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Outpatient tricuspid regurgitation in the community: Clinical context and outcome☆

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A R T I C L E I N F O

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A B S T R A C T

Background and aims: Epidemiology of tricuspid regurgitation (TR) is poorly known and its burden in the community is challenging to define. We aimed to evaluate the prevalence of TR in a geographically defined area and its outcome, in particular overall survival and hospitalization, considering different clinical contexts.
Methods: We retrospectively analyzed consecutive outpatients referred between 2006 and 2013 for echocardiography and clinical evaluation. Patients with at least moderate TR were included and five different clinical settings were defined: concomitant significant left-sided valvular heart disease (LVHD-TR), heart failure (HF-TR), previous open-heart valvular surgery (postop-TR), pulmonary hypertension (PHTN-TR) and isolated TR (isolated-TR). Primary endpoint was a composite outcome of all-cause mortality or first hospitalization for HF.
Results: Of 6797 consecutive patients with a clinical visit and echocardiograms performed in routine practice in a geographically defined community, moderate or severe TR was found in 4.8% of patients (327) . During median follow-up of 6.1 years, TR severity was a determinant of event-free survival. Analyzed for each clinical subset, eight-year event-free survival was 87 ± 7% for postop-TR subgroup, 75 ± 7% for isolated-TR, 67 ± 6% for PHTN-TR, 58 ± 6% for LHVD -TR and 52 ± 11% for HF-TR.
Conclusion: Moderate or more TR is a notable finding in the community and has impact on event-free survival in all clinical settings, with the worst outcomes when associated with relevant left-sided valvular heart disease and HF.

1. Introduction

The burden of tricuspid regurgitation (TR) is difficult to define in the community as it is often diagnosed for serendipity in the echocardiography laboratory. Furthermore, patients often complain vague or non-specific (fatigue, abdominal pain) symptoms which rarely elicit the request for an echocardiographic exam.

TR prevalence is mostly derived from studies conducted in patients with an indication for echocardiographic exam focused on the assessment of left-sided heart diseases, such as heart failure or mitral regurgitation, and it has been shown to increase with age and, when present, it portends poor outcome [1–3]. However, TR data are limited to large registries from referral institutions, where both in- and out-patients were included and only few community studies on TR burden are available [1,4,5]. TR is a dynamic condition and it is more frequently encountered in patients with decompensated HF, therefore studies including hospitalized patients may not reflect the true prevalence of this disease in the community.

Moreover, data from TR surgical series are available [6], biased by minimal proportion of patients with severe TR ever referred to surgical intervention in routine practice, particularly for isolated-TR [1].

The etiology of TR is largely functional (> 90%), which is an heterogenous pathological entity occurring in different clinical conditions (left-sided structural disease, atrial enlargement, or pulmonary hypertension) [4]. Each TR clinical scenario seems to be characterized by different prevalence, clinical course and outcome. Consequently, the

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

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context is a key variable that influences the natural history of associated right-sided valve disease.

The aim of the study was to determine the prevalence of moderate or severe TR in a geographically defined population across different clinical contexts, and to assess its prognostic impact.

2. Material and methods

2.1. Study setting and population

We retrospectively analyzed all consecutive outpatients, who underwent clinically indicated echocardiography at University of Verona, the largest outpatient clinic and only Hospital of the selected area, between 2006 and 2013. We only included patients resident in the geographically defined area aiming to obtain a picture of the disease prevalence and complete follow-up information.

We identified patients with first diagnosis of at least moderate TR, and a complete clinical examination within 3 months from the echocardiogram.

Patients with primary TR including endocarditis, congenital, carcinoid or flail were excluded. Patients with TR mainly due to Pacemaker and ICD leads were not considered in our cohort. Other exclusion criteria were age under 18, congenital heart disease and poor-quality echocardiography window.

2.2. Clinical and echocardiographic characteristics

General patients' features included sex, age, weight, height. From clinical history cardiovascular risk factors were noted: arterial hypertension, dyslipidemia, diabetes, coronary artery disease.

The heart rhythm was evaluated as sinus rhythm or atrial fibrillation at the time of echocardiographic exam, history of paroxysmal or chronic atrial fibrillation was also collected.

A comprehensive two-dimensional and Doppler echocardiography was performed for all patients referring to American Society of Echocardiography guidelines [7]. Left and right ventricular function were assessed, and mitral and aortic valvular diseases or valve prostheses were noted. RV dysfunction was defined by TAPSE <17 mm or visual estimation. Tricuspid valve regurgitation grading was assessed with an integrated semi-quantitative approach [8,9], through evaluation of color jet area, vena contracta width, proximal isovelocity surface area method, continuous Doppler, right ventricle (RV) and right atrium (RA) sizes. RV size and function were graded using multiple parameters, varying from visual assessment (mainly when the acoustic window was suboptimal) to fully quantitative data (from either 2D, tissue doppler or MMode) and summarized in the final report as semiquantitative evaluation. Moderate-severe TR were included in the group of severe TR.

