example, severe aortic stenosis is in a state of flux shifting from a valve-centered perspective to a more comprehensive view capturing the valvular damage in its functional and structural context of additional cardiopulmonary affections.[26,27] Moreover, it could be shown that not the disease-defining severity of aortic stenosis at initial presentation but rather the (potentially irreversible) extra-aortic valve cardiac damage determines prognosis after transcatheter aortic valve replacement.[28–30] Similarly, in patients with severe TR, the initial severity of TR expressed as TV EROA does not allow reliable prognostication for survival after TTVI as demonstrated by multivariable regression analysis (Table 5). A much better predictor for 2-year mortality would be the residual TR severity grade (HR [increment per 1 grade]: 1.3 [95% CI, 1.0–1.6]; *P*=0.049 [as confirmed by multivariable regression analysis; Table 5]); however, this

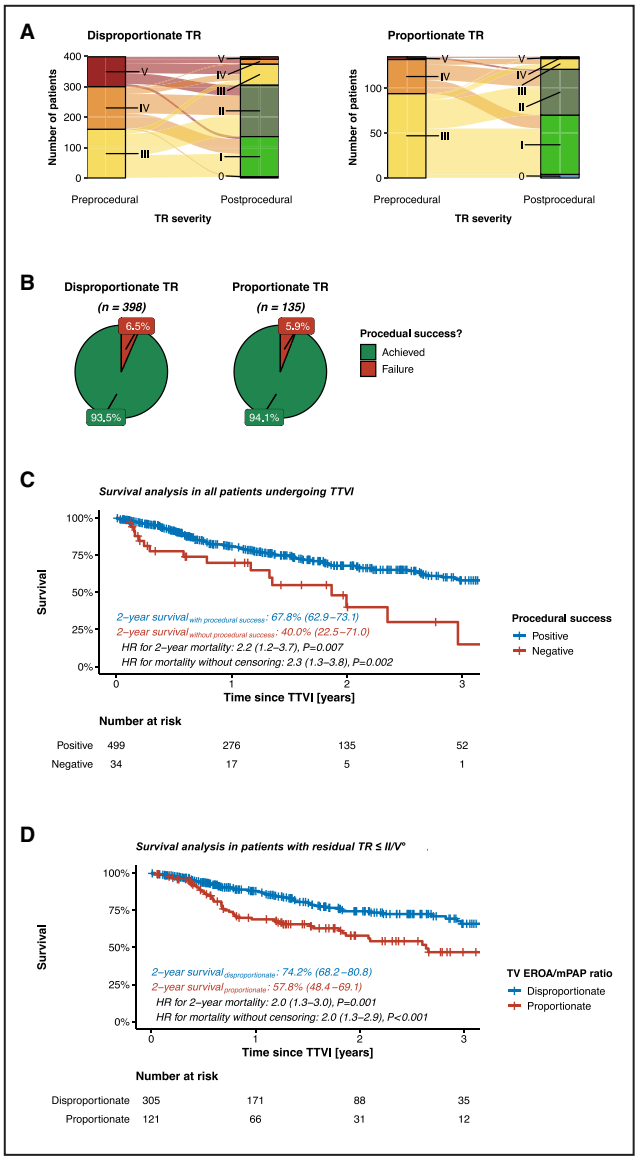

Figure 5. Comparison of residual TR as a confounder for mortality after TTVI (entire study population).
A, Alluvial diagrams comparing pre- and postprocedural TR severity in accordance with TR proportionality. **B**, Pie charts comparing rates of procedural success in accordance with TR proportionality (see Methods section for definition of procedural success). **C**, Kaplan–Meier survival plot comparing survival rates in accordance with procedural success. **D**, Kaplan–Meier survival plot comparing survival rates in accordance with TR reduction and TV EROA/mPAP ratio. HR indicates hazard ratio; mPAP, mean pulmonary artery pressure; TR, tricuspid regurgitation; TTVI, transcatheter tricuspid valve intervention; and TV EROA, tricuspid valve effective regurgitant orifice area.

parameter is obviously not available ex ante to optimize patient selection. Challenging the traditional perception that a large coaptation defect would translate into high mortality, the present study demonstrates that it is indeed possible to assign a relatively good prognosis to patients undergoing TTVI because of disproportionately extensive defects of the tricuspid valve. In other words, it is not the absolute severity of TR at initial presentation that matters but the severity corrected by the imposed pressure burden from the pulmonary circulation (which is potentially irreversible) that determines prognosis. This prognostic assessment for patients undergoing TTVI stands in contrast with the natural course of TR (focusing on the tricuspid valve), meaning that our proportionality framework could guide future patient selection and shared decision-making before TTVI.

