

# Risk assessment in PAH using quantitative CMR tricuspid regurgitation: relation to heart catheterization

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## Abstract

**Aims** Improved risk stratification is of value for decision making in pulmonary arterial hypertension (PAH). Right heart catheterization combined with quantitative tricuspid regurgitation (TR) by cardiovascular magnetic resonance (CMR) may provide this. The aims were to study: (i) to what extent quantitative TR is associated with event-free survival; (ii) how quantitative TR is related to known prognostic markers in PAH; and (iii) to what extent quantitative TR and right atrial pressure determine right atrial dilation.

**Methods and results** Fifty patients (63 ± 17 years) with PAH referred for CMR were included. Volumes and pulmonary artery flow by CMR and pressure and vascular resistance by right heart catheterization were obtained. Composite outcome was lung transplantation or death. Four transplantations and 27 deaths occurred over a median of 2.7 years. A trend towards higher hazard ratio was shown for TR volume (TRV; 2.1, 95% CI 1.0–4.4) and TR fraction (TR%; 1.6, 95% CI 0.8–3.3) above median. TRV and TR% correlated with right ventricular (RV) end-diastolic (TRV  $r = 0.50$ ; TR%  $r = 0.39$ ) and end-systolic (TRV  $r = 0.35$ ; TR%  $r = 0.30$ ) volumes, pulmonary vascular resistance (TRV  $r = 0.28$ ; TR%  $r = 0.43$ ), N terminal pro brain natriuretic peptide (TRV  $r = 0.65$ ; TR%  $r = 0.68$ ), cardiac index (TRV  $r = -0.32$ ; TR%  $r = -0.54$ ), pulmonary artery stroke volume (TRV  $r = -0.32$ ; TR%  $r = -0.58$ ) and effective RV ejection fraction by pulmonary artery quantitative flow (TRV  $r = -0.56$ ; TR%  $r = -0.69$ ), but not RVEF. Both TR% and right atrial pressure determined right atrial volumes ( $r^2 = 0.38$ ;  $r^2 = 0.48$ ).

**Conclusions** A clear trend towards worse outcome with larger TRV or TR% was shown; however, the number of events was insufficient for significant outcome differences. Prognostic value of quantitative TR should be investigated in a larger multicentre cohort. Effective RV ejection fraction may be considered an improved measure of RV function in PAH.

**Keywords** Pulmonary arterial hypertension; Tricuspid valve regurgitation; Cardiac magnetic resonance imaging; Right heart catheterization; Outcome

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## Introduction

Pulmonary arterial hypertension (PAH) is a rare, severe and progressive pathophysiological condition exhibiting increased pressure in the pulmonary circulation. The increased pressure affects the right side of the heart, which remodels to adapt to the altered pressure conditions. When right heart failure

occurs, mortality is high unless lung transplantation is performed.<sup>1</sup>

Echocardiography is the first-line non-invasive modality applied to evaluate right ventricular and atrial volumes and tricuspid regurgitation (TR). TR is commonly found in PAH and associated with heart failure and poor prognosis<sup>2,3</sup> and is a cornerstone for estimation of pulmonary arterial pressure.<sup>4</sup>

However, TR by echocardiography is assessed qualitatively by visual grading and not quantitatively. Invasive right heart catheterization (RHC) measuring pressure and resistance in the pulmonary circulation is required to either confirm or rule out PAH.<sup>1,5</sup> Considering the disease severity and progression, early detection and risk stratification are important to improve treatment and outcome.<sup>6</sup> Whereas advanced treatment options are available, however costly and with side effects,<sup>4,7</sup> current methods for risk evaluation and assessment of individual benefit of treatment are lacking.<sup>8</sup> There is thus a need for improved non-invasive prognostic methods.

Cardiovascular magnetic resonance (CMR) imaging is both accurate and precise and provides quantitative data. Right ventricular ejection fraction by CMR has been shown to be a powerful outcome predictor in PAH.<sup>9</sup> Further, increased right atrial volume by CMR indicates decreased transplantation-free survival, independent of right ventricular ejection fraction.<sup>10–12</sup> Right ventricular ejection fraction, as commonly calculated based on planimetry, does however not take into account the effective volume ejected into the pulmonary artery when TR is present. As CMR provides quantitative measures of regurgitant volumes across valves,<sup>13–15</sup> it can be used to measure effective pulmonary artery stroke volume and based on this effective right ventricular ejection fraction. Hence, it could be used to elucidate how TR volume affects prognosis in PAH. It is however unclear whether the main culprit for right atrial dilation in PAH is an increase in right atrial pressure or an increase in TR. While right atrial dilation and increased right atrial pressure both imply poor outcome, the prognostic value of quantitative TR by CMR has not been investigated.

The aims were therefore to study (i) to what extent increased TR quantified by CMR is associated with event-free survival; (ii) how TR quantified by CMR is related to known prognostic markers in PAH; and (iii) to what extent TR quantified by CMR and right atrial pressure by RHC determines right atrial dilation.

## Methods

The Regional Ethical Review Board approved the study (2013/891), which conformed to the Declaration of Helsinki. Patients provided written informed consent before participating.

### Study population

Adult patients with PAH who underwent CMR between 2003 and 2015 were retrospectively identified. Between 2015 and 2017, adult patients undergoing de-novo investigation for PAH were prospectively and consecutively included. Inclusion criteria were mean pulmonary arterial pressure (mPAP)

$\geq 25$  mmHg and pulmonary arterial wedge pressure (PAWP)  $\leq 15$  mmHg with normal or reduced cardiac output without evidence of congenital heart disease or a haemodynamically significant shunt. Exclusion criteria were missing image data, i.e. not full coverage of the heart or no phase-contrast pulmonary artery flow data, and more than 30 days between RHC and CMR, to avoid bias from pressure conditions changing over time. Further, patients with claustrophobia or other CMR contraindications such as ferromagnetic devices were not included. Patients were classified as idiopathic or familial PAH, PAH associated with systemic sclerosis, and PAH associated with connective tissue disorders other than systemic sclerosis.

