ESC European Society of Cardiology

European Journal of Heart Failure (2025) **27**, 1511–1522
doi:10.1002/ejhf.3532

RESEARCH ARTICLE

The prognostic value of the Dandel's index in patients undergoing tricuspid transcatheter edge-to-edge repair

Mohammad Kassar[1,2,3*†], Nicolas Brugger[1†], Lukas Stolz[4], Muhammed Gerçek[3], Vera Fortmeier[3], Karl-Patrik Kresoja[5,6], Jennifer von Stein[7], Benedikt Koell[8,9], Wolfgang Rottbauer[10], Bjoern Goebel[11], Paolo Denti[12], Paul Achouh[13], Tienush Rassaf[14], Manuel Barreiro-Perez[15], Peter Boekstegers[16], Andreas Rück[17], Monika Zdanyte[18], Marianna Adamo[19], Flavien Vincent[20], Philipp Schlegel[21], Ralph-Stephan von Bardeleben[6], Mirjam G. Wild[22], Stefan Toggweiler[23], Mathias H. Konstandin[21], Eric Van Belle[20], Marco Metra[19], Tobias Geisler[18], Rodrigo Estévez-Loureiro[15], Peter Luedike[14], Nicole Karam[13], Francesco Maisano[12], Philipp Lauten[11], Mirjam Kessler[10], Daniel Kalbacher[8,9], Christos Iliadis[7], Philipp Lurz[6], Stephan Windecker[1], Jörg Hausleiter[4,24], Volker Rudolph[3‡], and Fabien Praz[1‡]

[1]Department of Cardiology, Inselspital, Bern, Switzerland; [2]Graduate School for Health Sciences, University of Bern, Bern, Switzerland; [3]Clinic for General and Interventional Cardiology/Angiology, Heart and Diabetes Center, Bad Oeynhausen, Germany; [4]Medizinische Klinik und Poliklinik I, LMU Klinikum, LMU München, Munich, Germany; [5]Department of Cardiology, Heart Center Leipzig, University of Leipzig, Leipzig, Germany; [6]Department of Cardiology, Cardiology I, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany; [7]Department of Cardiology, Heart Center, University of Cologne, Cologne, Germany; [8]Department of Cardiology, University Heart and Vascular Centre Hamburg, Hamburg, Germany; [9]German Center of Cardiovascular Research (DZHK), Partner Site Hamburg/Kiel/Lübeck, Hamburg, Germany; [10]Department of Cardiology, University Heart Center Ulm, Ulm, Germany; [11]Department of Cardiology, Heart Center, Zentralklinik Bad Berka, Bad Berka, Germany; [12]Heart Valve Center, Cardio-Thoracic-Vascular Department, IRCCS San Raffaele Scientific Institute, Milan, Italy; [13]Cardiology Department, European Hospital Georges Pompidou, Université Paris Cité, Paris, France; [14]University Hospital Essen, University Duisburg-Essen, West German Heart- and Vascular Center, Department of Cardiology and Vascular Medicine, Essen, Germany; [15]Hospital Álvaro Cunqueiro, Vigo, Spain; [16]Department of Cardiology, Helios Klinikum Siegburg, Siegburg, Germany; [17]Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden; [18]Medical Clinic III, University Hospital Tübingen, Tübingen, Germany; [19]ASST Spedali Civili di Brescia and Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy; [20]Cardiology Department, Centre Hospitalier Universitaire De Lille, Lille, France; [21]Division of Cardiology, Department of Internal Medicine III, University Hospital Heidelberg, Ruprecht-Karl University Heidelberg, Heidelberg, Germany; [22]University Heart Center Freiburg/Bad Krozingen, Bad Krozingen, Germany; [23]Heart Center Lucerne, Luzerner Kantonsspital, Lucerne, Switzerland; and [24]German Center for Cardiovascular Research (DZHK), Partner Site Munich Heart Alliance, Munich, Germany

Received 23 July 2024; revised 28 October 2024; accepted 30 October 2024; online publish-ahead-of-print 2 December 2024

*Corresponding author. Department of Cardiology, Inselspital, Freiburgstrasse 10, 3010 Bern, Switzerland. Tel: +41 31 6640590, Email: mohammadkassar@outlook.de

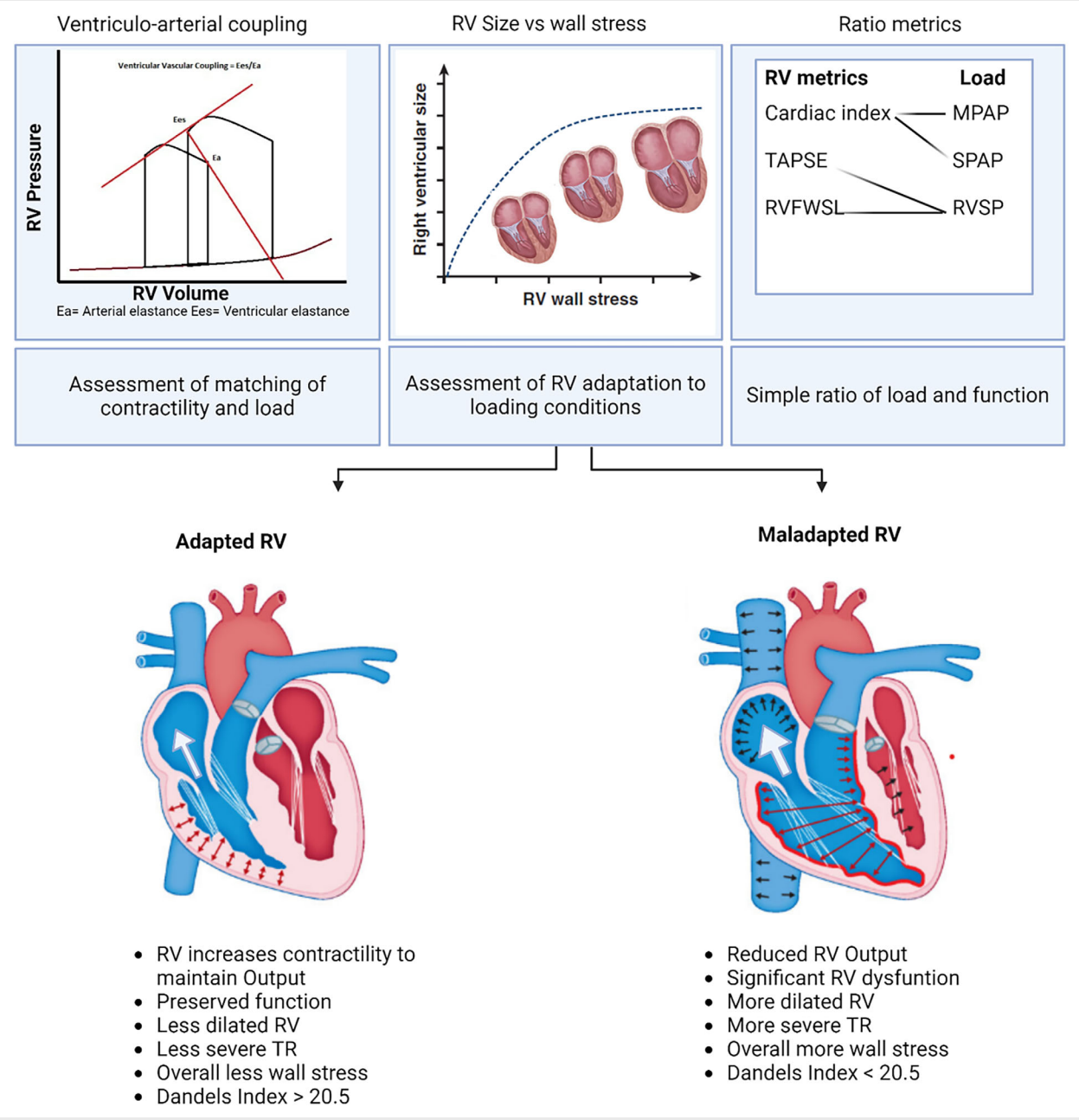
[†]Contributed equally as co-first authors.
[‡]Contributed equally as co-last authors.