Comparison of Proportionality Frameworks for Mitral and Tricuspid Regurgitation: Learning From a Controversy

Notably, the proportionality concept for functional mitral regurgitation was developed to explain apparently discordant results from 2 randomized controlled trials of transcatheter mitral valve repair,[31,32] and by relating the degree of mitral regurgitation severity (expressed as mitral valve effective regurgitant orifice area) to the severity of left ventricular remodeling (expressed as left ventricular end-diastolic volume), it postulates that correction of mitral regurgitation by transcatheter mitral valve repair might be particularly effective in improving outcomes in patients with disproportionate mitral regurgitation (proposed threshold, 0.15 cm^2/100 mL).[10] In fact, there were profound differences in baseline characteristics of the patient populations enrolled in the MITRA-FR (Percutaneous Repair With the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) and COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trials: COAPT enrolled patients whose mitral valve effective regurgitant orifice area was larger and whose left ventricular end-diastolic volume was smaller than those in MITRA-FR, resulting in a higher proportion of patients with disproportionate mitral regurgitation in the COAPT trial. Supporting the proportionality concept, transcatheter mitral valve repair was shown to reduce rates of mortality and heart failure hospitalizations only in the COAPT trial. However, a post hoc analysis of the MITRA-FR trial failed to demonstrate better efficacy of transcatheter mitral valve repair in patient subsets with disproportionate than in those with proportionate mitral regurgitation.[33] Another (retrospective multicenter) study reported that more pronounced early reduction in mitral regurgitation severity was not durable in patients with disproportionate mitral regurgitation, and ultimately resulted in similar rates of mortality and heart failure hospitalization between patients with proportionate and disproportionate mitral regurgitation.[34] While substantial

Table 6. Procedural Success Rates in Accordance With TV EROA/mPAP Ratio (Entire Study Population)

	All (n=533)	TV EROA/mPAP ratio		*P* value
		Disproportionate (n=398)	Proportionate (n=135)	
TR reduction by at least I°, n (%)	499 (93.6)	372 (93.5)	127 (94.1)	0.964
Residual TR≤II/V°, n (%)	426 (79.9)	305 (76.6)	121 (89.6)	0.002

Categorical variables are presented as numbers and frequencies (%). mPAP indicates mean pulmonary artery pressure; TR, tricuspid regurgitation; and TV EROA, tricuspid valve effective regurgitant orifice area.

controversy about the proportionality concept for mitral regurgitation remains, the evaluation of proportionality in patients with severe TR promises to provide a more physiological approach for the treatment of severe TR because PH as the true culprit causing dilatation of the right ventricular free wall, papillary muscle displacement, leaflet tethering, and failure of leaflet coaptation in the majority of cases (72.2% of patients were diagnosed with mPAP levels ≥25 mm Hg; 59.3% of patients were diagnosed with secondary ventricular etiology of TR) is unlikely to be ameliorated by TTVI, and it will hence persist to cause maladaptive right ventricular remodeling with its fatal consequences. Importantly, the threshold to define disproportionate mitral regurgitation is based on a predictive model for left ventricular remodeling,[10] while we calculated an outcome-oriented threshold to predict 2-year mortality after TTVI and confirmed its prognostic significance by external validation. Because patients with severe TR typically suffer from advanced heart failure symptoms and experience repeated heart failure hospitalizations, it will be interesting for future studies to investigate further end points such as heart failure hospitalizations and quality of life after TTVI in accordance with proportionality of TR.

Is Mortality in Patients With Proportionate TR Driven by Reduced Afterload Reserve?

Upon ameliorating TR severity by TTVI and hence reducing the regurgitant blood flow to the low-pressure right atrium, the right ventricle is acutely forced to eject blood into the high-pressure pulmonary circulation. It is therefore of paramount importance that the right ventricle has a sufficiently preserved contractile function to compensate for the increased afterload burden, as otherwise accelerated cardiac deterioration would result. Right ventricular–to–pulmonary artery coupling expressed as TAPSE/sPAP ratio captures right ventricular contractility related to afterload burden imposed from the pulmonary circulation,[35,36] and high ratios indicate a preserved afterload reserve with good prognosis following TTVI.[37] The reduced right ventricular–to–pulmonary artery coupling indices expressed as TAPSE/sPAP ratio as found in patients with proportionate TR (0.353±0.151 [95% CI, 0.326–0.378] mm/mm Hg in patients with proportionate TR versus 0.522±0.275 [95% CI, 0.495–0.549] mm/mm Hg in patients with disproportionate TR; $P=5.4\times10^{-15}$) provide a further mechanistic explanation for poorer survival rates in these patients (Figure S3) and possibly explain that the survival curves immediately diverge after TTVI (Figure 4). It is inherent to the nature of this observational study that one cannot draw conclusions about the benefit of TTVI in patients with proportionate TR, as a (randomized) conservative treatment group as control was missing. While randomized controlled trials analyzed the effect of transcatheter interventions on survival in patients with severe mitral regurgitation,[31,32] comparable studies are lacking for patients with severe TR. Two propensity-matched analyses provide the best level of evidence to date, both describing beneficial effects on survival for patients undergoing TTVI compared with conservative treatment.[8,9] Whether this survival-prolonging effect also holds true in a subset of patients with proportionate TR seems questionable, as the 1-year mortality rate of conservatively treated patients (36% and 26%) appears like that from patients with proportionate TR (32%; 1-year mortality rate of patients with disproportionate TR, 16%).

