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CLINICAL RESEARCH

Characteristics and prognosis of patients with significant tricuspid regurgitation

Caractéristiques et pronostic des patients présentant une insuffisance tricuspide significative

Yohann Bohbot[a,b], Gagandeep Chadha[a], Justine Delabre[a], Thomas Landemaine[a], Christophe Beyls[a], Christophe Tribouilloy[a,b,*]

[a] *Department of Cardiology, Amiens University Hospital, avenue René-Laënnec, 80054, Amiens cedex 1, France*
[b] *EA 7517, MP3CV, Jules Verne University of Picardie, chemin du Thil, 80054, Amiens cedex, France*

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KEYWORDS
Tricuspid regurgitation;
Prognosis;
Right heart failure;
Tricuspid valve surgery;
Isolated tricuspid regurgitation

Summary
Background. — Severe tricuspid regurgitation (TR) usually remains asymptomatic for a long period, and the diagnosis is often delayed until an advanced stage of right heart failure (RHF). Only a minority of patients are referred for surgery.
Aim. — To describe the characteristics and prognosis of patients with significant TR, according to aetiology.
Method. — Two-hundred and eight consecutive patients with moderate-to-severe (grade III) or severe (grade IV) TR were included from echocardiography reports between 2013 and 2017. Median follow-up was 18 (6—38) months.
Results. — Patients (mean age 75 years; 46.6% men) were divided into four groups according to TR aetiology: group 1, primary TR (14.9%); group 2, TR secondary to left heart disease with a history of left heart valve surgery (24.5%); group 3, TR secondary to left heart or pulmonary disease with no history of left valvular surgery (26.5%); and group 4, idiopathic TR (34.1%). During follow-up, 61 patients (29.3%) experienced at least one episode of RHF decompensation requiring hospitalization. Only 11 patients (5.3%) underwent tricuspid valve surgery during

Abbreviations: CI, confidence interval; HR, hazard ratio; ITVS, isolated tricuspid valve surgery; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RHF, right heart failure; RV, right ventricular; S', peak systolic velocity of the tricuspid annulus; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

* Corresponding author at: Department of Cardiology, Amiens University Hospital, avenue René-Laënnec, Amiens cedex 1, 80054, France.
E-mail address: tribouilloy.christophe@chu-amiens.fr (C. Tribouilloy).

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follow-up. The 4-year survival was much lower than the expected survival of age- and sex-matched individuals in the general population (56 ± 4% vs. 74%). After adjustment for outcome predictors, patients with idiopathic TR had a higher risk of mortality (adjusted hazard ratio 1.83, 95% confidence interval 1.05—3.21; $P = 0.034$) compared with other groups.

Conclusions. — Moderate-to-severe or severe TR is associated with a high risk of hospitalization for RHF and death at 4 years, and a low rate of surgery. Idiopathic TR is associated with worse outcome than other aetiologies.

MOTS CLÉS
Insuffisance tricuspide ;
Pronostic ;
Insuffisance cardiaque droite ;
Chirurgie valvulaire tricuspide ;
Insuffisance tricuspide isolée

Résumé

Contexte. — L'insuffisance tricuspide (IT) sévère reste le plus souvent asymptomatique pendant une longue période, souvent diagnostiquée avec un retard important au stade d'insuffisance cardiaque droite (IVD) avancée. Seule une minorité de patients est opérée.

Objectif. — —De décrire les caractéristiques ainsi que le pronostic des patients présentant une IT significative selon l'étiologie de l'IT.

Méthodes. — Deux cent huit patients consécutifs porteurs d'une IT moyenne (grade III) ou sévère (grade IV) ont été inclus à partir des comptes rendus d'échocardiographie entre 2013 et 2017. Le suivi médian était de 18 (6—38) mois.

Résultats. — Les patients (âge moyen 75 ans; 46,6 % d'hommes) ont été divisés en 4 groupes en fonction de l'étiologie de l'IT: groupe 1, IT primaire (14,9 %); groupe 2, IT secondaire à une cardiopathie gauche avec antécédents de chirurgie valvulaire gauche (24,5 %); groupe 3, IT secondaire à une cardiopathie gauche ou à une maladie pulmonaire sans antécédents de chirurgie valvulaire gauche (26,5 %); et groupe 4, IT idiopathiques (34,1 %). Au cours du suivi, 61 patients (29,3 %) ont présenté au moins une poussée d'IVD nécessitant une hospitalisation. Seuls 11 patients (5,3 %) ont bénéficié d'une chirurgie valvulaire tricuspide au cours du suivi. La survie à 4 ans était très inférieure à la survie attendue dans la population générale appariée pour l'âge et le sexe (56 ± 4 % vs 74 %). Après ajustement aux paramètres associés au pronostic, les patients avec une IT idiopathique avaient un risque de mortalité plus élevé (HR ajusté 1,83, 1,05—3,21; $P = 0,034$) que les autres groupes.

