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Functional tricuspid regurgitation and recurrent admissions in patients with acute heart failure☆

Rafael De la Espriella [a,b,c,d], Enrique Santas [a,b,c,d], Francisco J. Chorro [a,b,c,d], Gema Miñana [a,b,c,d], Meritxell Soler [a,b,c,d], Vicent Bodí [a,b,c,d], Ernesto Valero [a,b,c,d], Eduardo Núñez [a,b,c,d], Antoni Bayés-Genis [d,e,f], Josep Lupón [d,e,f], Juan Sanchis [a,b,c,d], Julio Núñez [a,b,c,d,]*

[a] Cardiology Department, Hospital Clínico Universitario, Valencia, Spain
[b] INCLIVA, Spain
[c] Universitat de València, Valencia, Spain
[d] CIBER Cardiovascular, Spain
[e] Cardiology Service and Heart Failure Unit, Hospital Universitari Germans Trias i Pujol, Badalona, Spain
[f] Department of Medicine, Autonomous University of Barcelona, Barcelona, Spain

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ABSTRACT

Background: Functional tricuspid regurgitation (TR) is a common echocardiographic finding in patients with heart failure (HF), and its role in disease progression and prognosis stratification is becoming increasingly relevant in recent years. However, data regarding its association with the burden of HF-readmission is scarce. In this work, we sought to evaluate the association between TR severity and HF-related readmissions following a hospitalization for acute heart failure (AHF).
Methods: We prospectively included a cohort of 2101 patients admitted with the diagnosis of AHF. TR severity was assessed using a multiparametric integrative approach, and classified as none, mild, moderate, and severe. We used negative binomial regression to identify the association between TR grade and HF-related recurrent admissions. The risk associated to severity of TR was expressed as incidence rate ratio (IRR).
Results: At a median follow-up of 2.53 years (IQR: 1.03–4.36), 978 (46.5%) patients died, and 1657 HF-readmissions occurred in 842 patients (40.0%). The proportion of patients with two or more admissions was 18.4%. The proportion of patients with moderate to severe TR was 17.2%. There was a stepwise increase in the incidence of readmissions from none to severe TR. After multivariable adjustment, only patients with severe TR were independently associated with higher risk of recurrent HF admissions (IRR = 1.34, CI 95%: 1.05–1.71; p = .019).
Conclusions: In patients with AHF, severe functional TR is independently associated with an increased risk of long-term recurrent HF hospitalizations.

1. Introduction

Heart failure (HF) is a clinical syndrome characterized by recurrent episodes of acute clinical decompensations, many of them resulting in hospital admissions. Readmissions due to worsening HF are associated with an increased mortality risk, deeply affect patients' quality of life, and account for significant and growing health care expenditure [1]. Unfortunately, the identification of the vulnerable patient at risk of rehospitalization is still an unmet clinical need [2].

Tricuspid regurgitation (TR) has been traditionally an overlooked valvular lesion in patients with HF. In this scenario, the etiology is often functional due to right ventricular (RV) dilatation, distortion of subvalvular apparatus, tricuspid annular dilatation, or a combination of these [3]. The association between hemodynamically significant TR and adverse outcomes in patients with left-side valvular disease is well described [4,5]. Furthermore, significant functional TR has been recently associated with a higher risk of mortality [6,7]. However, the importance of TR severity for selecting those patients at higher risk of hospitalizations has not been yet evaluated. In recent years, evaluating the risk of recurrent events, instead of classical "time-to-first" event methodology, has been recommended for the assessment of HF rehospitalization burden [8]. The aim of the present study was to evaluate

☆ All above authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Cardiology Department. Hospital Clínico Universitario, INCLIVA. Universitat de València. Valencia, Spain, Avda. Blasco Ibáñez 17, CP 46010, Valencia, Spain.
E-mail address: yulnunez@gmail.com (J. Núñez).

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the association between the severity of TR and long-term recurrent HF admissions following a hospitalization for acute heart failure (AHF).

2. Methods

2.1. Study design and population

We prospectively recruited 2244 consecutive patients admitted for AHF in the cardiology department of a tertiary-care teaching hospital in Spain (Hospital Clínico Universitario de Valencia) from 2009 to 2017. AHF diagnosis was performed by trained cardiologists according to the guidelines that were operating at the time the patients were included in the registry [9–11]. Either patients with new onset or decompensated chronic HF were eligible. By design, patients who died during the index hospitalization (n = 98) and those lost to follow-up after discharge (n = 40) were not included in the final analysis. Patients with primary TR were also excluded (n = 5). The final sample included in this study was 2101 patients (Supplemental file 1).