Table 7. Etiology of TR in Accordance With TV EROA/mPAP Ratio (Entire Study Population)

	All (n=533)	TV EROA/mPAP ratio		*P* value
		Disproportionate (n=398)	Proportionate (n=135)	
Ventricular (secondary)	316 (59.3)	230 (57.8)	86 (63.7)	0.268
Atrial (secondary)	163 (30.6)	121 (30.4)	42 (31.1)	0.963
CIED related	29 (5.44)	27 (6.78)	2 (1.48)	0.033
Primary	25 (4.69)	20 (5.03)	5 (3.70)	0.695

Categorical variables are presented as numbers and frequencies (%). CIED indicates cardiac implantable electronic device; mPAP, mean pulmonary artery pressure; and TV EROA, tricuspid valve effective regurgitant orifice area.

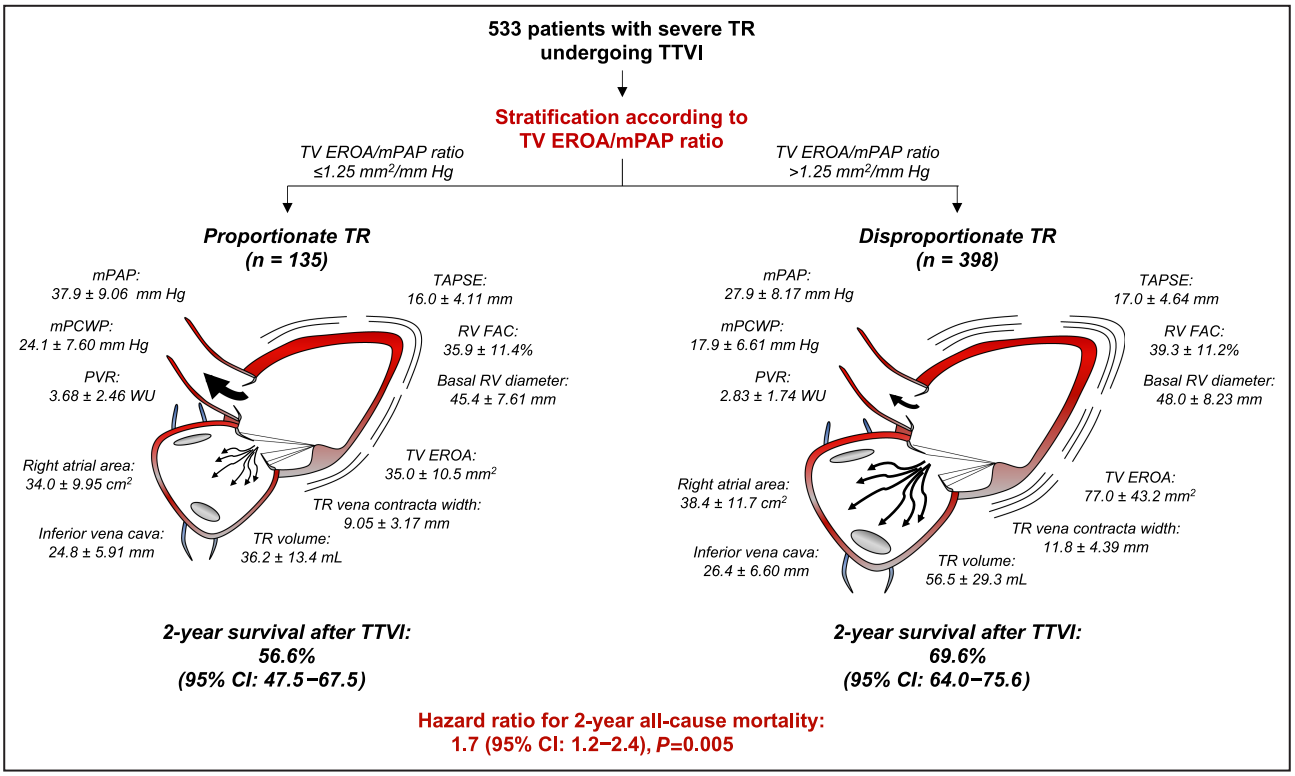

Figure 6. A conceptual framework to determine whether individual cases of TR represent a prognostically relevant interventional target or merely an indicator of worse prognosis in patients suffering from pulmonary hypertension (graphical summary).

A novel proportionality framework to correct the degree of TR severity expressed as TV EROA for the levels of mPAP shows that patients with a TV EROA/mPAP ratio >1.25 mm²/mm Hg (defining disproportionate TR) feature significantly better 2-year survival rates after transcatheter tricuspid valve intervention than patients with proportionate TR (69.6% [95% CI, 64.0–75.6] versus 56.6% [95% CI, 47.5–67.5]; *P*=0.005). mPAP indicates mean pulmonary artery pressure; mPCWP, mean postcapillary wedge pressure; PVR, pulmonary vascular resistance; RV, right ventricular; RV FAC, right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TTVI, transcatheter tricuspid valve intervention; and TV EROA, tricuspid valve effective regurgitant orifice area.

Can Resolving PH in Patients With Proportionate TR Prove More Beneficial Than Correction of the TR Itself?