Medical records were used for retrieving patient characteristics, N terminal pro brain natriuretic peptide (NT-proBNP) values, lung transplantation, and vital status data. Composite endpoints were lung transplantation or death.

### Cardiac magnetic resonance image acquisition

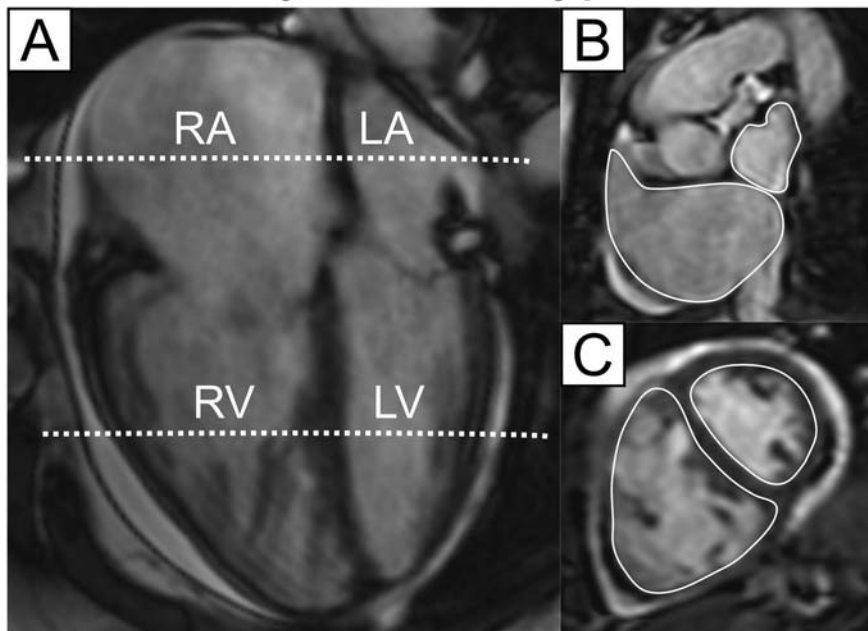
Cardiovascular magnetic resonance data were acquired using one of two 1.5 T scanners (Philips Achieva, Best, the Netherlands, between 2003 and 2015, and Siemens MAGNETOM Aera, Erlangen, Germany, between 2015 and 2017). Standard ECG-gated short-axis and long-axis cine balanced steady-state free precession images covering the heart were acquired at end-expiratory breath-hold using a cardiac phased-array coil either in combination with a second cardiac phased-array coil (Philips) or in combination with a spine phased-array coil (Siemens). Typical image parameters were  $1.4 \times 1.4 \times 8$  mm<sup>3</sup>, flip angle 60°, TR/TE 3/1.4 ms, with an acquired temporal resolution of 50 ms reconstructed to 30 (Philips) or 25 (Siemens) time frames per cardiac cycle. A standard 2D gradient recalled echo with retrospective ECG-gating was used to acquire phase-contrast quantitative flow data in the pulmonary artery during free breathing. Typical parameters were  $1.3 \times 1.3 \times 8$  mm<sup>3</sup>, TR/TE 20/3 ms, flip angle 10°/20°. Acquisition time was approximately 2 min averaged to 30 or 35 phases per cardiac cycle (<30 ms per phase). If arrhythmia was present, real-time phase-contrast flow sequences over 5 s were acquired. Typical parameters were  $3 \times 3 \times 9$  mm<sup>3</sup>, TR/TE 5/5 ms, flip angle 15°. Velocity encoding was set to 150–250 cm/s on an individual basis.

### Cardiac magnetic resonance image analysis

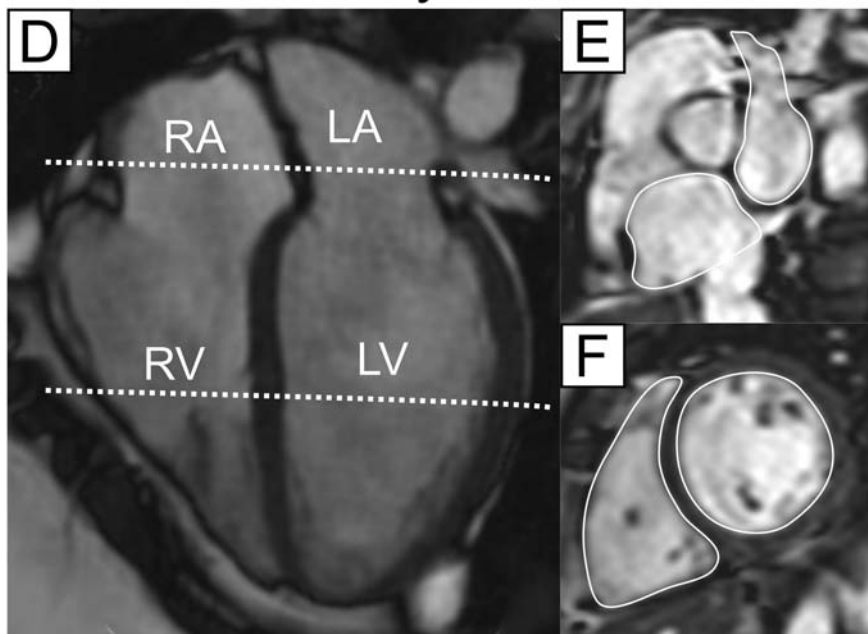
Analysis was performed using Segment v2.1 (<http://www.medviso.com>).<sup>16</sup> Right and left atrial and ventricular volumes were quantified by manual delineation of endocardial borders in the cine short-axis stack at ventricular end-systole and end-diastole, respectively (*Figure 1*). Atrial appendages were included, whereas the inferior and superior vena cava,