Clinical variables, including laboratory analysis, vital signs, demographics and comorbidities, were assessed by reviewing medical records and using pre-established registry questionnaires. Treatment and other therapeutic strategies were individualized following established guidelines that were operating at the time the patient was included in the registry [9–11].

All patients were followed-up on an outpatient heart failure clinic including a HF nurse and HF-specialized cardiologists. An early visit within the first 15th days after discharge was scheduled for evaluating residual congestion and other reversible potentially decompensating conditions. Based on the first evaluation and treatment upon discharge, drug titration, devices, revascularization, and surgical procedures were individualized according to clinical guidelines. Diuretics were adjusted based on the patient's congestive state, and intravenous treatments, such as furosemide, ferric carboxymaltose, and red blood cell transfusions, were administered as necessary. Further visits were scheduled according to physician clinical judgment allowing as many extra visits as required.

2.2. Echocardiographic evaluation

A comprehensive transthoracic echocardiographic examination was performed using commercially available systems (Agilent Sonos 5500 or IE33 Philips, MA, USA) at mid-late hospitalization (90 ± 20 h after admission), and after initial clinical stabilization was reached. Clinical stabilization was defined as cessation of intravenous therapy, reinstitution of oral diuretics and hemodynamic stability without the need for mechanical ventilation or ventilator support (other than for sleep apnea, if required). Two-dimensional and Doppler measurements were made according to the international recommendations [12,13] using standard views and techniques. TR severity was determined by a multiparametric integrative approach according to accepted criteria [14–16] and graded as none, mild, moderate, and severe. Small, narrow and central jets with a vena contracta width (VCW) <0.3 cm and normal tricuspid leaflets were considered as mild. By contrast, large jets with color flow jet area >10 cm^2, VCW >0.7 cm, and/or systolic flow reversal in hepatic veins were considered as severe. Intermediate jets were graded as moderate. Quantitative measures of the TR jet using the proximal isovelocity surface area method and/or regurgitant volume were available in <5% of patients, so it was not used in this analysis. TR severity was graded by the cardiac sonographer and confirmed by another study investigator blinded to clinical data. Pulmonary artery systolic pressure (PASP) was estimated from peak TR systolic pressure gradient and inferior vena cava size and respiratory variation [13]. Pulmonary hypertension (PH) was defined using the cut-off of PASP ≥50 mm Hg [17,18].

2.3. Study endpoint

The primary endpoint of this study was the number of HF-related readmissions. Only unplanned readmissions were included. The clinical endpoint was ascertained by a physician blinded to the exposure through a review of hospital and/or outpatient national electronic medical records.

2.4. Ethics

The study was prospectively designed, conformed to the principles outlined in the Declaration of Helsinki, and was approved by the institutional local review ethical committee. All patients gave informed consent.

2.5. Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]), as appropriate. Discrete variables were presented as percentages. Comparisons across TR groups were performed by χ^2 test for categorical variables. For continuous variables, one-way analysis of variance (ANOVA) and Kruskal–Wallis test were used for those variables with a parametric and non-parametric distribution, respectively. All variables listed in Table 1 were evaluated for prognostic purposes.

The rehospitalization endpoint was evaluated by determining the incidence rate ratio (IRR). To that end, a multivariable negative binomial regression (NBreg) was used to assess the association between TR severity and the number of readmissions that have occurred during the entire follow-up. To account for differences in the length of follow-up, the log of post-discharge follow-up (in years) from each patient was used as offset in the model. Because an increase in rehospitalization is most likely associated with an increased risk of subsequent death, it has been suggested that any analysis of recurrent admissions should also account for death as a terminal event [19]. Therefore, and as suggested by Pocock et al., each death was included as an additional event in the NBreg model but only if it occurred outside any rehospitalization [20]. This means that if a patient died during any rehospitalization, this was counted as a single event. Covariate selection was performed based on previous medical knowledge; then, a backward stepwise selection, with AIC as stopping criterion, was used to achieve a parsimonious model and to prevent model's overfitting. During this process, the linearity assumption for continuous variables was simultaneously tested, and transformed if appropriate, with fractional polynomials. The final model included the following covariates: age, sex, prior history of HF, diabetes mellitus, dyslipidemia, ischemic heart disease, valvular heart disease, left bundle brunch block, atrial fibrillation, hypertension, systolic blood pressure, heart rate, tricuspid annular plane systolic excursion, left ventricular ejection fraction (LVEF) < 40%, estimated glomerular filtration rate (eGFR), serum sodium, plasma antigen carbohydrate 125 (CA125), amino-terminal pro-brain natriuretic peptide (NT-proBNP), anemia, discharged on beta-blockers, ACE inhibitors/angiotensin II receptor blockers, and furosemide-equivalent dose at discharge.