The proportionality framework for TR might not only help to identify patients who benefit from TTVI, while preventing other patients from potentially futile or even harmful interventions, but it also points at future treatment targets to improve survival in patients with proportionate TR. Evidently, all indices of TR severity such as TV EROA, TR volume, and tricuspid valve vena contracta width were less elevated in patients with proportionate TR than in patients with disproportionate TR, but patients with proportionate TR featured more pronounced PH and more severely impaired right ventricular systolic function (Figure 6). Both factors, that is, PH expressed as mPAP and right ventricular systolic function expressed as TAPSE, were significantly associated with 2-year mortality after TTVI as shown by univariable analysis (Table 5). Because left ventricular function was statistically indifferent between patient subsets and also comorbidities such as coronary artery disease, atrial fibrillation, and chronic obstructive pulmonary disease were similarly prevalent (Tables S4 and S5), long-standing PH and concomitant remodeling of the pulmonary vasculature (expressed as elevated pulmonary vascular resistance levels) might have caused right ventricular contractile dysfunction and concomitant right ventricular–to–pulmonary artery uncoupling in patients with proportionate TR. The coexistence of proportionate TR and right ventricular–to–pulmonary artery uncoupling illustrates the intricate interplay between tricuspid valve, right ventricle, and pulmonary vasculature, and both concepts should be used synergistically to predict outcomes after TTVI. Interestingly, sPAP levels as estimated by echocardiography were not significantly associated with 2-year mortality—the reason could be that sPAP levels from echocardiography fail to detect the true severity of pulmonary hypertension in patients with severe TR and reduced right ventricular systolic function.[14] Future studies are therefore necessary to refine the metrics

for right ventricular–to–pulmonary artery coupling in patients with severe TR.[38]

Should We Just Avoid Treating Patients With PH to Obtain Better 2-Year Survival Rates?

Mainly 3 strategies can be pursued to improve survival outcomes after TTVI: improvement of transcatheter techniques, reinforced treatment of comorbidities, and stricter patient selection. To withhold TTVI from patients diagnosed with PH would surely improve the overall survival rate of the remaining population of relatively healthy patients, but it would also imply excluding many patients. In fact, resolving PH in patients with TR remains a challenge. On average, patients in this study presented with mPAP levels of 30.4±9.46 (95% CI, 29.6–31.2) mm Hg and mean postcapillary wedge pressure levels of 19.5±7.39 (95% CI, 18.7–20.2) mm Hg (Table 2), indicating backwards transmission of elevated left-sided filling pressures. To date, there exists no specific pharmacotherapy to lower pulmonary artery pressure levels in patients with PH attributable to left-sided heart disease.[19] Treatment with phosphodiesterase type 5 inhibitor sildenafil in patients with persistent PH after successful correction of left-sided valvular heart disease was even shown to be associated with worse clinical outcomes (death, hospital admission, worsening functional class, global symptom burden) as compared with placebo.[39] Acknowledging the prognostic significance of PH, it is therefore of paramount importance to invent pharmacotherapeutic options to ameliorate pulmonary artery pressure levels caused by left-sided heart disease. Our proportionality concept aims to evaluate whether TR represents a prognostically relevant interventional target or just an indicator of worse prognosis in patients with PH, and it might thus identify patients with proportionate TR who are in urgent need for better treatment of PH.

Limitations

Being a retrospective, observational, nonrandomized register study with inherent weaknesses, 4 major limitations of our analysis merit consideration.

First, the proportionality framework is based on dichotomization into 2 categories (proportionate versus disproportionate) relying on only 2 parameters, that is, mPAP and TV EROA. Dichotomization comes with the disadvantage to be prone to oversimplification, especially when dealing with a continuous variable such as TV EROA/mPAP ratio. Moreover, a multiparametric approach incorporating several indices for PH (eg, mPAP and pulmonary vascular resistance) as well as for TR severity (eg, TV EROA, TR volume, and tricuspid valve vena contracta width) could have compensated for inaccurateness in respective measurements at the cost of simplicity. Quantification of TR severity is particularly challenging because of its dependency on loading conditions, dynamicity throughout the cardiac and respiratory cycle, and unpredictable TV EROA geometry, which is neither flat nor circular.[40]

Second, this study is based on data that were generated during clinical routine in a real-life scenario, meaning that no central core laboratory was involved to prevent any potential interobserver biases regarding echocardiography or right heart catheterization. Moreover, 99 of 702 patients were excluded because of missing measurements of mPAP levels during preprocedural right heart catheterization. Using echocardiographic estimates of pulmonary artery pressure levels was no option, as echocardiography systematically underestimates PH in patients with advanced stages of right heart dysfunction and severe TR.[12] We have therefore decided to employ a previously established extreme gradient boosting algorithm for mPAP prediction based on 9 parameters from routine echocardiography. Because the TV EROA/$mPAP_{predicted}$ ratio also enabled patients to be stratified into low-risk and high-risk cohorts according to TR proportionality, we hereby provide a framework that has the potential to be broadly applicable for almost every (resident) cardiologist trained in echocardiography. It needs to be further acknowledged that pulmonary artery pressure levels may vary during a time course, and circumstances, when pulmonary artery pressure levels were assessed by echocardiography, may not have been the same as for right heart catheterization.

Third, we can only speculate on the mechanism(s) resulting in poor survival among patients with proportionate TR, because neither postprocedural hemodynamic trajectories nor echocardiographic follow-up data were available. A follow-up study is needed to test whether a postprocedural increase in right ventricular filling pressure leads to accelerated right heart decompensation in patients with proportionate TR (which were also diagnosed with impaired right ventricular–to–pulmonary artery coupling).