Aims Conventional parameters of right ventricular (RV) function are load-dependent and therefore do not accurately reflect contractility in patients with relevant tricuspid regurgitation (TR). RV adaptability to load has been characterized using the Dandel's index in patients with heart failure, but its prognostic value in patients undergoing tricuspid transcatheter edge-to-edge repair (T-TEER) has not been investigated so far.

Methods and results From the EuroTR registry (2019 to 2022), patients with complete datasets and a minimum of 2-years of follow-up were included. RV functional parameters (i.e. tricuspid annular plane systolic excursion [TAPSE], fractional area change [FAC], TAPSE/systolic pulmonary arterial pressure [sPAP]), as well as a echocardiographic RV load adaptation index (Dandel's index) were assessed and their predictive value in terms of all-cause mortality evaluated using logistic multivariate logistic regression. The majority of the 364 patients had secondary TR (96%) and were severely symptomatic (New York Heart Association class ≥III; 92%). At 2-year follow-up, 36% of patients had died. Functional RV parameters (TAPSE: hazard ratio [HR] 0.72, 95% confidence interval [CI] 0.62−0.84; FAC: HR 0.73, 95% CI 0.59−0.91), coupling index (TAPSE/sPAP: HR 0.8, 95% CI 0.65−0.99) and Dandel's index (HR 0.67, 95% CI 0.53−0.85) were all associated with mortality at 2 years in univariable analyses. In a multivariate logistic regression model, the Dandel's index maintained its predictive value ($p < 0.001$), along with TAPSE and absence of signs of right heart failure, with an optimal threshold of 20.5 determined by the receiver-operating characteristic analysis. This threshold also successfully predicted cardiac hospital readmission. A multivariate analysis was conducted to identify parameters linked to RV function and predicting clinical outcomes.

Conclusion Assessment of the RV capacity to adjust for changes in loading conditions predicted mortality in patients with severe symptomatic TR undergoing T-TEER. The use of a multiparametric approach including the Dandel's index to assess RV function had an incremental value for the stratification of patients into subgroups with different prognosis.

Graphical Abstract



Load adaptation indices and concepts. An adapted right ventricle in response to overload increases wall thickness to normalize wall stress and preserve function and morphology. If hemodynamic overload is sustained, it can progress to a maladaptive state and lead eventually to heart failure. CI, cardiac index; Ees, ventricular elastance; Ea, arterial elastance; MPAP, mean pulmonary arterial pressure; PP, pulse pressure; RV, right ventricle/right ventricular; RVFWSL, right ventricular free wall strain; RVSP, right ventricular systolic pressure; SPAP, systolic pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion.

Keywords Tricuspid regurgitation • Tricuspid transcatheter edge-to-edge repair • Preload and afterload • Load adaptability • Mid-term prognosis

Introduction

Tricuspid regurgitation (TR) leads to volume overload of the right ventricle, resulting in adverse remodelling and dysfunction. The haemodynamic consequences of TR are complex with both acute and chronic effects on the cardiovascular system.[1] Chronic severe TR exposes the right ventricle to an increased preload due to the regurgitant volume and, in early stages, to a decreased afterload due to the high resistance, but low-pressure outlet into the right atrium (RA). This is gradually followed by a remodelling process with right ventricular (RV) eccentric hypertrophy.[2] As long as these changes permit to keep the forward stroke volume sufficient and the right ventricle is able to couple with pulmonary vascular resistance (PVR), patients have little or no symptoms: RV load adaptability may be a key factor for survival.[3] Eventually, RV dilatation leads to increased wall stress (i.e. afterload according to Laplace's law) resulting in further chamber enlargement and impaired contractile function.[4]

The gold standard for assessing contractility is the end-systolic elastance (Ees) and RV–pulmonary artery (PA) coupling, which is calculated as the ratio of end-systolic to arterial elastance (Ees/Ea)[5–7] both derived from invasive pressure–volume loops. Non-invasive surrogates have been proposed, such as the tricuspid annular plane systolic excursion to systolic pulmonary arterial pressure (TAPSE/sPAP),[8,9] and the ratio of stroke volume to end-systolic volume (*Graphical abstract*).

As TR increases, the reliability of classic load-dependent parameters like TAPSE and fractional area change (FAC) for assessing RV contractility diminishes. RV size, geometry, sPAP, and TR severity are crucial variables in the direct evaluation of RV contractile function by echocardiography and their interrelation suggests that an integrative assessment may be most reliable. Therefore, the RV load adaptation index (RVLAI), also known as Dandel's index, has been introduced.[3]

Rather than consisting of a single load-dependent parameter to assess RV function, this index integrates information about RV afterload [ΔP(RV-RA)], preload (RV end-diastolic volume [RVEDV]) and geometry (RV end-diastolic length [RVEDL] vs. RVEDV) using echocardiographic measurements/surrogates in patients with severe TR. A slender right ventricle with a low volume relative to its long-axis size, along with a high value of the velocity time integral through the tricuspid valve (VTI_{TR}), indicates good adaptation to load, reflected in a high RVLAI (adapted right ventricle). Conversely, a short rounded severely dilated right ventricle with low VTI_{TR} (low RVLAI) suggests impaired RV contractile function (maladapted right ventricle) (*Graphical abstract*). This concept evaluating the changes in RV morphology and size linked to the wall stress (preload and afterload) has been investigated in populations with advanced diseases such as severe pulmonary hypertension[10] or end-stage left ventricular dysfunction requiring assist device implantation.[3] The evaluation of the prognostic significance of RV adaptability indexes to changes in load has been limited to single-centre investigations without comprehensive external validation. Additionally, no study has compared them to standard RV remodelling or functional parameters in the setting of severe TR (such as RV end-systolic dimension or strain).

Using data of patients with severe TR who underwent tricuspid transcatheter edge-to-edge repair (T-TEER) included into the EuroTR registry, our aim was to assess the predictive value of indexes of RV load adaptability compared to classical RV size and function parameters. Death was chosen as primary, and hospital readmission for heart failure as secondary endpoint.

Methods

Study design and patient selection

Patients from tertiary European heart valve centres who underwent T-TEER for treatment of relevant TR between 2019 and 2022 were retrospectively included into the EuroTR registry (NCT06307262). Each patient's treatment strategy was individually determined by an interdisciplinary Heart Team. The T-TEER procedure was conducted using either the PASCAL (Edwards Lifesciences, Irvine, CA, USA) or the TriClip system (Abbott, Santa Clara, CA, USA) as previously detailed.[1,5] Heart failure symptoms were classified using New York Heart Association (NYHA) functional class. Echocardiographic evaluations were performed by experienced physicians at each centre in line with current guidelines.[11–14] In a subgroup of this cohort, advanced three-dimensional (3D) echocardiograms were available. Patients were followed for 2 years according to each centre's standard of care. The study was approved by each centres' local ethics committee and adheres to the principles of the Declaration of Helsinki.

Study procedures

Transthoracic echocardiograms were performed within 1 month prior T-TEER; within a week in 60% of patients. Measurements included RV areas (RV end-diastolic area [RVEDA] and RV end-systolic area [RVESA]), RVEDL, VTI_{TR} and right atrial maximal area obtained from the apical 4-chamber view. In a subgroup of 190 patients, advanced 3D echocardiographic parameters (3D RV volumes, ejection fraction, as well as free wall and septal strain) were compared to the conventional functional parameters. Classical RV functional parameters, including TAPSE, FAC and echocardiographic TAPSE/sPAP were evaluated. The Dandel's index evaluating RV adaption to loading condition was calculated as follows[3]:

$$(\text{RVLAI} = [\Delta P(\text{RV} - \text{RA})]/[\text{RVEDV}/\text{RVEDL}]) \approx \text{VTI}_{\text{TR}}/$$

$$(\text{RVEDA}/\text{RVEDL}) = \left[\text{VTI}_{\text{TR}}\ (\text{cm}) * \text{RVEDL}\ (\text{cm})\right] /$$

$$\text{RVEDA}\ \left(\text{cm}^2\right)\ \text{as a dimensionless index}$$

where ΔP(RV-RA) is the maximum systolic pressure gradient between the right ventricle and RA and RVEDV is the RV end-diastolic volume. RVEDA is used as substitute for RVEDV and VTI_{TR} for $\Delta P_{(RV\text{-}RA)}$.