The cumulative probabilities of all-cause mortality and time-to-first HF-rehospitalization were also evaluated. The incidence of HF-readmission was analyzed by drawing the accumulated incidence curves, and between-TR categories differences were analyzed by Gray's test. The risk effect was determined using a regression model based on cumulative incidence function (CIF) that takes into account the effect of all-cause mortality as competing event (method of Fine and Gray). Kaplan-Meier survival plot was generated for all-cause mortality and tested by the log-rank test.

Along the follow-up, only 10 tricuspid surgical procedures were registered. In these cases, the follow-up was censored at the time of tricuspid intervention.

A 2-sided p-value of <0.05 was considered to be statistically significant for all analyses. All analyses were performed using STATA 14.1 (StataCorp. 2014. Stata Statistical Software: Release 14.1. College Station, TX: StataCorp LP).

3. Results

3.1. Baseline characteristics across TR severity

Mean age was 73 ± 11 years, 1047 of the patients were woman (49.8%), and 1127 (53.6%) patients had preserved left ventricular ejection fraction (HFpEF). The median (IQR) of NT-proBNP before discharge was 4186 pg/mL (IQR: 2161–7697). The distribution of patients across TR categories was as follows: Moderate or severe TR was observed in 361 (17.2%) and 202 (9.6%) patients respectively, whereas 781 (37.2%) and 757 (36%) had mild or no regurgitation. Table 1 summarizes the baseline characteristics stratified according to TR severity. History of hypertension and ischemic etiology were inversely associated with TR severity. By contrast, atrial fibrillation was positively associated with higher TR grade. Patients with right ventricular dysfunction (RVD), significant mitral regurgitation, and higher PASP were more likely to display more severe TR. Likewise, increasing TR severity was associated with a graded increase in NT-proBNP, CA125, total bilirubin, and gamma-glutamyltransferase (Fig. 1). At discharge, loop diuretics at higher doses were also more frequently prescribed among patients with greater TR.

3.2. Outcomes

At a median follow-up of 2.53 years (IQR: 1.03–4.36), 978 (46.5%) patients died, 1657 HF-readmissions occurred in 842 patients (40.0%) and, 386 (18.4%) patients had two or more admissions during the follow-up.

Cumulative incidence curve and Kaplan-Meier curve revealed a significant divergent risk trajectory for HF-readmission and mortality respectively, among patients with severe TR (Supplemental files 2 and 3).

3.3. TR and recurrent hospitalizations

Crude HF-readmissions rates across TR severity are shown in Fig. 2A. Overall, there was a stepwise increased incidence of recurrent HF- hospitalizations when moving from none to severe TR. In univariate analysis, and compared to none-TR, patients with moderate and severe-TR showed higher risk of the end-point (IRR = 1.34, CI 95%: 1.07–1.67; p = .011) and (IRR = 2.16, CI 95%: 1.65–2.80; p < .001), respectively. Those, with

Table 1
Baseline characteristics stratified according to TR before discharge.