Systolic pulmonary artery pressure (sPAP) was obtained using TR velocity with the addition of right atrium pressure (RAP), estimated using inferior vena cava (IVC) and its collapsibility [10]. The presence of pulmonary hypertension was defined by SPAP measured in the index echo as well as in the previous examination and in the medical history, knowing that SPAP may underestimate pulmonary hypertension in the presence of concomitant severe TR. RAP based upon IVC was used to evaluate central venous overload, arbitrarily defined as increased by RAP ≥8 mmHg.

2.3. Definition of clinical contexts and morphologic types

TR was evaluated in five different clinical contexts: distribution patterns were obtained through a step-by-step classification with the following approach. Firstly, we identified TR with concomitant left-sided valvular heart disease (LVHD-TR): in other words, moderate or severe mitral regurgitation, or aortic valve stenosis. In second step we defined Heart Failure related TR (HF-TR), including patients without concomitant relevant LVDH and with at least one of the following: left ventricular ejection fraction (LVEF) < 30%, previous hospital admission for heart failure, or, importantly, relevant clinical symptoms and high diuretic doses therapy (HF Stage C, dyspnea according to NYHA ≥ II). Third and fourth subgroups were respectively made of patients with previous open-heart valvular surgery (post-TR) and patients with pulmonary hypertension (PHTN-TR), defined as sPAP >50 mmHg unrelated to left-sided heart disease [10]. The remaining patients were classified as isolated TR (isolated-TR) in the fifth subgroup.

Moreover, we provided the morphologic stratification in atrial and ventricular TR (A-TR and V-TR) according to the latest classification of functional TR [11].

2.4. Follow-up and outcome

Outcome was obtained by electronic medical record and telephone contact. Primary endpoint was a composite outcome of all-cause mortality or first hospitalization for HF. The date of latest available medical report or patient telephone contact was considered the last follow-up date. Consent to be enrolled in the study was obtained from all patients. The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Verona's Hospital.

2.5. Statistical analysis

Categorical variables were expressed as percentage, while continuous variables as mean ± standard deviation. To establish the association between the several variables and TR severity as well as differences across clinical settings, we implemented X^2 or ANOVA.

Patients were followed up from TR diagnosis until death, heart failure hospitalization, or last medical contact. Kaplan-Meyer curves were generated to graphically display the event rates in function of time by severity of TR and by different clinical contexts.

Univariable and Multivariable Cox proportional hazards models were applied to compare event-free survival distributions by each of the five TR clinical settings and by TR severity; covariate were chosen based on their univariable association with outcome.

Statistical analysis was performed through JMP Version 16 SAS Institute Inc., Cary, NC.

3. Results

3.1. TR prevalence and clinical characteristics

Among 6797 consecutive outpatients evaluated in the laboratory from the selected area, 327 (4.8%) were diagnosed with at least moderate TR and formed the study cohort.

Table 1 summarizes main demographic and clinical characteristics of the cohort. Mean age was 76 ± 10 years old and 39% of patients had >80 years; 56% were women and mean BMI was 24.91 ± 4.01 kg/m^2. Arterial hypertension was present in 80% and atrial fibrillation was diagnosed in 68% of patients.

3.2. Distribution pattern of functional TR according to the clinical context

Fig. 1 shows the distribution of study patients according to the clinical context. The largest group included patients with concomitant left-sided valvular heart disease (LVHD-TR; 39%), consisting of moderate or severe mitral regurgitation (85%), and aortic stenosis (15%). PHTN-TR prevalence was 27%, isolated-TR 14% (n = 46), HF-TR 10% (n = 34) and postop-TR 10% (n = 31). In elderly (> 80 years) patients LHVD-TR was the most common form. Except for patients with post-op TR who were younger, age was similar among the other groups, furthermore in patients with postop-TR arterial hypertension was less frequent. No other relevant differences were found between other cardiovascular risk factors across TR clinical contexts (Table 1).

Table 1
Baseline and clinical characteristics by different TR subcategories.