**Figure 1** Atrial and ventricular delineations in cardiovascular magnetic resonance (CMR) images. End-diastolic CMR image in a patient with pulmonary arterial hypertension in the four-chamber view (A), indicating by dotted lines the slice locations of the atrial (B) and ventricular (C) short-axis images. Corresponding CMR images in a healthy volunteer (D–F). Solid white lines show examples of atrial (B, E) and ventricular (C, F) endocardial delineations. Note the enlarged right atrium and ventricle and the flattened septum as signs of increased pulmonary pressure in the patient with pulmonary arterial hypertension (A–C). LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

## Pulmonary arterial hypertension



## Healthy control



coronary sinus, and pulmonary veins were excluded. All volumes were indexed to body surface area. Right ventricular stroke volume was calculated as differences in end-diastolic and end-systolic volumes by planimetry. Right ventricular ejection fraction by planimetry was computed as right ventricular stroke volume by planimetry/end-diastolic volume by planimetry  $\times$  100.

Pulmonary artery stroke volume was quantified from phase-contrast data by manually tracing the pulmonary artery lumen in all time phases. For patients with atrial fibrillation, real-time phase-contrast data were analysed and stroke volume was averaged over all full heartbeats acquired in the individual patient (three–five heartbeats). Linear Eddy current compensation was performed when needed. In cases where baseline shift was still evident, manual baseline correction was performed.

Tricuspid regurgitation volume (TRV) was calculated as the volume difference between right ventricular stroke volume and pulmonary artery stroke volume. TR fraction (TR%) was calculated as TRV/right ventricular stroke volume  $\times$  100. Heart rate variation between flow and planimetric acquisitions could lead to a false negative value of TR volume and TR volume was in these cases set to 0.

Effective right ventricular ejection fraction was computed as pulmonary stroke volume by quantitative flow measured in the pulmonary artery divided by right ventricular end-diastolic volume by planimetry  $\times$  100. Effective right ventricular ejection fraction is thus the truly ejected volume into the pulmonary circulation and is not dependent on TR.

## Right heart catheterization

All included patients were clinically referred for RHC, performed according to clinical routine at rest in supine position under local anaesthesia. A triple-lumen 7.3 Fr balloon-tipped Swan-Ganz catheter was inserted through an 8 Fr introducer placed in the right internal jugular vein. Pulsatile and mean right atrial pressures, mean pulmonary arterial pressure, and pulmonary artery wedge pressure were recorded. Cardiac output was calculated via thermodilution, and pulmonary vascular resistance was expressed as (mean pulmonary arterial pressure – pulmonary artery wedge pressure) /cardiac output.

## Statistical analyses

Statistical analyses were performed using GraphPad Prism (8.0.2 for Mac OS X, La Jolla, California, USA), SPSS 24 (IBM SPSS Statistics 24.0.0.0, New York, USA) and R 3.5.3 (R Core Team, Vienna, Austria).<sup>17</sup> Data are presented as mean  $\pm$  SD or median (range) as appropriate. Normal distribution was evaluated by histograms. Linear regression and

nonparametric Spearman correlation coefficients and determination coefficients were assessed. Kaplan–Meier curves with results expressed in survival and hazard ratio were used to analyse event-free survival. As the proportional hazards assumption was violated and early censoring did not occur, the Gehan–Breslow–Wilcoxon test was applied. Cox-regression univariate analyses of CMR measures were performed to test for variables associated with outcome. Multivariate multiple linear regression was performed to assess to what extent TR quantified by CMR and right atrial pressure by RHC determine right atrial dilation. A post-hoc power calculation was performed using an  $\alpha = 0.05$  and  $\beta = 0.2$ , i.e. power = 0.8, based on data from the current study. Group cut-offs was defined above vs. below medians to yield same-size groups. *P* values  $<0.05$  were considered to show statistically significant differences or associations.

## Results

Seventy-nine patients with PAH who had undergone CMR were retrospectively identified or prospectively and consecutively included. Of the 79 identified patients, 15 were excluded due to incomplete image data and 14 due to more than 30 days between CMR and RHC. Thus, 50 patients fulfilled the study protocol criteria and were included in the current study. Systemic blood pressure and NT-proBNP were not available in medical records for one and four patients, respectively. Twenty-seven patients (54%) were de-novo PAH patients (Table 1). Twenty-three (46%) patients were treatment naïve of PAH-specific medication at inclusion, and 45 patients (90%) received PAH-specific treatment after RHC and CMR. Median follow-up time was 2.7 years (0.1–8.9 years). The composite endpoints occurred in 31 patients, consisting of 27 deaths and four successful lung transplantations. Manual baseline shift was performed in five patients in whom automatic Eddy current compensation could not be performed. There was no pulmonary regurgitation as measured by phase-contrast CMR. Median TRV and TR% were 10.785 mL/m<sup>2</sup> (0–33.5 mL/m<sup>2</sup>) and 24.18% (0–66%), respectively.

