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ORIGINAL PAPER

Annular remodelling predicts outcome in isolated severe tricuspid regurgitation: a registry-based echocardiographic analysis

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Aims Depending on volume status, secondary tricuspid regurgitation (sTR) has a strong dynamic component. In contrast, associated structural dilatation of the tricuspid annulus and the right heart chambers may be less volume dependent. This study aimed to assess the prognostic value of right heart remodelling in isolated severe sTR (isoTR).

Methods and results A total of 36 000 patients from the longitudinal echocardiographic database of our tertiary centre were screened for severe isoTR [vena contracta (VC) ≥ 7 mm] in the absence of atrial fibrillation (AF), other valve disease, and/or reduced systolic left ventricular function. Echocardiographic examinations were re-read, focusing on right ventricular (RV) parameters and on quantitative and qualitative parameters of isoTR. All-cause mortality was defined as the primary endpoint. Two hundred and sixteen patients fulfilled the inclusion criteria. Severe TR was predominant; only few were classified in the new grades massive [$n = 23$ (10%)] and torrential TR [$n = 4$ (2%)]. During a median follow-up of 35 months (20–53), all-cause mortality was 31% ($n = 67$). Multivariate Cox regression analysis revealed no association of VC, effective regurgitant orifice area, or regurgitant volume with all-cause mortality. However, indexed RV end-diastolic diameter ($P < 0.001$), indexed right atrial dimensions ($P = 0.019$), and particularly tricuspid valve (TV) annulus diameter diastole index ($P = 0.002$) and TV annulus diameter systole index ($P = 0.001$) were significantly associated with outcome.

Conclusion Severe isolated TR in the absence of AF is a rare finding with a grim prognosis. Tricuspid annular diameter dimensions rather than quantitative measures of TR proved to be of significant prognostic value indicating a continuous remodelling leading to a 'point of no return' with a dismal outcome.

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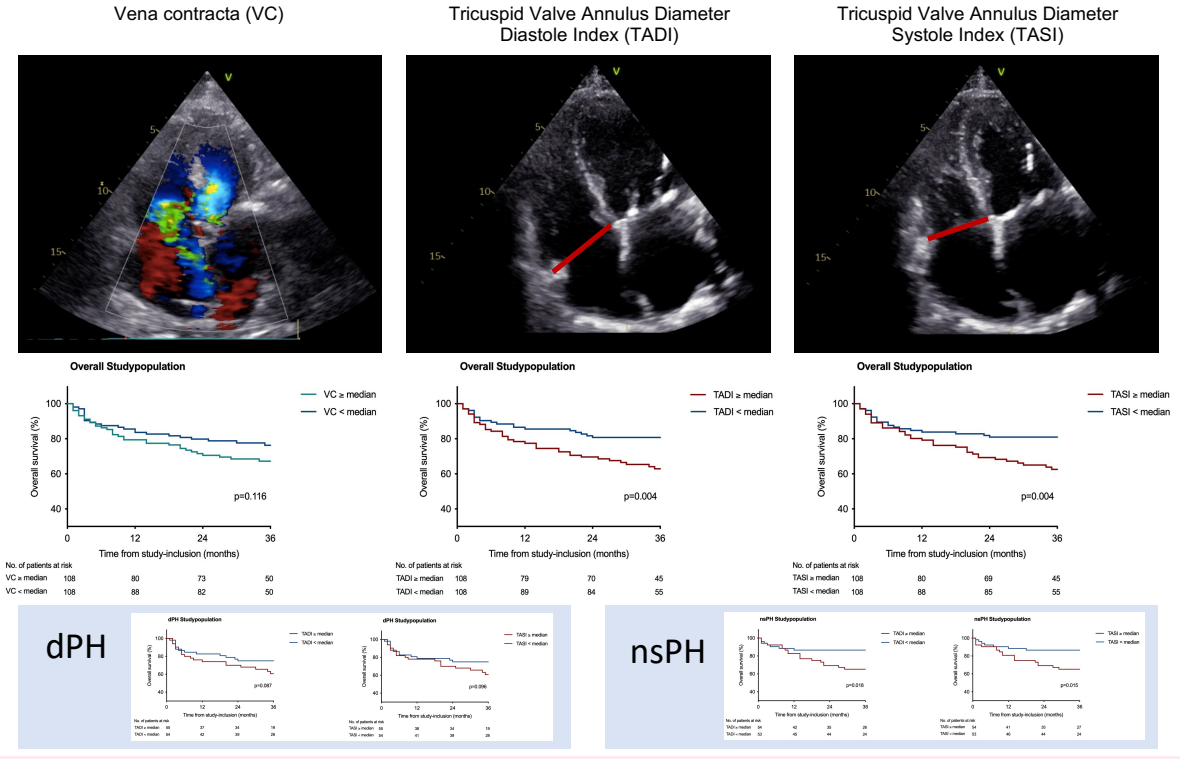
Graphical Abstract

Central Illustration: Annular Remodelling predicts Outcome in Isolated Severe Tricuspid Regurgitation: A Registry-based Echocardiographic Analysis.