Variables	None TR (n = 757)	Mild TR (n = 781)	Moderate TR (n = 361)	Severe TR (n = 202)	p-Value
Demographics and medical history					
Age, years	72.4 ± 12.2	73.1 ± 11.6	74.6 ± 10.5	72.8 ± 12.1	<0.01
Female gender, n (%)	355 (46.9)	394 (50.4)	179 (49.6)	119 (58.9)	0.02
Hypertension, n (%)	630 (83.2)	625 (80.1)	276 (76.4)	141 (69.8)	<0.01
Diabetes Mellitus, n (%)	365 (48.2)	344 (44.1)	149 (41.3)	78 (38.6)	0.03
Dyslipidemia, n (%)	400 (52.8)	430 (55.1)	172 (47.7)	90 (44.5)	0.01
Chronic lung disease, n (%)	169 (22.3)	181 (23.2)	73 (20.2)	40 (19.8)	0.59
Ischemic HF etiology, n (%)	312 (41.2)	268 (34.3)	89 (24.6)	55 (27.2)	<0.01
Prior admission for AHF, n (%)	335 (44.2)	334 (42.8)	178 (49.3)	116 (57.4)	<0.01
Atrial fibrillation, n (%)	236 (31.2)	349 (44.7)	212 (58.7)	123 (60.9)	<0.01
Pacemaker, n (%)	28 (3.7)	32 (4.1)	20 (5.5)	17 (8.4)	0.02
Vital signs					
Heart rate, bpm	101 ± 28	99 ± 28	99 ± 29	91 ± 93	<0.01
SBP, mm Hg	156 ± 36	147 ± 32	140 ± 30	132 ± 26	<0.01
DBP, mm Hg	84 ± 21	82 ± 19	78 ± 18	75 ± 17	<0.01
Laboratory data at admission					
Hemoglobin, g/dL	12.8 ± 1.9	12.4 ± 1.9	12.3 ± 1.8	12.1 ± 1.8	<0.01
Creatinine, mg/dL	1.2 ± 0.6	1.2 ± 0.5	1.3 ± 0.6	1.3 ± 0.6	0.39
eGFR (MDRD), mL/min/1.73 m^2	62 ± 25	65 ± 34	60 ± 23	59 ± 25	0.01
Serum sodium, mEq/L	139 ± 4	139 ± 4	138 ± 5	137 ± 5	<0.01
NT-proBNP, pg/mL[a]	5075 (4502)	6395 (5613)	7248 (6549)	8162 (8083)	<0.01
CA-125, U/mL[a]	75 (75)	93 (99)	120 (115)	151 (154)	<0.01
Total bilirubin, mg/dL	0.8 ± 0.3	0.9 ± 0.4	1.0 ± 0.6	1.1 ± 0.5	<0.01
Gamma-glutamyltransferase, IU/L	57 ± 62	71 ± 78	82 ± 99	108 ± 123	<0.01
Echocardiographic data					
LVEF (%)	51 ± 15	48 ± 15	49 ± 16	50 ± 16	0.07
Moderate/severe mitral regurgitation, n (%)	70 (9.2)	125 (16.1)	109 (30.2)	80 (39.6)	<0.01
PASP, mmHg	–	40 ± 11	49 ± 13	58 ± 17	<0.01
Right ventricular dysfunction (TAPSE <16 mm), n (%)	87 (11.4)	157 (20.1)	93 (25.7)	80 (39.6)	<0.01
Medication at discharge					
Loop diuretics, n (%)	516 (68.2)	638 (81.7)	293 (81.2)	173 (85.6)	<0.01
Furosemide equivalent dose, mg/day	67.9 ± 37.9	77.8 ± 101.2	77.5 ± 36.8	90.2 ± 42.2	<0.01
Spironolactone, n (%)	229 (30.2)	282 (36.1)	122 (33.8)	76 (37.6)	0.06
Beta-blockers, n (%)	470 (62.1)	595 (76.2)	248 (68.7)	127 (62.9)	<0.01
ACEI/ARB, n (%)	526 (69.8)	523 (67.4)	231 (64.3)	131 (65.5)	0.23
Digoxin, n (%)	124 (16.4)	140 (17.9)	95 (26.3)	59 (29.2)	<0.01

Abbreviations: HF, heart failure; AHF, acute heart failure; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease formula, NT-proBNP, amino-terminal pro-brain natriuretic peptide; CA-125, antigen carbohydrate 125; LVEF, left ventricle ejection fraction; PASP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers.
Continuous variables are expressed as mean ± 1 standard deviation, unless otherwise specified.
[a] Variable expressed as median (interquartile range).

mild-TR showed a border-line increased risk (IRR = 1.17, CI 95%: 0.97–1.41; p = .094).

After comprehensive multivariate adjustment, only severe-TR remained significantly associated with the risk of recurrent HF-hospitalizations (IRR = 1.34, CI 95%: 1.05–1.71; p = .019). Adjusted estimates of risk are shown in Fig. 2B.