## Event-free survival

Median event-free survival was 2.8 years (hazard ratio 2.1; 95% CI 1.032–4.419; *P* = 0.098) in patients with TRV above median and 3.9 years in patients with TRV below median. Median event-free survival was 2.8 years (hazard ratio 1.6; 95% CI 0.784–3.300; *P* = 0.44) in patients with TR% above median and 3.7 years in patients with TR% below median (Figure 2). Cox regression univariate analysis showed that none of the analysed CMR variables at baseline was

**Table 1** Patient characteristics at baseline, defined as time point of cardiovascular magnetic resonance imaging

Age (years)	63 ± 17
Body surface area (mL/m <sup>2</sup> )	1.83 ± 0.23
Time between RHC and CMR, days	1 [1–2.25]
NT-proBNP (ng/L)	2,376 [929–5,830]
Systemic systolic blood pressure (mmHg)	123 ± 17
Systemic diastolic blood pressure (mmHg)	78 ± 11
Mean pulmonary arterial pressure (mmHg)	46 ± 12
Systolic pulmonary arterial pressure (mmHg)	76 ± 19
Pulmonary arterial wedge pressure (mmHg)	8 [5–11]
Mean right atrial pressure (mmHg)	8 [3–11]
Cardiac index by RHC (mL/min/m <sup>2</sup> )	2.55 ± 0.73
Pulmonary vascular resistance (Wood units)	8 [6–12]
Men/Women, n (%)	12/38 (24%/76%)
de-novo Diagnosis, n (%)	27 (54%)
IPAH/FPAH, n (%)	23 (46%)
SSc-PAH, n (%)	18 (36%)
CTD-PAH, n (%)	9 (18%)
<b>Medication</b>	
PAH dedicated, n (%)	27 (54%)
Calcium channel blocker, n (%)	16 (32%)
Prostanoids, n (%)	2 (4%)
Endothelin receptor antagonist, n (%)	23 (46%)
Phosphodiesterase Type 5 inhibitor, n (%)	10 (20%)
Betablocker, n (%)	17 (34%)
ACE-inhibitor or ARB, n (%)	19 (38%)
Diuretic, n (%)	31 (62%)
<b>Comorbidities</b>	
Smoking, n (%)	2 (4%)
Previous smoking, n (%)	20 (40%)
Diabetes, n (%)	12 (24%)
Chronic obstructive pulmonary disease, n (%)	9 (18%)
Ischemic heart disease, n (%)	6 (12%)
Systemic hypertension, n (%)	19 (38%)
Thyroid disease, n (%)	7 (14%)
Atrial fibrillation, n (%)	9 (18%)
Stroke, n (%)	5 (10%)

Data are expressed as mean ± standard deviation, median [interquartile range] or in absolute number (percentage). ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CMR, cardiovascular magnetic resonance; CTD, connective tissue disorder; RHC, right heart catheterization; IPAH/FPAH, idiopathic or familial PAH; RHC, right heart catheterization; PAH, pulmonary arterial hypertension; SSc, systemic sclerosis.

significantly associated with poor outcome defined as lung transplantation or death (Table 2).

Even though the Kaplan–Meier plots in Figure 2 seem to show clear trends towards worse outcome for larger TR, the post-hoc power calculation showed that 57 and 142 events (TRV and TR%, respectively) and a minimum of 62 and 167 patients per group (TRV and TR%, respectively) were required to show statistically significant differences in event-free survival between groups. As 31 events occurred in the current

study, the above results are not conclusive, and larger studies are needed.

## Quantitative tricuspid regurgitation and its relation to known prognostic markers

Tricuspid regurgitation volume correlated to right ventricular end-diastolic ( $r = 0.50$ ;  $P = 0.0002$ ) and end-systolic ( $r = 0.35$ ;  $P = 0.012$ ) volumes and correlated inversely to cardiac index ( $r = -0.32$ ;  $P = 0.03$ ), pulmonary artery stroke volume ( $r = -0.32$ ;  $P = 0.02$ ), and effective right ventricular ejection fraction based on quantitative flow measurements ( $r = -0.56$ ;  $P < 0.0001$ ), but not by planimetry alone ( $r = -0.07$ ,  $P = 0.65$ ) (Figure 3). TR volume also correlated to pulmonary vascular resistance ( $r = 0.28$ ;  $P = 0.026$ ) and NT-proBNP ( $r = 0.65$ ;  $P < 0.0001$ ). TR volume was, however, not correlated to systolic pulmonary artery pressure ( $r = 0.16$ ;  $P = 0.14$ ).

Tricuspid regurgitation fraction correlated to right ventricular end-diastolic ( $r = 0.39$ ;  $P = 0.005$ ) and end-systolic ( $r = 0.30$ ;  $P = 0.034$ ) volumes, and correlated inversely to cardiac index ( $r = -0.54$ ;  $P < 0.0001$ ), pulmonary artery stroke volume ( $r = -0.58$ ;  $P < 0.0001$ ) and effective right ventricular ejection fraction based on quantitative flow measurements ( $r = -0.69$ ;  $P < 0.0001$ ), but not by planimetry alone ( $r = -0.21$ ;  $P = 0.07$ ) (Figure 4). TR fraction also correlated to pulmonary vascular resistance ( $r = 0.43$ ;  $P = 0.0008$ ), systolic pulmonary artery pressure ( $r = 0.26$ ;  $P = 0.03$ ), and NT-proBNP ( $r = 0.68$ ;  $P < 0.0001$ ).