Keywords tricuspid regurgitation • echocardiography • vena contracta width • regurgitant volume • EORA

Introduction

Secondary tricuspid regurgitation (sTR) is frequently observed but insufficiently defined and understood both anatomically and in terms of its clinical significance.[1–4] There is an increasing recognition of a subgroup of patients with isolated sTR, defined as the absence of other associated cardiac morphologic abnormalities, e.g. concomitant valvular disease, and left ventricular systolic dysfunction.[5] Aetiologies of isolated sTR include severe pulmonary hypertension, severe atrial dilatation due to longstanding atrial fibrillation (AF), and heart failure with preserved ejection fraction.[6] Left untreated, isolated sTR has been shown to significantly worsen survival.[7,8] Invasive therapy is often managed as a case-by-case decision and treatment of isolated sTR alone is rarely performed since the average operative risk is high and data demonstrating improved survival are scarce.[9–12]

Generally, a holistic assessment of the tricuspid valve (TV) is necessary to evaluate TR, including qualitative, quantitative, and semi-quantitative measures of transvalvular regurgitant flow but also structural valve anatomy and measurements of the right atrium and the right ventricle to not neglect the extent of potential right heart remodelling.[13,14] However, the extent of functional regurgitation is highly volume dependent and can vary tremendously between two subsequent examinations according to the preload, afterload, and right ventricular (RV) function.[15]

In contrast, structural dilatation of the tricuspid annulus as part of right heart remodelling processes within the progressive disease seems less volume/pressure dependent than the dimensions of the tricuspid regurgitant blood flow.[16] Hence, considerable tricuspid dilatation can be present even in the absence of substantial sTR initially, but will lead to severe sTR over time.[16] With this study, we sought to evaluate the prognostic value of quantitative echocardiographic parameters representing the degree of isolated sTR as well as parameters rather describing the stage of right heart remodelling in these patients.

Methods

Study population

Adult patients from the longitudinal echocardiographic database of the Vienna General Hospital, a university-affiliated tertiary centre, were consecutively recruited in this observational, non-interventional study. Patients diagnosed with severe isolated sTR were included in the present analysis. Among these, patients were excluded when showing impaired left ventricular systolic function (LVEF < 50%), AF, congenital heart disease, or any concomitant valvular defect with a severity greater than mild to moderate, as well as repeat examinations of the same patient.

The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the local Ethics Committee (#1179/2019).

Echocardiographic assessment

Echocardiographic examinations were performed using commercially available equipment (Vivid E9, Vivid7, GE Healthcare, Chicago, IL, USA). For this study, all stored images were re-read and measurements of the cardiac

chamber size and function were repeated according to the recommendations of the European Association of Cardiovascular Imaging.[17–19]

The TV annulus diameter was measured in end-diastole and in end-systole in an apical four-chamber view. All measurements were reported as absolute values; dimensions were indexed to body surface area.

Tricuspid regurgitation was quantified by measurement of vena contracta (VC) width from a four-chamber view, and by calculation of the effective regurgitant orifice area (EROA), as well as of the regurgitant volume (RegV). Moreover, tricuspid leaflet tenting area and coaptation distance were measured as described previously.[20] Only patients with a VC ≥7 mm were included in the final analysis.

Pulmonary hypertension

Patients were classified as pulmonary hypertensive (PH) according to the respective maximal TR velocity signal (TR-Vmax).[21] Regarding the presence of PH, two groups were defined: (i) TR-Vmax <3.5 m/s [absence of severe PH, non-severe (ns) PH], and (ii) TR-Vmax ≥3.5 m/s (definite PH, dPH) as previously described by our group.[6]

The investigated hospital is a national reference centre for pulmonary hypertension. Therefore, a high prevalence of severe pulmonary hypertension can be expected in this cohort.

Clinical measures, follow-up, and study endpoints

Patient characteristics were recorded by systematic retrieval from the centralized patient management system. All-cause mortality was chosen as the primary endpoint and obtained via inquiry from the Austrian Death Registry.

Statistical analysis

Differences between groups were analysed by the Mann–Whitney *U* test for continuous data and χ^2 test for discrete data, respectively. The correlation between assessed echocardiographic parameters was compared by the Spearman rho correlation coefficient. For outcome analysis, Cox proportional hazard regression analysis (correcting for the possible confounders age, sex, creatinine, and presence of pulmonary hypertension) and restricted cubic spline curve graphs were applied to estimate and visualize hazard ratios (HRs) with 95% confidence interval (CI). The Kaplan–Meier analysis estimates illustrate the prognostic ability of the new parameters.

A two-sided *P*-value of <0.05 was used to indicate statistical significance. SPSS Version 27 (IBM SPSS, USA) software package was used for all statistical analyses. Illustrations were created with GraphPad Prism version 9.1.0 and R Studio (R Foundation for Statistical Computing, Vienna, Austria) version 1.3.1073.

Results

Patient selection

A total of 36 000 patients received transthoracic echocardiography at our institution between 1 January 2013 and 31 December 2016. Out of these, 590 met the predefined inclusion criteria of severe isolated TR (initial diagnosis in the report) with normal systolic left ventricular function and no other valvular pathology graded as more than mild-to-moderate. After the exclusion of 352 patients due to insufficient image quality, measurements were performed on the remaining 258 patients. Subsequently, 42 patients were excluded due to less than severe TR indicated by a VC < 7 mm (Supplementary data online, *Figure S1*).

