ESC European Society of Cardiology

European Journal of Heart Failure (2024)
doi:10.1002/ejhf.3235

RESEARCH ARTICLE

Congestion patterns in severe tricuspid regurgitation and transcatheter treatment: Insights from a multicentre registry

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Received 4 December 2023; revised 22 March 2024; accepted 28 March 2024

Aims While invasively determined congestion holds mechanistic and prognostic significance in acute heart failure (HF), its role in patients with tricuspid regurgitation (TR)-related right- heart failure (HF) undergoing transcatheter tricuspid valve intervention (TTVI) is less well established. A comprehensive understanding of congestion patterns might aid in procedural planning, risk stratification, and the identification of patients who may benefit from adjunctive therapies before undergoing TTVI. The aim of this study was to investigate the role of congestion patterns in patients with severe TR and its implications for TTVI.

Methods and results Within a multicentre, international TTVI registry, 813 patients underwent right heart catheterization (RHC) prior to TTVI and were followed up to 24 months. The median age was 80 (interquartile range 76–83) years and 54% were women. Both mean right atrial pressure (RAP) and pulmonary capillary wedge pressure (PCWP) were associated with 2-year mortality on Cox regression analyses with Youden index-derived cut-offs of 17 mmHg and 19 mmHg, respectively ($p < 0.01$ for all). However, RAP emerged as an independent predictor of outcomes following multivariable adjustments. Pre-interventionally, 42% of patients were classified as euvolaemic (RAP <17 mmHg, PCWP <19 mmHg), 23% as having left-sided congestion (RAP <17 mmHg, PCWP ≥19 mmHg), 8% as right-sided congestion (RAP ≥17 mmHg, PCWP <19 mmHg), and 27% as bilateral congestion (RAP ≥17 mmHg, PCWP ≥19 mmHg). Patients with right-sided or bilateral congestion had the lowest procedural success rates and shortest survival times. Congestion patterns allowed for discerning specific patient's physiology and specifying prognostic implications of right ventricular to pulmonary artery coupling surrogates.

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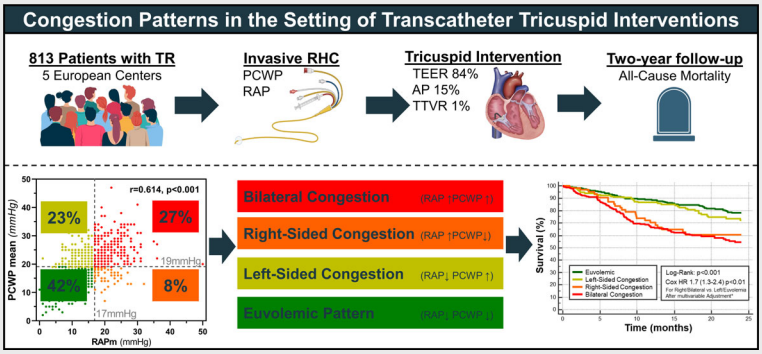
Conclusion In this large cohort of invasively characterized patients undergoing TTVI, congestion patterns involving right-sided congestion were associated with low procedural success and higher mortality rates after TTVI. Whether pre-interventional reduction of right-sided congestion can improve outcomes after TTVI should be established in dedicated studies.

Graphical Abstract



Congestion patterns in transcatheter tricuspid valve interventions. AP, annuloplasty; HR, hazard ratio; RAP, right atrial pressure; RAPm, mean right atrial pressure; PCWP, pulmonary capillary wedge pressure; RHC, right heart catheterization; TEER, transcatheter edge-to-edge repair; TR, tricuspid regurgitation; TTVR, transcatheter tricuspid valve repair.

Keywords Right heart failure • Tricuspid regurgitation • Haemodynamics • Transcatheter tricuspid valve repair • Central venous congestion

Introduction

Severe tricuspid regurgitation (TR) is now widely recognized as an independent risk factor for a poor prognosis and an adverse clinical course in patients with various types of heart failure (HF).[1,2] Aetiologically, TR can be associated with left-sided HF, increased left-sided filling pressures, and the accompanying pulmonary hypertension.[3] The underlying left-sided congestion is quantified by pulmonary capillary wedge pressures (PCWP), which hold prognostic relevance in a wide variety of left HF subtypes.[4] Functionally, progressive TR results in chronic volume overload of the right heart chambers and right-sided HF, leading to subsequent elevations in right-sided filling pressures. These pressures are quantified by right atrial pressures (RAP), which are linked to central venous congestion.[5] RAP has been shown to be of prognostic significance in patients with chronic or acute left HF, but its implications in right-sided HF remain contentious.[6,7]

The recent advent of transcatheter tricuspid valve interventions (TTVI) has not only provided safe and effective means to reduce TR but also offers a model for studying right-sided HF by partly attenuating its haemodynamic basis.[5] Initial observations in patients with TR-associated right-sided HF have reported reductions in RAP following TTVI, but they found no significant associations between PCWP or RAP and outcomes.[8] However, we recently demonstrated that patients with severe TR and a hypercirculatory phenotype or elevated levels of stressed blood volumes actually exhibit the highest degrees of right-sided congestion. In addition, these patients experience the least reductions in RAP despite effective TR amelioration in response to TTVI and, consequently, have the worst prognosis.[9,10]

We therefore sought to investigate haemodynamic and prognostic implications of invasively determined, pre-procedural bilateral filling pressures in a large cohort of patients with TR-related right-sided HF undergoing TTVI.

Methods

Patient cohort

This study uses data from a multicentre, binational, prospective registry of patients with severe, symptomatic TR undergoing right heart catheterization (RHC) prior to TTVI between 2016 and 2022.[11] Patients were included on the basis of a diagnosis of severe TR and an interventional therapeutic approach according to a local heart team decision. The analysis was approved by the local ethics committees of each centre and all patients gave written informed consent. The study

cohort and the investigation conform to the principles outlined in the Declaration of Helsinki.

Echocardiographic assessment

Pre-procedural assessment included a comprehensive echocardiography according to current guideline recommendations, as previously described.[11] In brief, grading of TR severity was based on the assessment of vena contracta, effective regurgitant orifice area and estimated regurgitant volume according to proximal isovelocity surface area. TR severity grades of mild, moderate, and severe were extended to include grade IV and V TR (massive and torrential, respectively).[12] Right ventricular (RV) systolic function was estimated based on tricuspid annular plane systolic excursion (TAPSE) measurements. Echocardiographic systolic pulmonary artery pressure (PAPs) levels were approximated from the TR regurgitant jet and RAP.[13]

Invasive haemodynamics

All patients underwent elective RHC prior to the valvular intervention, as previously described.[11] PCWP, PAPs, diastolic pulmonary artery pressure (PAPd), mean pulmonary artery (PA) pressure, mean RAP and aortic pressures were assessed. Cardiac output was measured using the indirect Fick method. Cardiac index (CI) was derived by indexing cardiac output to body surface area. Pulmonary vascular resistance (PVR) was calculated as previously described.[9,14] RV/PA coupling was estimated from the ratio of TAPSE on echocardiography divided by PAPs as determined invasively (TAPSE/iPAPs). TR associated hypercirculatory cardiac output states were defined as CI >2.6 L/min/m^2, as previously suggested.[9] Transmural filling pressures (TMFP) were calculated as PCWP−RAP.[15] Pulmonary artery pulsatility index (PAPi) was calculated as (PAPs−PAPd)/RAP.