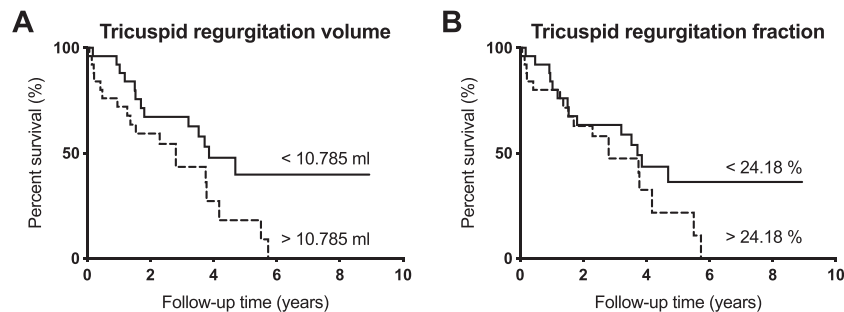
## Tricuspid regurgitation and right atrium dilation

Both TR% (volume overload) and right atrial pressure (pressure overload) determined right atrial maximum ( $r^2 = 0.38$  and  $r^2 = 0.43$ ;  $P < 0.0001$ ) and minimum ( $r^2 = 0.45$  and  $r^2 = 0.48$ ;  $P < 0.0001$ ) volumes to a similar extent. Further, TR% and right atrial pressure were related, indicating co-existence but not by necessity co-dependence ( $r = 0.53$ ;  $P < 0.0001$ ; Figure 5). Considering the low co-determination ( $r^2 = 0.28$ ) between TR% and right atrial pressure, it remains to reveal the cause and effect between volume overload and pressure overload for right atrial dilation.

## Discussion

This study showed a clear trend towards worse outcome with increasing TRV or TR% quantified by MR flow measurements. None of the CMR or RHC measures showed a statistically significant association with event-free survival. Post-hoc power analysis however showed the study to be underpowered for this purpose. Therefore, the prognostic value of quantitative

**Figure 2** Kaplan–Meier analysis for event-free survival vs. tricuspid regurgitation (TR) volume and fraction. Patients were divided into two groups based on TR volume and fraction above (dashed lines) and below (solid lines) median values in the studied population. Survival of patients with TR volume (A) above vs. below median was 2.8 and 3.9 years, respectively, with a hazard ratio of 2.1 (95% CI 1.032–4.419;  $P = 0.098$ ). Survival of patients with TR fraction (B) above vs. below median was 2.8 and 3.7 years, respectively, with a hazard ratio of 1.6 (95% CI 0.784–3.300;  $P = 0.44$ ).



**Table 2** Cardiovascular MR data at baseline and Cox-regression results for event-free survival

	Mean $\pm$ SD or median [IQR]	Hazard ratio	95% confidence interval	$P$ value
RV-EDV (mL/m <sup>2</sup> )	128 $\pm$ 36	1.001	0.992–1.011	0.76
RV-ESV (mL/m <sup>2</sup> )	85 $\pm$ 33	1.001	0.991–1.011	0.86
RV ejection fraction (by planimetry) (%)	36 $\pm$ 11	0.997	0.967–1.028	0.85
Tricuspid regurgitation volume (mL/m <sup>2</sup> )	11 [5–17]	1.023	0.986–1.061	0.23
Tricuspid regurgitation fraction (%)	24 [14–39]	1.013	0.994–1.032	0.20
Pulmonary regurgitation volume (mL/m <sup>2</sup> )	1 $\pm$ 1	0.981	0.728–1.323	0.90
Pulmonary regurgitation fraction (%)	3 [1–7]	1.013	0.949–1.082	0.69
Pulmonary stroke volume (mL/m <sup>2</sup> )	30 $\pm$ 8	0.988	0.959–1.018	0.43
Effective RV ejection fraction (by quantitative flow/planimetry) (%)	23 [18–32]	0.983	0.983–1.023	0.40
Cardiac index by CMR (L/min/m <sup>2</sup> )	2.39 $\pm$ 0.68	0.942	0.549–1.618	0.83
RA maximum volume (mL/m <sup>2</sup> )	78 [54–111]	1.005	0.996–1.015	0.27
RA minimum volume (mL/m <sup>2</sup> )	51 [32–82]	1.004	0.995–1.014	0.37
LV-EDV (mL/m <sup>2</sup> )	61 $\pm$ 15	0.984	0.959–1.009	0.20
LV-ESV (mL/m <sup>2</sup> )	27 $\pm$ 9	0.966	0.923–1.012	0.15
LV ejection fraction (%)	55 $\pm$ 8	1.014	0.974–1.055	0.50

All volumes are indexed for body surface area. EDV, end-diastolic volume; ESV, end-systolic volume; IQR, interquartile range; LV, left ventricular; RA, right atrial; RV, right ventricular.