Baseline characteristics

The final study cohort consisted of 216 patients. The median age was 69 years [interquartile range (IQR): 52–79)], and 86 (40%) were male. A total of 144 (67%) received diuretic medication at the time of the echocardiogram, 119 (55%) presented in NYHA functional Class I. Forty-nine per cent ($n = 107$) revealed a TR-Vmax <3.5 m/s (nsPH group), and 51% ($n = 109$) a TR-Vmax ≥3.5 m/s (dPH group). Further details on baseline characteristics are displayed in *Table 1* and Supplementary data online, *Table S1*.

Tricuspid regurgitation

Tricuspid regurgitation was severe in all patients defined by a VC ≥7 mm. The median VC was 9.7 mm (IQR: 8.2–11.7), median EROA 0.40 cm^2 (IQR: 0.26–0.53), and median RegV was 44 mL (IQR: 33–60). Considering the new gradation recommendations,[22,23] 189 patients (88%) had severe TR (VC 7–13 mm), 23 (10%) had massive TR (VC 14–20 mm), and 4 (2%) had torrential TR (VC ≥21 mm) (*Table 1*).

Patients in the dPH group had higher N-terminal pro-brain natriuretic peptide (NT-proBNP) levels and more severe iron deficiency levels compared with patients in the nsPH group. No significant differences in parameters reflecting renal or liver function could be observed (*Table 1*).

Pulmonary hypertension

Right heart catheterization was performed in 114/216 (52.5%) of the included patients. The mean mPAP was 38 mmHg in the overall cohort. In the nsPH group, mPCWP was 15 mmHg and LVEDP was 15 mmHg, indicating a high prevalence of elevated left heart filling pressures in this group (*Table 2*). Data on PH medication are presented in Supplementary data online, *Table S1*.

A separate analysis of the subgroup of patients with dPH and available invasive haemodynamics was performed ($n = 70$, 54 with pre-capillary and 16 with post-capillary PH). Pulmonary pressures were significantly higher in the pre-capillary PH group (systolic PAP 79 vs. 58 mmHg, mean PAP 50 vs. 38 mmHg, PVR 587 vs. 247 dynes s/cm^5, all *P*-values <0.05). Right atrial and ventricular remodelling was significantly more pronounced in the pre-capillary PH group (RV basal diameter 50 vs. 40 mm, RA volume 138 vs. 102 mL, all *P*-values <0.05). RV function was better in the post-capillary PH group (FAC 30 vs. 41%, RV FW strain −11 vs. −17%, tricuspid annular plane systolic excursion (TAPSE)/systolic pulmonary artery pressure (sPAP) ratio 0.15 vs. 0.20 mm/mmHg, all *P*-values <0.05). In both groups, 3-year mortality was 31%, and NT-proBNP was the same with 1919 and 1914 pg/mL (see Supplementary data online, *Table S2*).

Right heart dimensions and function

RV dilatation occurred in the overall study cohort with a median basal right ventricular end-diastolic diameter of 45 mm (IQR: 40–51). The RV was significantly larger in the dPH group when compared with the nsPH group (49 vs. 42 mm, $P < 0.001$). Also, in the dPH group, RV systolic function was more severely reduced (TAPSE, FAC, RV-S′, RV free wall strain: $P \leq 0.05$ for all measurements) and RV-PA uncoupling was more pronounced [nsPH: TAPSE/sPAP: 0.42 mm/mmHg (IQR: 0.33–0.48) vs. dPH: 0.17 mm/mmHg (IQR: 0.13–0.25), *P*-value <0.001] (*Table 1*). Dimensions of TV annulus diameter diastole (TADD), TADI, TV annulus diameter systole (TADS), and TASI were enlarged [TADD: 43 mm (IQR: 40–47), TADI: 24 mm/m^2 (IQR: 22–26), TADS: 39 mm (IQR: 35–43), and TASI: 21 mm/m^2 (IQR: 19–24)]. Among these, only the TADI differed significantly between the two investigated sub-groups ($P = 0.047$). In the overall analysis, the median coaptation distance was 1.17 cm (IQR: 0.96–1.44), and the median tenting area was 3.3 cm^2 (IQR: 2.26–4.43) (*Table 1*).

The parameters TADI and TASI were not associated with sTR severity reflected by EROA, VC, and RegVol but with disease severity reflected by NT-proBNP (TADI: $r_s = 0.43$, $P < 0.001$; TASI: $r_s = 0.42$, $P < 0.001$) and with survival (see below).