Conclusions. — L'IT de grade III ou IV est associée à un risque élevé d'hospitalisation pour IVD et de décès et à un faible taux de chirurgie à 4 ans. L'IT idiopathique est associée à un plus mauvais pronostic que les autres étiologies.

Background

The tricuspid valve is often called the ''forgotten valve'' because its echocardiographical assessment is relatively difficult and the management of patients with tricuspid valve diseases remains poorly defined [1—4]. Significant (at least moderate) tricuspid regurgitation (TR) is common, affecting about 0.5% of the general population [5], and its prevalence increases markedly after the age of 75 years, especially in women and in the presence of atrial fibrillation [6]. Whereas trivial TR is extremely frequent and benign, significant TR is associated with a poor prognosis [7,8]. The mechanisms of TR are mainly secondary [9,10], while primary TR is less common. Idiopathic (or isolated secondary) TR, defined by structurally normal tricuspid valves, no overt organic TR cause, no left-sided valvular heart disease and preserved left ventricular ejection fraction (LVEF), is not rare [9,10], especially in older patients. TR usually remains asymptomatic for a long time and is often diagnosed only at an advanced stage of right heart failure (RHF). A minority of patients (< 1%) are referred for surgery because the operative mortality risk is often considered unacceptable in older patients, especially in the presence of right ventricular (RV) dysfunction [11,12]. Guidelines from Europe [1] and the USA [13] concerning isolated tricuspid valve surgery (i.e. without left-sided valve surgery) remain vague in view of the small number of prognostic studies and their contradictory findings [14,15], which are often influenced by the patients' major comorbidities [14]. The dynamic nature of TR also highlights the difficulty in identifying patients who are likely to benefit from a surgical procedure. It is therefore crucial to acquire more data to understand more clearly the natural history and prognosis of TR, and to try to define the optimal timing of surgery.

The aims of this study were to:

- describe the clinical and echocardiographic characteristics of patients with significant TR who were followed in our heart valve centre;

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- assess the long-term survival of these patients relative to that of the general population;
- evaluate the frequency of ''idiopathic'' TR among moderate-to-severe and severe TR;
- evaluate the long-term prognosis of ''idiopathic TR'' compared with other causes of TR.

Methods

Inclusion criteria

Between January 2013 and December 2017, 208 consecutive patients aged ≥ 18 years, with a diagnosis of moderate-to-severe or severe TR on echocardiography, were identified prospectively and included in an electronic database. Patients were divided into four groups according to TR aetiology: group 1, primary TR (including drug-induced valve diseases, rheumatic valvular disease, myxomatous disease, infective endocarditis, carcinoid syndrome, congenital heart disease, traumatic and postiatrogenic); group 2, TR secondary to left heart disease with previous left heart valve surgery; group 3, TR secondary to left heart or pulmonary disease without previous cardiac surgery; and group 4, idiopathic TR. Idiopathic TR was defined by structurally normal tricuspid valves with no overt organic TR cause, no left-sided valvular heart disease, preserved LVEF and no previous cardiac surgery [6,10].

Data on baseline clinical and demographic characteristics, including age, sex, body mass index and cardiovascular risk factors, were collected. The Charlson Comorbidity Index, comprising the sum of individual comorbidities, was calculated for each patient [16]. Renal failure was defined by a creatinine clearance < 50 mL/min. This study was approved by an independent ethics committee, and was conducted in accordance with institutional policies, French legislation and the revised Declaration of Helsinki (ID-RCB: 2017-A03233-50).