In a subgroup analysis, we found no significant interactions between TR severity and any of the following subgroups: pulmonary hypertension (PASP>50 mm Hg) (p-value for the interaction = 0.670), LVEF categories (p-value for interaction = 0.840), right ventricular systolic dysfunction (TAPSE <16 m) (p-value for interaction = 0.516), history of atrial fibrillation (p-value for the interaction = 0.518), NT-proBNP lower than median (4186 pg/mL) (p-value for interaction = 0.877), GFR lower than 60 mL/min/m^2 (p-value for interaction = 0.729), gender (p for interaction = 0.747) or age (p for interaction = 0.607) (Fig. 3).

4. Discussion

The present study shows a significant and independent association between the presence of severe functional TR and the risk of recurrent HF admissions in a large non-selected cohort of AHF patients. In addition, the magnitude of the association between TR severity and the end-point was not significantly influenced by important confounders such as echo-derived pulmonary hypertension, right ventricular systolic dysfunction or LVEF categories.

Health-care strategies designed for reducing the morbidity burden in HF remain a major challenge [2]. Along this line of thought, identifying the risk factors associated with the risk of readmission is still an unmet need.

Traditionally the risk of readmission has been assessed by time-to-first-event methods. However, counting only the first event means neglecting subsequent hospitalizations, fact that is frequent in patients with HF [21,22]. Therefore, recent initiatives advocate a more comprehensive approach of disease burden by analyzing all hospitalizations that occur during follow-up [8].

Even though TR is a common echocardiographic finding in patients with HF, its clinical or prognostic relevance has been historically neglected. Nevertheless, in the last years there is a growing interest in the clinical consequences and prognostic role of functional TR in different cardiovascular scenarios [23]. In the field of HF, recent evidence linked significant TR with adverse outcomes both in chronic and acute setting [6,7,24]. However, data is relatively scarce and limited to certain subgroups of patients. For instance, Neuhold et al. reported an independent association between TR severity and the combined end-point death/heart transplantation/left ventricular-assist device implantation in patients with mild to moderate chronic HF, whereas it was not related to the composite end-point in patients with a more advanced disease

