Association of Tricuspid Regurgitation With Outcome in Acute Heart Failure

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BACKGROUND: Tricuspid regurgitation (TR) is common in chronic heart failure (HF) and is associated with negative prognosis. However, evidence on prognostic implications of TR in acute HF is lacking. We sought to investigate the association between TR and mortality and the interaction with pulmonary hypertension (PH) in patients admitted for acute HF.

METHODS: We enrolled 1176 consecutive patients with a primary diagnosis of acute HF and with available noninvasive estimation of TR and pulmonary arterial systolic pressure.

RESULTS: Moderate-severe TR was present in 352 patients (29.9%) and was associated with older age and more comorbidities. The prevalence of PH (ie, pulmonary arterial systolic pressure >40 mm Hg), right ventricular dysfunction, and mitral regurgitation was higher in moderate-severe TR. At 1 year, 184 (15.6%) patients died. Moderate-severe TR was associated with higher 1-year mortality risk after adjustment for other echocardiographic parameters (pulmonary arterial systolic pressure, left ventricle ejection fraction, right ventricular dysfunction, mitral regurgitation, left and right atrial indexed volumes; hazard ratio, 1.718; P=0.009), and the association with outcome was maintained when clinical variables (eg, natriuretic peptides, serum creatinine and urea, systolic blood pressure, atrial fibrillation) were added to the multivariable model (hazard ratio, 1.761; P=0.024). The association between moderate-severe TR and outcome was consistent in patients with versus without PH, with versus without right ventricular dysfunction, and with versus without left ventricle ejection fraction <50%. Patients with coexistent moderate-severe TR and PH had 3-fold higher 1-year mortality risk compared with patients with no TR or PH (hazard ratio, 3.024; P<0.001).

CONCLUSIONS: In patients hospitalized for acute HF, the severity of TR is associated with 1-year survival, regardless of the presence of PH. The coexistence of moderate-severe TR and estimated PH was associated with a further increase in mortality risk. Our data must be interpreted in the context of potential underestimation of pulmonary arterial systolic pressure in patients with severe TR.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: heart failure ■ pulmonary hypertension ■ tricuspid valve ■ tricuspid valve insufficiency ■ ventricular dysfunction

Moderate or severe tricuspid regurgitation (TR) was found to have a prevalence of 0.55% in community setting,[1] increasing in elderly, female sex, and heart failure (HF).[2] In most of the cases, the cause of TR is secondary to left-sided heart disease, pulmonary hypertension (PH) or right ventricular dysfunction (RVD), whereas primary TR, due to structural valvular abnormalities, is rare.[3]

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CLINICAL PERSPECTIVE

Secondary tricuspid regurgitation (TR) is associated with poor prognosis in chronic heart failure (HF), but the role in acute HF is more controversial. In this series of patients admitted for acute de novo or acute decompensated chronic HF, moderate or severe secondary TR was highly prevalent and associated with increased risk of mortality, independently from right ventricle impairment and pulmonary hypertension. Furthermore, the combination of moderate-severe TR and pulmonary hypertension conferred a further incremental mortality risk. Previous studies did not clearly demonstrate the incremental mortality associated with significant TR in the overall acute HF population. To the best of our knowledge, this is the first study demonstrating the strong and consistent association between TR severity and short- and long-term survival in acute HF, and the detrimental interaction of pulmonary hypertension and TR on prognosis. The mechanisms underlying secondary TR in the acute setting, the response to medical interventions for the treatment of acute HF, and the identification of the subset of patients who can potentially benefit from direct strategies for the correction of TR deserve dedicated studies which can inform the future management of patients admitted for acute HF.

Nonstandard Abbreviations and Acronyms

AHF	acute heart failure
HF	heart failure
HR	hazard ratio
LA	left atrial
LV	left ventricular
LVEF	left ventricular ejection fraction
MR	mitral regurgitation
NPs	natriuretic peptides
PASP	pulmonary arterial systolic pressure
PH	pulmonary hypertension
RA	right atrial
RV	right ventricular
RVD	right ventricular dysfunction
TR	tricuspid regurgitation

Secondary TR has long been considered a bystander in HF, without prognostic implications and in general reversible after the correction of the primary disorder.[4] In the last years, several large studies and meta-analyses on chronic HF confirmed that TR contributes to increased morbidity and mortality, with increasing risk observed for more severe TR grades.[5–7] In the setting of acute HF (AHF), the evidence on the prognostic implications of secondary TR is poor and more controversial.[8,9]

In this study, we sought to assess the prevalence and the characteristics associated with secondary TR and to explore the association of secondary TR with the mortality/morbidity risk and the interaction with PH in a large retrospective cohort of patients admitted for AHF.

METHODS

Study Design and Data Collection

In this retrospective longitudinal study, we analyzed consecutive patients >18 years old hospitalized with a primary diagnosis of AHF in our Institution (ASUGI, Azienda Sanitaria Universitaria Giuliano-Isontina and University Hospital of Trieste, Italy) between November 22, 2010 and November 29, 2020, and with available echocardiographic assessment of TR and pulmonary arterial systolic pressure (PASP). The study population was derived from the electronic records stored in the institutional data warehouse and extracted through queries based on a coded diagnosis of AHF. Extracted cases were retrospectively reviewed by selected investigators (D.C., M.P., S.C., D.B., G.S., J.R., D.S.), and data of interest, including outcome information, were collected in a dedicated electronic registry after full anonymization. All the data used for the analysis are available in anonymized format upon reasonable request by contacting the corresponding author.

AHF diagnosis was based on the attending Cardiologist clinical judgment. All patients were managed and treated as per local clinical practice, in accordance with European Society of Cardiology HF guidelines.[10] Primary TR cases were excluded. Patients admitted with AHF secondary to acute myocardial infarction, pulmonary embolism, type I pulmonary arterial hypertension, congenital heart disease, or endocarditis were also excluded from the study.

The study was approved by the institutional review committee, and the subjects gave informed consent.

Echocardiographic Examination

Echocardiograms were recorded on digital media storage devices at the echocardiographic core laboratory of our Institution and analyzed offline, according to current international guidelines (see Appendix in the Supplemental Material).[11–14] Data from the first echocardiographic assessment, generally performed within 24 hours from admission by institutional protocol, were collected.