Finally, this study was designed to develop an easily comprehensible, prognostically meaningful mechanistic model that relates TR severity to pulmonary artery pressure levels. By detecting cases of TR that are more severe than expected from the degree of PH, we aspire to improve prognostication in patients undergoing TTVI. Importantly, this model did not intend to predict futility with the consequence of withholding the option of TTVI from patients with proportionate TR in the future. To better understand the impact of TTVI on longevity in patients with proportionate TR, a randomized study with a conservative treatment arm as a control group is mandatory.

CONCLUSIONS

The proposed proportionality framework for patients with severe TR demonstrates that low TV EROA/mPAP levels are associated with poor survival after TTVI. Importantly, patients with proportionate TR (defined as TV EROA/mPAP ratio ≤1.25 mm^2/mm Hg) were characterized by less severe TR but more pronounced PH. Distinct from the natural course of the disease, where rising stages of TR severity directly translate into increased mortality, we show in patients treated by TTVI that it is of prognostic importance to identify those cases where the degree of TR severity exceeds the expectation on the basis of pulmonary artery pressure levels. Our proposed proportionality framework could therefore serve physicians in tailoring individual treatment plans for a heterogeneous disease entity such as severe TR. While patients with disproportionate TR featured a favorable outcome after TTVI, treatment success of TTVI in patients with proportionate TR was limited. Before influencing clinical decision-making, randomized controlled trials evaluating the net benefit of TTVI in patients with proportionate TR are mandatory.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Table S1–S5
Figures S1–S3

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Supplemental Material

Table S1. R packages employed in this study.

Amelia	*grDevices*	*readxl*
base	*iterators*	*reshape2*
datasets	*itertools*	*stats*
dplyr	*methods*	*stringr*
forcats	*missForest*	*survival*
foreach	*mlbench*	*survminer*
gcookbook	*mvtnorm*	*tibble*
ggalluvial	*plotROC*	*tidyr*
ggbeeswarm	*pROC*	*tidyverse*
ggExtra	*purrr*	*timeROC*
ggplot2	*randomForest*	*utils*
ggpubr	*rcompanion*	*xgboost*
ggrepel	*Rcpp*	
graphics	*readr*	

Table S2. Demographic and clinical characteristics in accordance with study enrollment.

	All (n = 702)	Included (n = 533)	Excluded (n = 169)	*p*-value
Age, mean ± SD [95% CI], years	78.0 ± 7.86 [77.4-78.6]	78.0 ± 7.55 [77.4-78.7]	77.9 ± 8.77 [76.6-79.2]	0.332
Men, No. (%)	316 (45.0%)	250 (46.9%)	66 (39.1%)	0.089
BMI, mean ± SD [95% CI], kg/m²	26.1 ± 4.81 [25.7-26.4]	26.2 ± 4.83 [25.8-26.6]	25.6 ± 4.73 [24.9-26.3]	0.188
Arterial hypertension, No. (%)	593 (84.5%)	464 (87.1%)	129 (76.3%)	0.001
Diabetes mellitus, No. (%)	192 (27.4%)	144 (27.0%)	48 (28.4%)	0.800
NYHA class ≤ II, No. (%)	70 (9.97%)	57 (10.7%)	13 (7.69%)	0.323
NYHA class III, No. (%)	533 (75.9%)	398 (74.7%)	135 (79.9%)	0.202
NYHA class IV, No. (%)	99 (14.1%)	78 (14.6%)	21 (12.4%)	0.554
EuroScore II (%)	7.22 ± 7.16 [6.69-7.76]	7.36 ± 7.25 [6.74-7.98]	6.78 ± 6.87 [5.73-7.84]	0.828
eGFR, mean ± SD [95% CI], mL/min	50.3 ± 21.9 [48.7-51.9]	51.8 ± 21.5 [50.0-53.7]	45.4 ± 22.6 [42.0-48.9]	< 0.001
NT-proBNP, mean ± SD [95% CI], pg/mL	4,738 ± 8,616 [4,090-5,390]	4,764 ± 8,457 [4,030-5,490]	4,655 ± 9,150 [3,210-6,100]	0.697
CAD, No. (%)	304 (43.3%)	229 (43.0%)	75 (44.4%)	0.815
COPD, No. (%)	131 (18.7%)	97 (18.2%)	34 (20.1%)	0.657
Atrial fibrillation, No. (%)	632 (90.0%)	479 (89.9%)	153 (90.5%)	0.917
Pacemaker, No. (%)	197 (28.1%)	153 (28.7%)	44 (26.0%)	0.565

BMI: body mass index; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; NYHA: New York Heart Association.

Categorical variables are presented as numbers and frequencies (%), whilst continuous variables are given as means ± standard deviation and 95% confidence interval.

Table S3. Echocardiographic and hemodynamic characteristics in accordance with study enrollment.