Table 1 Baseline characteristics and 2D echocardiography

	Overall study population	nsPH group: TR-Vmax <3.5 m/s	dPH group: TR-Vmax ≥3.5 m/s	*P*-value
N (%)	216 (100)	107 (49)	109 (51)	
Baseline characteristics				
Age, years (IQR)	69 (52–79)	71 (58–80)	66 (48–77)	0.055
Male sex, *n* (%)	86 (40)	43 (40)	43 (39)	0.912
NYHA class, *n* (%)				0.099
I	119 (55)	65 (61)	54 (50)	
II	24 (11)	14 (13)	10 (9)	
III	33 (15)	15 (14)	18 (17)	
IV	8 (4)	1 (1)	7 (6)	
3-year mortality, *n* (%)	67 (31)	28 (26)	39 (36)	0.127
Laboratory parameters				
Bilirubin, mg/dL (IQR)	0.76 (0.51–1.21)	0.69 (0.50–1.14)	0.83 (0.52–1.14)	0.197
Cholinesterase, kU/L (IQR)	5.81(3.92–7.46)	6.10 (3.92–7.67)	5.67 (3.92–7.29)	0.313
Albumin, g/L (IQR)	39.7 (33.5–43.0)	40.3 (34.6–44.3)	39.4 (32.8–41.6)	0.066
Creatinine, mg/dL (IQR)	0.97 (0.80–1.33)	0.96 (0.81–1.31)	0.97 (0.78–1.33)	0.694
NT-proBNP, pg/mL (IQR)	1910 (940–3720)	1547 (652–2634)	2367 (1198–5350)	**<0.001**
TSAT	17.1 (12.4–24.8)	21.3 (14.3–29.8)	14.3 (10.1–20.9)	**0.040**
Transferrin	253 (199–294)	242 (191–284)	283 (234–309)	**0.046**
Echocardiography measurements				
Right heart remodelling				
RA area, cm^2 (IQR)	31.8 (26.5–38.8)	31.0 (26.5–37.3)	32.3 (26.5–39.1)	0.478
RA volume, mL (IQR)	132 (104–183)	126 (99–176)	137 (107–191)	0.219
RV basal diameter, mm (IQR)	45 (40–51)	42 (37–47)	49 (42–55)	**<0.001**
TV annulus diameter diast., mm (IQR)	43 (40–47)	43 (39–46)	43 (40–47)	0.195
TV annulus diameter diast. index, mm/m^2 (IQR)	24 (22–26)	23 (21–25)	24 (22–27)	**0.047**
TV annulus diameter syst., mm (IQR)	39 (35–43)	38 (35–43)	39 (36–43)	0.386
TV annulus diameter syst. index, mm/m^2 (IQR)	21 (19–24)	21 (19–23)	21 (19–24)	0.128
Coaptation distance, cm (IQR)	1.17 (0.96–1.44)	1.04 (0.90–1.25)	1.26 (1.03–1.54)	**<0.001**
Tenting area, cm^2 (IQR)	3.30 (2.26–4.43)	2.87 (2.08–3.80)	3.48 (2.41–4.62)	**0.013**
TR-Vmax, m/s (IQR)	3.5 (3.0–4.4)	3.0 (2.6–3.2)	4.4 (3.9–4.9)	**<0.001**
Right ventricular systolic function				
TAPSE, mm (IQR)	19 (15–22)	20 (18–24)	17 (14–21)	**<0.001**
FAC, % (IQR)	42 (30–52)	49 (42–55)	32 (26–43)	**<0.001**
RV-S′, cm/s (IQR)	11 (9–12)	11 (9–12)	10 (8–12)	**0.041**
RV free wall strain, % (IQR)	−19.7 (−11.3 to −27.0)	−26 (−22 to −29)	−13 (−9 to −20)	**<0.001**
TAPSE/sPAP ratio, mm/mmHg (IQR)	0.28 (0.16–0.41)	0.42 (0.33–0.48)	0.17 (0.13–0.25)	**<0.001**
Left ventricular filling pressures				
LA volume index, mL/m^2 (IQR)	40 (26–59)	46 (34–60)	33 (21–54)	**<0.001**
Tricuspid regurgitation severity				
Vena contracta, mm (IQR)	9.7 (8.2–11.7)	10.0 (8.7–12.3)	9.5 (8.0–11.0)	**0.001**
EROA (PISA), cm^2	0.40 (0.26–0.53)	0.51 (0.38–0.77)	0.30 (0.22–0.41)	**<0.001**
RegV, mL (IQR)	44 (33–60)	48 (36–62)	42 (31–57)	**0.044**

FAC, fractional area change; IQR, interquartile range; LA, left atrium; LDH, lactate dehydrogenase; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association functional classification; PISA, proximal isovolumetric surface area; RA, right atrium; RegV, regurgitant volume; RV, right ventricle; sPAP, systolic pulmonary artery pressure; syst., systolic; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TSAT, transferrin saturation; TV, tricuspid valve; Vmax, maximal velocity.

Table 2 Haemodynamic parameters of right heart catheterization

	Overall study population	nsPH group: TR-Vmax <3.5 m/s	dPH group: TR-Vmax ≥3.5 m/s	*P*-value
N (%)	114/216 (52.5)	44/107 (41)	70/109 (64)	
Haemodynamic parameters				
LVED pressure, mmHg (IQR)	13 (9–19)	15 (12–20)	11 (8–16)	**0.003**
sPAP, mmHg (IQR)	61 (42–82)	41 (26–60)	75 (55–94)	**<0.001**
mPAP, mmHg (IQR)	38 (28–51)	26 (18–37)	47 (35–56)	**<0.001**
PCWP, mmHg (IQR)	12 (9–17)	15 (10–21)	11 (9–15)	**0.024**
PVR, dynes s/cm^5 (IQR)	329 (158–643)	160 (95–306)	549 (347–941)	**<0.001**

Data of the entire cohort and for the sub-groups nsPH group (TR-Vmax <3.5 m/s) and dPH group (≥3.5 m/s) are shown.
IQR, interquartile range; LVED, left ventricular end-diastolic; mPAP, mean pulmonary arterial pressure; PA, pulmonal artery; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; sPAP, systolic pulmonary arterial pressure; TR, tricuspid regurgitation.