Baseline and clinical characteristics	Overall ($n = 327$)	LVHD-TR ($n = 127$)	HF-TR ($n = 34$)	Postop-TR ($n = 31$)	PHTN-TR ($n = 89$)	Isolated-TR ($n = 46$)	*P*-Value
Age	76 ± 10	77 ± 10	76 ± 9	71 ± 2	76 ± 10	74 ± 7	0.04
Age > 80	126 (39%)	54 (43%)	15 (44%)	5 (16%)	40 (45%)	12 (26%)	0.02
Male	144 (44%)	55 (43%)	17 (50%)	9 (29%)	37 (42%)	26 (57%)	0.17
Weight (kg)	69.2 ± 12.4	66.7 ± 12.2	69.3 ± 13.6	69.8 ± 10.7	68.1 ± 13.0	70.0 ± 12.0	0.59
Height (m)	1.65 ± 0.08	1.64 ± 0.08	1.66 ± 0.08	1.63 ± 0.07	1.66 ± 0.08	1.68 ± 0.07	0.08
BMI (kg/m^2)	24.91 ± 4.01	24.66 ± 4.16	25.18 ± 4.99	26.28 ± 4.14	24.70 ± 3.62	24.70 ± 3.31	0.40
Hypertension	261 (80%)	107 (84%)	24 (71%)	16 (52%)	76 (85%)	38 (83%)	0.0003
Dyslipidemia	149 (46%)	55 (43%)	14 (41%)	11 (36%)	40 (45%)	29 (63%)	0.13
Diabetes	78 (24%)	34 (27%)	9 (26%)	4 (13%)	21 (24%)	10 (22%)	0.55
Coronary artery disease	105 (32%)	43 (34%)	13 (38%)	6 (19%)	28 (31%)	15 (33%)	0.34
AF	223 (68%)	87 (69%)	24 (71%)	25 (81%)	56 (63%)	31 (67%)	0.39
AF during echo	159 (49%)	63 (50%)	16 (47%)	17 (55%)	41 (46%)	22 (49%)	0.12

AF: atrial fibrillation (paroxysmal, persistent or permanent); HF-TR: Tricuspid Regurgitation with Heart Failure; LVHD-TR: TR with concomitant significant left-sided valvular heart disease; PHTN-TR: TR with pulmonary hypertension; postop-TR: TR after previous open-heart valvular surgery.

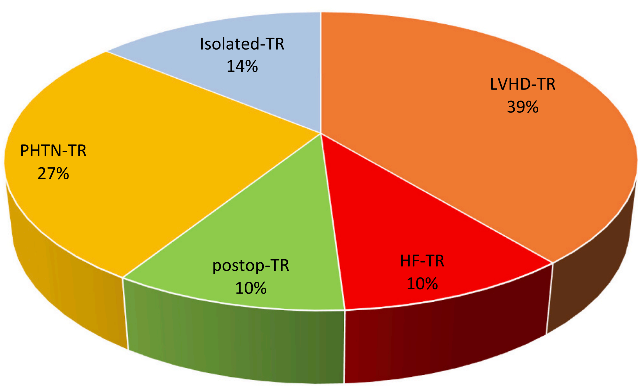

Fig. 1. Distribution Patterns of TR.
HF-TR: Tricuspid Regurgitation with Heart Failure; LVHD-TR: TR with concomitant significant left-sided valvular heart disease; PHTN-TR: TR with pulmonary hypertension; postop-TR: TR after previous open-heart valvular surgery.

Among morphologic phenotypes, V-TR was predominant (63%). A-TR patients were younger and more frequently presenting with AF vs. V-TR (Supplementary Data, Table 1).

3.3. *Echocardiographic characteristics*

The mean LVEF was 54 ± 14% and mean estimated sPAP was 48 ± 13 mmHg. Relevant PHTN (defined as sPAP ≥50 mmHg) was found in 37% of patients ($n = 119$), mostly related to V-TR ($n = 103$), and severe TR in 33% of patients ($n = 108$) (Table 2). Right atrial dilation was almost invariably present in all subgroups while right ventricle dilation, found in 48% of cases, was less common in the isolated-TR group (37%, $n = 17$) and more common in HF-TR group, where 56% had mild dilation and 15% had relevant dilation. RV dysfunction was more frequent in HF-TR (21%, $n = 7$) and LHVD-TR (13%, $n = 16$). LVEF was lower in HF-TR and LVHD-TR groups. Isolated-TR was associated with a lower grade of TR severity ($P < 0.0001$), lower sPAP ($P < 0.0001$) and lower rate of increased RAP ($P = 0.01$).

3.4. *TR clinical outcome*

During a median follow-up of 6.1 [interquartile range 1.9–8.7] years, 95 (29%) patients died and 20 (6%) patients had HF hospitalization after diagnosis of at least moderate TR. Survival curves for the composite of HF or death showed worse outcome for severe vs. moderate TR. Four years event-free survival was 72% ± 5 in patients with severe-TR and 87% ± 3 in moderate TR, while at eight years it was respectively 59% ± 6 for severe-TR versus 70% ± 4 for moderate-TR (Fig. 2).

Moreover, comparing severe-TR versus moderate-TR, observed event-free survival was significantly lower in the first group with a HR of 1.75 [95% CI 1.12–2.73; $P = 0.01$]. These results were confirmed also in a multivariate model after adjustment for AF, age, sex, sPAP and LVEF with a HR of 1.76 [95% CI 1.08–2.88; $P = 0.02$] (Table 3). We found no interaction between AF and TR grades' prognostic impact ($P = 0.5$).