	All (n = 702)	Included (n = 533)	Excluded (n = 169)	*p*-value
LVEF, mean ± SD [95% CI], %	53.6 ± 11.6 [52.7-54.5]	53.4 ± 11.5 [52.4-54.5]	54.0 ± 12.1 [51.9-56.1]	0.574
LVESD, mean ± SD [95% CI], mm	39.2 ± 14.1 [38.1-40.4]	39.7 ± 14.2 [38.4-41.0]	37.6 ± 13.6 [35.3-39.9]	0.121
LVEDD, mean ± SD [95% CI], mm	47.9 ± 8.24 [47.2-48.6]	47.8 ± 8.07 [47.0-48.6]	48.3 ± 8.72 [46.9-49.8]	0.789
LA area, mean ± SD [95% CI], cm^2	31.4 ± 9.90 [30.6-32.1]	31.3 ± 9.62 [30.4-32.2]	31.6 ± 10.8 [29.8-33.4]	0.886
$sPAP_{echo}$, mean ± SD [95% CI], mmHg	41.1 ± 14.9 [40.0-42.2]	40.4 ± 14.7 [39.2-41.7]	43.4 ± 15.3 [40.9-45.8]	0.016
TAPSE, mean ± SD [95% CI], mm	16.6 ± 4.54 [16.3-17.0]	16.7 ± 4.53 [16.3-17.1]	16.4 ± 4.56 [15.7-17.1]	0.379
RV FAC, mean ± SD [95% CI], %	38.2 ± 11.0 [37.2-39.2]	38.5 ± 11.3 [37.3-39.7]	37.2 ± 9.95 [35.2-39.2]	0.228
Basal RV diameter, mean ± SD [95% CI], mm	47.0 ± 8.06 [46.4-47.6]	47.3 ± 8.15 [46.6-48.0]	46.0 ± 7.68 [44.8-47.2]	0.098
TR volume, mean ± SD [95% CI], mL	51.3 ± 28.0 [49.1-53.6]	51.2 ± 27.5 [48.7-53.6]	52.1 ± 30.4 [45.9-58.2]	0.852
TR vena contracta width, mean ± SD [95% CI], mm	11.2 ± 4.27 [10.9-11.5]	11.1 ± 4.29 [10.8-11.5]	11.4 ± 4.18 [10.7-12.1]	0.426
TR ≤ III/V°, No. (%)	354 (50.4%)	254 (47.7%)	100 (59.2%)	0.012
TR = IV/V°, No. (%)	219 (31.2%)	178 (33.4%)	41 (24.3%)	0.033
TR = V/V°, No. (%)	129 (18.4%)	101 (18.9%)	28 (16.6%)	0.560
RA area, mean ± SD [95% CI], cm^2	36.9 ± 11.6 [36.0-37.8]	37.3 ± 11.4 [36.3-38.2]	35.8 ± 12.0 [33.9-37.6]	0.062
Inferior vena cava diameter, mean ± SD [95% CI], mm	25.8 ± 6.42 [25.3-26.3]	26.0 ± 6.47 [25.4-26.6]	25.3 ± 6.24 [24.3-26.2]	0.285

Basal RV diameter: basal right ventricular diameter; LA area: left atrial area; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; RA area: right atrial area; RV FAC: right ventricular fractional area change; $sPAP_{echo}$: systolic pulmonary artery pressure (as assessed by echocardiography); TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation; TR vena contracta width: tricuspid regurgitation vena contracta width; TR volume: tricuspid regurgitation volume. Continuous variables are given as means ± standard deviation and 95% confidence interval.

Table S4. Demographic and clinical characteristics in accordance with TV EROA/mPAP ratio (entire study population).

	TV EROA/mPAP ratio		
	Disproportionate (n = 398)	Proportionate (n = 135)	*p*-value
Age, mean ± SD [95% CI], years	78.2 ± 7.47 [77.4-78.9]	77.7 ± 7.80 [76.3-79.0]	0.667
Men, No. (%)	189 (47.5%)	61 (45.2%)	0.716
BMI, mean ± SD [95% CI], kg/m²	26.2 ± 4.79 [25.8-26.7]	26.1 ± 4.97 [25.3-27.0]	0.632
Arterial hypertension, No. (%)	339 (85.2%)	125 (92.6%)	0.039
Diabetes mellitus, No. (%)	99 (24.9%)	45 (33.3%)	0.072
NYHA class ≤ II, No. (%)	39 (9.80%)	18 (13.3%)	0.324
NYHA class III, No. (%)	306 (76.9%)	92 (68.1%)	0.057
NYHA class IV, No. (%)	53 (13.3%)	25 (18.5%)	0.181
EuroScore II (%)	6.99 ± 6.28 [6.37-7.62]	8.45 ± 9.52 [6.82-10.1]	0.606
eGFR, mean ± SD [95% CI], mL/min	52.7 ± 21.8 [50.5-54.8]	49.4 ± 20.4 [45.9-52.8]	0.124
NT-proBNP, mean ± SD [95% CI], pg/mL	4,232 ± 7,866 [3,440-5,020]	6,318 ± 9,856 [4,620-8,020]	$4.9x10^{-7}$
CAD, No. (%)	165 (41.5%)	64 (47.4%)	0.269
COPD, No. (%)	67 (16.8%)	30 (22.2%)	0.203
Atrial fibrillation, No. (%)	361 (90.7%)	118 (87.4%)	0.352
Pacemaker, No. (%)	122 (30.7%)	31 (23.0%)	0.110
Pulmonary hypertension defined as mPAP ≥ 25 mmHg, No. (%)	255 (64.1%)	130 (96.3%)	$1.1x10^{-12}$
Pulmonary hypertension defined as mPAP ≥ 20 mmHg, No. (%)	338 (84.9%)	135 (100%)	$3.6x10^{-6}$

BMI: body mass index; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; mPAP: mean pulmonary artery pressure (as assessed by right heart catheterization); NYHA: New York Heart Association. Categorical variables are presented as numbers and frequencies (%), whilst continuous variables are given as means ± standard deviation and 95% confidence interval.