Outcome analysis

For this analysis, patients were included who received an echo between 2013 and 2016. During this time, no interventional procedures of the TV were performed at our institution. None of the included patients had cardiac surgery of the TV. In the dPH group, 10 patients consequently received lung transplantation, 9 patients received pulmonary endarterectomy, and 2 patients were treated by balloon pulmonary angioplasty.

During a median follow-up of 35 months (IQR: 20–53), all-cause mortality was 31% ($n = 67$). Multivariate Cox regression analysis correcting for the possible confounders age, sex, creatinine, and presence of pulmonary hypertension revealed no statistically significant association of VC, EROA, or RegV with all-cause mortality. However, RV basal diameter index (HR 1.09, 95% CI 1.05–1.14, $P < 0.001$), indexed RA dimensions (RA area index: HR 1.06, 95% CI 1.01–1.12, $P = 0.019$; RA volume index: HR 1.01, 95% CI 1.00–1.02, $P = 0.020$), and particularly indexed diastolic and systolic TV annulus (TADI: HR 2.50, 95% CI 1.36–4.59, $P = 0.003$; TASI: HR 3.06, 95% CI 1.58–5.90, $P = 0.001$, respectively) were significantly associated with outcome (see Supplementary data online, *Figure S3*). Results remained virtually unchanged, when assessed in the nsPH group. In the dPH group, only TASI (HR 2.58, 95% CI 1.07–6.25, $P = 0.035$) and indexed basal RV diameter (HR 1.09, 95% CI 1.03–1.15, $P = 0.003$) were significantly associated with outcome. Adjusted cubic spline curve analysis further defined the association between right heart remodelling and outcome showing an increased risk with advancing right heart remodelling. Cubic spline modelling and the hazards for the assessed parameter strata and outcome are depicted in *Figure 1A* and *B* and Supplementary data online, *Figure S2*.

The Kaplan–Meier estimates showed a significant increase in long-term mortality when TADI and TASI were more enlarged in the overall and the nsPH study population (log-rank $P < 0.018$ for all). A similar effect of TADI or TASI was not seen in the dPH-only group (log-rank $P =$ ns) (*Figure 2*).

Discussion

This large-scale observational study shows a low prevalence of severe isolated secondary TR. However, if present these patients suffer from a dismal short-term prognosis. The results particularly highlight that not sTR severity quantified by VC, EROA, and RegV, but parameters of right heart remodelling are associated with disease severity and predict poor outcome in the investigated patient population with isolated TR. In addition to indexed RA area, indexed RA volume, and indexed RV basal diameter, the presented data introduce for the first time the indexed systolic and diastolic tricuspid annulus dimensions (TASI and TADI) as valuable prognostic parameters.

Isolated secondary TR: a rare disease encompassing two underlying entities

In contrast to sTR associated with systolic heart failure and left heart valvular disease,[24] severe isolated TR is hardly seen, with a prevalence of only 590 cases (1.6%) during a four-year observational period at a large tertiary centre. Nevertheless, all-cause mortality after a median follow-up of 35 months is high with 31% in this patient population, underlining its clinical importance.

Atrial functional TR due to severe bi-atrial dilatation caused by long-standing AF is a common form of isolated TR. Its degree can vary considerably depending on rate and rhythm control. In addition, due to beat-to-beat variability, measurements regarding degree of TR and RV remodelling can be less reliable. Therefore, these patients were excluded from this retrospective analysis. The aetiology of isolated sTR in patients with sinus rhythm is not well characterized. It can be assumed that this cohort consists of two groups of patients: (i) patients with significant pre-capillary pulmonary hypertension and (ii) patients with heart failure with preserved ejection fraction (HFpEF).[6]

Considering the significant differences in the clinical course of the named disease entities PH and HFpEF, as well as diagnostic and therapeutic consequences, patients presenting with isolated sTR must be further subclassified according to the presence or absence of significantly elevated pulmonary pressures.

The present data show an approximately equal distribution, with 51% of patients in this analysis presenting with high pulmonary pressure (TR-Vmax ≥3.50 m/s; dPH), and 49% of patients with non-significantly elevated pulmonary pressure (TR-Vmax <3.50 m/s; nsPH). However, the high number of dPH patients in this study cohort might be a selection bias caused by the fact that the investigated hospital is a national reference centre for pulmonary hypertension, thus leading to a high number of patients with severe PH.

The nsPH patients may represent the previously described subgroup of HFpEF patients with severe TR.[25] In a subgroup of the included nsPH patients (44/107, 41%) right heart catheterization data were available. The mean PAP was 26 mmHg, and with a mean PCWP of 15 mmHg and a mean LVEDP of 15 mmHg, there was a high prevalence of post-capillary pulmonary hypertension due to HFpEF.