Preserved systolic function was defined as left ventricular ejection fraction (LVEF) ≥50%. RVD was defined as right ventricular fractional area change <35% or tricuspid annular plane excursion <17 mm. We evaluated TR severity using quantitative (PISA) or semi-quantitative (vena contracta width) methods (both, when feasible), while qualitative approach was used mainly as a support for quantitative/semi-quantitative ones[14] (see Appendix in the Supplemental Material for complete description). In the rare cases of discordance between PISA and vena contracta width severity grade, the more severe estimation was used, to avoid underestimation of the severity of TR. According to the severity of TR, patients were divided in 2 groups: trivial-mild TR versus moderate-severe TR (Figure 1).

TR peak velocity was measured with continuous wave Doppler, and TR gradient was calculated by the modified

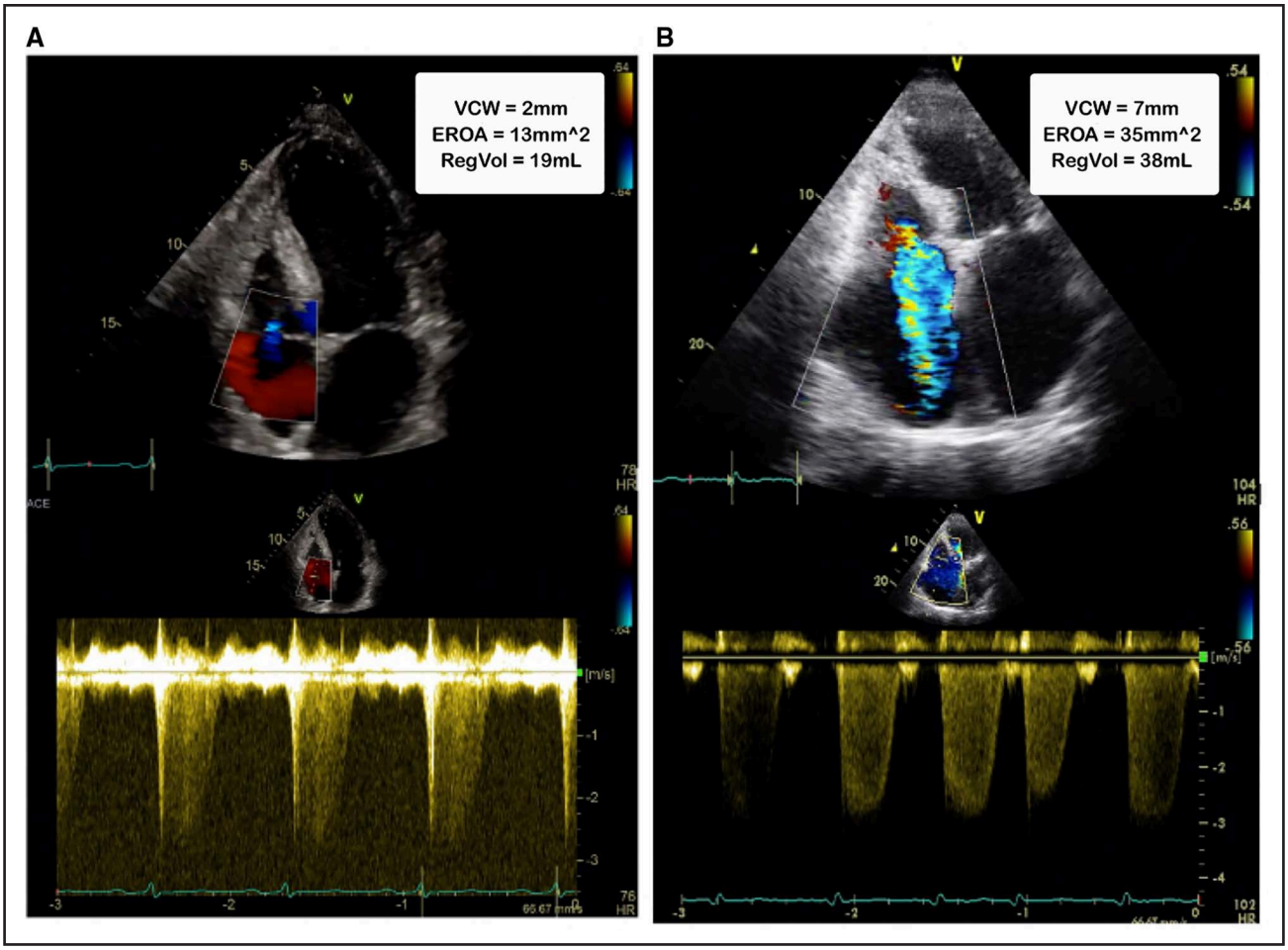

Figure 1. Echocardiographic definition of the severity of tricuspid regurgitation (TR).
Echocardiographic visualization of TR with EchoColorDoppler and with continuous wave Doppler imaging. **A** and **B**, Respectively an example of trivial-mild TR and moderate-severe TR. EROA indicates effective regurgitant orifice area; RegVol, regurgitant volume; and VCW, vena contracta width.

Bernoulli equation.[15] PASP was estimated by the sum of TR gradient and estimated right atrial pressure, calculated by the inferior vena cava size and inspiratory variation.[15] We acknowledged the possibility of PASP underestimation in patients with severe TR.[16] PH was defined as PASP >40 mm Hg, since in previous studies this cutoff was found to have a fairly high sensitivity and specificity.[17,18] To explore the incremental prognostic correlations of the combination of moderate-severe TR and PH, patients were also divided according to the presence of (1) both moderate-severe TR and PASP >40 mm Hg, (2) either moderate-severe TR or PASP >40 mm Hg, (3) trivial-mild TR and PASP ≤40 mm Hg.

Study Outcomes

The primary end point was 1-year all-cause mortality. Secondary end points were 5-years all-cause mortality, and the composite of 1-year all-cause mortality and time to first HF re-hospitalization. Information regarding the outcome was obtained from official reports drawn up by hospitals, direct contact with patients, their families or general practitioners, queries of regional health-care data warehouse and registers of death of the municipalities of residence.