Procedural outcomes

Transcatheter tricuspid valve intervention procedural success was defined as a device successfully implanted and delivery system retrieved with residual TR grade ≤2/5 as assessed on transthoracic echocardiography before discharge (i.e. 2−5 days after the procedure).[16,17]

Clinical outcomes

The primary clinical outcome was post-procedural 2-year all-cause mortality. Survival data were ascertained by review of the German civil registry, hospital documentation, or contact to the general practitioner.

Statistical analyses

Continuous variables are presented as medians with interquartile range (IQR) and between-group differences were tested with Mann−Whitney U tests or Kruskal−Wallis tests where appropriate. Paired data were analysed with Wilcoxon rank tests. Categorical variables are presented as frequencies and percentages and were compared with Chi^2 or McNemar's tests where appropriate. Post-hoc analyses were carried out with Dunn's tests and pairwise Z tests. Correlations between continuous variables were assessed by Spearman's rho. Receiver operating characteristic (ROC) curve statistics were calculated to identify optimal cut-off values for mortality prediction according to the Youden index (YI).

Congestion profiles were defined as euvoleamic (RAP < YI associated cut-off, PCWP < YI associated cut-off), left-sided congestion (RAP < 1 YI associated cut-off, PCWP ≥ YI associated cut-off), right-sided congestion (RAP ≥ YI associated cut-off, PCWP < YI associated cut-off) and bilateral congestion (RAP ≥1 YI associated cut-off, PCWP ≥ YI associated cut-off), similar to previous studies.[7,10]

Univariable and multivariable Cox regression analyses were performed to investigate the prognostic value of congestion patterns. All variables in *Tables 1* and *2* were tested in univariable analyses. Continuous variables that showed significant relationships with mortality in univariable regression, were additionally tested as dichotomized variables. Dichotomization was guided by cut-offs defined within our manuscript (e.g. RAP, PCWP, TAPSE/iPAPs), prior literature (e.g. CI),[9] or the cohort's median values. Stepwise multivariable regression was performed using dichotomized variables demonstrating statistical significance in univariable testing ($p < 0.05$), exhibiting minimal contextual or mathematical interrelations, and representing distinct facets of the categories 'patient characteristics', 'echocardiographic measures', 'invasive haemodynamics', and 'RV function'. For variables in the multivariable model, variance inflation factors were assessed, considering a threshold of 5 as an indicator of multicollinearity with other variables in the model. Results are presented as hazard ratios (HR) and 95% confidence intervals (CI).

Kaplan−Meier survival estimates were used to compare the time of the first occurrence of the clinical endpoints between groups.

A two-sided significance level of $\alpha = 0.05$ was defined appropriate to indicate statistical significance. Statistical analyses were performed using SPSS (version 29.0.0.0) and figures were illustrated using GraphPad Prism (version 8.0.2).

Results

Overall patient cohort

A total of 813 patients were included in the current analysis, with a median age of 80 years (IQR 76−83) and a slight female predominance (54%). The cohort presented an elevated surgical risk, as indicated by a EuroSCORE II of 4.7% (IQR 2.8−8.3). Predominantly, patients displayed New York Heart Association class III and IV symptoms (88%). Echocardiography revealed a median preserved left ventricular (LV) ejection fraction of 55% (IQR 48−61) and preserved RV function (TAPSE 17 mm, IQR 14−20). About 47% of the cohort exhibited massive or torrential TR, with severe TR in the remaining cases.

Invasive assessments demonstrated elevated biventricular filling pressures, with a RAP of 14 (IQR 10−19) mmHg and PCWP of 19 (IQR 14−23) mmHg. The 1-year mortality rate was 18%, and up to the 2-year mark, 208 patients died, resulting in a 2-year survival rate of 67%.

Univariable Cox regression analysis revealed that both RAP (HR 1.06, 95% CI 1.04−1.08, $p < 0.001$) and PCWP (HR 1.7, 95% CI 1.3−2.2, $p < 0.001$) were associated with 2-year mortality. ROC analyses showed an area under the curve (AUC) of 0.65 (CI 0.62−0.68, $p < 0.001$) for mortality prediction by RAP, with an optimized cut-off value of 17 mmHg. The AUC for PCWP was 0.59 (95% CI 0.56−0.63, $p < 0.01$), with an optimized cut-off value for mortality prediction at 19 mmHg. Consequently, patients with