Echocardiography

All patients underwent a comprehensive Doppler echocardiographic assessment, using commercially available ultrasound systems. Three consecutive measurements in patients in sinus rhythm and five consecutive measurements in patients in atrial fibrillation were systematically averaged. TR was graded according to an integrative approach [17,18], using semiquantitative (colour flow jet area, vena contracta width, proximal isovelocity surface area [PISA] radius, hepatic vein flow and tricuspid inflow) and quantitative variables (effective regurgitant orifice area, regurgitant volume) [17—20]. Tricuspid valve morphology was evaluated using a multiview approach (parasternal long-axis, parasternal short-axis, apical four-chamber and subcostal views). Right ventricular (RV) assessment was based on multiple views. RV function was evaluated using tricuspid annular plane systolic excursion (TAPSE) and peak systolic velocity of the tricuspid annulus (S') [21]. RV dilation was defined by a basal linear diameter and/or a proximal outflow diameter > 42 mm, and RV dysfunction was defined by either TAPSE < 14 mm and/or S' < 10 cm/s [21]. Left and right atrial areas were measured in the apical four-chamber view, and were considered to be enlarged when > 20 cm^2 and > 18 cm^2, respectively [21]. Tricuspid annular diameter was considered to be dilated when > 4 cm in the standard apical four-chamber view [21]. Left ventricular (LV) wall thickness and dimensions were assessed from parasternal long-axis views by two-dimensional guided M-mode, using the leading-edge methodology at end-diastole and end-systole. LV dilatation was defined by end-diastolic diameter > 60 mm and/or end-systolic diameter > 40 mm. LVEF was calculated using Simpson's biplane method [21].

Follow-up and endpoints

Median (interquartile range) follow-up was 18 (6—38) months. Most patients were followed by clinical consultations and echocardiography in the outpatient clinic at Amiens Hospital. A few patients were followed in public hospitals or private practices by referring cardiologists working in collaboration with our centre. All surviving patients (n = 139) were followed until the end of the study, with an inclusion date corresponding to the date of baseline echocardiography. No patients were lost to follow-up. Information on follow-up was obtained by direct patient interview and clinical examination and/or repeated follow-up letters, questionnaires and telephone calls to physicians, patients and (if necessary) next of kin. The primary endpoint was all-cause mortality. The two secondary endpoints were hospitalization for RHF and the combination of hospitalization for RHF and cardiovascular mortality. Clinical decisions regarding medical management or referral for surgery were made by the Heart Team, with the approval of the patient's cardiologist, based on the European Society of Cardiology guidelines [1].

Statistical analysis

Continuous variables are expressed as means ± standard deviations or medians (interquartile ranges), and categorical variables are expressed as numbers (percentages). The relationship between baseline continuous variables and the various groups was explored using 1-way analysis of variance tests. The χ^2 test was used to compare categorical variables between groups. The independent-sample t-test or the Mann—Whitney U—test was used to compare continuous variables with normal or skewed distribution between groups. Event rates ± standard errors were estimated using the Kaplan-Meier method, and compared using two-sided log-rank tests. Survival of patients was compared with the expected survival of the age- and sex-matched population. Control data were obtained from Somme (a French department with 555,551 inhabitants) life tables, established on the basis of the 1999 population census carried out by the French Institute of National Statistics (INSEE) [22]. Relative survival was computed as the ratio of observed-to-expected survival (observed number of deaths in the TR population/expected number of deaths in the general population). Mortality and predictors of hospitalization for RHF analyses were performed using Cox proportional hazards models. Covariates considered to have a potential prognostic impact were tested in a univariate analysis. All significant variables in univariate analysis with P < 0.1 were included in the multivariable Cox analysis. The limit of statistical significance was

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Table 1 Distribution of tricuspid regurgitation aetiologies ($n = 208$).

Tricuspid regurgitation aetiologies	Number of patients (%)
Primary TR (group 1)	31/208 (14.9)
Valve prolapse	11/31 (34.4)
Active endocarditis	3/31 (9.4)
Drug-induced	3/31 (9.4)
Radiotherapy-induced	1/31 (3.1)
Post-traumatic	3/31 (9.4)
Postembolic	2/31 (6.2)
Pacemaker lead-induced	7/31 (21.9)
Carcinoid tumour	1/31 (3.1)
TR secondary to left heart or pulmonary disease	106/208 (51.0)
Previous left valvular surgery (group 2)	51/208 (24.5)
Aortic valve replacement	25/51 (49.0)
Mitral valve replacement	13/51 (25.5)
Mitral valve repair	8/51 (15.7)
Aortic + mitral valve replacement	5/51 (9.8)
No previous left valvular surgery (group 3)	55/208 (26.5)
Left heart disease	51/55 (92.7)
Pulmonary disease	4/55 (7.3)
Idiopathic TR (group 4)	71/208 (34.1)

TR: tricuspid regurgitation.

$P < 0.05$, and all tests were two-tailed. Data were analysed using SPSS 25.0 (SPSS Inc. Chicago, IL, USA).