In a subgroup with sufficient image quality, Lagrangian longitudinal strain of the free wall and septum was assessed. Lagrangian longitudinal strain was derived from the manually traced endocardial end-diastolic and end-systolic lengths as (end-systolic length − end-diastolic length)/(end-diastolic length). RV systolic pressure was either approximated from the TR maximal velocity and estimated right atrial pressure or measured using right heart catheterization.

Invasive haemodynamic assessment

Pulmonary artery pressures were evaluated using right heart catheterization. A 6 or 7 Fr Swan–Ganz catheter was introduced via the

femoral access and measurements of the pulmonary artery wedge pressure (PAWP), sPAP, diastolic pulmonary artery pressure, and mean pulmonary artery pressure (mPAP) were conducted. The cardiac output was estimated utilizing the indirect Fick method integrating calculated oxygen uptake values. PVR was defined as PVR = (mPAP − PAWP)/cardiac output.

Clinical outcomes

The predictive value of RV size and function parameters for all-cause mortality at 2 years as the primary endpoint and hospital readmission for right heart failure (RHF) as the secondary endpoint was assessed using multivariate logistic regression. Vital status at the time of enrolment was assessed by review of medical charts and of follow-up records.

Statistical analysis

Normality was assessed using the Shapiro–Wilk test. In case of normal distribution, quantitative values were expressed as mean ± standard deviation and compared using *t*-test for independent samples; otherwise values appeared as median and 25th–75th percentiles and were compared by Mann–Whitney test. Uni- and multivariate regression analysis of continuous variables were performed to determine relevant predictors of the primary outcome. In addition, adjusted univariable analysis per standard deviation were performed to compare echocardiographic parameters. Variables were included in the univariable analyses based on previous literature, pathophysiological considerations and the statistical significance for inclusion in the multivariate model was set at $p < 0.1$. A variance inflation factor >5 was considered as marker for a significant collinearity. Event rates were based on Kaplan–Meier estimates in time-to-first-event analyses. Receiver-operating characteristic (ROC) analyses were used to determine the optimal cut-offs for different RV parameters to predict the primary endpoint. For the prediction of the secondary endpoint, the incremental value of Dandel's index and of a multiparametric echocardiographic assessment of RV function were assessed using a Kaplan–Meier analysis to develop a multiparametric echocardiographic risk score incorporating data of RV function and geometry, we conducted a subsequent multivariate analysis only taking these elements into account and we also tested for collinearity. The most pertinent echocardiographic parameters were employed in a non-hierarchical additive risk score, after testing for collinearity: one point was given for each pathological value (risk factors) according to the guidelines for chamber quantification[15] (except for the Dandel's index whose cut-off was defined according to a ROC analysis). A *p*-value <0.05 was considered to indicate statistical significance. Analyses were performed with XLSTAT Premium, version 2022.1.2 (Addinsoft, New York, NY, USA) or IBM SPSS Statistics for Windows, version 26 (IBM, Armonk, NY, USA).

Results

Baseline characteristics

The analysed cohort consisted of 364 patients with complete datasets. Mean age was 78 ± 8 years, 48% were women, and the mean surgical risk was high (EuroSSCORE 6.9 ± 5.3; STS score 7.9 ± 6.2) (*Table 1*). TR was secondary in 95% of the subjects with TR classified as torrential in 64 (17.6%), massive in 130 (35.7%), severe in 161 (44.2%), and moderate in 9 individuals (2.9%). The majority had dyspnoea NYHA class III–IV (92%) with elevated N-terminal pro-B-type natriuretic peptide levels (6104 ± 12 035). Before treatment, 78% of patients presented with signs of RHF, and renal function was impaired in most participants (estimated glomerular filtration rate <45 ml/min in 63% of the population). Detailed echocardiographic quantitative TR parameters are presented in *Table 2*. Left ventricular function was preserved, while according to conventional parameters, RV function was borderline in the context of significant RV dilatation.

Echocardiographic parameters/indices and their correlations

Online supplementary *Figure S1* presents the correlation heatmap of echocardiographic load adaptability indices and standard RV parameters. The Dandel's index showed moderate correlations with both RVEDA and RVESA ($r = 0.51$, $p < 0.0001$; and $r = 0.42$, $p < 0.0001$, respectively), weak correlation with RV-PA coupling index (TAPSE/sPAP: $r = 0.31$, $p < 0.0001$) and TR severity, as evaluated by vena contracta width ($r = 0.36$, $p < 0.0001$), but no correlation with free wall longitudinal function, i.e. TAPSE ($r = 0.02$, $p = 0.740$). In contrast, the RV-PA coupling index demonstrated no correlation with RV size (RVEDA and RVESA; $r = 0.04$, $p = 0.421$; and $r = 0.05$, $p = 0.321$, respectively) or TR severity ($r = 0.08$, $p = 0.153$).

Clinical outcomes according to right ventricular adaptivity

During the follow-up period of 2 years, 36% of patients died (*Figure 1*). The univariable analyses of echocardiographic parameters per standard deviation[16] in relation to death are presented in *Figure 2*.

Higher values of functional RV parameters (TAPSE and FAC), of left ventricular ejection fraction, as well as of RV-PA coupling and Dandel's index were linked to a lower risk of mortality at 2 years (*Figure 2*). In contrast, bigger vena contracta width values were associated with a higher probability of meeting the primary endpoint. Interestingly, the quantitative evaluation of TR by the PISA method was not predictive of the outcome. The span of the area under the curve (AUC) of all significant parameters was relatively small ranging from 0.538 to 0.624, with Dandel's index having the highest but still modest AUC for a single parametric approach. In the subset examination of 190 individuals who underwent 3D echocardiography, the 3D RV ejection fraction, as well as the septal and free wall strain were not associated with the primary endpoint in the univariable analysis. However, higher RV end-systolic volume and RVEDV were linked to a higher mortality at 2 years (*Table 3*).

The univariate logistic regression analysis adjusted for all selected clinical and echocardiographic variables is detailed in online supplementary *Table S1*. Using the pre-specified criterion of $p < 0.1$ and after checking for collinearity, the optimal model