Analyzed for each clinical subset (Fig. 3), eight-year event-free survival was 87 ± 7% for postop-TR subgroup, 75 ± 7% for isolated-TR, 67 ± 6% for PHTN-TR, 58 ± 6% for LVHD-TR and 51 ± 11% for HF-TR.

Table 2
Echocardiographic characteristics by different TR subcategories.

Echo characteristics	Overall (n = 327)	LVHD-TR (n = 127)	HF-TR (n = 34)	Postop-TR (n = 31)	PHTN-TR (n = 89)	Isolated-TR (n = 46)	P-Value
LVEF (%)	54 ± 14	49.9 ± 14.8	50.2 ± 17.5	55.4 ± 12.1	57.8 ± 12.8	56.4 ± 10.0	0.0009
RV dysfunction	31 (9%)	16 (13%)	7 (21%)	1 (3%)	4 (4%)	3 (7%)	0.03
RV dilation							
-Mild/Mod	140 (43%)	56 (44%)	19 (56%)	12 (39%)	37 (42%)	16 (35%)	0.03
-Severe	17 (5%)	3 (2%)	5 (15%)	3 (10%)	5 (6%)	1 (2%)	
RA dilation							
-Mild/Mod	133 (41%)	56 (44%)	13 (38%)	11 (36%)	30 (34%)	23 (50%)	0.79
-Severe	130 (40%)	46 (36%)	16 (47%)	13 (42%)	38 (43%)	17 (37%)	
sPAP (mmHg)	48 ± 13	49.5 ± 11.8	52.1 ± 17.4	43.1 ± 8.5	51.3 ± 11.4	34.5 ± 2.9	< 0.0001
TR severity (moderate/severe or severe)	108 (33%)	40 (32%)	34 (100%)	8 (25%)	20 (23%)	6 (13%)	< 0.0001
Increased RAP (> 10 mmHg)	107 (33%)	43 (34%)	13 (38%)	12 (39%)	34 (38%)	5 (11%)	0.02

HF-TR: Tricuspid Regurgitation with Heart Failure; LVEF: left ventricular ejection fraction; LVHD-TR: TR with concomitant left-sided valvular heart disease; PHTN-TR: TR with pulmonary hypertension; postop-TR: TR after previous open-heart valvular surgery; RA: right atrium; RAP: right atrium pressure; RV: right ventricle; sPAP: systolic pulmonary artery pressure.

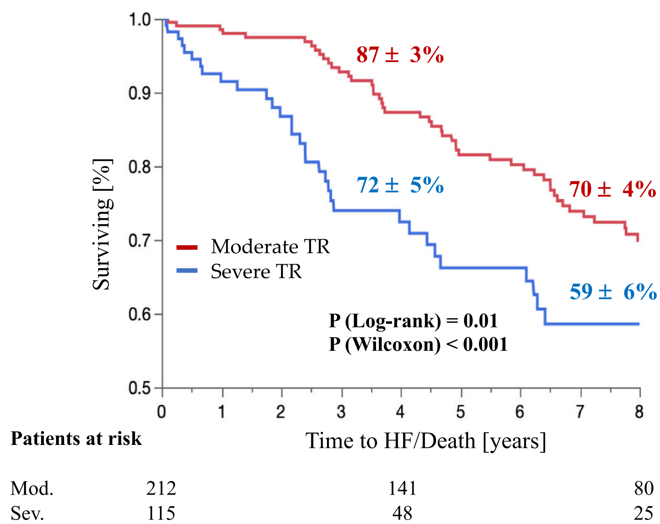

Fig. 2. Kaplan Meier event-free survival by TR severity.

Table 3
Univariable and multivariable Cox proportional hazard models (Cox PH) for mortality and hospitalization for HF of severe vs. moderate TR.

	Univariable model		Multivariable model: adjustement for AF, sPAP ≥ 50, LVEF ≤ 30%, age and sex	
	HR (95% CI)	P – value	HR (95% CI)	P – value
Severe TR vs. Moderate TR	1.75 (1.12–2.73)	0.01	1.76 (1.08–2.88)	0.02

AF: atrial fibrillation; HF: Heart Failure; HR: hazard ratio; LVEF: left ventricular ejection fraction; sPAP: systolic pulmonary artery pressure; TR: tricuspid regurgitation.