Table 1 Baseline characteristics

	Euvolaemic profile (*n* = 344, 42%)	Left-sided congestion (*n* = 184, 23%)	Right-sided congestion (*n* = 63, 8%)	Bilateral congestion (*n* = 222, 27%)	*p*-value	Available data, *n* (%)
Age, years	80 (77–83)[3,4]	80 (76–83)[3,4]	78 (74–81)[1,2]	79 (75–83)[1,2]	0.009	813 (100)
Male sex, *n* (%)	140 (41)[4]	85 (46)	33 (52)	115 (52)[1]	0.047	813 (100)
BMI, kg/m^2	25.1 (22.7–28.1)[4]	25.2 (23.2–28.5)[4]	24.7 (22.5–27.4)[4]	27.1 (23.8–30.8)[1–3]	<0.001	813 (100)
EuroSCORE II, %	4.1 (2.5–6.9)[2,4]	5.2 (3.2–9.0)[1]	4.7 (3.1–9.5)	5.3 (3.2–9.1)[1]	<0.001	802 (99)
Arterial hypertension, *n* (%)	290 (84)[4]	155 (84)	51 (81)[4]	206 (93)[1,3]	0.01	813 (100)
Atrial fibrillation, *n* (%)	307 (89)	172 (93)	56 (89)	204 (92)	0.4	813 (100)
Diabetes mellitus, *n* (%)	76 (22)[4]	50 (27)	11 (17)[4]	88 (40)[1,3]	<0.001	813 (100)
Chronic lung disease, *n* (%)	55 (16)[4]	43 (23)	9 (14)[4]	59 (27)[1,3]	0.008	813 (100)
Coronary artery disease, *n* (%)	128 (37)[4]	71 (39)	22 (35)[4]	108 (49)[1,3]	0.033	813 (100)
RV lead present, *n* (%)	88 (26)[3,4]	44 (24)[3,4]	20 (32)[1,2]	79 (36)[1,2]	0.027	813 (100)
Prior cardiac intervention, *n* (%)	62 (28)	44 (38)	14 (30)	49 (32)	0.32	540 (66)
Ascites, *n* (%)	20 (9)[4]	16 (14)	10 (21)	41 (27)[1]	<0.001	540 (66)
Peripheral oedema, *n* (%)	137 (61)[4]	84 (72)	31 (66)	119 (78)[1]	0.007	540 (66)
Pleural effusion, *n* (%)	45 (13)[3,4]	36 (20)	20 (32)[1]	65 (29)[1]	<0.001	540 (66)
NYHA class ≥III, *n* (%)	295 (86)	162 (88)	55 (87)	201 (91)	0.4	813 (100)
eGFR, ml/min/1.73 m^2	49 (40–65)[3,4]	47 (36–62)[3,4]	42 (33–48)[1,2]	39 (27–56)[1,2]	<0.001	810 (99)
eGFR <30 ml/min/1.73 m^2, *n* (%)	38 (11)[4]	28 (15)	11 (18)	66 (30)[1]	<0.001	810 (99)
Total bilirubin, mg/dl	0.75 (0.53–1.01)[3,4]	0.71 (0.50–1.00)[3,4]	0.91 (0.80–1.20)[1,2]	0.97 (0.60–1.40)[1,2]	<0.001	462 (57)
Gamma-glutamyl transferase, U/L	83 (42–160)[3,4]	97 (50–189)[4]	129 (60–250)[1]	120 (73–243)[1,2]	<0.001	462 (57)
Aspartate transaminase, U/L	28 (23–34)	28 (24–36)	26 (22–33)	27 (23–35)	0.70	513 (63)
Alanine transaminase, U/L	20 (15–26)	19 (14–26)	17 (14–23)	18 (13–23)	0.068	513 (63)
NT-proBNP, ng/L	1800 (1074–3365)[2–4]	2369 (1356–4452)[1,3,4]	3178 (1749–6386)[1,2]	2885 (1441–6076)[1,2]	<0.001	791 (97)
Haemoglobin, g/dl	12.7 (11.2–13.8)[3,4]	12.4 (10.9–13.4) [3,4]	11.8 (9.8–12.7)[1,2]	11.0 (9.7–12.2)[1,2]	<0.001	647 (80)
Aldosterone antagonist, *n* (%)	78 (35)	48 (41)	14 (30)	69 (45)	0.12	540 (66)
Loop diuretics, *n* (%)	210 (94)	108 (92)	46 (98)	150 (98)	0.108	540 (66)
Diuretic therapy, *n* (%)	212 (95)	111 (95)	46 (98)	151 (99)	0.22	540 (66)

BMI, body mass index; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RV, right ventricular.
Superscript numbers indicate significant pairwise between-group differences on post-hoc testing with.
[1] Euvolaemic profile.
[2] Left-sided congestion.
[3] Right-sided congestion.
[4] Bilateral congestion.

RAP ≥17 mmHg and PCWP ≥19 mmHg exhibited shorter survival times than their counterparts (*Figure 1*).

Restricted cubic spline analyses revealed a sigmoid association between RAP and mortality risk, with a steep linear slope between 10 and 25 mmHg (*Figure 1*). PCWP exhibited a rather linear association with mortality risk, albeit with a shallower slope (*Figure 1*).

Congestion patterns

Right atrial pressure and PCWP demonstrated a moderate linear correlation ($r = 0.61$, $p < 0.01$; *Figure 2*). Combining the two parameters based on their prognostic cut-offs resulted in 322 patients (42%) with a euvolaemic pattern (RAP <17 mmHg, PCWP <19 mmHg), 184 patients (23%) with a left-sided congestion pattern (RAP <17 mmHg, PCWP ≥19 mmHg), 63 patients (8%) with a right-sided congestion pattern (RAP ≥17 mmHg, PCWP <19 mmHg), and 222 patients (27%) with a bilateral congestion pattern (RAP ≥17 mmHg, PCWP ≥19 mmHg). Patient characteristics according to these groups are displayed in *Table 1* and *Figure 2*.

Euvolaemic patients exhibited the highest age, were predominantly female, had the lowest EuroSCORE II, the best renal function, and the lowest N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. Similarly, patients with left-sided congestion were relatively old and predominantly female, with preserved renal function but a high EuroSCORE II. Patients with a right-sided congestion profile were the youngest, showed male predominance, the lowest body mass index, the lowest rates of chronic conditions, but the highest NT-proBNP levels. Bilaterally congested patients showed the highest EuroSCORE II, the most extensive comorbidity profile, including coronary artery diseases, and the worst renal function.

Patients with right-sided or bilateral congestion presented more often with ascites or pleural effusions, while the presence of peripheral oedema was more variable among groups. Similarly, levels of bilirubin and gamma-glutamyl transferase were higher in patients with right-sided or bilateral congestion, while transaminase levels were similar across congestion patterns. Haemoglobin levels gradually decreased from euvolaemic to left-sided, to right-sided, to bilateral congestion patterns (*Table 1*).

Echocardiographic and haemodynamic characteristics are displayed in *Table 2* and *Figure 2*. Euvolaemic patients had the best LV and RV function, relatively low PA pressures, and thus the best TAPSE/iPAPs ratios and preserved PAPi. TMFP as well as RAP/PCWP ratio were in a physiological range in the setting of low RAP and PCWP values. Patients with left-sided congestion