Table 1 Baseline characteristics of the study population

Variable	All ($n = 364$)	Patients reaching the primary endpoint ($n = 124$)	Patients not reaching the primary endpoint ($n = 240$)	*p*-value
Age (years)	78 ± 8	78 ± 8	78 ± 8	0.244
Sex, *n* (%)				0.089
Female	176 (48)	69 (56)	107 (45)	
Male	188 (52)	55 (44)	133 (55)	
TR aetiology, *n* (%)				**0.027**
Primary	20 (5)	10 (8)	10 (4)	
Secondary	344 (95)	114 (92)	230 (96)	
NYHA class, *n* (%)				**0.0002**
I	3 (1)	0 (0)	3 (1)	
II	28 (8)	5 (4)	23 (10)	
III	265 (73)	82 (66)	183 (76)	
IV	68 (19)	37 (30)	31 (13)	
TR severity grade, *n* (%)				**0.003**
I	0 (0)	0 (0)	0 (0)	
II	9 (2.4)	0 (0)	9 (4)	
III	161 (44.2)	42 (34)	119 (50)	
IV	130 (35.7)	50 (40)	80 (30)	
V	64 (17.6)	32 (26)	32 (13)	
TR aetiology, *n* (%)				0.151
Primary	20 (6)	9 (7)	12 (5)	
Secondary atrial	81 (22)	27 (22)	53 (22)	
Secondary ventricular	263 (72)	88 (71)	175 (73)	
Any signs of right heart failure, *n* (%)	284 (78)	104 (84)	180 (75)	**0.002**
Peripheral oedema, *n* (%)	265 (73)	105 (85)	160 (67)	**0.006**
Ascites, *n* (%)	57 (16)	35 (28)	22 (9)	**<0.0001**
Jugular vein distention, *n* (%)	44 (12)	31 (25)	13 (5)	**0.006**
Pleural effusion, *n* (%)	100 (34)	71 (57)	29 (12)	**<0.0001**
Diabetes mellitus, *n* (%)	82 (22)	27 (22)	55 (23)	0.965
Hypertension, *n* (%)	317 (87)	110 (89)	207 (86)	0.314
Previous myocardial infarction, *n* (%)	33 (9)	12 (10)	21 (9)	0.324
Dyslipidaemia, *n* (%)	99 (33)	40 (32)	59 (25)	0.199
Pervious stroke or TIA, *n* (%)	44 (12)	17 (14)	27 (11)	0.329
Coronary artery disease, *n* (%)	163 (45)	60 (48)	103 (43)	0.466
Chronic obstructive pulmonary disease, *n* (%)	63 (17)	26 (21)	37 (15)	0.273
History of atrial fibrillation or flutter, *n* (%)	336 (92)	107 (86)	229 (95)	**0.009**
History of cardiac surgery, *n* (%)	105 (29)	42 (34)	63 (26)	0.229
Previous CRT, *n* (%)	13 (4)	7 (6)	6 (3)	0.191
Previous ICD, *n* (%)	14 (4)	9 (7)	5 (2)	0.252
Previous pacemaker, *n* (%)	90 (25)	32 (26)	58 (24)	0.778
Pacemaker lead crossing the RV, *n* (%)	108 (30)	39 (31)	65 (27)	0.624
ACE-inhibitor or ATII-antagonist, *n* (%)	183 (50)	55 (44)	128 (53)	0.494
Beta-blocker, *n* (%)	302 (83)	105 (85)	197 (82)	0.478
Aldosterone antagonist, *n* (%)	162 (45)	57 (46)	105 (44)	0.424
Loop diuretics, *n* (%)	344 (95)	118 (95)	226 (94)	0.842
EuroSCORE II	6.9 ± 5.3	7.1 ± 6.8	5.6 ± 4.8	0.032
STS score	7.9 ± 6.2	7.1 ± 5.9	6.8 ± 5.1	0.690
TRI-SCORE	6 [4–7]	5 [4–7]	7 [6–8]	**<0.0001**
Total bilirubin (mg/dl)	1.0 ± 0.7	1.1 ± 0.6	1.0 ± 0.7	0.247
AST (U/L)	31.6 ± 13.3	33.1 ± 14.1	31 ± 13.8	0.219
ALT (U/L)	20.7 ± 11.8	20.9 ± 11.9	20.6 ± 11.8	0.865
GGT (U/L)	156.2 ± 141.3	212.2 ± 176.4	139.6 ± 124.9	**0.001**
Creatinine clearance (ml/min)	46 ± 22	43 ± 26	47 ± 21	0.162
NT-proBNP (pg/ml)	6104 ± 12 035	9772 ± 15 970	4992 ± 10 339	**0.001**

ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATII, angiotensin II; CRT, cardiac resynchronization therapy; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; GGT, gamma glutamyl transferase; ICD, implantable cardioverter-defibrillator; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RV, right ventricle; STS, Society of Thoracic Surgeons; TIA, transient ischaemic attack; TR, tricuspid regurgitation.

Table 2 Pre-interventional echocardiographic and invasive characteristics of the study population

Variable	All ($n = 364$)	Patients reaching the primary endpoint ($n = 124$)	Patients not reaching the primary endpoint ($n = 240$)	p-value
LVEF (%)	54 ± 11	52 ± 12.8	54 ± 10.9	**0.040**
LVEDD (mm)	48 ± 8	49 ± 8	48 ± 8	0.505
LA volume (ml)	107 ± 59	118 ± 49	104 ± 61	0.071
TR EROA (cm^2)	0.65 ± 0.54	0.67 ± 0.4	0.64 ± 0.58	0.689
TR RegVol (ml)	46 ± 23	44 ± 19	47 ± 24	0.497
TR VTI (cm)	80.9 ± 30.6	79.9 ± 24.6	83.9 ± 30.67	0.057
TR vena contracta width (mm)	10.9 ± 4.4	12.2 ± 5.2	10.6 ± 4.1	**0.003**
RV FAC (%)	36.1 ± 10.5	33.7 ± 9.4	36.7 ± 10.7	**0.020**
RVEDA (cm^2)	28.1 ± 9	30.3 ± 10.5	27.4 ± 8.4	**0.009**
RVESA (cm^2)	18.1 ± 6.8	20.1 ± 7.7	17.5 ± 6.4	**0.002**
RV mid diameter (mm)	40.1 ± 8.5	42.9 ± 9.9	39.3 ± 7.8	**0.047**
RV base diameter (mm)	48.4 ± 9.1	48.6 ± 9.4	48.5 ± 9.1	0.926
RV length (mm)	71.3 ± 11.6	73.2 ± 12	70.8 ± 11.4	0.090
TV annular diameter (mm)	47.2 ± 9.2	47.3 ± 9.6	47.2 ± 9.1	0.979
RA area (cm^2)	37.6 ± 12.1	39.4 ± 12.6	37.1 ± 11.8	0.118
TAPSE (mm)	17.3 ± 4.8	15.7 ± 4.6	17.7 ± 4.7	**0.001**
Echo sPAP	41.4 ± 13.5	41.1 ± 14.3	41.5 ± 13.3	0.816
Dandel's index	22.2 ± 10.8	20.1 ± 10.3	22.8 ± 10.9	**0.005**
Ventriculo–arterial coupling (TAPSE/sPAP)	0.46 ± 0.2	0.43 ± 0.2	0.47 ± 0.2	0.084
PAP systolic (mmHg)	47.9 ± 15.3	50.2 ± 14.5	47.3 ± 13.4	0.081
PAP diastolic (mmHg)	21.3 ± 7.6	23.3 ± 7.1	20.7 ± 6.7	**0.002**
PAP mean (mmHg)	31.4 ± 9.7	33.5 ± 9.2	30.7 ± 8.4	**0.010**
PAWP mean (mmHg)	19.2 ± 7.1	19.9 ± 6.5	19.1 ± 4.9	0.199
PVR (WU)	2.8 ± 1.8	3.5 ± 2.4	2.8 ± 1.6	0.108
Cardiac output (L/min)	4.7 ± 1.9	4.2 ± 1.3	4.8 ± 2	0.166

EROA, effective regurgitant orifice area; FAC, fractional area change; LA, left atrial; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; PAP, pulmonary artery pressure; PAWP pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RA, right atrial; RegVol, regurgitant volume; RV, right ventricular; RVEDA, right ventricular end-diastolic area; RVESA, right ventricular end-systolic area; sPAP, systolic pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TV tricuspid valve; VTI, velocity time integral; WU, Wood unit.

consisting of six variables (TAPSE, FAC, RV Dandel's index, mPAP, absence of atrial fibrillation and indicators of RHF as defined by peripheral oedema, ascites, pleural effusion, or jugular venous distention) was included in the multivariate logistic regression analysis: Dandel's index was the echocardiographic parameter that best predicted the primary endpoint (*Table 4*), and according to the ROC analysis, the optimal cut-off for predicting mortality was 20.5 (AUC 0.624, sensitivity 0.64, specificity 0.80), which also allowed to predict the risk of hospital readmission for RHF, as shown in *Figure 3*. This model was compared to the now well-established TRI-SCORE.[17] The AUCs derived from the ROC analysis for the prediction of all-cause mortality at 2 years were 0.760 for the new model and 0.745 for TRI-SCORE, with no significant difference ($p = 0.7364$; online supplementary *Figure S2*). Interestingly, when Dandel's index is excluded from the analysis, the optimal model, consisting of five variables (FAC, mPAP, TAPSE/sPAP, absence of atrial fibrillation, and indicators of RHF as previously defined), identifies TAPSE/sPAP as the echocardiographic parameter that most accurately predicts the primary endpoint (online supplementary *Table S2*).