Statistical Analysis

Continuous variables were reported as mean (±SD) or median (interquartile range) and compared by analysis of variancor Mann-Whitney *U* test as appropriate, whereas categorical variables were reported as counts (percentages) and compared by χ^2 test. Cumulative event-free survival estimates were plotted using the Kaplan-Meier estimator. Differences between survival curves were tested with the log-rank test. Univariable and multivariable Cox regression were fitted to identify the association between moderate-severe TR and outcomes. Two different multivariable models were tested; in the first one, only echocardiographic variables were included (ie, TR severity, PASP as a continuous variable, presence of RVD, LVEF as a continuous variable, MR severity, right atrial and left atrial indexed volumes; model 1), whereas the second one was generated with the addition of clinical variables (NPs [natriuretic peptides] above the median, serum creatinine, serum urea, systolic blood pressure, diabetes, ischemic cause of HF, peripheral artery disease and atrial fibrillation; model 2). To explore the association between moderate-severe TR and the primary end point in specific subgroups (ie, PH, RVD, and LVEF ≥50% versus <50%), an interaction term between each subgroup and TR

severity was included in the multivariable Cox regression. The presence of a statistically significant interaction was tested by the Wald test. A 2-tailed *P* value of <0.05 was considered statistically significant. IBM SPSS Statistics software (IBM Corp, Released 2016, IBM SPSS Statistics for Windows, Version 26.0,s Armonk, NY) and Stata version 14.2 (Stata Corp, College Station, TX) were used for analysis, GraphPad Prism, Version 7 (GraphPad Software, La Jolla, CA) was used for illustrations.

RESULTS

Study Population and Patient Characteristics

Among 1650 patients with AHF admitted to our institution during the study period potentially eligible for the study, 1176 were included whereas the remaining 474 were excluded owing to lacking estimation of TR severity or PASP. No statistically significant differences in the outcomes of interest were found between the final study cohort and the excluded patients, as shown in Table S1. Table 1 summarizes the baseline characteristics of the study population. Mean age was 70±12 years, 66% of patients were males, 52% had a history of chronic HF, 39.5% had ischemic heart disease, and 33% chronic kidney disease.

Patients with moderate-severe TR were 352 (29.9%, 260 patients with moderate TR and 92 with severe TR). The remaining 824 patients had trivial-mild TR (70.1%, 50 patients with trivial TR and 774 with mild TR). The main characteristics of patients according to TR severity are shown in Table 1. Patients with moderate-severe TR were older, less frequently had de-novo HF, showed higher prevalence of chronic kidney disease, and accordingly, higher creatinine at admission. They also had higher values of NPs (NPs above the median in 60.0% versus 45.8% of patients with trivial-mild TR, *P*<0.001). Prevalence of female sex was not statistically different between the 2 groups. Figure 2 shows the distribution of the main echocardiographic characteristics according to TR severity. Compared with patients with trivial-mild TR, those with moderate-severe TR had higher PASP (53.30±15.74 versus 42.18±12.74 mm Hg, *P*<0.001; PASP >40 mm Hg in 80.4% versus 54.7%, *P*<0.001), more frequent RVD (59.9% versus 44.1%, *P*<0.001) and moderate-severe MR (68.5% versus 46.1%, *P*<0.001), larger left atrial (71±37 versus 58±24 mL/m^2) and right atrial (50±29 versus 35±18 mL/m^2) volumes. LVEF was not different in the 2 groups.

Association Between TR Severity and Outcome

During the first 12 months after discharge, 184 patients died (15.6%), 104 (12.6%) among patients with trivial-mild TR and 80 (22.7%) among patients with moderate-severe TR. At Kaplan-Meier analysis, patients with moderate-severe TR showed lower survival compared with patients with trivial-mild TR (*P*<0.001, Figure 3A).

As shown in Table 2, at multivariable analysis, moderate-severe TR was significantly associated with higher risk of 1-year all-cause mortality after adjustment for echocardiographic covariates (model 1) with hazard ratio (HR), 1.718 (95% CI, 1.147–2.573; *P*=0.009). Moreover, moderate-severe TR remained significantly associated with increased risk of 1-year all-cause death after additional adjustment for clinical variables (model 2) with HR, 1.761 (95% CI, 1.078–2.879; *P*=0.024).

The association between TR severity and 1-year mortality was consistent across different subgroups, as shown in Figure 4. Specifically, no significant interactions were observed for the association with the primary outcome between TR severity and PH (PASP >40 mm Hg versus PASP ≤40 mm Hg), RVD (presence versus absence), and LVEF (LVEF <50% versus LVEF ≥50%).

Survival curves assessing the secondary study outcomes demonstrated a lower 5-years survival and a lower 1-year survival free from HF hospitalization in patients with moderate-severe TR compared with patients with trivial-mild TR (Figures 3B and 3C). As reported in Tables S2 and S3, multivariable analysis showed a significant association between moderate-severe TR and increased risk of 5-years mortality in both model 1 (HR, 1.577 [95% CI, 1.227–2.027]; *P*<0.001) and model 2 (HR, 1.363 [95% CI, 1.020–1.820]; *P*=0.036), whereas for the composite outcome of 1-year mortality/first HF hospitalization, moderate-severe TR showed an association with an increased risk after adjustment for echocardiographic parameters (HR, 1.323 [95% CI, 1.002–1.746]; *P*=0.048), but not when adjusted also for clinical variables (HR, 1.218 [95% CI, 0.882–1.683]; *P*=0.232).

Incremental 1-Year Mortality Risk of the Combination of Moderate-Severe TR and Pulmonary Hypertension

In the study cohort, 283 patients (24.1%) had both moderate-severe TR and PASP>40 mm Hg, 520 patients (44.2%) had either moderate-severe TR or PASP >40 mm Hg, and the remaining 373 patients (31.7%) showed trivial or mild TR and PASP ≤40 mm Hg.

Kaplan-Meier survival curves showed a clear divergence between the 3 groups, with the highest 1-year mortality in patients with concomitant moderate-severe TR and PASP >40 mm Hg (Figure 5). After adjustment for LVEF, RVD, moderate-severe MR, left atrial and right atrial indexed volume (model 1), the combination of moderate-severe TR and PASP >40 mm Hg was associated with a 3-fold higher risk of 1-year all-cause death (HR, 3.024 [95% CI, 1.735–5.271]; *P*<0.001) compared with patients with trivial-mild TR and PASP ≤40 mm Hg, and a 80% higher risk compared with the presence of either moderate-severe TR or PASP >40 mm Hg (HR, 1.795 [95% CI, 1.195–2.703]; *P*=0.005; Table 3).