Table 2 Echocardiographic and haemodynamic characteristics

	Euvolaemic profile ($n = 344$, 42%)	Left-sided congestion ($n = 184$, 23%)	Right-sided congestion ($n = 63$, 8%)	Bilateral congestion ($n = 222$, 27%)	*p*-value	Available data, *n* (%)
LV ejection fraction, %	57 (51–63)[3,4]	56 (50–61)[3]	50 (45–59)[1,2]	55 (45–60)[1]	<0.001	781 (96)
LV ejection fraction <50%, *n* (%)	63 (19)[3,4]	40 (23)[3]	26 (43)[1,2]	78 (36)[1]	<0.001	781 (96)
LV end-diastolic diameter, mm	47 (43–53)[4]	50 (43–55)	49 (44–54)	50 (45–57)[1]	0.009	794 (98)
LA area, cm^2	29 (24–35)[2]	32 (26–40)[1]	28 (25–35)	30 (25–38)	0.031	679 (84)
Mitral regurgitation > mild, *n* (%)	63 (28)	33 (28)	12 (26)	42 (28)	0.98	532 (65)
RA area, cm^2	35 (29–44)	35 (30–43)	39 (33–50)	38 (30–47)	0.12	795 (98)
RV basal diameter, mm	45 (40–50)[3,4]	44 (40–49)[3,4]	48 (44–55)[1,2]	47 (42–54)[1,2]	<0.001	803 (99)
TAPSE, mm	18 (15–21)[3,4]	17 (14–20)	16 (13–19)[1]	17 (13–19)[1]	<0.001	789 (97)
RV FAC, %	44 (36–52)[2–4]	41 (34–49)[1,4]	39 (31–47)[1]	37 (29–45)[1,2]	<0.001	760 (93)
PAP systolic (echo), mmHg	40 (32–48)[2,4]	46 (38–56)[1,3]	35 (28–47)[2,4]	44 (35–57)[1,3]	<0.001	800 (98)
Vena cava diameter, mm	25 (20–28)[3,4]	25 (21–28)[3,4]	27 (23–33)[1,2]	28 (24–31)[1,2]	<0.001	785 (97)
TV EROA, cm^2	0.51 (0.40–0.70)	0.47 (0.38–0.60)	0.68 (0.51–0.90)	0.60 (0.42–0.93)	<0.001	785 (97)
TR vena contracta, mm	9.6 (8.0–13.0)[2–4]	9.0 (7.0–11.0)[1,3,4]	12.0 (9.9–14.0)[1,2]	11.0 (8.6–14.0)[1,2]	<0.001	796 (98)
TR grade, *n* (%)						
3	185 (54)[2,3]	122 (66)[1,3,4]	20 (32)[1,2,4]	98 (44)[2,3]	**<0.001**	813 (100)
4	102 (30)	48 (26)	24 (38)	73 (33)		
5	57 (17)[2]	14 (7.6)[1,3,4]	19 (30)[2]	51 (23)[2]		
TR aetiology, *n* (%)						
Atrial	125 (36)	73 (40)	17 (27)	53 (24)	0.009	813 (100)
Ventricular	185 (54)[4]	102 (55)[4]	40 (64)	149 (67)[1,2]		
Primary	16 (5)	3 (2)	4 (6)	6 (3)		
CIED-related	18 (5)	6 (3)	4 (6)	6 (3)		
Cardiac index, L/min/m^2	2.00 (1.71–2.44)	2.10 (1.70–2.54)	1.98 (1.71–2.40)	2.20 (1.75–2.76)	0.071	769 (95)
PAP systolic (invasive), mmHg	37 (32–44)[2–4]	50 (44–58)[1,3,4]	40 (37–47)[1,2,4]	55 (48–65)[1–3]	<0.001	800 (98)
PAP diastolic, mmHg	14 (10–17)[2–4]	19 (17–23)[1,4]	19 (16–23)[1,4]	24 (21–27)[1–3]	<0.001	798 (98)
PAP mean, mmHg	23 (20–27)[2–4]	32 (29–36)[1,3,4]	28 (24–31)[1,2,4]	36 (32–42)[1–3]	<0.001	805 (99)
PVR, WU	2.60 (1.66–3.74)	2.80 (1.68–4.10)	3.10 (2.12–4.35)	2.71 (1.83–4.30)	0.2	754 (93)
TPG, mmHg	10 (7–13)[4]	10 (6–14)	10 (8–15)	11 (8–14)[1]	0.009	805 (99)
PCWP, mmHg	14 (11–17)[2–4]	22 (20–25)[1,3,4]	16 (15–18)[1,2,4]	25 (22–29)[1–3]	<0.001	813 (100)
RAP mean, mmHg	10 (7–13)[2–4]	13 (11–15)[1,3,4]	20 (18–23)[1,2]	21 (19–25)[1,2]	<0.001	813 (100)
TAPSE/PAP systolic (invasive), ratio	0.47 (0.38–0.60)[2–4]	0.34 (0.25–0.42)[1,4]	0.38 (0.28–0.48)[1,4]	0.29 (0.22–0.36)[1–3]	<0.001	777 (96)
TMFP, mmHg	4 (1–7)[2,3]	9 (7–12)[1,3,4]	−4 (−8 to −1)[1,2,4]	4 (1–7)[2,3]	<0.001	813 (100)
RAP/PCWP, ratio	0.72 (0.50–0.88)[2–4]	0.57 (0.47–0.67)[1,3,4]	1.27 (1.06–1.53)[1,2,4]	0.85 (0.75–0.97)[1–3]	<0.001	813 (100)
PAPi, ratio	2.5 (1.8–3.6)[3,4]	2.4 (1.9–3.2)[3,4]	1.0 (0.8–1.5)[1,2,4]	1.4 (1.0–1.9)[1–3]	<0.001	798 (98)

CIED, cardiac implantable electronic device; EROA, effective regurgitant orifice area; FAC, fractional area change; LA, left atrial; LV, left ventricular; PAP, pulmonary artery pressure; PAPi, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RA, right atrial; RAP, right atrial pressure; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; TMFP, transmural filling pressure; TPG, transpulmonary gradient; TR, tricuspid regurgitation; WU, Wood units.
Superscript numbers indicate significant pairwise between-group differences on post-hoc testing with.
[1] Euvolaemic profile.
[2] Left-sided congestion.
[3] Right-sided congestion.
[4] Bilateral congestion.

displayed the largest LV and left atrial dimensions but the smallest dimensions of the right-sided chambers and the least severe TR. Invasively, PA pressures were elevated, and the patients showed the highest TMFP and lowest RAP/PCWP ratios.

Patients in the right-sided congestion pattern exhibited the lowest LV and RV function, the largest RV and right atrial dimensions but the smallest left atrial dimensions. These patients were characterized by the most severe TR but relatively low PA pressures, resulting in preserved TAPSE/iPAPs ratios despite the lowest PAPi. Notably, these patients exhibited the lowest, and in fact, negative TMFP and the highest RAP/PCWP ratios (exceeding 1). Patients with bilateral congestion showed an intermediate echocardiographic phenotype; however, they displayed the largest diameter of the vena cava, the highest PA pressures, and the lowest TAPSE/iPAPs values along with low PAPi levels.

Procedural outcomes

The predominant TR therapy in the cohort was transcatheter edge-to-edge repair (TEER, $n = 681$, 84%), followed by interventional annuloplasty ($n = 125$, 15%), and transcatheter replacement ($n = 7$, 1%), with no differences in the distribution among congestion profile groups ($p = 0.70$). Procedural success was achieved in 654 (80.4%) of patients, but success rates gradually declined from euvolaemic to left-sided, right-sided, and bilateral congestion (87%, 84%, 73%, and 70%, respectively, $p < 0.01$). Success rates were higher in patients with euvolaemic or left-sided congestion patterns (86%) compared to patients with right-sided or bilateral congestion patterns (71%, $p < 0.01$; *Figure 3*). Procedural success was observed in 83% of patients undergoing TEER, 64% of patients undergoing annuloplasty, and 100% of patients undergoing replacement ($p < 0.01$).