Clinical outcomes using a multiparametric approach

This study aimed to identify optimal echocardiographic parameters, independent of each other, to provide insight into different aspects of RV function and geometry. Using validated cut-offs for conventional parameters (TAPSE <17 mm, FAC <35%, pulmonary coupling index (TAPSE/sPAP) <0.32, combined with a Dandel's index <20.5), subgroups of patients were created: Group 1 = all values within normal range; Group 2 = one or two abnormal value(s); Group 3 = more than two abnormal values. These subgroups had significantly different prognoses, suggesting the value of an assessment of RV function integrating the Dandel's index (log-rank <0.0001, AUC 0.79 vs. AUC for TAPSE <17 mm 0.576, FAC <35% 0.593, pulmonary coupling index (TAPSE/sPAP) <0.32 0.594, Dandel's index 0.614; *Figure 4*).

Discussion

This study investigated a novel predictor of survival among patients undergoing transcatheter tricuspid valve intervention, specifically

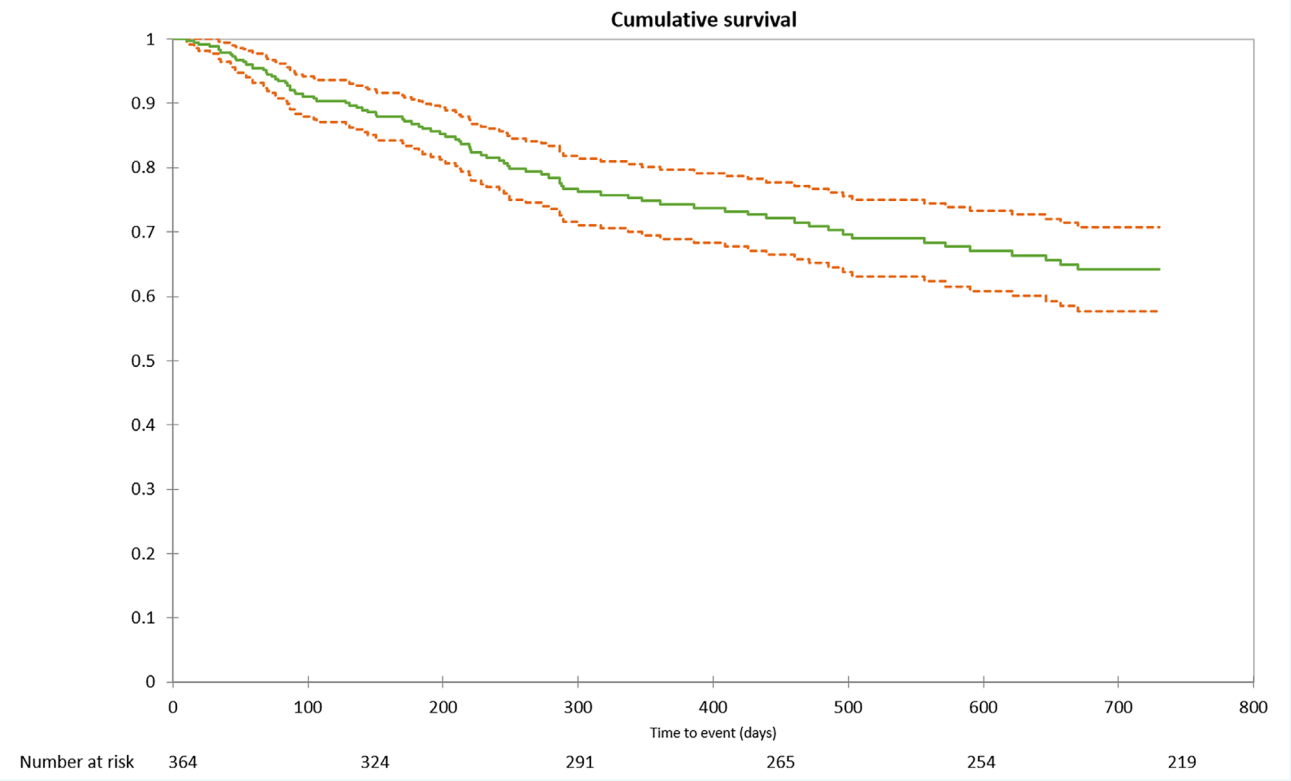


Figure 1 Two-year Kaplan–Meier heart cumulative survival curve of patients who underwent tricuspid transcatheter edge-to-edge repair with 95% confidence intervals (in orange).

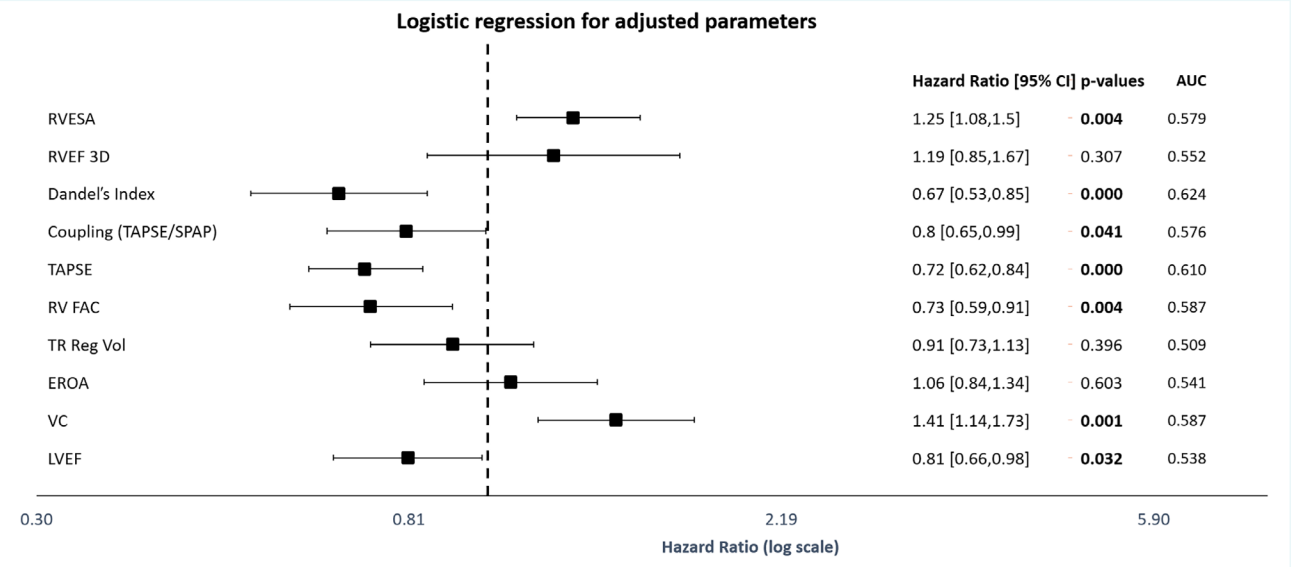


Figure 2 Displayed is a forest plot illustrating a logistic regression model for various echocardiographic parameters for the primary outcome, adjusted per standard deviation. CI, confidence interval; EROA, effective regurgitant orifice area; FAC, fractional area change; LVEF, left ventricular ejection fraction; RV, right ventricular; RVEF, right ventricular ejection fraction; RVESA, right ventricular end-systolic area; SPAP, systolic pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; TR Reg Vol, tricuspid regurgitation volume; VC, vena contracta.