Although not conclusively understood, the pathomechanism of annular dilation may include degenerative alterations in the tricuspid annular fibrous structure.[7,26] Prospective studies should focus on the longitudinal progression of disease, particularly right atrial, RV, and

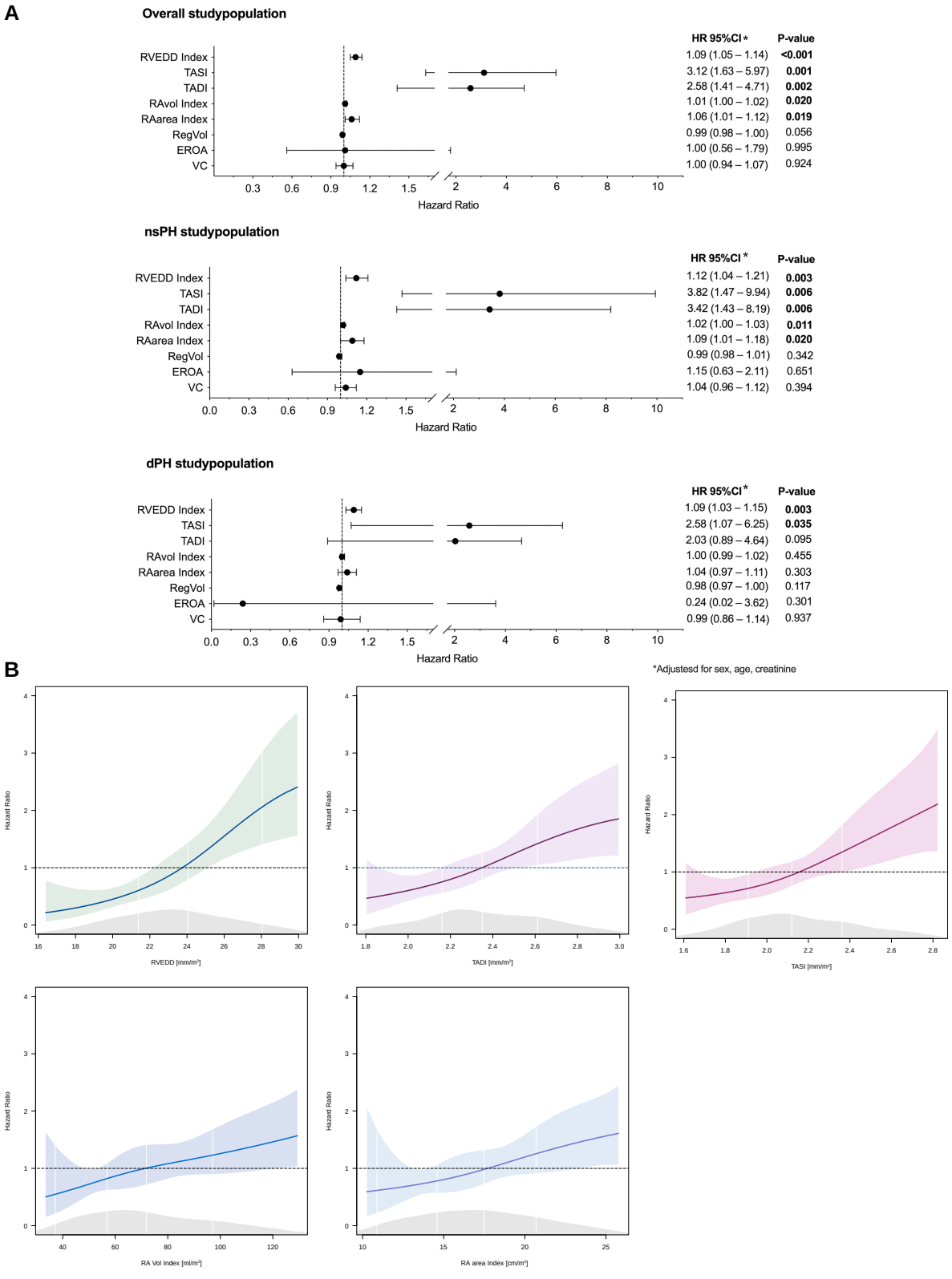


Figure 1 Association of echocardiographic parameters with outcome in severe isolated secondary TR patients ($n = 216$). The HRs for all-cause mortality with 95% CIs according to the respective echocardiographic measure strata (*A*) and restricted spline curves examining the association of the extend of right heart remodelling and outcome adjusted for sex, age, creatinine (*B*) are shown. Curves represent adjusted HRs (solid line) and the 95% CIs (shades). The distributions of measures are shown at the bottom (grey). CI, confidence interval; dPH, definite pulmonary hypertension; EROA, effective regurgitation orifice area; HR, hazard ratio; nsPH, non-significant pulmonary hypertension; RA, right atrium; RegVol, regurgitant volume; RVEDD, right ventricular end-diastolic diameter; TADI, tricuspid valve annulus diameter diastole index; TASI, tricuspid valve annulus diameter systole index.