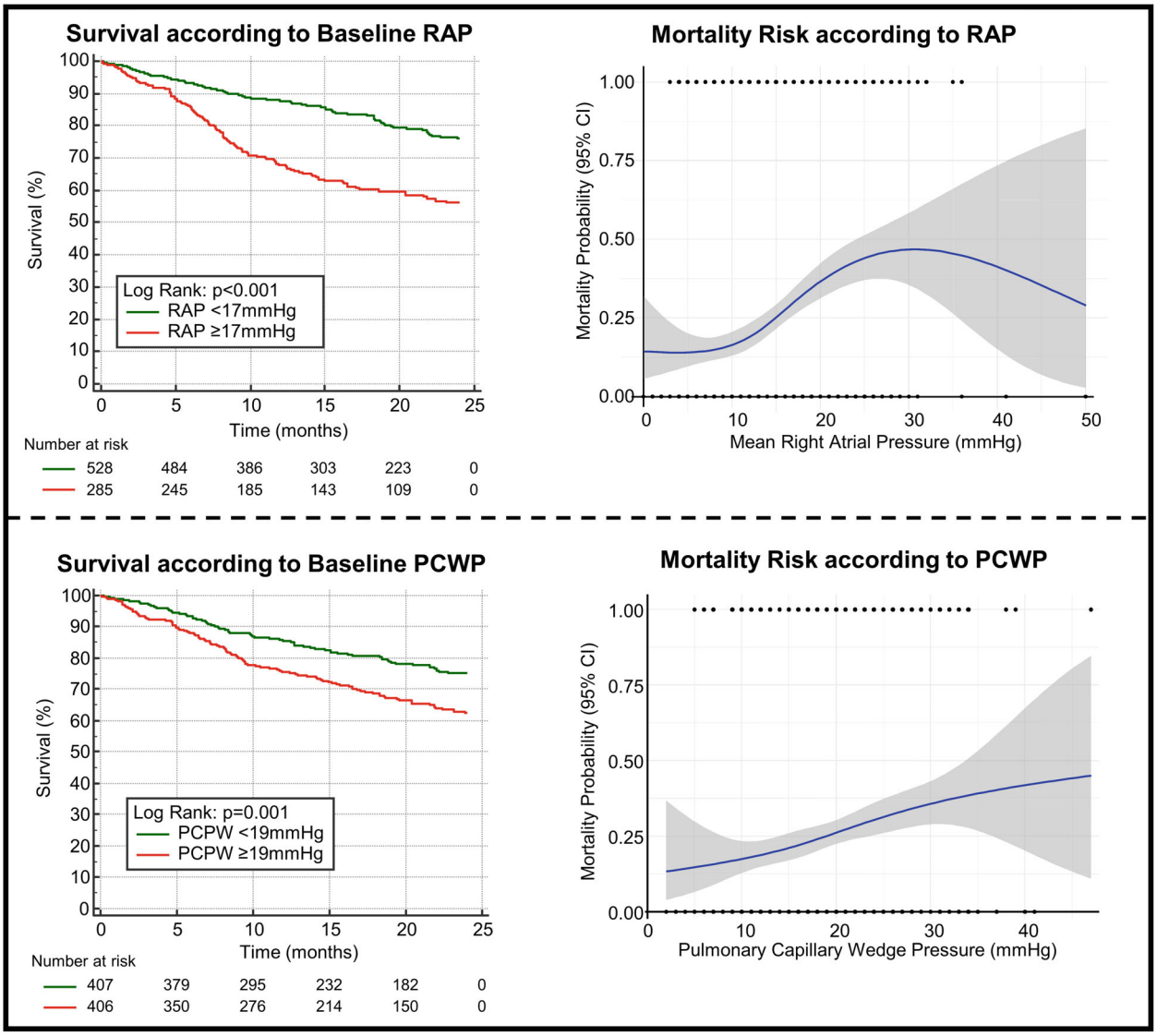


Figure 1 Association between biventricular filling pressure and mortality. CI, confidence interval; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure.

Clinical outcomes

The 1-year mortality gradually increased, and the 2-year survival gradually decreased from the euvolaemic pattern to left-sided, right-sided, and biventricular congestion patterns (1-year mortality: 11%, 12%, 29%, 32%, $p < 0.001$; 2-year survival: 83%, 79%, 63%, 60%, $p < 0.01$, respectively). Kaplan–Meier analyses demonstrated similar survival times in the right-sided and bilateral congestion group, significantly lower than that of the euvolaemic or left-sided congestion pattern ($p < 0.01$; *Figure 2*). This translated into a HR of 2.33 (95% CI 1.78–3.06, $p < 0.01$) for 2-year mortality in the right-sided or bilateral congestion group compared to the euvolaemic or left-sided congestion pattern on univariable Cox regression (*Table 3*). The assignment to the right-sided or bilateral congestion group remained significantly associated with 2-year survival on multivariable Cox regression, in a model that included the TAPSE/iPAPs ratio <0.31 mm/mmHg, PVR >4.5 Wood units, CI >2.6 L/min/m^2, TR grade, and estimated glomerular filtration rate <30 ml/min/m^2 (*Table 3*). The same held true when considering patients classified with a mean RAP ≥17 mmHg; however, the prognostic value of PCWP ≥19 mmHg was attenuated when adjusted in the multivariable model (HR 1.47, 95% CI 0.97–1.95, $p = 0.06$). Variance inflation factors for all variables considered for multivariable analysis were <2.

While procedural failure was significantly associated with 2-year survival (HR 2.39, 95% CI 1.79–3.18, $p < 0.01$), right-sided or bilateral congestion remained independently associated even after adjusting for residual TR grade >2 (HR 1.45, 95% CI 1.01–2.09, $p = 0.04$). In fact, ineffective procedural TR reduction was associated with adverse outcomes in both patients with

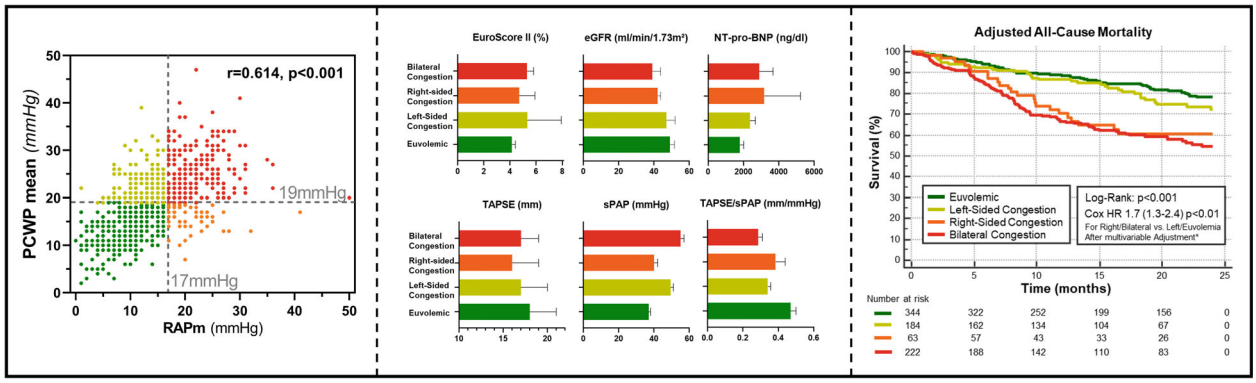


Figure 2 Definition, patients characteristics and outcome among congestion profiles. eGFR, estimated glomerular filtration rate; HR, hazard ratio; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; PCWP, pulmonary capillary wedge pressure; RAPm, mean right atrial pressure; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion. *Multivariable adjustment for eGFR, tricuspid regurgitation grade, cardiac index, pulmonary vascular resistance, TAPSE/sPAP.