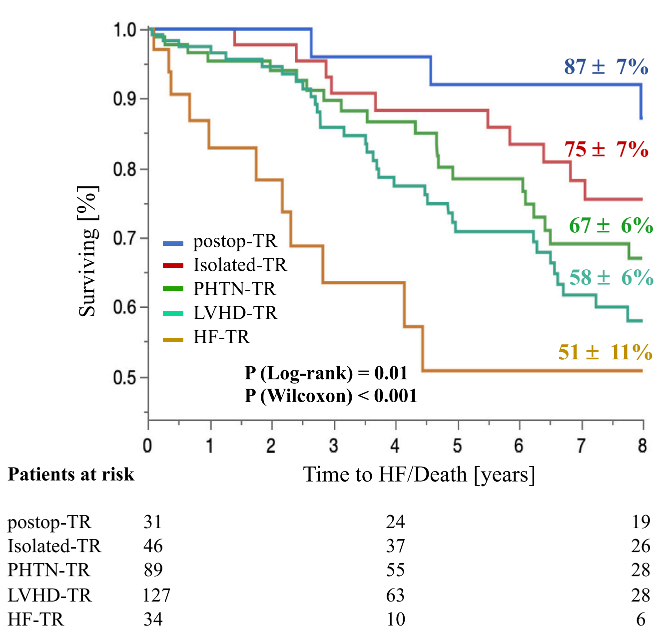

Fig. 3. Kaplan Meier event-free survival by different clinical subsets.
HF-TR: Tricuspid Regurgitation with Heart Failure; LVHD-TR: TR with concomitant significant left-sided valvular heart disease; PHTN-TR: TR with pulmonary hypertension; postop-TR: TR after previous open-heart valvular surgery.

HRs for HF-TR were respectively 4.80 [95% CI 1.63–14.13; P = 0.004] vs. postop-TR, 2.41 [95% CI 1.06–5.43; P = 0.04] vs. isolated-TR, and 2.18 [95% CI 1.03–4.62; P = 0.04] vs. PHTN-TR.

HRs for LVHD-TR were 3.10 [95% CI 1.21–7.97; P = 0.02] vs. postop-TR while no difference was found vs. isolated-TR [HR 1.56; 95% CI 0.84–2.89; P = 0.16] and PHTN-TR [HR 1.41; 95% CI 0.83–2.40; P = 0.21] (Table 4). After adjustment for RV e RA parameters, HF-TR, LVHD-TR and PHTN-TR were related to worse outcome vs. postop-TR (P = 0.008, P = 0.008, P = 0.05, respectively). In the subset of LVHD-TR, aortic stenosis and mitral regurgitation did not significantly impact the event-free rates at survival analysis (P = 0.1).

Finally, considering the morphologic phenotypes of TR, V-TR showed worse event-free survival than A-TR (Supplementary Data, Fig. 1): 59 ± 4% vs. 75% ± 4 at eight years [HR 1.91; 95% CI 1.21–2.99, P = 0.005].

Of note, only 9 patients (2.8%) of the overall cohort underwent TR surgical treatment during the follow-up.

4. Discussion

The main findings of the present study are the following:

- Moderate or severe TR is found in 4.8% patients in the community,
- TR severity significantly affects clinical outcome,
- The clinical context in which TR occurs has remarkable impact on absolute event rate.

4.1. *TR prevalence and clinical characteristics*

The prevalence of moderate or more TR in our cohort of outpatients from a geographically defined area in northern Italy is in agreement with other studies. *Vieitz* et al. observed a prevalence of at least moderate TR of 6% in a population of 35,088 patients undergoing clinically indicated echocardiography [4], while *Chorin* et al. reported a prevalence of 4.45% in 13,026 outpatients undergoing echocardiography in Tel Aviv Medical Center Echo Laboratory [12]. Therefore, TR should be regarded as a noteworthy condition in the general population, comparable to the prevalence of left valve diseases [13,14]. Moreover, it is in line with the 4.5% prevalence of moderate or severe aortic stenosis in patients aged >75 years [15] in a community cohort of 16,543 adults referred for clinically indicated echocardiography in Olmsted County, Minnesota.

The outcome data reported reported in the present study also confirms the findings in literature [1,4,16] that at least moderate TR constituted a strong independent predictor of adverse outcome, especially with increasing severity of TR. *Fortuni* et al. studied a population of 1129 patients with significant TR and found 1-, 5- and 10-year survival rates of 79%, 56%, and 42%, respectively [17].

However, in the present study compared to previous data, we observed an overall higher event free survival (the four-year event-free survival rates in severe and moderate TR were respectively 72% ± 5 and

Table 4
Relevant risk ratios for mortality and hospitalization for HF by clinical subsets.

Risk ratio by clinical subsets		HR (95% CI)	P – value
HF-TR	vs. postop-TR	4.80 (95% CI 1.63–14.13)	0.004
	vs. Isolated-TR	2.41 (95% CI 1.06–5.43)	0.04
	vs. PHTN-TR	2.18 (95% CI 1.03–4.62)	0.04
LHVD-TR	vs. postop-TR	3.10 (95% CI 1.21–7.97)	0.02
	vs. Isolated-TR	1.56 (95% CI 0.84–2.89)	0.16
	vs. PHTN-TR	1.41 (95% CI 0.83–2.40)	0.21

HF-TR: Tricuspid Regurgitation with Heart Failure; LVHD-TR: TR with concomitant significant left-sided valvular heart disease; PHTN-TR: TR associated with pulmonary hypertension; postop-TR: TR after previous open-heart valvular surgery.