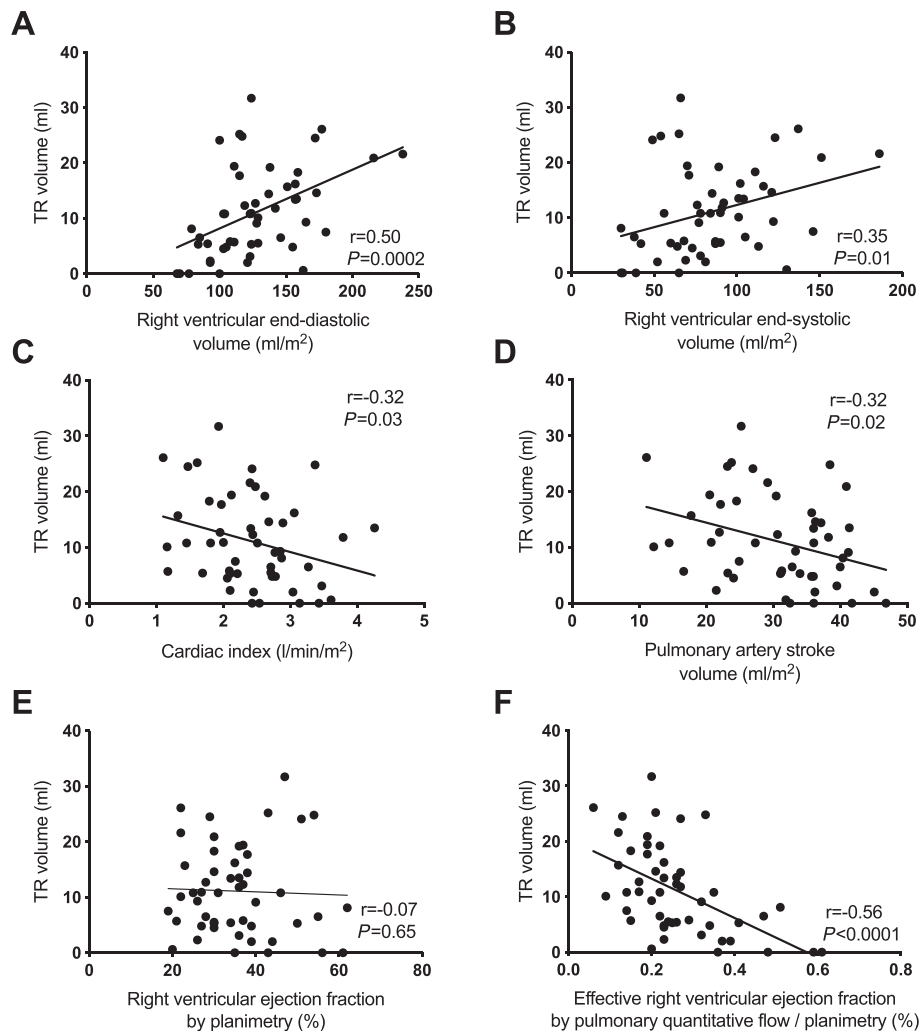
measures of TR should be investigated in a larger cohort, preferably in a multicentre design. TR quantified by CMR correlated to known prognostic markers in PAH, particularly cardiac index, pulmonary artery stroke volume, and NT-proBNP. Furthermore, TR correlated to right ventricular ejection fraction by quantitative pulmonary flow. Finally, this study showed that right atrial volume was determined to a similar extent by TR% (volume overload) and right atrial pressure (pressure overload).

The current study is the first to quantify TR in PAH by CMR, whereas echocardiography assesses TR as visually graded in arbitrary degrees of severity. In previous studies using echocardiographic ordinal grading, severe TR or progression of TR was indicative of worse prognosis.<sup>2,3,18</sup> In the study by Chen et al. on newly diagnosed patients with PAH, 23% had severe TR by visual grading.<sup>2</sup> In the study by Medvedofsky et al., 21% were deemed to have severe TR, and progression was defined as less or equal to mild TR at baseline and more

or equal to moderate TR at follow-up examination.<sup>3</sup> In the study by Bustamante-Labarta et al., two patients (8%) had severe TR.<sup>18</sup> Qualitative grading of TR by echocardiography, however, misclassified 39% of patients using quantitative 4D CMR flow as reference, with more evident misclassification in severe TR.<sup>19</sup> This emphasizes an additive value of accurate and precise CMR-based TR quantification for refining PAH diagnostics based on TR measurements, as performed in the current study.

Chen et al.<sup>2</sup> showed qualitatively severe TR by echocardiography to be a strong predictor of 5-year mortality. The current results indicate a clear trend towards worse outcome with larger quantitative TR. The lack of statistical significance in the current study may be related to that only a minority of patients had severe TR, and in part also explained by the sample size as confirmed by the post-hoc power calculation. The post-hoc power calculation showed that a minimum of 62 (TR volume) and 167 (TR fraction) patients per group would be

**Figure 3** Relationships between tricuspid regurgitation (TR) volume and prognostic markers in PAH. TR volume correlated with right ventricular end-diastolic (A) and end-systolic volumes (B), cardiac index (C), and pulmonary artery stroke volume (D). TR volume did not correlate to ejection fraction calculated by planimetry (i.e. not taking into account the blood volume ejected through the TR into the atrium) (E) but did correlate to effective right ventricular ejection fraction by quantitative pulmonary artery flow divided by right ventricular end-diastolic volume by planimetry (F), thereby indicating effective ejection fraction by quantitative flow and planimetry rather than standard ejection fraction by planimetry alone as a promising marker in future studies of TR.