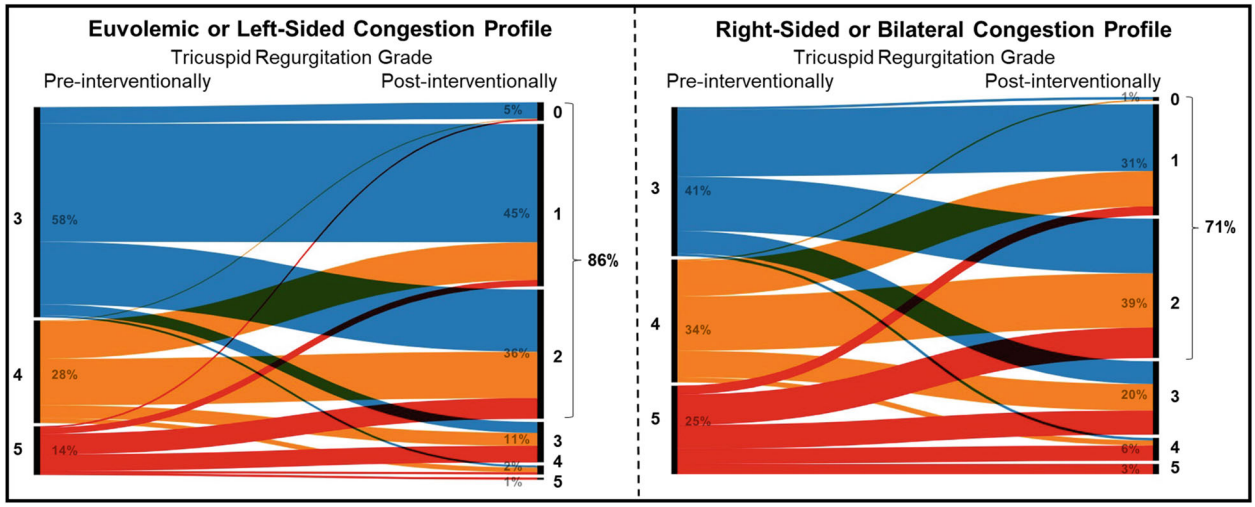


Figure 3 Changes in tricuspid regurgitation grades according to congestion patterns. Alluvial plot for changes in tricuspid regurgitation grade after transcatheter tricuspid valve interventions in patients with euvolaemic or left-sided congestion pattern.

euvolaemic or left-sided congestion pattern (HR 2.44, 95% CI 1.55–3.82, $p < 0.01$) and right-sided or bilateral congestion pattern (HR 1.82, 95% CI 1.24–2.65, $p < 0.01$).

Conversely, the assignment to congestion patterns was associated with a differential prognostic impact of the TAPSE/iPAPs ratio in the sense that a prognostic value was only evident in patients with a congestion pattern involving RAP elevations (*Figure 4*).

Discussion

This multicentre study represents the largest analysis to date concerning patients with TR who underwent TTVI and pre-interventional invasive RHC. Our investigation focused on evaluating the physiological and prognostic implications of invasively determined bilateral filling pressures, yielding the following key findings: (i) while both PCWP and RAP were associated with a higher risk of 2-year mortality, elevated RAP emerged as an independent predictor of outcomes following multivariable adjustments; (ii) congestion patterns, derived from combining information on PCWP and RAP represent a straightforward method to discern specific patient's physiology; and (iii) central venous congestion is linked to reduced procedural success and associated with differential prognostic implications of the TAPSE/iPAPs ratio after TTVI (*Graphical Abstract*).

Biventricular filling pressures have come a long way in diagnosing, classifying and managing patients with left-sided HF.[7,18,19] Only recently right HF has gained more widespread attention. Specifically, right HF in the presence of severe TR, a highly prevalent condition, is now acknowledged for its association with substantially elevated morbidity and mortality.[1,2] TTVI for TR has recently