87% ± 3), which might be related to the selected outpatients' setting of our study.

The prevalence and outcome of TR confirmed by our data corroborate the fact that TR is a public health problem, also considering the global progressive aging of the population [18].

4.2. TR: Different clinical settings

Our study shows that TR is mostly occurring in the context of left heart diseases, notably heart failure and mitral regurgitation, with LVHD-TR and HF-TR subgroups representing half of cases of relevant TR. This finding is aligned with evidence from other institutions [1,4].

Furthermore, this study highlights the remarkable variability of event-free survival related to the different clinical settings, little described in other reports. As expected, the outcome was particularly poor in patients with TR associated with left heart disease (HF-TR and LVHD-TR). While the mutual relation between TR and HF had long been a matter of debate, solid evidence of independent excess mortality together with increasing TR grade and the reported survival benefit of TR correction [19] highly suggested that TR was not only a marker or bystander but the cause of worsening HF with impact on outcome [16,20].

Conversely, postop-TR patients had the best outcome among all groups. This result can be explained considering that these patients were younger (mean age 71 ± 9 years), with only 5 patients >80 years old, have less severe TR, intrinsically lower surgical risk vs. those medically managed, and have already undergone correction of a concomitant life-threatening disease. Indeed, only 8 patients had severe TR (25% of postop-TR), and left ventricular performance was mostly within normal limits (mean LVEF 55.4 ± 12.1). While a more favorable natural history of postop-TR and isolated-TR vs. other subsets have been reported also by other authors [21], TR progression and at least moderate TR after mitral valve surgery were related to worsening NYHA class, heart failure, redo mitral valve surgery and stroke by other groups [22]. In the present study, the outcome of postop-TR and isolated-TR may result from the outpatient setting design of our study; nonetheless, the heterogeneity of the cohorts of postop-TR patients and the presented outcomes might be additional sources of discrepancies. Accumulation of evidence is needed for the individual contexts, especially in view of emerging therapeutic perspectives for TR [23].

According to the most recent insights into TR classification [11], V-TR was associated with worse prognosis, agreeing with recent research [24]. Nevertheless, the distinction between A-TR and V-TR may not always be unequivocal: long-standing A-TR may lead to RV dilatation and dysfunction, resulting in a mixed phenotype [11].

Our study underscores the critical prognostic role of the clinical setting in which TR occurs to understand the patient outcome and the natural history of the pathology. This evaluation is complementary to the severity of the TR. In our vision the clinical context may give a prognostic stratification of the patients with TR, useful to determine patient management and timing of potential interventional treatment [23,25,26].

Only a very low percentage of patients in the overall cohort underwent TR surgical treatment (2.8%), confirming that TR, despite its poor outcome, remains almost undertreated in routine practice. Current guidelines advocate surgical repair or replacement only in limited cases and the chance to have TR surgery concomitant to other procedures depends on the patient's risk profile and the centers' expertise [27]. Less invasive techniques including percutaneous treatment are being introduced and might become an option in the future particularly for patients at high surgical risk [19,23,28,29].

5. Limitations

The main limitation of the present study is the retrospective observational nature, and that it does not analyze systematic echocardiograms of the entire population or a random sample. Nevertheless, it represents a picture of the largest outpatient clinic in the area, aiming to display the burden of TR and its natural history based on diverse clinical settings. Furthermore, data were retrieved unaltered form the clinical notes, representing a picture of the outpatient routine practice without additional interpretation or elaboration.

Despite the exclusion of patients with relevant TR mainly related to device leads, we cannot completely exclude interference from PM lead as a component of TR. Pacemaker carriers were however only 19% (n = 63), and 22% of them (n = 14) had an implantable defibrillator.

The definition of TR contexts slightly differs from the study of Topilsky et al., particulary considering HF-TR as we decided to apply more strict echocardiographic criteria and add related HF clinical features to better suit the outpatient setting in which the study was conducted [1].

In addition, SPAP was assessed by echocardiography only: in presence of severe TR, this measure could underestimate the actual pulmonary artery pressure. This aspect does not affect our hierarchical classification, particularly for the first four groups defined by a step-by-step approach. Nonetheless, even if the outcome link suggests otherwise, we cannot exclude that some of the patients of isolated – TR may present underestimated sPAP by echocardiography and thus truly belong to the PHTN – TR group.

Finally, quantitative TR grading and right chamber size were not homogeneously available for all patients limiting the possibility to identify more than severe TR grades [30].

6. Conclusions

Relevant TR is a notable finding in the outpatient community and holds significant prognostic value, particularly when severe, with the worst outcomes occurring in the context of relevant left-sided valvular heart disease or HF. Furthermore, despite its frequency TR is rarely treated.

These results underscore the importance of early diagnosis and accurate evaluation through comprehensive echocardiography, and renew the interest in novel and safe, less invasive percutaneous intervention to improve patients' survival.