Results

Baseline demographic and clinical characteristics

Table 1 summarizes the distribution of TR aetiologies. Of the 208 patients included, 119 (57%) had severe TR and 89 (43%) had moderate-to-severe TR. Secondary TR was the predominant aetiology in 177 patients (85.1%), 51 (24.5%) of whom had a history of left heart valve surgery (group 2), 55 (26.5%) had TR secondary to left heart or pulmonary disease with no history of left heart valve surgery (group 3) and 71 (34.1%) had idiopathic TR (group 4), while primary TR was diagnosed in only 31 patients (14.9%) (group 1).

Baseline demographic and clinical characteristics of the 208 patients (mean age 75 ± 14 years; 46.6% men) and the results of comparisons between the four groups are displayed in Table 2. About two-thirds of patients were classified as New York Heart Association (NYHA) stage I or II at the time of baseline echocardiography, and 52.4% of patients had a history of RHF. Patients with primary TR (group 1) were younger, with a mean age of 65 years ($P < 0.001$). Group 1 patients had lower rates of atrial fibrillation ($P < 0.05$), hypertension ($P < 0.05$), diuretics ($P < 0.001$) and comorbidities (lower Charlson Comorbidity Index score; $P < 0.05$) than the other groups. Patients in the idiopathic TR group (group 4) ($n = 71$; mean age 77 years) were mostly women (63.4%). Thirty-nine patients (54.9%) from this group had a history of RHF, 88.7% were in atrial fibrillation and 35.2% were NYHA stage III or IV. Fifty-eight patients from group 4 (81.7%) were treated with diuretics, at an average daily dose of 122 mg.

Only 11 patients (5.3%) underwent tricuspid valve surgery during follow-up: five tricuspid valve repairs; and six tricuspid valve replacements (five biological prostheses and one mechanical prosthesis). Tricuspid valve surgery was performed in two patients in group 1 (one valvular prolapse and one drug-induced TR), three patients in group 2 (one with previous mitral valve replacement and two with previous aortic valve replacement), four patients in group 3 (all had associated severe mitral regurgitation) and two patients in group 4.

Echocardiographic characteristics

Baseline echocardiographic variables are displayed in Table 3. Compared to patients with idiopathic TR (group 4), those with TR secondary to left heart disease (groups 2 and 3) had a more enlarged left ventricle (all $P < 0.001$), a lower LVEF ($P < 0.001$) and poorer RV function, with more impaired S'-waves and TAPSE (both $P < 0.001$). Patients with primary TR (group 1) had a smaller left atrial area ($P < 0.05$) and a lower LVEF ($P < 0.05$) compared with group 4. There were no significant differences between groups in terms of cardiac output ($P = 0.28$), TR severity ($P = 0.61$), inferior vena cava size ($P = 0.28$) and maximum velocity of TR ($P = 0.37$).

Overall mortality

Sixty-nine (33.2%) deaths were recorded during follow-up, 41 of which were cardiovascular-related deaths (59%). Overall survival rates were low: 74 ± 3% at 1 year; 65 ± 3% at 2 years; 61 ± 4% at 3 years; and 56 ± 4% at 4 years (Fig. 1). The 4-year survival of patients with TR was lower than the expected survival of the general population (56 ± 4% vs 74%). One-year and 4-year relative survival rates (observed number of deaths in the TR population/expected number of deaths in the general population) were 79.6% and 75.7%, respectively (Fig. 1).

Clinical and laboratory variables associated with mortality in univariate Cox analysis were age, male sex, NYHA stage ≥ III, signs of RHF, Charlson Comorbidity Index, low haemoglobin, renal failure and a diuretic dose > 125 mg/day (Table 4). In the multivariable Cox analysis, male sex, NYHA stage ≥ III, renal failure and a diuretic dose > 125 mg/day remained independently associated with mortality (Table 4).

Echocardiographic variables associated with mortality in the univariate Cox analysis were the presence of significant (i.e. at least moderate) left-sided valvular heart disease and the presence of RV systolic dysfunction (Table 5). In the multivariable analysis, only RV systolic dysfunction was independently associated with mortality (Table 5).

After pooling clinical, laboratory and echocardiographic variables, only male sex (adjusted hazard ratio [HR] 1.93, 95% confidence interval [CI] 1.14–3.75; $P = 0.014$), NYHA stage ≥ III (adjusted HR 1.58, 95% CI 1.01–2.65; $P = 0.050$) and a diuretic dose > 125 mg/day (adjusted HR 1.66, 95% CI

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Table 2 Clinical characteristics of patients with tricuspid regurgitation, according to aetiology.