Table 1. Patient Characteristics of the Entire Study Population and Divided According to the TR Grade (Trivial-Mild TR vs Moderate-Severe TR)

	Missing rate (N, % of 1176)	Study population (N=1176)	Trivial or mild TR (N=824; 70.1%)	Moderate or severe TR (N=352; 29.9%)	*P* value
Demographics, past medical history, therapy before admission					
Males	0 (0.0%)	773 (65.7%)	555 (67.4%)	218 (61.9%)	0.073
Age, y	0 (0.0%)	70±12	69±12	73±12	<0.001*
BMI, kg/m^2	4 (0.3%)	27±5	27±5	26±4	<0.001*
Worsening HF	0 (0.0%)	614 (52.2%)	407 (49.4%)	207 (58.8%)	0.003*
Ischemic cause of HF	0 (0.0%)	465 (39.5%)	328 (39.8%)	137 (38.9%)	0.776
Diabetes	0 (0.0%)	414 (35.2%)	289 (35.1%)	125 (35.5%)	0.885
Previous myocardial infarction	0 (0.0%)	253 (21.5%)	168 (20.4%)	85 (24.1%)	0.151
Peripheral artery disease	0 (0.0%)	254 (21.6%)	174 (21.1%)	80 (22.7%)	0.539
Stroke/TIA	0 (0.0%)	105 (8.9%)	66 (8.0%)	39 (11.1%)	0.091
CKD	0 (0.0%)	385 (32.7%)	240 (29.1%)	145 (41.2%)	<0.001*
COPD	0 (0.0%)	180 (15.3%)	121 (14.7%)	59 (16.8%)	0.365
ACE inhibitor/ARB/ARNI	14 (1.2%)	615 (52.9%)	428 (52.6%)	187 (53.7%)	0.718
Beta-blockers	6 (0.5%)	541 (46.2%)	365 (44.6%)	176 (50.1%)	0.080
MRA	6 (0.5%)	173 (14.8%)	106 (12.9%)	67 (19.1%)	0.007*
Furosemide	6 (0.5%)	555 (47.4%)	342 (41.8%)	213 (60.7%)	<0.001*
Clinical characteristics and in-hospital treatments					
Systolic blood pressure, mm Hg	60 (5.1%)	132±28	134±29	127±24	<0.001*
Heart rate, bpm	59 (5.0%)	93±29	95±29	90±29	0.005*
Atrial fibrillation	0 (0.0%)	470 (40.0%)	309 (37.5%)	161 (45.7%)	0.008*
Vasodilators	0 (0.0%)	247 (21.0%)	184 (22.3%)	63 (17.9%)	0.087
Inotropes or vasopressors	0 (0.0%)	289 (24.6%)	179 (21.7%)	110 (31.3%)	0.001*
Laboratory findings					
Creatinine, mg/dL	10 (0.9%)	1.13 (0.91–1.49)	1.11 (0.88–1.41)	1.22 (0.97–1.64)	<0.001*
Urea, mg/dL	68 (5.8%)	49 (36–69)	46 (34–64)	56 (41–80)	<0.001*
Glycemia, mg/dL	22 (1.9%)	121 (103–159)	122 (103–165)	120 (101–151)	0.082
NA^+, mEq/L	25 (2.1%)	138±4	138±4	137±4	<0.001*
K^+, mEq/L	33 (2.8%)	4.04±0.56	4.03±0.55	4.05±0.58	0.611
Hemoglobin, g/dL	14 (1.2%)	12.8±2.1	13.0±2.1	12.5±2.1	0.001*
C-reactive protein, mg/dL	150 (12.8%)	8.4 (3.3–20.5)	8.7 (3.3–20.9)	7.6 (3.0–19.5)	0.114
BNP, pg/mL	262 (22.3%)	839 (450–1505)	730 (405–1365)	1107 (584–1837)	<0.001*
NT-proBNP, pg/mL	1056 (89.8%)	4858 (2585–11342)	4323 (2582–10828)	5528 (2583–13706)	0.462
High NPs (BNP or NT-proBNP > median)†	147 (12.5%)	515 (50.0%)	329 (45.8%)	186 (60.0%)	<0.001*
Albumin, g/dL	199 (16.9%)	3.53±0.47	3.54±0.48	3.50±0.43	0.340
Echocardiography					
LV EDV index, mL/m^2	95 (8.1%)	78±33	79±33	76±34	0.183
LV EF, %	61 (5.2%)	37±16	37±15	37±17	0.607
LV EF ≥50%	8 (0.7%)	268 (22.9%)	175 (21.4%)	93 (26.5%)	0.059
RV dysfunction	18 (1.5%)	566 (48.9%)	358 (44.1%)	208 (59.9%)	<0.001*
MR, moderate-severe	29 (2.5%)	606 (52.8%)	371 (46.1%)	235 (68.5%)	<0.001*
TR, moderate-severe	0 (0.0%)	352 (29.9%)	//	//	//
Restrictive pattern	0 (0.0%)	411 (34.9%)	274 (33.3%)	137 (38.9%)	0.062
E/E′	475 (40.4%)	19 (14–26)	19 (14–25)	20 (14–27)	0.204

(*Continued*)

Table 1. Continued

	Missing rate (N, % of 1176)	Study population (N=1176)	Trivial or mild TR (N=824; 70.1%)	Moderate or severe TR (N=352; 29.9%)	*P* value
PASP, mm Hg	0 (0.0%)	45.51±14.62	42.18±12.74	53.30±15.74	<0.001*
PASP >40 mm Hg (PH)	0 (0.0%)	734 (62.4%)	451 (54.7%)	283 (80.4%)	<0.001*
LA ESV index, mL/m^2	71 (6.0%)	62±29	58±24	71±37	<0.001*
RA ESV index, mL/m^2	117 (9.9%)	40±22	35±18	50±29	<0.001*

Data are presented as n (%), mean±SD or median (Q25–Q75). *P value* were obtained by ANOVA or Mann-Whitney *U* test (as appropriate) for comparation of continuous variables; whereas categorical variables were compared by χ^2 test. ACE indicates angiotensin converting enzyme; ARB, angiotensin II receptor blockers; ARNi, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; BNP, brain natriuretic peptide; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; LA ESV, left atrial end-systolic volume; LV EDV, left ventricular end-diastolic volume; LV EF, left ventricular ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonists; NPs, natriuretic peptides; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PASP, pulmonary artery systolic pressure; RA ESV, right atrial end-systolic volume; RV, right ventricle; TIA, transient ischemic attack; and TR, tricuspid regurgitation.