Table 3 Pre-interventional echocardiographic subgroup analysis ($n = 190$)

Variable	
RVEDV 3D (ml)	203 ± 76
RVESV 3D (ml)	116 ± 46
RVEF 3D (%)	42 ± 9
RV septal longitudinal strain (%)	−15.1 ± 5.7
RV free wall longitudinal strain (%)	−23.2 ± 5.9

3D, three-dimensional; RV, right ventricular; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-systolic volume.

Table 4 Multivariate logistic regression for the primary outcome of death

Parameters	Odds ratio	95% CI	*p*-value
No signs of right heart failure	0.292	0.126–0.680	**0.004**
Dandel's index	0.639	0.464–0.881	**0.006**
TAPSE	0.735	0.556–0.971	**0.03**
No atrial fibrillation	2.321	0.987–5.46	0.054
mPAP	1.211	1.050–1.67	**0.042**
RV FAC	0.930	0.703–1.23	0.609

CI confidence interval; mPAP, mean pulmonary artery pressure; RV FAC, right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion.

addressing the significance of RV load adaptation in predicting contractility reserve and prognosis. Several echocardiographic RV parameters were associated with all-cause mortality at 2 years: TAPSE, FAC, TAPSE/sPAP, and the Dandel's index, which had the highest AUC among individual parameter.

Assessment of right ventricular function in the setting of severe tricuspid regurgitation

Previous research on TR has emphasized its complex haemodynamic consequences, leading to RV dysfunction and adverse outcomes.[18] In relevant TR, the high preload associated with regurgitant volume and the low afterload due to the low pressure outlet in the RA reduce the reliability of classic markers of RV contractile function or reserve.[19] TAPSE is an imperfect one-dimensional, single-location, angle-dependent parameter. FAC appears to be slightly more accurate because it captures both the longitudinal and circumferential function of the right ventricle.[18] However, despite these limitations, these parameters were predictive of higher mortality in our study population, as well as in reports by other groups,[20,21] while not always consistent.[8,22]

The TAPSE/sPAP ratio stands out as the only RV-PA coupling surrogates validated against the invasive gold-standard pressure–volume loop-derived Ees/Ea, as demonstrated in different studies.[23] It has been extensively evaluated in patients suffering from pulmonary hypertension.[24] Recently, the 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension incorporated TAPSE/sPAP as an echocardiographic parameter for risk assessment.[25]

In the setting of severe TR, TAPSE/sPAP may have limitations because of the specific haemodynamics with low resistance

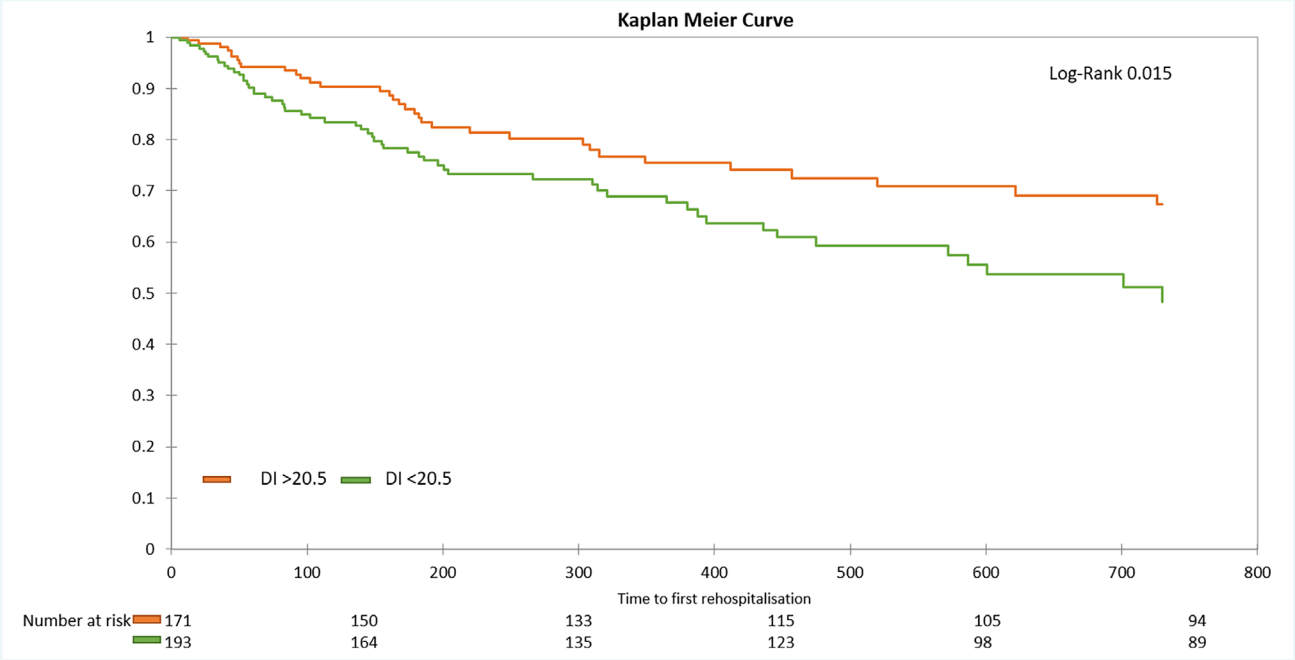


Figure 3 Kaplan–Meier curve predicting the risk of cardiac hospital readmission for a follow-up of 2 years stratified by Dandel's index (DI).

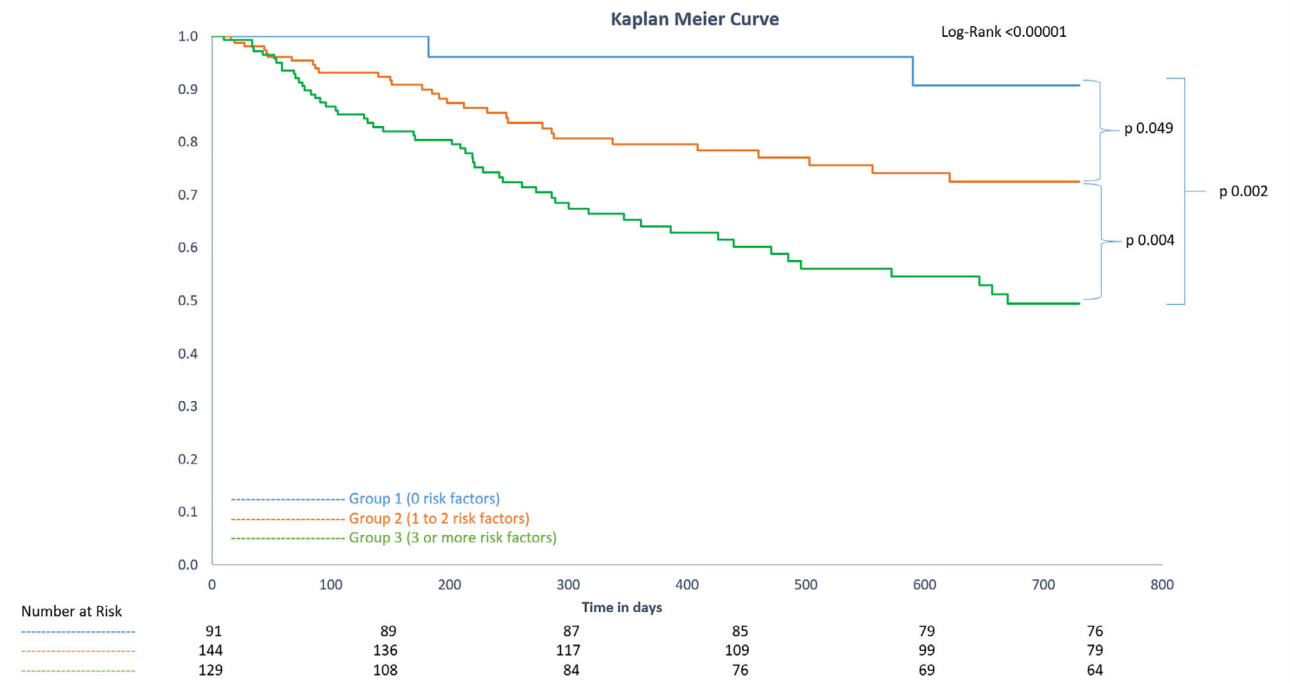


Figure 4 Kaplan–Meier curve predicting the risk of death for a follow-up of 2 years according to risk stratification utilizing established thresholds (tricuspid annular plane systolic excursion [TAPSE] <17 mm, fractional area change <35%, TAPSE/systolic pulmonary arterial pressure <0.32 and Dandel's index < 20.5).