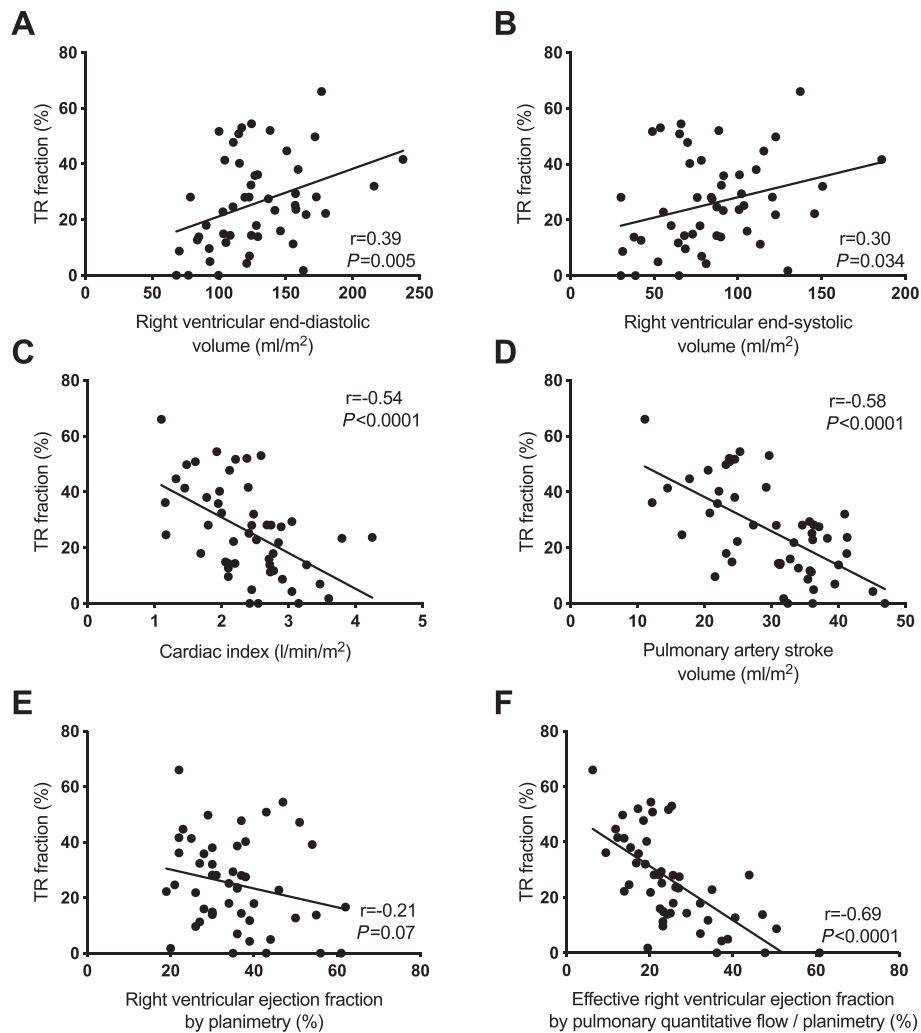
needed to reach statistical power for survival analysis, respectively. This reiterates the importance of multicentre studies for PAH.

The findings in the current study support the results by Hinderliter et al.<sup>20</sup> They concluded that TR is a result of right ventricular remodelling and that ventricular dilation shifts the tricuspid leaflets from its original position allowing for regurgitation of blood. Moreover, the current study showed an inverse association between TR and pulmonary artery stroke volume and cardiac index. This is indicative of TR as relieving the right ventricle after remodelling related to the forward failure with increased pulmonary pressure and increased right ventricular volume.

Hoeper et al.<sup>21</sup> suggested that right ventricular ejection fraction by planimetry is limited as regurgitation volume can be falsely accounted for as forward volume. This is supported by the current study in which no correlation between TR and right ventricular ejection fraction by planimetry was found. Effective right ventricular ejection fraction that index pulmonary stroke volume by quantitative phase-contrast CMR to right ventricular end-diastolic volume, as performed in the current study, could hence be considered a relevant measure of right ventricular function in PAH.

Whereas right atrial dilation is dependent on both volume overload and pressure overload, it has been shown that

**Figure 4** Relationships between tricuspid regurgitation (TR) fraction and prognostic markers in PAH. TR fraction correlated with right ventricular end-diastolic (A) and end-systolic volumes (B), cardiac index (C), and pulmonary artery stroke volume (D). TR fraction did not correlate to ejection fraction calculated by planimetry (i.e. not taking into account the blood volume ejected through the TR into the atrium) (E) but did correlate to effective right ventricular ejection fraction by quantitative pulmonary artery flow divided by right ventricular end-diastolic volume by planimetry (F), thereby indicating effective ejection fraction by quantitative flow and planimetry, rather than standard ejection fraction by planimetry alone, as a promising marker in future studies of TR.