*P<0.05

†Median value for BNP=839pg/mL, median value for NT-proBNP=4858pg/mL.

DISCUSSION

TR has become an important focus of research in HF and several studies demonstrated a negative association with outcome in chronic HF.[2,5-7,19,20] However, in AHF data are less conclusive and more controversial, with TR demonstrating an association with prognosis only in specific subgroups of patients.[8,9] Therefore, we decided to specifically focus on TR in a relatively large real-world cohort of patients with AHF. The main findings are that (1) moderate-severe secondary TR is frequent (ie, about 30%) in patients admitted with AHF, and it is associated with clinical and echocardiographic markers of worse clinical status; (2) moderate-severe TR is associated with higher risk of 1-year mortality independently from other main echocardiographic and clinical/laboratory variables; (3) the association between moderate-severe TR and mortality risk is consistent across different subgroups of patients; and (4) the combination of moderate-severe TR and PH conferred an incremental risk of death in patients with AHF.

Characteristics of Patients With Moderate-Severe TR

Although secondary TR is highly prevalent in chronic HF,[2] less data is available in cohorts of patients with AHF or acutely decompensated HF. In our study, the observed prevalence of moderate-severe TR was 30%, in line with previous reports.[8,9] Patients with moderate-severe TR were older, with more comorbidities and more severe HF compared with patients with trivial-mild TR. Renal function was worse in patients with moderate-severe TR, and this is probably partially explained by the effect of the venous congestion worsened by TR on renal function since, as previously reported, central venous congestion is the major determinant of acute renal failure in patients with AHF.[21] Estimated values of pulmonary pressures were also higher in patients with moderate-severe TR, in line with the role of PH as a major contributor to RV overload and, consequently, to TR.[22,23] Of note, distribution of reduced LVEF was not different between patients with moderate-severe versus trivial-mild TR.

Association Between Moderate-Severe TR and Outcomes in AHF

In the present study, moderate-severe TR was associated with an increased risk of 1-year mortality that was independent from several echocardiographic and clinical variables, and in particular, it was not influenced by the adjustment for PASP. We hypothesized that secondary TR in AHF is not just a marker of congestion or merely the consequence of RV remodeling or increased RV afterload, but it might worsen the hemodynamic status towards progressive instability and, finally overt acute decompensation. In a previous study on secondary TR in AHF, the association between TR and prognosis was confirmed only in patients with elevated pulmonary pressures.[9] However, the loss of right ventriculo-arterial coupling can affect the linear relation between pulmonary pressure and outcome and it is a known strong prognostic marker of negative outcome.[24,25] In this condition, the adverse remodeling of the right heart chambers can have immediate effect on the severity of TR which could have an impact on prognosis that is not directly related to the severity of PH. Future studies should explore the dynamic trends of TR in response to diuretics and other medical treatments and the association of improved TR with prognosis. Moreover, atrial phenotype of TR has been recently recognized in literature.[26] The distinction of atrial versus ventricular cause of TR might have important implications in the clinical and prognostic characterization of TR and deserves future dedicated studies in AHF. In our cohort, the identification of atrial forms was limited to the more recent patients, after the recognition of this