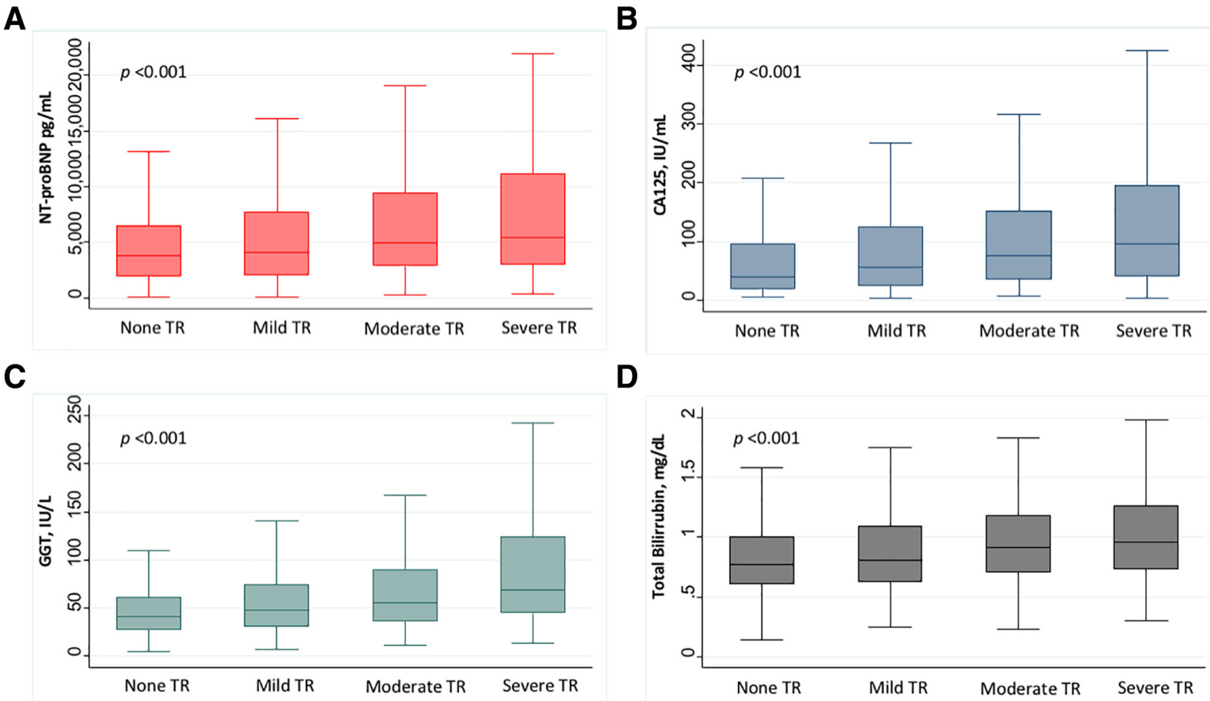

Fig. 1. NT-proBNP levels (A), CA-125 levels (B), GGT (C) and total bilirubin (D) across TR severity. NT-proBNP, amino-terminal pro-brain natriuretic peptide; CA-125, antigen carbohydrate 125; GGT, Gamma-glutamyltransferase.

(LVEF<35% and higher levels of NT-proBNP) [24]. Our group previously described a differential prognostic effect of TR severity on 1-year mortality following an admission for AHF according to LVEF status. Remarkably, the significant association between TR severity and mortality only persisted in patients with HFpEF [6]. In the same line, recently Mutlak et al. [7] observed that significant TR was associated with an increased risk of the composite end point of HF rehospitalizations and mortality only in patients with PH. In the present work, TR was homogeneously associated with the burden of HF-readmission in most important subgroups of the disease, including the different LVEF phenotypes. We speculate that the strong association with mortality and readmission in HFpEF reinforce the crucial pathophysiological role of right ventricular failure in this syndrome [25,26]. In HFrEF, despite the reported neutral association with mortality, was also associated with HF-readmissions, pointing out the crucial role of parameters linked to congestion with the burden of morbidity in HF regardless LVEF status [27].

According to our findings, we postulate that the presence of severe-TR before discharge in patients with AHF, would identify a subgroup of subjects with incomplete decongestion and tendency to experience new decompensations after discharge. Along this line, and regardless of the primary mechanism leading to severe TR, there is strong evidence supporting the causal association between TR severity, fluid overload and progression of the disease [6,7,24]. Once the patient experience significant right-side pressure overload, symptoms of right-sided heart failure and congestion will become clinically evident [3]. At this point, TR promotes increasing venous pressures which is further transmitted into different organs promoting organ dysfunction [28–30]. For instance, the increase in renal veins pressures are a well-recognized factor causally related with worsening renal function in patients with HF [31].

From a clinical point of view, patients with severe TR after an episode of AHF represent one of the most important subgroups that could benefit from transitional care programs aimed to reduce readmission

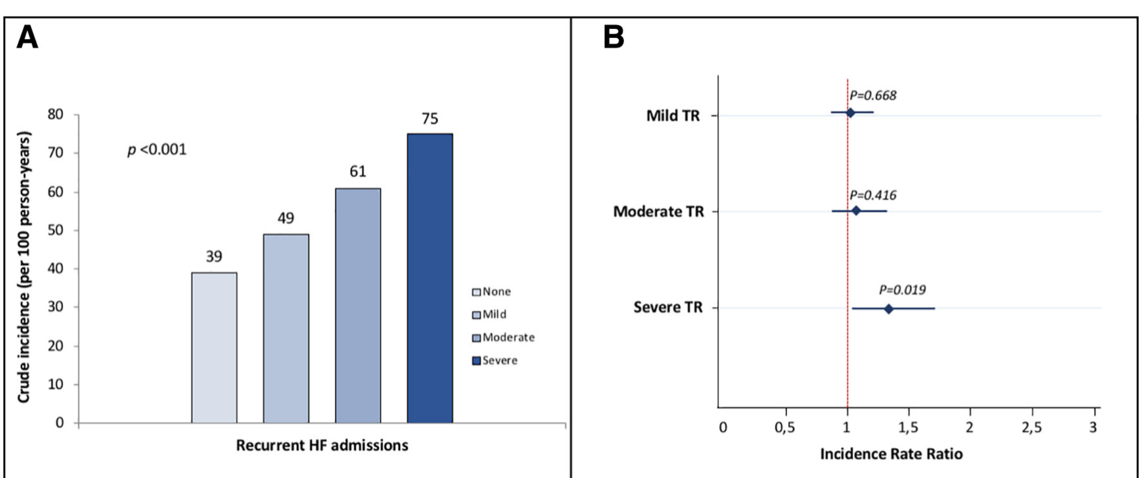

Fig. 2. Crude incidence rates for HF recurrent hospitalizations across TR severity (A). Adjusted estimate risk of recurrent HF admissions across TR severity (B).