towards the RA: in this case this parameter evaluate RV-RA-PA coupling and not only RV-PA coupling. After optimal TR treatment, afterload increases leading to a decrease of TAPSE, while right ventricles with a better contractile reserve are still able to produce increasing sPAP leading to a decrease of TAPSE/sPAP. Our data support the findings by Brener *et al.*[8] by linking TAPSE/sPAP before T-TEER to mortality after T-TEER with an almost identical optimal cut-off value of 0.404 (vs. 0.406).

In contrast, the RVLAI integrates information about RV afterload [ΔP(RV-RA)], preload (RVEDV) and geometry (RVEDL vs. RVEDV) using echocardiographic measurements/surrogates. The synthesis of several parameters may better account for RV remodelling due to TR volume overload and increasing wall stress. This index is not load-independent but takes into account load variables and should allow, better than RVEDA, TAPSE or FAC, to distinguish between adapted and maladapted right ventricle.[3] As single parameter, Dandel's index had the highest AUC for the prediction of the primary outcome in our study, which supports its value for the evaluation of RV adaptation. This optimal cut-off value of 20.5 also demonstrated effectiveness in anticipating RHF hospital readmission, as shown by the log-rank analysis.

Multiparametric approach, is it the way to go?

The RV has a complex morphology and its adaptability to volume overload due to severe TR depends on the chronicity of valvular heart disease and on the afterload determined by PVR. No single echocardiographic parameter can account for this complexity. The Integration of the Dandel's index as part of a multiparametric approach including TAPSE, FAC, and RV-PA coupling index was best able to stratify patients into subgroups with different prognosis (log-rank <0.0001).

Limitations

The retrospective design introduces inherent bias: less than one-third of the patients included in EuroTR had complete data sets allowing inclusion in the present study. The high risk characteristics of the cohort may limit generalizability. In addition, the study did not evaluate advanced echocardiographic parameters in the entire cohort. The reliance on a single cut-off for the Dandel's index may oversimplify its predictive value. Although the study provides important contributions, these limitations warrant cautious interpretation of the results and further validation is needed.

Conclusions

Assessment of the RV capacity to adjust for changes in loading conditions using the RV load adaptation index predicted mortality in patients with ≥ severe symptomatic TR undergoing T-TEER better than classical RV function and size parameters. The use of a multiparametric approach including the Dandel's index to assess RV function had an incremental value for the stratification of patients into subgroups with different prognosis.

Clinical perspectives

The RV load adaptation index (Dandel's index) incorporates several RV echocardiographic parameters evaluating the RV response to volume overload due to severe TR. It enables to differentiate adapted and maladapted right ventricles and consequently to predict mortality in patients treated with T-TEER better than traditional metrics. Such indexes should be incorporated into the risk assessment of patients suffering from ≥ severe TR to optimize decision-making processes for the choice of treatment.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflict of interest: L.S. received speaker honoraria from Edwards Lifesciences. K.P.K. reports travel expenses from Edwards Lifesciences. J.v.S. received speaker honoraria and travels expenses from Edwards Lifesciences. W.R. received speaker honoraria from Edwards and Abbott. P.D. served as consultant for InnovHeart, Picardia, HVR, Approxima and received speaker honoraria from Abbott and Edwards. T.R. received speaker honoraria and consulting fees from AstraZeneca, Bayer, Pfizer, Daiichi Sankyo. M.B.P. received speaker fees from Abbott Vascular, Edwards Lifesciences and Venus Medtech. A.R. received consulting honoraria for Edwards, Boston Scientific, Anteris and institutional research support from Boston Scientific. M.A. received consulting fees in the last 3 years from Abbott Structural Heart and Edwards Lifesciences. R.S.v.B. has received institutional grants and served as speaker to Abbott Vascular and Edwards Lifesciences. S.T. has received personal honoraria from Medtronic, Boston Scientific, Biosensors, Abbott Vascular, Medira, Shockwave, Teleflex, atHeart Medical, Cardiac Dimensions, Polares Medical, Amarin, Sanofi, AstraZeneca, ReCor Medical, Daiichi Sankyo; has received institutional research grants from Edwards Lifesciences, Boston Scientific, Fumedica, Novartis, Boehringer Ingelheim; and holds equity in Hi-D Imaging. M.M. received consulting fees in the last 3 years from Abbott Structural Heart, AstraZeneca, Bayer, Boehringer Ingelheim, Edwards Lifesciences, Roche Diagnostics. T.G. received speaker honoraria/research grants from AstraZeneca, Bayer, Bristol Myers Squibb/Pfizer, Ferrer/Chiesi, Medtronic and Edwards Lifesciences, none of them was related to this study. R.E.L. received speaker fees from Abbott Vascular, Edwards Lifesciences, Boston Scientific and Venus Medtech. N.K. has received consultant fees from Abbott, Medtronic and Boston. F.M. received grant and/or research institutional support from Abbott, Medtronic, Edwards Lifesciences, Biotronik, Boston Scientific Corporation, NVT, Terumo, Venus and consulting fees, honoraria, personal and institutional from Abbott, Medtronic, Edwards Lifesciences, Xeltis, Cardiovalve, Occlufit, Simulands, Mtex, Venus, Squadra, Valgen Royalty Income/IP Rights Edwards Lifesciences and is shareholder (including share options) of Magenta, Transseptalsolutions, 4Tech. P.La. received speaker honoraria and consulting fees from AstraZeneca, Bayer, Pfizer, Edwards Lifesciences, and research honoraria from Edwards Lifesciences. M.K. received speaker honoraria Edwards and Abbott. D.K. has received personal fees from Abbott Medical, Edwards Lifesciences and Pi-Cardia Ltd. C.I. received consultant fees and travel expenses from Abbott Medical and Edwards Lifesciences. P. Lurz received institutional grants from Edwards Lifesciences and honoraria from Innoventrics. S.W. reports research and educational grants to the institution from Abbott, Amgen, BMS, Bayer, Boston Scientific, Biotronik, Cardinal Health, CardioValve, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Johnson & Johnson, Medtronic, Querbet, Polares, Sanofi, Terumo, and Sinomed; serves as an unpaid advisory board member and/or unpaid member of the steering/executive group of trials funded by Abbott, Abiomed, Amgen, AstraZeneca, BMS, Boston Scientific, Biotronik, Cardiovalve, Edwards Lifesciences, MedAlliance, Medtronic, Novartis, Polares, Sinomed, V-Wave, and Xeltis but has not received personal payments by pharmaceutical companies or device manufacturers; is a member of the steering/executive committee group of several investigated/initiated trials that receive funding by industry without impact on his personal remuneration; and is an unpaid member of the Pfizer Research Award selection committee in Switzerland. J.H. reports research grant support and speaker honoraria from Edwards Lifesciences. V.R. received research grants from Abbott Medical, Boston Scientific, Medtronic Inc. and Edwards Lifesciences. F.P. was compensated for travel expenses by Edwards Lifesciences, Abbott Vascular, Medira, Siemens Healthineers, and inQB8 Medical Technologies; has received a research grant to the institution from Abbott Vascular. All other authors have nothing to disclose.