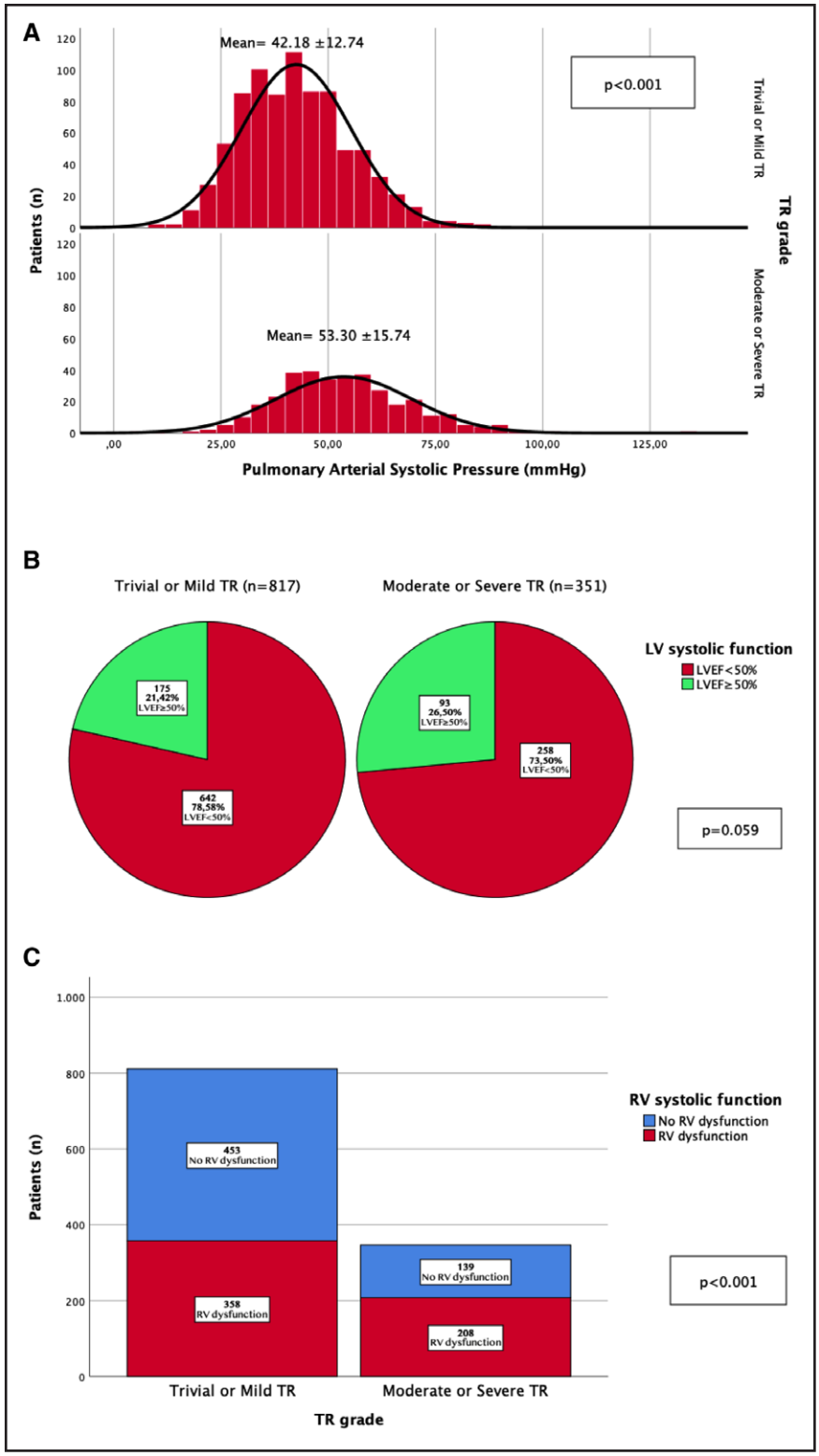

Figure 2. Echocardiographic characteristics according to the severity of tricuspid regurgitation (TR).
Distribution of pulmonary arterial systolic pressure (PASP, **A**), prevalence of left ventricle (LV) systolic dysfunction (**B**), and prevalence of right ventricle (RV) systolic dysfunction (**C**) in patients with trivial-mild TR vs moderate-severe TR. Pulmonary hypertension and RV dysfunction were more frequent in patients with moderate-severe TR compared with patients with trivial-mild TR. LVEF indicates left ventricle ejection fraction. *P* values in this picture were obtained by ANOVA (for PASP) and by χ^2 test (for RV dysfunction and LV systolic function).

specific entity.[26] However, in multivariable models we included atrial volumes and atrial fibrillation, which are major determinants of atrial TR, to minimize the potential confounding effect of TR phenotype.

In the secondary analysis, the association of moderate-severe TR with the risk of mortality was confirmed at 5-years follow-up, with a larger separation of the survival curves after the first year, that might suggest the utility in the long-term prognostic stratification of AHF. The lacking association in the clinical-echocardiographic model for the composite 1-year mortality/HF hospitalization end point suggested a stronger

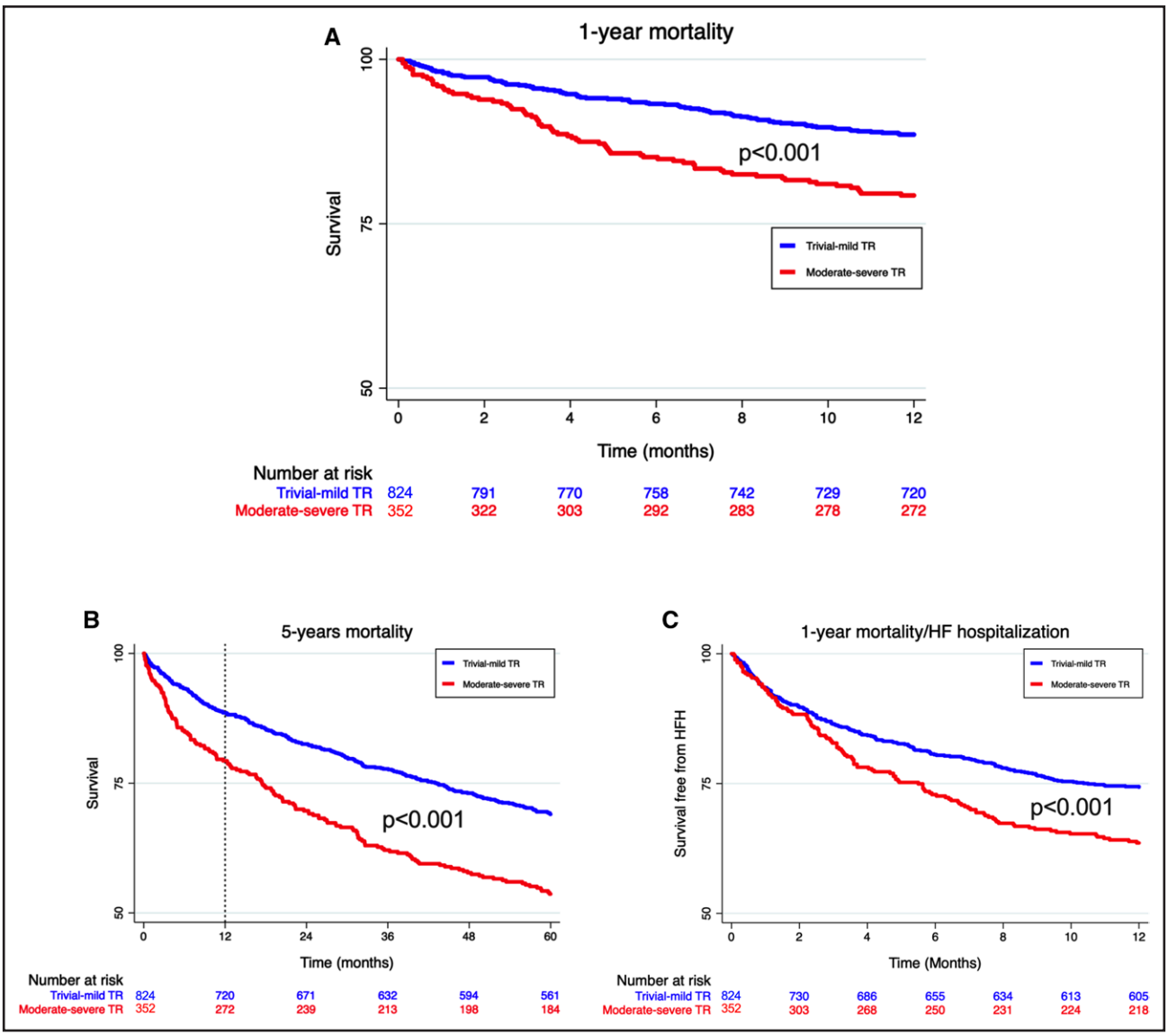

Figure 3. Kaplan-Meier survival curves for primary and secondary end points, according to the severity of tricuspid regurgitation (TR). Among 1176 patients admitted for acute heart failure (AHF), 352 (29.9%) had moderate-severe TR. Patients with moderate-severe TR were more likely to die in the first year of follow-up (**A**) and in the first 5 years of follow-up (**B**); in this group of patients, the combined risk of 1-year death or HF re-hospitalization was also higher (**C**). *P* values were obtained by Log-rank test.

influence of clinical variables on the HF hospitalization component of the end point.