Author contributions

Conceptualization, G.B. and D.L.; methodology, G.B.; software, G.B.; validation, G.B., F.B., M.E.S. and F.L.R.; formal analysis, G.B.; investigation, D.L.; resources, G.B.; data curation, D.L.; writing—original draft preparation, D.L., F.B. and P·S; writing—review and editing, F.B., A.D., L.C., P·S and D.F.; visualization, C·B, E.T., C.M., R.S.; supervision, G.B., M.E.S. and F.L.R.; critical review, M.E.S; project administration, G.B., F. L.R. All authors have read and agreed to the published version of the manuscript.

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Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Verona's Hospital.

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Declaration of Competing Interest

The authors declare no conflict of interest.

Data availability

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2023.131443.

References

[1] Y. Topilsky, S. Maltais, J. Medina Inojosa, et al., Burden of tricuspid regurgitation in patients diagnosed in the community setting, JACC Cardiovasc. Imaging 12 (3) (2019) 433–442, https://doi.org/10.1016/j.jcmg.2018.06.014.

[2] C.M. Otto, R.A. Nishimura, R.O. Bonow, et al., 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines, Circulation. 143 (5) (2021), https://doi.org/10.1161/CIR.0000000000000923.

[3] A. Vahanian, F. Beyersdorf, F. Praz, et al., 2021 ESC/EACTS guidelines for the management of valvular heart disease, Eur. Heart J. 43 (7) (2022), https://doi.org/10.1093/eurheartj/ehab395.

[4] J.M. Vieitez, J.M. Monteagudo, P. Mahia, et al., New insights of tricuspid regurgitation: a large-scale prospective cohort study, Eur. Heart J. Cardiovasc. Imaging 22 (2) (2021) 196–202, https://doi.org/10.1093/ehjci/jeaa205.

[5] J.L. D'Arcy, S. Coffey, M.A. Loudon, et al., Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE population cohort study, Eur. Heart J. 37 (47) (2016) 3515–3522a, https://doi.org/10.1093/eurheartj/ehw229.

[6] M.E. Staab, R.A. Nishimura, J.A. Dearani, Isolated tricuspid valve surgery for severe tricuspid regurgitation following prior left heart valve surgery: analysis of outcome in 34 patients, J. Heart Valve Dis. 8 (5) (1999) 567–574. https://pubmed.ncbi.nlm.nih.gov/10517400/.

[7] A.W. Zoghbi, M. Enriquez-Sarano, E. Foster, et al., Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and doppler echocardiography, JASE. 16 (7) (2003) 777–802, https://doi.org/10.1016/S0894-7317(03)00335-3.

[8] R.T. Hahn, J.D. Thomas, O.K. Khalique, J.L. Cavalcante, F. Praz, W.A. Zoghbi, Imaging assessment of tricuspid regurgitation severity, JACC Cardiovasc. Imaging 12 (3) (2019) 469–490, https://doi.org/10.1016/j.jcmg.2018.07.033.

[9] L.P. Badano, D. Muraru, M. Enriquez-Sarano, Assessment of functional tricuspid regurgitation, Eur. Heart J. 34 (25) (2013) 1875–1884, https://doi.org/10.1093/eurheartj/ehs474.

[10] L.G. Rudski, W.W. Lai, J. Afilalo, L. Hua, et al., Guidelines for the Echocardiographic Assessment of the Right Heart in Adults: A Report from the American Society of Echocardiography, in: Endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography vol. 23, JASE, 2010, https://doi.org/10.1016/j.echo.2010.05.010.

[11] R.T. Hahn, Tricuspid regurgitation, N. Engl. J. Med. 388 (20) (1876), https://doi.org/10.1056/NEJMra2216709, 1876–1891.

[12] E. Chorin, Z. Rozenbaum, Y. Topilsky, et al., Tricuspid regurgitation and long-term clinical outcomes, Eur. Heart J. Cardiovasc. Imaging 21 (2) (2020) 157–165, https://doi.org/10.1093/ehjci/jez216.

[13] J. Hung, S. Elmariah, The forgotten valve finally gets some respect, JACC Cardiovasc. Imaging 12 (3) (2019) 398–400, https://doi.org/10.1016/j.jcmg.2018.12.006.

[14] E.A. Prihadi, Tricuspid valve regurgitation: no longer the "forgotten valve", ESC E-J. Cardiol. Pract. 16 (30) (2018) 1–14, https://doi.org/10.33590/emjcardiol/10314906.

[15] V.T. Nkomo, J.M. Gardin, T.N. Skelton, J.S. Gottdiener, C.G. Scott, M. Enriquez-Sarano, Burden of valvular heart diseases: a population-based study, Lancet. 368 (9540) (2006) 1005–1011, https://doi.org/10.1016/S0140-6736(06)69208-8.