Characteristic	Group 1	Group 2	Group 3	Group 4	*P* for trend
	(*n* = 31)	(*n* = 51)	(*n* = 55)	(*n* = 71)	
Age (years)	65 ± 19[b]	77 ± 9	77 ± 12	77 ± 13	< 0.001
Male sex	14 (45.2)	27 (52.9)	30 (54.5)	26 (36.6)	0.17
BMI (kg/m^2)	25 ± 5	27 ± 4	27 ± 6	27 ± 6	0.36
NYHA stage					
I—II	27 (87.1)	38 (74.5)	36 (65.5)	46 (64.8)	0.10
III—IV	4 (12.9)	13 (25.5)	19 (34.5)	25 (35.2)	
History of RHF	13 (41.9)	30 (58.8)	27 (49.1)	39 (54.9)	0.45
Hypertension	16 (51.6)[a]	39 (76.5)	46 (83.6)	53 (74.6)	0.012
Diabetes mellitus	4 (12.9)	16 (31.4)	17 (30.9)	19 (26.8)	0.26
Dyslipidaemia	12 (38.7)	34 (66.7)[a]	27 (49.1)	27 (38.0)	0.011
Charlson Comorbidity Index	2.5 ± 2[a]	3.8 ± 1.4	3.8 ± 2	3.6 ± 2	0.019
Atrial fibrillation	13 (41.9)[a]	43 (84.3)	47 (85.4)	63 (88.7)	0.024
Cirrhosis	1 (3.2)	2 (3.9)	4 (7.3)	5 (7.0)	0.77
Treatment					
ACE-I	12 (38.7)	13 (25.5)	22 (40.0)	18 (25.4)	0.20
ARB	1 (3.2)	11 (21.6)	9 (16.4)	10 (14.1)	0.15
Aldactone	5 (16.1)	16 (31.4)	13 (23.6)	18 (25.4)	0.48
Beta-blockers	18 (58.1)	38 (74.5)	36 (65.5)	49 (69.0)	0.46
Diuretics	16 (51.6)[b]	45 (88.2)	47 (85.5)	58 (81.7)	< 0.001
Dose of diuretics (mg/day)	105 ± 143	183 ± 271	162 ± 195	122 ± 140	0.33

Data are expressed as mean ± standard deviation (continuous variables) or number (%) (categorical variables). ACE-I: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; BMI: body mass index; NYHA: New York Heart Association; RHF: right heart failure; TR: tricuspid regurgitation. Group 1: primary TR; Group 2: TR secondary to left heart disease with previous left heart valve surgery; Group 3: TR secondary to left heart or pulmonary disease without previous cardiac surgery; and Group 4: idiopathic TR.
[a] $P < 0.05$ versus group 4.
[b] $P < 0.001$ versus group 4.

1.03—2.87; $P = 0.045$) were independently associated with mortality.

Four-year survival rates were 67 ± 7% for group 1, 65 ± 9% for group 2, 47 ± 11% for group 3 and 50 ± 7% for group 4 (log-rank $P = 0.63$) (Fig. 2A). In the multivariable Cox analysis, no significant difference in terms of survival was observed between the four groups ($P = 0.40$) (Fig. 2B), with no difference between primary and secondary TR ($P = 0.65$) or between TR secondary to left heart or pulmonary disease (group 2 + group 3) and the other groups ($P = 0.68$).

In the Kaplan-Meier analysis, there was no significant difference in terms of survival between patients with idiopathic TR and the rest of the population ($P = 0.42$) (Fig. 3A). However, in the multivariable analysis, idiopathic TR (group 4) was independently associated with significant excess mortality compared with the other causes of TR (adjusted HR 1.83, 95% CI 1.05—3.21; $P = 0.034$) (Fig. 3B).

RHF

During follow-up, 61 patients (29.3%) experienced at least one episode of RHF decompensation requiring hospitalization: six patients in group 1 (18.8%); 16 patients in group 2 (31.4%); 19 patients in group 3 (35.2%); and 20 patients in group 4 (28.2%) ($P = 0.43$).