Table 3 Cox regression for 2-year survival

	Univariable		Multivariable	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Patients characteristics				
Male sex, binary	1.57 (1.19–2.06)	0.001	–	–
EuroSCORE II, per %	1.02 (1.01–1.04)	0.008		
EuroSCORE ≥4.7%, binary	1.56 (1.18–2.07	0.002	–	–
Chronic lung disease, binary	1.42 (1.04–1.94)	0.030	–	–
NYHA class, per class	1.71 (1.31–2.24)	<0.001		
NYHA class ≥III, binary	1.95 (1.56–3.29)	0.013	–	–
Pleura effusion, binary[a]	2.05 (1.52–2.77)	<0.001		
Ascites, binary[a]	2.30 (1.65–3.21)	<0.001		
eGFR, per ml/min/1.73 m^2	0.98 (0.97–0.99)	<0.001		
eGFR <30 ml/min/1.73 m^2, binary	2.36 (1.74–3.19)	<0.001	2.02 (1.43–2.84)	<0.001
NT-proBNP, per ng/L	1.00 (1.00–1.01)	<0.001		
NT-proBNP ≥2000 ng/L, binary	1.96 (1.46–2.64)	<0.001	–	–
Echocardiography				
LV ejection fraction, per %	0.99 (0.98–0.99)	0.021		
LV ejection fraction <50%, binary	1.52 (1.40–2.03)	0.005	–	–
LVEDD, per mm	1.02 (1.01–1.04)	0.004		
LVEDD ≥49 mm, binary	1.36 (1.02–1.80)	0.035	–	–
RV basal diameter, mm	1.02 (1.01–1.04)	0.007		
RV basal diameter ≥45 mm, binary	1.35 (1.02–1.80)		–	–
TAPSE, per mm	0.95 (0.92–0.98)	0.001		
TAPSE <17 mm, binary	1.51 (1.14–1.99)	0.004		
RV FAC, per %	0.98 (0.96–0.99)	<0.001		
RV FAC <40%, binary	1.39 (1.04–1.85)	0.027		
Vena cava diameter, per mm	1.04 (1.02–1.06)	<0.001		
Vena cava diameter ≥25 mm, binary	1.66 (1.23–2.23)	<0.001	–	–
TV EROA, per cm^2	1.40 (1.03–1.89)	0.031		
TV EROA ≥0.5 cm^2, binary	1.06 (0.79–1.42)	0.68		
TR vena contracta, per mm	1.04 (1.01–1.07)	0.002		
TR vena contracta ≥10 mm, binary	1.31 (0.99–1.73)	0.058		
TR grade, per grade (3–5)	1.25 (1.06–1.48)	0.010	1.27 (1.04–1.55)	0.021
Invasive haemodynamics				
Cardiac index, per L/min/m^2	1.25 (1.07–1.46)	0.006		
Cardiac index >2.6 L/min/m^2, binary	1.52 (1.11–2.05)	0.009	1.50 (1.05–2.15)	0.027
PAP systolic (invasive), per mmHg	1.02 (1.01–1.03)	<0.001		
PAP systolic ≥50 mmHg, binary	1.64 (1.25–2.16)	<0.001		
PAP diastolic, per mmHg	1.05 (1.03–1.06)	<0.001		
PAP diastolic ≥18 mmHg, binary	1.99 (1.48–2.68)	<0.001		
PAP mean, per mmHg	1.04 (1.03–1.05)	<0.001		
PAP mean ≥30 mmHg, binary	1.80 (1.36–2.38)	<0.001		
PVR, per WU	1.12 (1.06–1.19)	<0.001		
PVR >4.5 WU, binary	1.70 (1.23–2.34)	0.001	1.70 (1.17–2.49)	0.006
TPG, per mmHg	1.04 (1.02–1.06)	<0.001		
TPG ≥12 mmHg, binary	1.60 (1.22–2.10)	<0.001		
PCWP, per mmHg	1.04 (1.02–1.06)	<0.001		
PCWP >19 mmHg, binary	1.68 (1.27–2.21)	<0.001		
RAP mean, per mmHg	1.06 (1.04–1.08)	<0.001		
RAP mean >17 mmHg, binary	2.33 (1.78–306)	<0.001		
TMFP, per mmHg	0.97 (0.95–0.99)	0.014		
TMFP <0 mmHg, binary	1.67 (1.24–2.25)	<0.001	–	–
RAP/PCWP, per ratio	2.13 (1.52–3.00)	<0.001		
RAP/PCWP <0.75, binary	1.59 (1.20–2.10)	0.001		
RV function				
TAPSE/iPAPs, per mm/mmHg	0.09 (0.03–0.24)	<0.001		
TAPSE/iPAPs <0.31 mm/mmHg, binary	2.08 (1.58–2.75)	<0.001	1.52 (1.09–2.13)	0.013
PAPi, per ratio	0.89 (0.81–0.98)	0.012		
PAPi <2.0, binary	1.48 (1.12–1.95)	0.006	–	–
Congestion patterns				
Right/bilateral congestion, binary	2.33 (1.78–3.06)	<0.001	1.74 (1.25–2.41)	<0.001

CI, confidence interval; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant orifice area; FAC, fractional area change; HR, hazard ratio; iPAPs, invasive systolic pulmonary artery pressure; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PAP, pulmonary artery pressure; PAPi, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; TMFP, transmural filling pressure; TPG, transpulmonary gradient; TR, tricuspid regurgitation; WU, Wood units.

Gray rows mark variables selected for multivariable stepwise regression based on statistical significance in univariable testing, minimal contextual or mathematical collinearity and representation of categories listed in the first column (for details please refer to the Methods section).

[a]Not considered for multivariable analysis because of missing data.

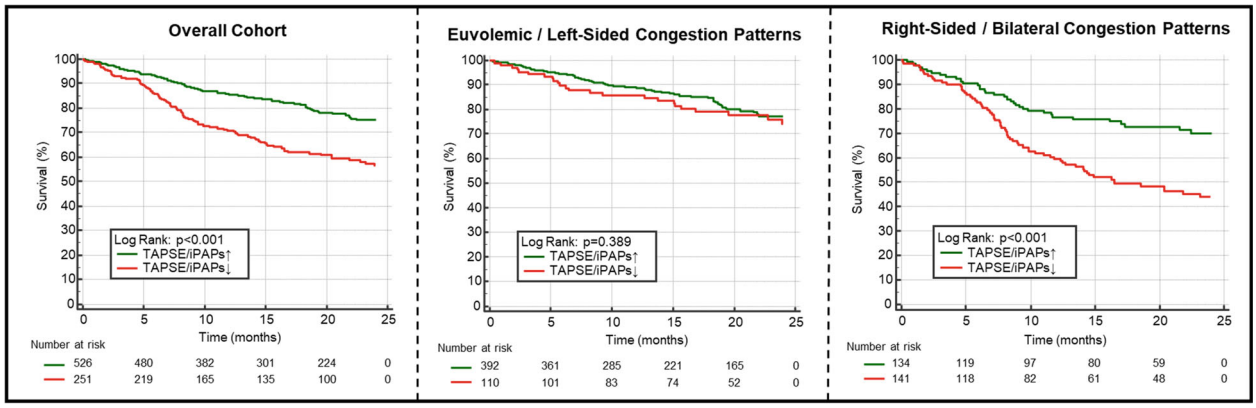


Figure 4 Survival according to tricuspid annular plane systolic excursion/invasive systolic pulmonary artery pressure (TAPSE/iPAPs) ratio and congestion patterns. TAPSE/iPAPs↑, ≥0.311 mm/mmHg; TAPSE/iPAPs↓, <0.311 mm/mmHg.

gained recognition in guidelines, in cases of prohibitive surgical risk, following evaluation by a Heart Team.[20] A large body of observational data suggests that successful TTVI improves clinical outcomes.[16,21,22] The TRILUMINATE Pivotal trial, the only randomized controlled study to date, demonstrated improvements in HF symptoms and quality of life with TTVI compared to medical therapy. However, it did not reveal any significant impact on survival or HF hospitalizations.[23]

In an effort to enhance patient selection for the procedure and identify criteria for enriching trial populations, various predictors for adverse outcomes have been pinpointed. Notably, the procedure's effectiveness in reducing TR has consistently correlated with improved survival.[3,24,25] Additionally, haemodynamic parameters, especially when invasively assessed, have proven to offer valuable prognostic information. This holds true, particularly for PA pressures, their pre-capillary component, and their integration with RV function, termed RV/PA coupling.[8,11,14,26,27]

Somewhat surprisingly, despite the intricate interplay of biventricular filling pressures with pathological RV loading, pre-interventional levels of RAP or PCWP had not been linked to outcomes in patients undergoing TTVI until now.[8] Speculation arises that this might be attributed to substantial changes in RV loading conditions with TTVI, diminishing the predictive value of pre-interventional assessments. However, the impact of TTVI on PCWP and RAP varies. Mean RAP, on average, is only reduced by about 15%, and a significant proportion of patients do not experience reductions in RAP despite effective TR alleviation.[8] Our recent observations indicate that cardiac output has a U-shaped relationship with mortality and patients with a hypercirculatory TR phenotype (cardiac index >2.6 L/min/m^2) derive the least benefit from TTVI in terms of RAP reduction and exhibit the poorest outcomes. The same is true for patients with elevated levels of stressed blood volumes prior to TTVI.[9,10] It is noteworthy that both phenotypes are characterized by elevated RAP levels at baseline. Changes in PCWP after TTVI might also vary as improvements in ventricular interdependence after reducing RV volume overload may potentially lead to a reduction in PCWP, while enhanced RV forward flow and consequently enhanced LV filling might counteract this mechanism, leading to an increase in PCWP.[5]

For the first time, we now demonstrate that both pre-interventional RAP and PCWP are associated with an impaired prognosis after TTVI. The determined cut-offs for optimal prognosis prediction were relatively high, at 17 and 19 mmHg, respectively, underscoring the overall elevated pressure levels in our cohort of patients with TR-related right HF.