Table S5. Comparison of echocardiographic and hemodynamic characteristics in accordance with TV EROA/mPAP ratio (entire study population).

	TV EROA/mPAP ratio		
	Disproportionate (n = 398)	Proportionate (n = 135)	*p*-value
LVEF, mean ± SD [95% CI], %	53.3 ± 11.1 [52.2-54.5]	53.8 ± 12.5 [51.6-56.0]	0.637
LVESD, mean ± SD [95% CI], mm	39.9 ± 13.9 [38.4-41.4]	39.2 ± 14.9 [36.6-41.9]	0.479
LVEDD, mean ± SD [95% CI], mm	47.8 ± 8.00 [46.9-48.7]	47.6 ± 8.31 [45.9-49.3]	0.726
LA area, mean ± SD [95% CI], cm^2	31.3 ± 9.96 [30.3-32.4]	31.1 ± 8.66 [29.6-32.7]	0.852
$sPAP_{echo}$, mean ± SD [95% CI], mmHg	37.0 ± 12.6 [35.8-38.3]	50.4 ± 15.8 [47.7-53.1]	$< 2.2x10^{-16}$
TAPSE, mean ± SD [95% CI], mm	17.0 ± 4.64 [16.5-17.4]	16.0 ± 4.11 [15.3-16.7]	0.012
RV FAC, mean ± SD [95% CI], %	39.3 ± 11.2 [38.0-40.6]	35.9 ± 11.4 [33.3-38.4]	0.005
Basal RV diameter, mean ± SD [95% CI], mm	48.0 ± 8.23 [47.2-48.8]	45.4 ± 7.61 [44.1-46.7]	0.001
TV EROA, mean ± SD [95% CI], mm^2	77.0 ± 43.2 [72.8-81.3]	35.0 ± 10.5 [33.2-36.8]	$< 2.2x10^{-16}$
TR volume, mean ± SD [95% CI], mL	56.5 ± 29.3 [53.4-59.5]	36.2 ± 13.4 [33.9-38.5]	$< 2.2x10^{-16}$
TR vena contracta width, mean ± SD [95% CI], mm	11.8 ± 4.39 [11.4-12.3]	9.05 ± 3.17 [8.51-9.60]	$1.9x10^{-13}$
TR ≤ III/V°, No. (%)	160 (40.2%)	94 (69.6%)	6.0x10-9
TR = IV/V°, No. (%)	140 (35.2%)	38 (28.1%)	0.164
TR = V/V°, No. (%)	98 (24.6%)	3 (2.22%)	$2.0x10^{-8}$
RA area, mean ± SD [95% CI], cm^2	38.4 ± 11.7 [37.2-39.6]	34.0 ± 9.95 [32.3-35.7]	< 0.001

Inferior vena cava diameter, mean ± SD [95% CI], mm	26.4 ± 6.60 [25.7-27.1]	24.8 ± 5.91 [23.8-25.9]	0.037
Cardiac output, mean ± SD [95% CI], L/min	4.06 ± 1.48 [3.91-4.21]	4.46 ± 2.00 [4.11-4.82]	0.096
Cardiac index, mean ± SD [95% CI], L/min/m²	2.18 ± 0.754 [2.10-2.25]	2.42 ± 1.02 [2.24-2.60]	0.027
PVR, mean ± SD [95% CI], WU	2.83 ± 1.74 [2.63-3.03]	3.68 ± 2.46 [3.20-4.17]	0.002
$sPAP_{invasive}$, mean ± SD [95% CI], mmHg	43.1 ± 12.7 [41.8-44.3]	59.2 ± 14.9 [56.6-61.8]	$< 2.2x10^{-16}$
dPAP, mean ± SD [95% CI], mmHg	18.0 ± 6.88 [17.3-18.7]	24.0 ± 7.99 [22.6-25.4]	$5.3x10^{-14}$
mPAP, mean ± SD [95% CI], mmHg	27.9 ± 8.17 [27.1-28.7]	37.9 ± 9.06 [36.3-39.4]	$< 2.2x10^{-16}$
mPCWP, mean ± SD [95% CI], mmHg	17.9 ± 6.61 [17.1-18.6]	24.1 ± 7.60 [22.6-25.5]	$4.2x10^{-14}$

Basal RV diameter: basal right ventricular diameter; dPAP: diastolic pulmonary artery pressure (as assessed by right heart catheterization); LA area: left atrial area; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; mPAP: mean pulmonary artery pressure (as assessed by right heart catheterization); mPCWP: mean postcapillary wedge pressure (as assessed by right heart catheterization); PVR: pulmonary vascular resistance; RA area: right atrial area; RV FAC: right ventricular fractional area change; $sPAP_{echo}$: systolic pulmonary artery pressure (as assessed by echocardiography); $sPAP_{invasive}$: systolic pulmonary artery pressure (as assessed by right heart catheterization); TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation; TR vena contracta width: tricuspid regurgitation vena contracta width; TR volume: tricuspid regurgitation volume; TV EROA: tricuspid valve effective regurgitant orifice area.