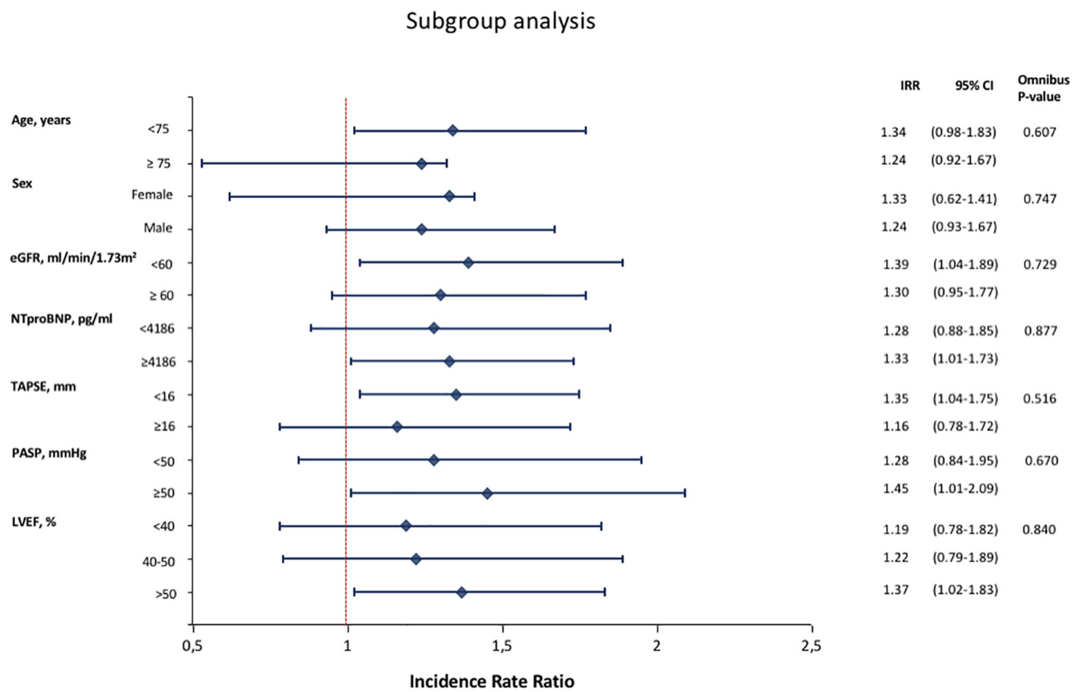

Fig. 3. Subgroup analysis. CI indicates confidence interval; IRR, incidence rate ratio; eGFR, estimated glomerular filtration rate (Modification of Diet in Renal Disease formula); NT-proBNP, amino-terminal pro-brain natriuretic peptide; TAPSE, tricuspid annular plane systolic excursion; PASP, systolic pulmonary artery pressure; LVEF, left ventricle ejection fraction.

risk burden. In addition, in clinical practice there is a growing group of elderly patients with severe functional TR and right-side HF without significant left-side valve disease, in which isolated tricuspid surgical therapy is associated with high mortality [32] and medical treatment is often problematic. Recently, the question of whether minimally invasive transcatheter repair provides an alternative therapeutic option for this high-risk subgroup of patients has arisen and a variety of transcatheter devices are currently under clinical testing [33,34]. Nonetheless, further longitudinal studies depicting the trajectory of TR after an episode of AHF are welcome to elucidate the dynamic behavior of TR severity and its contribution to HF progression.

There are several limitations in our study that need to be acknowledged. First, this is a single-center observational study in which some circumstances and hidden bias influencing the pattern of hospitalizations might be operating. Second, PASP was only available in 1196 (57%) patients, which precluded a formal prognostic assessment across TR severity. Third, we graded the severity of TR in a semi-quantitative manner and it has been recently reported that quantitative grading may allow more accurate risk stratification [35]. Fourth, echocardiographic images were not reviewed by an independent core laboratory external to the investigators. As strengths, the recurrent “state-of-the-art” event methodology applied in our study offers a more “realistic” picture of disease burden.

In conclusion, in patients with AHF, the presence of severe TR identifies a subgroup of patients at higher risk of HF-related recurrent hospitalizations.

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Conflicts of interest

None declared.

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