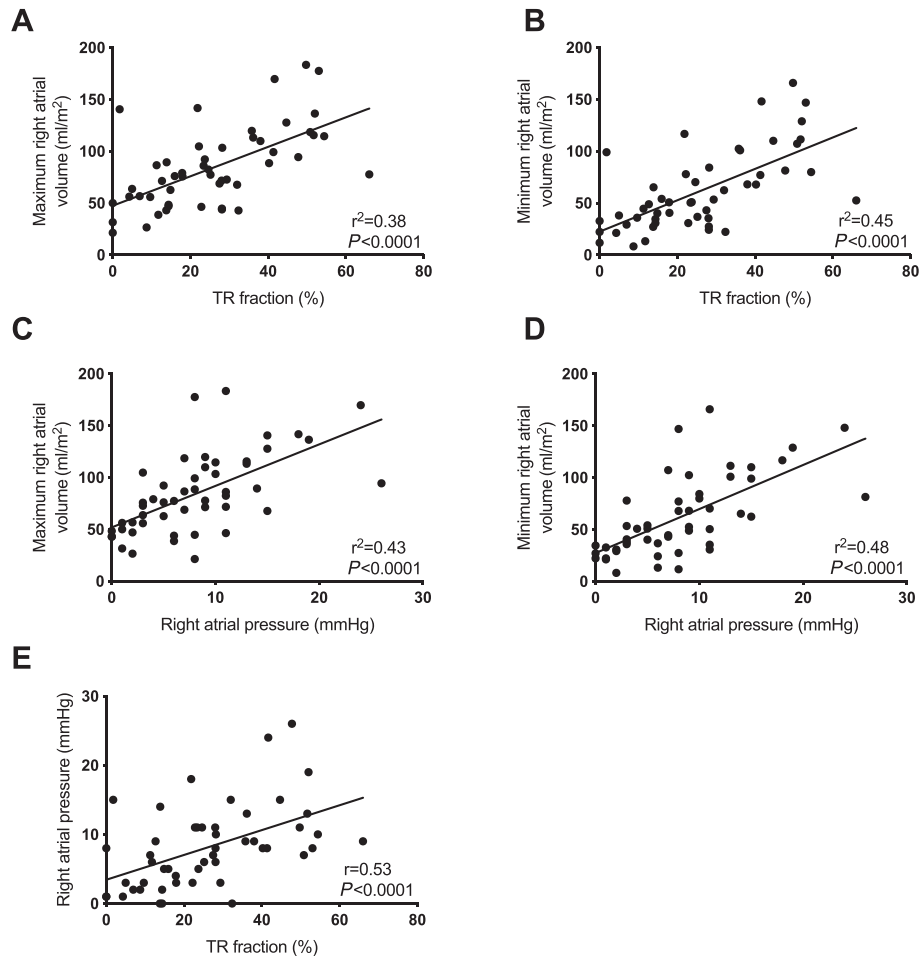


pulmonary pressure has no impact on right atrial volume in patients with TR graded as moderate or severe by echocardiography.<sup>22</sup> Pulmonary pressure has been indicated to only worsen right atrial dilation in the presence of mild TR as graded by echocardiography.<sup>22</sup> Volume overload and not pressure overload therefore seems to be the main culprit in producing severe TR. Both Hinderliter *et al.*<sup>20</sup> and Mutlak *et al.*<sup>23</sup> showed that remodelling of the right atrium and ventricle is crucial for development of TR. The current study supports this by showing that there is no statistically significant correlation between invasive systolic pulmonary arterial pressure and TR volume whereas pulmonary vascular resistance and TR correlate.

Mortality was relatively high in the current study with 27 deaths (54%) over a median follow-up time of 2.7 years (0.1–8.9 years). This may be related to comorbidities as listed in *Table 1* and to the age of included patients with  $n = 14$  over 75 years of age. Although diastolic dysfunction was not assessed in the current study, it may be assumed that diastolic dysfunction is more prevalent in this age group with the present comorbidities. As PAH treatment is less efficient in these patients, it may in part explain the relatively high degree of mortality. However, none of the patients in the current study had PAWP >15 mmHg. Furthermore, 45 patients (90%) received PAH-specific treatment after RHC and CMR, whereas 46% of the patients were treatment naïve regarding



**Figure 5** Tricuspid regurgitation (TR) by cardiovascular magnetic resonance imaging and right atrial pressure by right heart catheterization as determinants of right atrial volumes and correlation between TR and right atrial pressure. Both maximum (A, C) and minimum (B, D) atrial volumes were determined by TR fraction (A, B) and right atrial pressure (C, D). TR correlated with right atrial pressure (E).



PAH-specific medication at inclusion. The proportion of patients with PAH-specific treatment after RHC and CMR in the current study is similar to that in the study by Medvedofsky et al.<sup>3</sup> However, in that study, some patients had PAWP above 15 mmHg, which implies a component of left heart disease in their population. This affects treatment efficacy and survival. In the study by Chen et al., patients with congenital heart defects were included, and some of these had tricuspid valve repair or valve replacement during follow-up time.<sup>2</sup> This changes transplantation-free survival beyond mere changes in medical treatment, which was not accounted for in that study. The current study population is therefore not directly comparable with those of the two previous studies, as the current study excluded patients with PAH owing to shunts or congenital heart defects as well as patients with PAWP >15 mmHg. This is thus the first study to investigate quantitative TR as a continuous variable in a population with precapillary PAH.

## Limitations

The number of included patients was too small for determining statistically significant prognostic values, despite up to almost 9 years follow-up. As PAH is rare, multicentre studies would be needed to provide sufficiently large population samples. This may now be possible as more centres add CMR to their clinical diagnostic PAH protocol. Further, the quantitative flow images are sensitive to turbulent flow, more common in PAH, which could lead to underestimation of pulmonary stroke volume and cardiac output. Turbulence was however checked for and not evident in the current population. Finally, referral bias might have occurred as patients were investigated on clinical indication. The impact of this potential bias is unclear but likely negligible as all PAH patients were admitted through the same clinical team with both CMR and RHC performed as clinical routine with standardized protocols at a single centre.

## Conclusions

This study showed worse outcome with increased TRV or TR% whereas none of the CMR or RHC measures showed a statistically significant association with event-free survival due to insufficient power. Therefore, the prognostic value of quantitative measures of TR should be investigated in a larger cohort, preferably in a multicentre design. TR quantified by CMR is related to known prognostic markers in PAH, particularly cardiac index, pulmonary artery stroke volume, right ventricular ejection fraction by quantitative pulmonary flow, and NT-proBNP. Finally, this study showed that right atrial volume is determined to a similar extent by TR% quantified by CMR (volume overload) and right atrial pressure by RHC (pressure overload). Effective right ventricular ejection fraction may be considered an improved measure of right ventricular function in PAH.

## Perspectives

Effective right ventricular ejection fraction by quantitative phase-contrast magnetic resonance imaging may be considered an improved measure of right ventricular function in PAH. This may enhance risk stratification in PAH. The clinical implication of this work is thus that individualized treatment may be improved by quantitative measurements by CMR. A direct comparison between qualitative TR

by echocardiography and quantitative TR by CMR for risk assessment in PAH was not performed in the current study, and future research would benefit from this. As PAH is rare, multicentre studies would be needed to provide sufficiently large population samples. This may now be possible as more centres add CMR to their clinical diagnostic PAH protocol.

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## Conflict of interest

None declared.

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