Continuous variables are given as means ± standard deviation and 95% confidence interval.

Figure S1. Kaplan-Meier survival plot comparing survival rates between included and excluded patients.

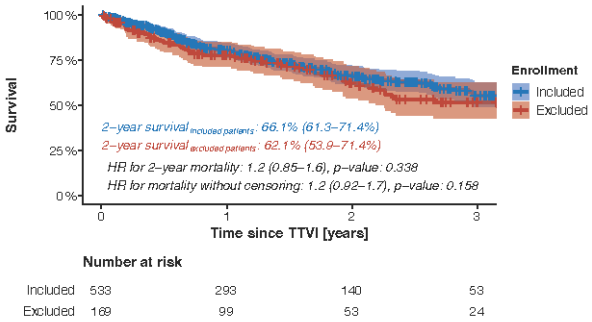
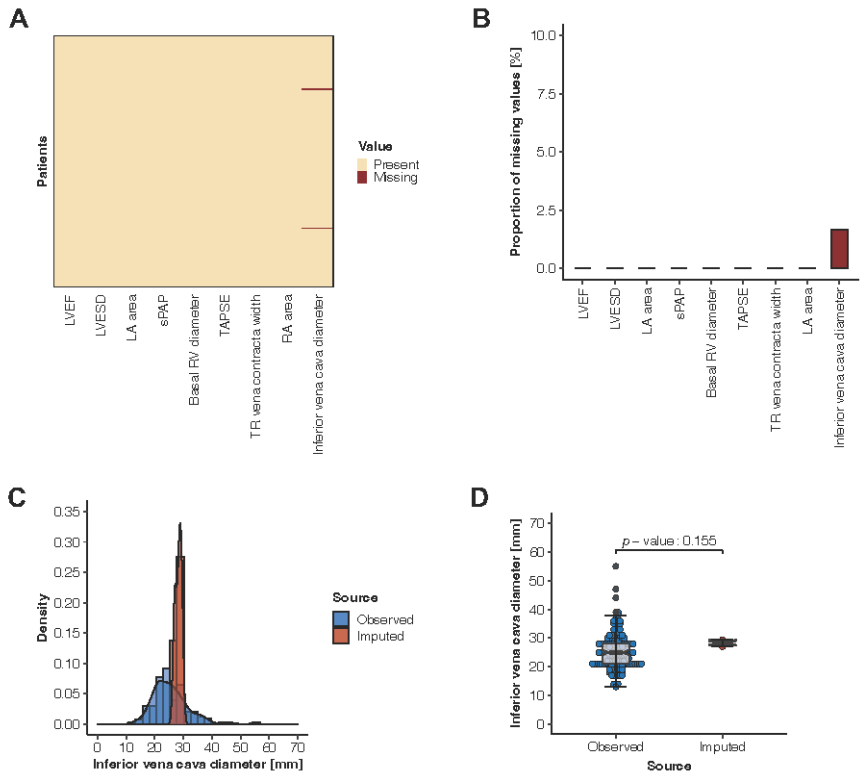


Figure S2. Imputation of missing values (validation cohort).



A: Illustration of missing and observed values.

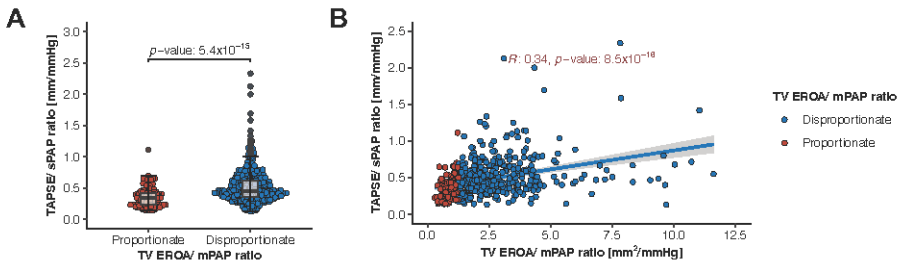
B: Bar plot showing the proportion of missing values per variable.

C: Density plot showing the distribution of sPAP levels as observed and imputed by a random forest algorithm.

D: Bee swarm plot comparing sPAP levels as observed and imputed.

Basal RV diameter: basal right ventricular diameter; LA area: left atrial area; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; RA area: right atrial area; sPAP: systolic pulmonary artery pressure (assessed by echocardiography); TAPSE: tricuspid annular plane systolic excursion; TR vena contracta width: tricuspid valve vena contracta width.

Figure S3. Analysis of right ventricular to pulmonary artery coupling in accordance with TR proportionality (entire study population).



A: Bee swarm plot comparing TAPSE/sPAP ratios in accordance with TR proportionality expressed as TV EROA/mPAP ratio.

B: Scatter plot relating TAPSE/sPAP levels to TV EROA/mPAP levels. R: correlation coefficient by Pearson correlating TAPSE and sPAP levels. Blue line: linear regression line. Gray area: 95% confidence interval.

mPAP: mean pulmonary artery pressure; sPAP: systolic pulmonary artery pressure (assessed by echocardiography); TAPSE: tricuspid annular plane systolic excursion; TV EROA: tricuspid valve effective regurgitant orifice area.