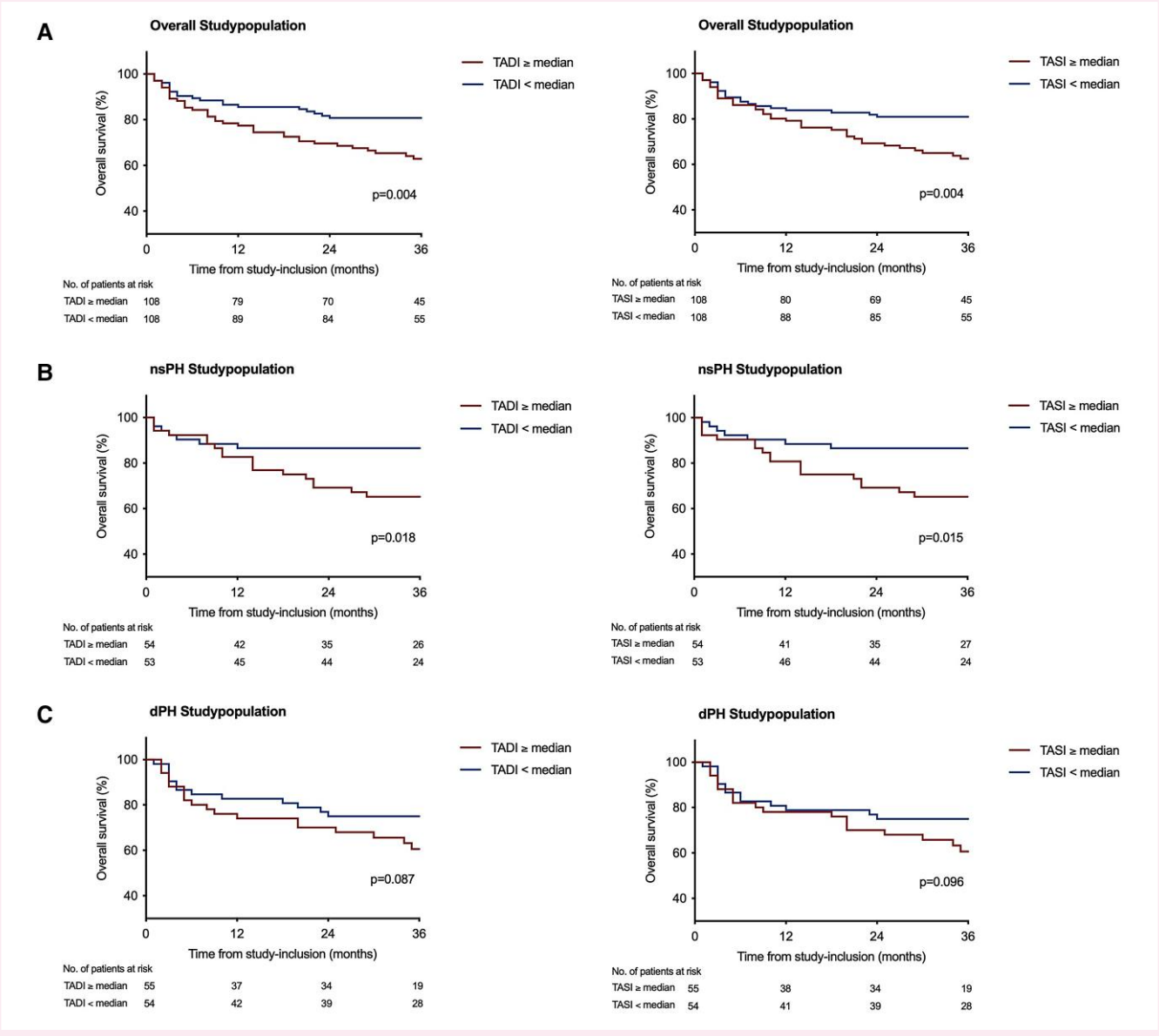


Figure 2 Kaplan–Meier estimates for overall survival in overall study population (*A*), nsPH study group (*B*), or dPH study group (*C*) according to TADI and TASI, respectively. Assessed for within-population median strata. Curves were compared by the log-rank test. dPH, definite pulmonary hypertension; nsPH, non-significant pulmonary hypertension; TADI, tricuspid valve annulus diameter diastole index; TASI, tricuspid valve annulus diameter systole index.

TV annular dimensions as well as quantitative measures of TR. Interventional techniques focusing on annular reduction may be beneficial in HFpEF patients with severe TR, to be addressed in future research.

Pulmonary hypertension: understanding the underlying disease

Severe TR can conceal the presence of PH due to pressure equalization between the RA and the RV and consequently low trans-tricuspid pressure gradients when measured by continuous wave Doppler only.[27] The mean pulmonary artery pressure in this cohort was 38 mmHg (28–51). This finding stresses the importance of a complete workup of patients with severe isolated TR including right heart catheterization. Oftentimes, the underlying disease will be pre-capillary PH which may be the driving force of clinical deterioration needing specific treatment. In pre-capillary PH, the onset of severe TR may be a late sign of severe disease, occurring only after significant RV dilatation and dysfunction. This may explain the observed high mortality in this subgroup.