Acknowledgement

Open Access funding enabled and organized by Projekt DEAL.

References

1. Fortuni F, Dietz MF, Butcher SC, Prihadi EA, van der Bijl P, Ajmone Marsan N, *et al.* Prognostic implications of increased right ventricular wall tension in secondary tricuspid regurgitation. *Am J Cardiol* 2020;**136**:131–139. https://doi.org/10.1016/j.amjcard.2020.09.022
2. Gold J, Akazawa Y, Sun M, Hunter KS, Friedberg MK. Relation between right ventricular wall stress, fibrosis, and function in right ventricular pressure loading. *Am J Physiol Heart Circ Physiol* 2020;**318**:H366–H377. https://doi.org/10.1152/ajpheart.00343.2019
3. Dandel M, Potapov E, Krabatsch T, Stepanenko A, Löw A, Vierecke J, *et al.* Load dependency of right ventricular performance is a major factor to be considered in decision making before ventricular assist device implantation. *Circulation* 2013;**128**:S14–S23. https://doi.org/10.1161/CIRCULATIONAHA.112.000335
4. Ross J Jr. Afterload mismatch in aortic and mitral valve disease: Implications for surgical therapy. *J Am Coll Cardiol* 1985;**5**:811–826. https://doi.org/10.1016/s0735-1097(85)80418-6
5. Lahm T, Douglas IS, Archer SL, Bogaard HJ, Chesler NC, Haddad F, *et al.*; American Thoracic Society Assembly on Pulmonary Circulation. Assessment of right ventricular function in the research setting: Knowledge gaps and pathways forward. An official American Thoracic Society research statement. *Am J Respir Crit Care Med* 2018;**198**:e15–e43. https://doi.org/10.1164/rccm.201806-1160ST
6. Vonk Noordegraaf A, Westerhof BE, Westerhof N. The relationship between the right ventricle and its load in pulmonary hypertension. *J Am Coll Cardiol* 2017;**69**:236–243. https://doi.org/10.1016/j.jacc.2016.10.047
7. Stolz L, Weckbach LT, Karam N, Kalbacher D, Praz F, Lurz P, *et al.*; EuroTR Investigators. Invasive right ventricular to pulmonary artery coupling in patients undergoing transcatheter edge-to-edge tricuspid valve repair. *JACC Cardiovasc Imaging* 2023;**16**:564–566. https://doi.org/10.1016/j.jcmg.2022.10.004
8. Brener MI, Lurz P, Hausleiter J, Rodés-Cabau J, Fam N, Kodali SK, *et al.* Right ventricular-pulmonary arterial coupling and afterload reserve in patients undergoing transcatheter tricuspid valve repair. *J Am Coll Cardiol* 2022;**79**:448–461. https://doi.org/10.1016/j.jacc.2021.11.031
9. Sugiura A, Kavsur R, Spieker M, Iliadis C, Mauri V, Tanaka T, *et al.* Impact of right ventricular-pulmonary arterial coupling on clinical outcomes of tricuspid regurgitation. *EuroIntervention* 2022;**18**:852–861. https://doi.org/10.4244/EIJ-D-22-00045
10. Amsallem M, Boulate D, Aymami M, Guihaire J, Selej M, Huo J, *et al.* Load adaptability in patients with pulmonary arterial hypertension. *Am J Cardiol* 2017;**120**:874–882. https://doi.org/10.1016/j.amjcard.2017.05.053
11. Hahn RT, Zamorano JL. The need for a new tricuspid regurgitation grading scheme. *Eur Heart J Cardiovasc Imaging* 2017;**18**:1342–1343. https://doi.org/10.1093/ehjci/jex139
12. Winkel MG, Brugger N, Khalique OK, Gräni C, Huber A, Pilgrim T, *et al.* Imaging and patient selection for transcatheter tricuspid valve interventions. *Front Cardiovasc Med* 2020;**7**:60. https://doi.org/10.3389/fcvm.2020.00060
13. Zamorano JL, Badano LP, Bruce C, Chan KL, Goncalves A, Hahn RT, *et al.* EAE/ASE recommendations for the use of echocardiography in new transcatheter

interventions for valvular heart disease. *Eur Heart J* 2011;**32**:2189–2214. https://doi.org/10.1093/eurheartj/ehr259
14. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, *et al.* Recommendations for noninvasive evaluation of native valvular regurgitation: A report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr* 2017;**30**:303–371. https://doi.org/10.1016/j.echo.2017.01.007
15. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, *et al.* Guidelines for the echocardiographic assessment of the right heart in adults: A report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010;**23**:685–713. https://doi.org/10.1016/j.echo.2010.05.010
16. Hopper JL. Odds per adjusted standard deviation: Comparing strengths of associations for risk factors measured on different scales and across diseases and populations. *Am J Epidemiol* 2015;**182**:863–867. https://doi.org/10.1093/aje/kwv193
17. Dreyfus J, Audureau E, Bohbot Y, Coisne A, Lavie-Badie Y, Bouchery M, *et al.* TRI-SCORE: A new risk score for in-hospital mortality prediction after isolated tricuspid valve surgery. *Eur Heart J* 2022;**43**:654–662. https://doi.org/10.1093/eurheartj/ehab679
18. Rako ZA, Kremer N, Yogeswaran A, Richter MJ, Tello K. Adaptive versus maladaptive right ventricular remodelling. *ESC Heart Fail* 2023;**10**:762–775. https://doi.org/10.1002/ehf2.14233
19. Hahn RT, Lawlor MK, Davidson CJ, Badhwar V, Sannino A, Spitzer E, *et al.* Tricuspid valve academic research consortium definitions for tricuspid regurgitation and trial endpoints. *J Am Coll Cardiol* 2023;**82**:1711–1735. https://doi.org/10.1016/j.jacc.2023.08.008
20. Schmeisser A, Rauwolf T, Groscheck T, Kropf S, Luani B, Tanev I, *et al.* Pressure-volume loop validation of TAPSE/PASP for right ventricular arterial coupling in heart failure with pulmonary hypertension. *Eur Heart J Cardiovasc Imaging* 2021;**22**:168–176. https://doi.org/10.1093/ehjci/jeaa285
21. Kuwajima K, Ogawa M, Ruiz I, Yamane T, Hasegawa H, Yagi N, *et al.* Comparison of prognostic value among echocardiographic surrogates of right ventricular-pulmonary arterial coupling: A three-dimensional echocardiographic study. *Echocardiography* 2024;**41**:e15717. https://doi.org/10.1111/echo.15717
22. Karam N, Mehr M, Taramasso M, Besler C, Ruf T, Connelly KA, *et al.* Value of echocardiographic right ventricular and pulmonary pressure assessment in predicting transcatheter tricuspid repair outcome. *JACC Cardiovasc Interv* 2020;**13**:1251–1261. https://doi.org/10.1016/j.jcin.2020.02.028
23. Richter MJ, Peters D, Ghofrani HA, Naeije R, Roller F, Sommer N, *et al.* Evaluation and prognostic relevance of right ventricular-arterial coupling in pulmonary hypertension. *Am J Respir Crit Care Med* 2020;**201**:116–119. https://doi.org/10.1164/rccm.201906-1195LE
24. Tello K, Wan J, Dalmer A, Vanderpool R, Ghofrani HA, Naeije R, *et al.* Validation of the tricuspid annular plane systolic excursion/systolic pulmonary artery pressure ratio for the assessment of right ventricular-arterial coupling in severe pulmonary hypertension. *Circ Cardiovasc Imaging* 2019;**12**:e009047. https://doi.org/10.1161/CIRCIMAGING.119.009047
25. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, RMF B, Brida M, *et al.* 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2022;**43**:3618–3731. https://doi.org/10.1093/eurheartj/ehac237