In contrast with previous reports, we demonstrated consistent results across important subgroups of patients, that is, with versus without PH, with versus without RVD, and reduced/mildly reduced versus preserved LVEF.[8,9] The consistent data in patients with reduced versus preserved LVEF add important insights in the prognostic stratification of the overall spectrum of AHF, whereas the prognostic implications of the severity of TR regardless of RV functional impairment or the presence of PH attested the reciprocal pathophysiological interaction between these 3 components and the importance of a comprehensive echocardiographic assessment of the right heart to correctly stratify the risk of patients with AHF.

The Combined Effect of TR and Pulmonary Hypertension

As reported in previous large studies,[27,28] PASP was strongly associated with mortality in AHF. Furthermore, in our cohort the combination of moderate-severe TR and PH determined a further reduction in survival with 3-fold higher probability of dying compared with patients without PH and moderate-severe TR, and 1.8-fold higher probability compared with patients with either PH or moderate-severe TR. In our opinion, this is an important finding,

Table 2. Factors Associated With the Risk of 1-Year Mortality at Multivariable Analysis

	Model 1			Model 2		
	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
TR, moderate-severe	1.718	1.147–2.573	0.009*	1.761	1.078–2.879	0.024*
PASP (per 1 mm Hg increase)	1.019	1.006–1.032	0.003*	1.003	0.987–1.018	0.750
RV dysfunction	1.387	0.923–2.083	0.115	0.985	0.614–1.582	0.951
LV EF (per 1% increase)	0.997	0.984–1.009	0.610	1.007	0.992–1.023	0.359
MR, moderate-severe	0.851	0.580–1.248	0.409	0.753	0.476–1.192	0.226
LA ESV index (per 1 mL/m^2 increase)	0.999	0.993–1.005	0.796	0.997	0.988–1.006	0.520
RA ESV index (per 1 mL/m^2 increase)	1.009	1.003–1.015	0.004*	1.003	0.995–1.012	0.457
High NPs (BNP or NT-proBNP >median) †				1.978	1.177–3.322	0.010*
Creatinine (per 1 mg/dL increase)				1.192	0.911–1.561	0.200
Urea (per 1 mg/dL increase)				1.009	1.003–1.015	0.002*
Systolic blood pressure (per 1 mm Hg increase)				0.972	0.963–0.982	<0.001*
Diabetes				0.877	0.545–1.411	0.589
Ischemic cause of HF				0.974	0.608–1.560	0.913
Peripheral artery disease				1.683	1.032–2.744	0.037*
Atrial fibrillation				1.568	1.008–2.441	0.046*

Model 1: echocardiographic variables; model 2: echocardiographic and clinical variables. HR and *P* value were obtained by multivariable Cox regression. BNP indicates brain natriuretic peptide; HF, heart failure; HR, hazard ratio; LA ESV, left atrial end-systolic volume; LV EF, left ventricular ejection fraction; MR, mitral regurgitation; NPs, natriuretic peptides; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PASP, pulmonary arterial systolic pressure; RA ESV, right atrial end-systolic volume; RV, right ventricular; and TR, tricuspid regurgitation.

*P<0.05.

†Median value for BNP=839 pg/mL, median value for NT-proBNP=4858pg/mL.

as it supports the importance of a careful assessment of both the components in the acute phase of HF and claims for interventional studies with the goal of a combined reduction in the entity of both TR and PH. As stated above, underestimation of PASP is possible in patients with severe TR and additional indirect echocardiographic signs of PH should be always assessed in clinical practice.[16] In our study, we cannot exclude misclassification and risk underestimation of part of the patients with moderate-severe TR due to PASP underestimation.

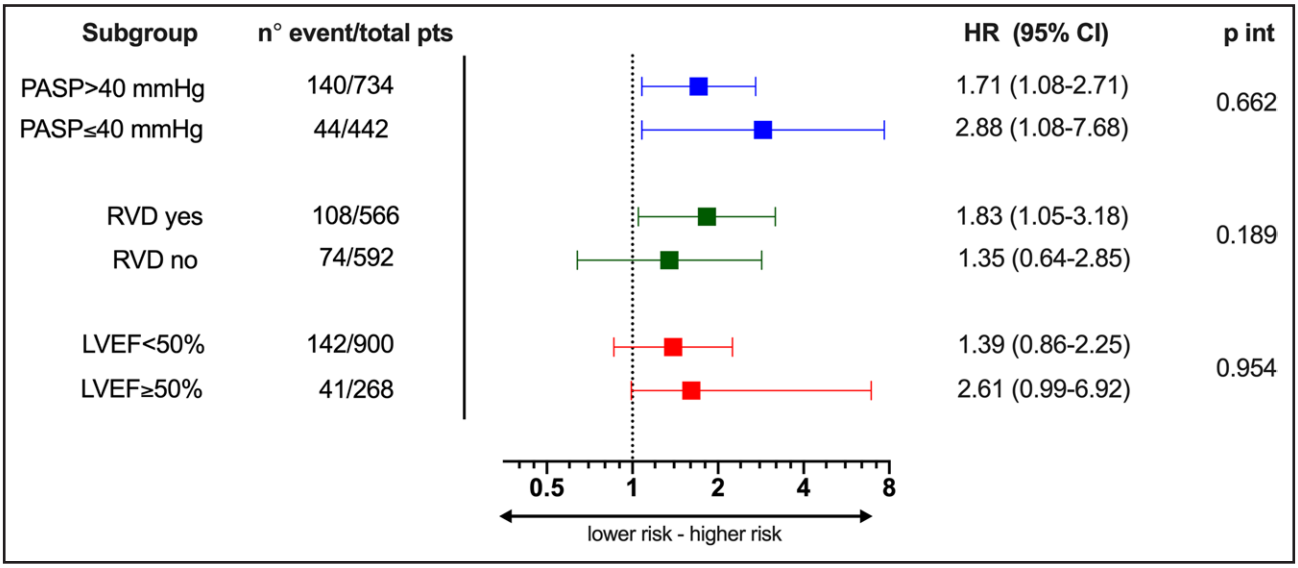

Figure 4. Association between severity of tricuspid regurgitation and 1-year survival across different subgroups.
No significant interactions were observed for the association with 1-year mortality risk between tricuspid regurgitation (TR) severity and pulmonary hypertension (PH; pulmonary arterial systolic pressure [PASP] >40 mm Hg vs PASP ≤40 mm Hg), right ventricle dysfunction (RVD; presence vs absence), and left ventricle ejection fraction (LVEF; <50% vs LVEF ≥50%). The association between TR severity and 1-year mortality was consistent across all different subgroups. Each analysis (multivariable Cox regression) was adjusted for PASP, RVD, LVEF, moderate-severe mitral regurgitation (MR), left atrial (LA), and right atrial (RA) indexed volume (model 1). HR indicates hazard ratio.