In the sub-analysis of those dPH patients where haemodynamic data were available, 54 patients had pre-capillary PH and 16 patients had severe post-capillary PH. While pulmonary pressures were significantly higher, and right atrial and RV remodelling was significantly more pronounced in those with pre-capillary PH, RV function was better in those with post-capillary PH. At the same time, TR severity, TADi and TASi, NT-proBNP values, and 3-year mortality were the same in the two groups, as was clinical state assessed by NYHA class. Future prospective research is needed to confirm these findings and to evaluate if

interventional repair of TR may be an option for patients with post-capillary PH and accompanied isolated severe TR.

The findings stress that specialized PH centres in collaboration with valve centres must be involved in the diagnosis and treatment of these complex patients.

Pitfalls and difficulties in the assessment and grading of (isolated) secondary TR

According to current heart valve guidelines,[13] quantification of secondary TR includes the assessment of EROA, VC, and RegVol—parameters with significant pitfalls when applied for the TV. The TV EROA increases with inspiration and is also dependent on preload and afterload.[15] VC measurements correlate with EROA if it is circular.[28] However, due to the three or more commissures of the TV, in most cases, the orifice is triangular, or star-shaped, rather than circular.[29] A possible solution for this predicament is the evaluation of the VC area by 3D colour Doppler visualization of the valve.[27]

Recently published new recommendations on TR classification propose a five-grade spectrum adding the categories 'massive' and 'torrential'.[22] However, in the presented cohort, 88% of patients had severe TR defined by a VC of 7–13 mm, and only 10 and 2% were classified as massive and torrential, respectively. The cohort showed an IQR of VC of 8–12 mm, of EROA of 0.26–0.53 cm^2, and of RegV of 33–60 mL. This finding leads to the hypothesis that in patients with isolated sTR, the degrees 'massive' and 'torrential' are uncommon. This needs to be investigated further in future prospective studies.

Right heart remodelling in different isolated sTR phenotypes and outcome

In patients with severe TR, depending on the cause of the disease, right heart remodelling can be observed predominantly in the right atrium or the right ventricle.[6] However, the present data suggest that not the heart chambers but the tricuspid annulus as the common structure affected by either chamber's dilation is the parameter significantly associated with prognosis. Indexed diastolic and systolic TV annulus diameters were significant predictors of survival with a multivariate HR of 2.5 and 3.06, respectively, while controversially, quantitative measures of severity of TR (VC, EROA, RegV) were not. The median diastolic annulus diameter was 43 mm and the indexed diastolic annulus diameter was 24 mm/m^2. Concordantly, an annular diameter of 21 mm/m^2 has previously been described as significantly dilated.[30]

The location of measurement of the tricuspid annulus remains to be clarified in a standardized way. Surgically, the extension from the anterior–septal commissure to the anterior–posterior commissure has previously been suggested.[16] This dimension could be measured in a 2D *en face* angulation; however, there will be uncertainty if the true valvular level has been reached.[31] In this cohort, dimensions were measured in an apical four-chamber view. With slight anterior angulation, this view will most likely be similar to the surgical dimension. Future studies should investigate a biplane average measurement and an indexed TV annulus 3D area.

Additional parameters of right heart remodelling in sTR have been described previously. Topilsky *et al.*[32] investigated the tenting height of the TV in patients with and without pulmonary hypertension. In line with their findings, in the presented cohort tenting height and tenting area were both significantly larger in the dPH group when compared with the nsPH group.

Considering the extreme variability of secondary TR being dependent on fluid status, heart rhythm and rate, and respiration, the main target of the description of sTR should not merely be the colour Doppler loops and quantitative measurements of a particular time point but should focus on the morphological status of the right heart, which includes not only RA and RV dimensions and function but importantly also the indexed TV annulus in systole and diastole. In addition, when grading TR, the volume state, including current body weight, presence of pleural effusion, and peripheral oedema, is an integral part and should be mentioned in the echo report.

Limitations

Due to the retrospective analysis of echocardiographic examinations from a prospective database, only measurements initially performed could be analysed. As no homogeneous follow-up intervals were available for this study population, serial echocardiographic analysis was omitted in order to avoid bias on outcome. The findings should be stimulating for future prospective projects. In this retrospective analysis, invasive haemodynamic data were not available for all patients; therefore, TR-Vmax was applied, and a cut-off of 3.5 m/s was chosen as suggested by the current PH guidelines.[21] To correct for potential bias on survival, all significant left heart valvular lesions (graded more than mild-to-moderate) and systolic dysfunction (LV systolic function graded not normal) were excluded. However, HFpEF was not excluded. While a limitation, it is an important finding and should lead to future prospective follow-up of HFpEF patients with sTR, as more accurate knowledge and possibly interventional treatment of TR may eventually provide treatment strategies for often highly symptomatic HFpEF patients.

Conclusion

Severe isolated TR in the absence of AF is a rare finding with a grim prognosis. Underlying diseases are significant (pre-capillary) pulmonary hypertension and HFpEF. The newly proposed TR grades 'massive' and 'torrential' are uncommon in these patients and therefore of lesser clinical relevance. Tricuspid annular diameter dimensions rather than quantitative measures of TR proved to be of significant prognostic value indicating a continuous remodelling leading to a 'point of no return' with a dismal outcome.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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Data availability

Research data are not shared.

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