While the presence of right-sided congestion (i.e. elevated central venous pressures) ultimately dictated the association with prognosis, it was the amalgamation of RAP and PCWP in the form of congestion patterns that yielded intriguing physiological insights. Euvolaemic patients exhibited a favourable outcome, characterized by the best biventricular function, the lowest PA pressures, and the best RV/PA coupling as indicated by the TAPSE/iPAPs ratio. Patients with left-sided congestion demonstrated a rather favourable outcome despite high levels of PCWP, an impaired RV/PA coupling, but overall the lowest TR grades and preserved RV dimensions.

The most interesting group comprised patients with a right-sided congestion pattern. These patients exhibited the worst biventricular function and right heart chamber dilatation, although the left-sided chamber dimensions were preserved. Importantly, this group demonstrated the most severe TR grades and relatively low PA pressures. Therefore, despite having the worst RV function and the lowest PAPi among all groups, the TAPSE/iPAPs ratios remained preserved. These observations collectively suggest that these patients, in particular, suffer from LV underfilling due to TR related severe RV volume overload and reduced RV forward stroke volume at rest. This is further supported by an unphysiological, negative TMFP and high RAP/PCWP ratios and may be exacerbated during exercise.[15,28,29]

Patients with bilateral congestion had the highest comorbidity burden, a relatively high number of patients with impaired LV function, relatively preserved RV function, but the highest PA pressures, and consequently the lowest TAPSE/iPAPs ratios, indicating the worst RV/PA coupling. Importantly, this group might comprise patients with elevated PCWP due to primary left-sided HF and

patients with advanced isolated TR with impaired ventricular interdependence. Whether discerning this distinction can further aid in predicting treatment responses to TTVI remains to be demonstrated. We have previously suggested that levels of stressed blood volumes and central venous congestion gradually increase from euvolaemia to left-sided to right-sided and bilateral congestion, which is indirectly supported in this study by a gradual decrease in haemoglobin levels and an increase in vena cava diameters across these groups.[10]

As such, we argue that straightforward simultaneous determination of PCWP and RAP constitutes a powerful tool for gaining essential insights into assessing individual patient physiology. Beyond aiding in treatment personalization, it could also serve as a readout for complex-to-assess parameters, such as stressed volume. The latter might potentially serve as adjunctive treatment target in patients with severe TR, provided treatments that have been suggested to impact stressed blood volume, like diuretics, sodium–glucose cotransporter 2 inhibitors, nitric oxide donors, sympathetic nerve modulation, milrinone or levosimendan, might prove beneficial in this vulnerable patient cohort.[30]

Furthermore, the assessment enabled effective prognostication, proving its independent value in a model alongside well-established prognostic factors such as renal dysfunction, pre-capillary component of PA pressures, TAPSE/iPAPs ratio, relative high cardiac output, TR grade, and procedural success. Notably, right-sided and bilateral congestion patterns carried the worst prognosis, highlighting that elevated RAP levels or central venous congestion indeed play a pivotal role in dictating prognosis, consistent with prior findings.[7,10]

Additionally, we demonstrate that TAPSE/iPAPs ratios identify heterogeneous patient groups, and varying RAP levels (and as such RV preload) or baseline risk are associated with various prognostic implications of the TAPSE/iPAPs ratio. This observation might help explain the consistent yet quantitatively only moderate prognostic value of TAPSE/PAPs ratios observed in prior studies and the limitations of the ratio to truly inform on RV/PA coupling.[26]

Further reflecting on prognosis, it is essential to acknowledge the higher mortality rates observed in our study compared to the TRILUMINATE trial.[23] While this discrepancy may be partly attributed to the real-world, less controlled setting of our present registry, it could also be linked to more advanced LV diseases in our study, evidenced by twice the incidence of patients with a LV ejection fraction <50%. The elevated incidences of LV impairment in the right-sided and bilateral congestion groups, which showed the highest mortality, further substantiate the concept of high event rates in the setting of a compromised left ventricle. Additionally, in comparison to the TRILUMINATE cohort, our patients exhibited higher PCWP and RAP levels (19 vs. 15 mmHg and 15 vs. 12 mmHg, respectively). Considering the significant prognostic implications of elevated RAP levels before and after the procedure, as demonstrated in this and prior studies, the disparity in outcomes could be attributed to better pre-procedural optimization of RAP levels and central venous congestion in the randomized trial.[9,10] Whether aggressively targeting these parameters with additional measures in the peri-interventional setting can indeed improve outcomes after TTVI will need to be determined in dedicated clinical trials in the future.

Limitations

While the current study is the largest invasive haemodynamic study in the setting of TTVI to date, based on a large, international multicentre registry, entailing real-world patients, the data were site-reported without core-lab adjudication and universal availability. The timing and conduct of invasive haemodynamic measurement and procedures were carried out according to the operator's discretion and were not standardized across centres. Cardiac output was measured using the indirect Fick method according to local practice, which might bias the results due to assumptions underlying the methods for estimating oxygen uptake. It has been shown that the indirect Fick method can provide cardiac output estimates with reasonable accuracy at a cohort level; however, the wide limits of agreement compared to the direct Fick method could significantly impact diagnostic and therapeutic decisions at an individual patient level. Therefore, we advocate for a comprehensive haemodynamic assessment that takes into account multiple variables, including cardiac output and the method used for its assessment. While we could establish central venous congestion as an important determinant of outcomes alongside several prognostic factors in patients undergoing TTVI in prior studies, the lack of a control group precludes conclusions on causality and futility.

Conclusion

In conclusion, we strongly advocate for comprehensive invasive haemodynamic characterization before TTVI to enhance the understanding of patients' physiology and assess prognosis. The current findings underscore that a simple, straightforward RHC assessment may offer a practical and scalable alternative to more sophisticated yet cumbersome approaches for patient phenotyping, such as artificial intelligence solutions, pending the implementation of practical clinical interfaces. Moreover, central venous congestion and RAP might serve as adjunctive treatment targets in the context of TTVI, which needs to be further substantiated in the future.

Funding

Dr. Rommel is supported by a research grant from the Else-Kroener-Fresenius-Foundation, Bad Homburg, Germany.

Conflict of interest: L.S. received speaker honoraria from Edwards Lifesciences. All other authors have nothing to disclose.

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