[16] G. Benfari, C. Antoine, W.L. Miller, et al., Excess mortality associated with functional tricuspid regurgitation complicating heart failure with reduced ejection fraction, Circulation. 140 (3) (2019) 196–206, https://doi.org/10.1161/CIRCULATIONAHA.118.038946.

[17] F. Fortuni, M.F. Dietz, E.A. Prihadi, et al., Prognostic implications of a novel algorithm to grade secondary tricuspid regurgitation, JACC Cardiovasc. Imaging 14 (6) (2021) 1085–1095, https://doi.org/10.1016/j.jcmg.2020.12.011.

[18] M. Enriquez-Sarano, D. Messika-Zeitoun, Y. Topilsky, C. Tribouilloy, G. Benfari, H. Michelena, Tricuspid regurgitation is a public health crisis, Prog. Cardiovasc. Dis. 62 (6) (2019) 447–451, https://doi.org/10.1016/j.pcad.2019.10.009.

[19] M. Taramasso, G. Benfari, P. van der Bijl, et al., Transcatheter versus medical treatment of patients with symptomatic severe tricuspid regurgitation, JACC. 74 (24) (2019) 2998–3008, https://doi.org/10.1016/j.jacc.2019.09.028.

[20] D. Margonato, F. Ancona, G. Ingallina, F. Melillo, S. Stella, F. Biondi, A. Boccellino, C. Godino, A. Margonato, E. Agricola, Tricuspid regurgitation in left ventricular systolic dysfunction: marker or target? Front. Cardiovasc. Med. (2021) https://doi.org/10.3389/fcvm.2021.702589.

[21] S. Nakagawa, H. Takahama, K. Hoshino, Y. Yanagi, Y. Irie, K. Moriuchi, M. Amano, A. Okada, M. Amaki, H. Kanzaki, K. Kusano, T. Noguchi, S. Yasuda, C. Izumi, Prevalence and predictive factors for clinical outcomes of isolated functional tricuspid regurgitation, J. Cardiol. 82 (1) (2023), https://doi.org/10.1016/j.jjcc.2022.12.008.

[22] P.B. Bertrand, J.R. Overbey, X. Zeng, R.A. Levine, G. Ailawadi, M.A. Acker, P. K. Smith, V.H. Thourani, E. Bagiella, M.A. Miller, L. Gupta, M.J. Mack, A. M. Gillinov, G. Giustino, A.J. Moskowitz, et al., Progression of tricuspid regurgitation after surgery for ischemic mitral regurgitation, J. Am. Coll. Cardiol. 77 (6) (2021), https://doi.org/10.1016/j.jacc.2020.11.066.

[23] M. Nabauer, M. Orban, Treatment of tricuspid valve regurgitation: the future is now, JACC Cardiovasc. Interv. [Internet] 14 (1) (2021) 51–53, https://doi.org/10.1016/j.jcin.2020.11.009.

[24] M. Gavazzoni, F. Heilbron, L.P. Badano, N. Radu, A. Cascella, M. Tomaselli, F. Perelli, S. Caravita, C. Baratto, G. Parati, D. Muraru, The atrial secondary tricuspid regurgitation is associated to more favorable outcome than the ventricular phenotype, Front. Cardiovasc. Med. (2022) 9, https://doi.org/10.3389/fcvm.2022.1022755.

[25] N. Karam, D. Braun, M. Mehr, et al., Impact of Transcatheter tricuspid valve repair for severe tricuspid regurgitation on kidney and liver function, JACC Cardiovasc. Interv. 12 (15) (2019), https://doi.org/10.1016/j.jcin.2019.04.018.

[26] M. Arsalan, T. Walther, R.L. Smith, P.A. Grayburn, Tricuspid Regurgitation Diagnosis and Treatment vol. 38, Eur Heart J. Oxford University Press, 2017, pp. 634–638, https://doi.org/10.1093/eurheartj/ehv487.

[27] A.P. Tagliari, D. Perez-Camargo, M. Taramasso, Tricuspid regurgitation: when is it time for surgery? Expert. Rev. Cardiovasc. Ther. 19 (1) (2021) 47–59, https://doi.org/10.1080/14779072.2021.1854734.

[28] O.M. Demir, D. Regazzoli, A. Mangieri, et al., Transcatheter tricuspid valve replacement: principles and design, Front. Cardiovasc. Med. 5 (2018), https://doi.org/10.3389/fcvm.2018.00129.

[29] M. Alkhouli, J.J. Lopez, V. Mathew, Transcatheter therapy for severe tricuspid regurgitation: learning to understand the forgotten valve, JACC. 74 (24) (2019) 3009–3012, https://doi.org/10.1016/j.jacc.2019.09.029.

[30] R.T. Hahn, J.L. Zamorano, The need for a new tricuspid regurgitation grading scheme, Eur. Heart J. Cardiovasc. Imaging 18 (12) (2017) 1342–1343, https://doi.org/10.1093/ehjci/jex139.