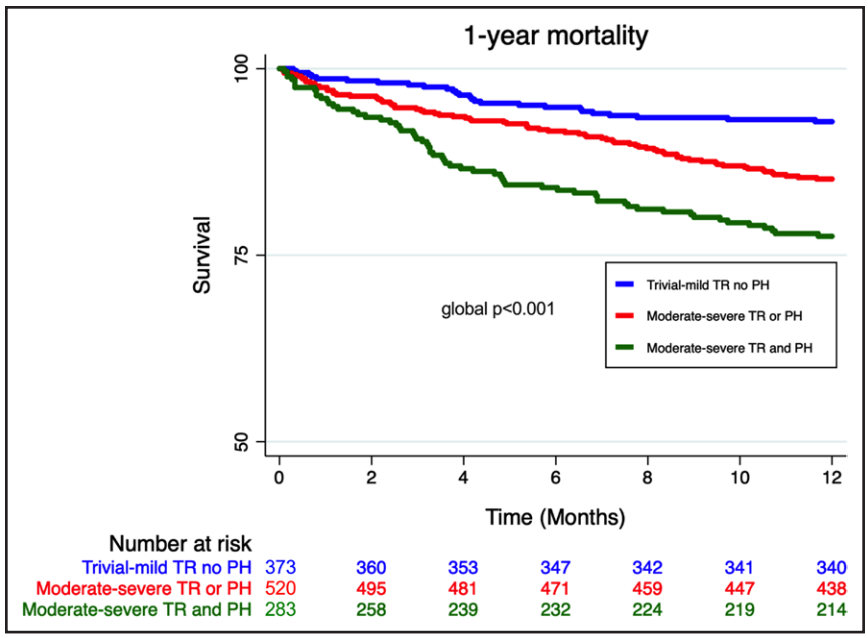

Figure 5. Kaplan-Meier survival curves for 1-year mortality according to the severity of tricuspid regurgitation (TR) and the presence of pulmonary hypertension (PH; that is, pulmonary arterial systolic pressure [PASP] >40 mm Hg). Two hundred eighty-three patients had concomitant moderate-severe TR and PASP >40 mm Hg, 520 patients had either moderate-severe TR or PASP >40 mm Hg, and 373 patients showed trivial-mild TR and PASP ≤40 mm Hg. Kaplan-Meier survival curves showed a clear divergence between the 3 groups, with the highest 1-year mortality in patients with both moderate-severe TR and PASP >40 mm Hg. *P* value in this figure was obtained by Log-rank test.

Study Limitations

The retrospective nature of the analysis limits the power of our conclusions. The study population was enrolled in a single third-level center for HF and cardiomyopathies, limiting the generalizability of results. The exclusion of patients without available estimation of TR or PASP might have generated a selection bias. However, survival rates at 1 year were similar among the study cohort and excluded patients (Table S1).

Unfortunately, due to the acute setting of our patients, systematic recording of RV size was not feasible owing to poor quality imaging. Correct noninvasive estimation of pulmonary pressure may be challenging. In this study, the paucity of invasive data from right heart catheterization (<5% of the total cohort) did not allow to specifically assess the correlation between PASP and invasive systolic pulmonary pressure. We recently validated main noninvasive hemodynamic measures in a broad multicenter cohort of unselected patients undergone simultaneous right heart catheterization and echocardiography for multiple indications.[29] However, the possible underestimation of PASP in patients with severe TR must be acknowledged.

The diagnosis of AHF at admission was based on physician judgment as in most of the observational studies on AHF, thus we cannot completely exclude potential misdiagnosis.

Table 3. Incremental 1-Year Mortality Risk Associated With the Combination of Moderate-Severe TR and PH (ie, PASP >40 mm Hg)

	Hazard ratio	95% CI	*P* value
Moderate-severe TR or PH vs no moderate-severe TR + no PH	1.684	0.994–2.854	0.053
Moderate-severe TR + PH vs moderate-severe TR or PH	1.795	1.195–2.703	0.005*
Moderate-severe TR + PH vs no moderate-severe TR + no PH	3.024	1.735–5.271	<0.001*
RV dysfunction	1.437	0.954–2.150	0.083
LV EF (per 1% increase)	0.998	0.986–1.011	0.800
MR, moderate-severe	0.827	0.564–1.214	0.332
LA ESV index (per 1 mL/m^2 increase)	0.999	0.993–1.005	0.781
RA ESV index (per 1 mL/m^2 increase)	1.009	1.003–1.015	0.003*

HR and *P value* were obtained by multivariable Cox regression. HR indicates hazard ratio; LA ESV, left atrial end-systolic volume; LV EF, left ventricular ejection fraction; MR, mitral regurgitation; PASP, pulmonary arterial systolic pressure; PH, pulmonary hypertension; RA ESV, right atrial end-systolic volume; RV, right ventricular; and TR, tricuspid regurgitation.

*P<0.05.

Conclusions

The severity of TR was strongly associated with survival in AHF, and this association was independent from the presence of PH and from several other clinical and echocardiographic parameters. Despite the possible underestimation of PASP in patients with severe TR, the combination of moderate-severe TR and PH was associated with additional incremental risk of death. Future dedicated studies are advocated to identify the optimal strategies for the management of secondary TR in AHF and their potential impact on the outcome.

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Sources of Funding

None.

Disclosures

Dr Stolfo reports personal fees from Novartis, Merck, GSK, and Acceleron outside the submitted work. Dr Merlo reports consultant and unrestricted fees at congresses, congress fees from Novartis and Vifor Pharma. Dr Sinagra reports consulting fees from Novartis, Impulse Dynamics and Biotronik, and speaker and honoraria from Novartis, Bayer, Astrazeneca, Boston Scientific, Vifor Pharma, Menarini and Akcea Therapeutics outside the submitted work. The other authors report no conflicts

Supplemental Material

Supplemental Methods
Tables S1–S3

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