In the univariate Cox analysis, clinical and laboratory variables associated with RHF decompensation requiring hospitalization were: NYHA stage III or IV (HR 2.53, 95% CI 1.53—4.18; $P < 0.001$); history of RHF (HR 2.71, 95% CI 1.51—4.89; $P = 0.001$); renal failure (HR 2.30, 95% CI 1.39—3.80; $P = 0.001$); and diuretic dose > 125 mg/day (HR 2.63, 95% CI 1.58—4.38; $P < 0.001$). In the multivariable Cox analysis, after inclusion of all of the above variables and cirrhosis ($P < 0.10$ in the univariate analysis), NYHA stage III or IV (adjusted HR 2.33, 95% CI 1.40—3.86; $P = 0.001$), history of RHF (adjusted HR 2.40, 95% CI 1.32—4.34; $P = 0.004$), renal failure (adjusted HR 2.03, 95% CI 1.21—3.41; $P = 0.007$) and diuretic dose > 125 mg/day (adjusted HR 1.90, 95% CI 1.12—3.21; $P = 0.017$) were independently associated with RHF decompensation requiring hospitalization.

Echocardiographic variables associated with RHF decompensation requiring hospitalization in the univariate Cox analysis were: LV dilatation (HR 1.82, 95% CI 1.08—3.07; $P = 0.024$); LVEF < 50% (HR 1.93, 95% CI 1.16—3.22; $P = 0.011$); RV dilatation (HR 1.91, 95% CI 1.14—3.21; $P = 0.015$); right atrial dilatation (HR 2.31, 95% CI 1.19—4.48; $P = 0.014$); and RV dysfunction (HR 1.89, 95% CI 1.14—3.13; $P = 0.013$). In the multivariable Cox analysis, after inclusion of all of the above variables and significant left valvular disease ($P < 0.10$ in the univariate analysis), only right atrial dilatation (adjusted HR 2.09, 95% CI 1.22—4.29; $P = 0.024$) and LVEF < 50% (adjusted HR 1.97, 95% CI 1.02—3.02; $P = 0.043$) were independently associated with RHF decompensation requiring hospitalization.

After pooling clinical, laboratory and echocardiographic variables, only NYHA stage III or IV (adjusted HR 2.38, 95%

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Table 3 Echocardiographic characteristics of patients with tricuspid regurgitation, according to aetiology.

Variable	Group 1 ($n=31$)	Group 2 ($n=51$)	Group 3 ($n=55$)	Group 4 ($n=71$)	P for trend
Left heart characteristics					
LV end diastolic diameter (mm)	47 ± 7	53 ± 9[a]	54 ± 9[a]	47 ± 6	< 0.001
LV end systolic diameter (mm)	34 ± 8	39 ± 11[b]	41 ± 9[a]	32 ± 7	< 0.001
LV end diastolic volume (mL)	98 ± 46	110 ± 57	126 ± 57[a]	78 ± 35	0.001
LV end systolic volume (mL)	53 ± 36	56 ± 48[b]	74 ± 48[a]	30 ± 15	< 0.001
LVEF (%)	54 ± 14[b]	53 ± 11[a]	43 ± 13[a]	61 ± 6	< 0.001
Left atrial area (cm^2)	25 ± 8[b]	31 ± 9	30 ± 9	28 ± 8	0.011
Cardiac output (L/min)	4.8 ± 1.3	4.7 ± 1.4	4.5 ± 1.5	5 ± 1.6	0.28
Right heart characteristics					
TAPSE (mm)	19 ± 6	15 ± 3[a]	16 ± 5[a]	19 ± 6	< 0.001
S' wave (cm/s)	11 ± 4	9 ± 2[a]	9 ± 2[a]	12 ± 4	< 0.001
Right atrial area (cm^2)	29 ± 14	31 ± 10	30 ± 11	30 ± 11	0.96
ERO of TR (mm^2)	53 ± 37	52 ± 42	44 ± 21	51 ± 34	0.61
IVC diameter (mm)	22 ± 6	25 ± 7	24 ± 5	24 ± 6	0.28
Peak jet velocity of TR (m/s)	2.8 ± 0.5	2.8 ± 0.7	2.9 ± 0.6	3 ± 0.7	0.37
Tricuspid annulus diameter (mm)	43 ± 6	45 ± 5	43 ± 6	44 ± 7	0.43

Data are expressed as mean ± standard deviation. ERO: effective regurgitant orifice; IVC: inferior vena cava; LV: left ventricular; LVEF: left ventricular ejection fraction; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation. Group 1: primary TR; Group 2: TR secondary to left heart disease with previous left heart valve surgery; Group 3: TR secondary to left heart or pulmonary disease without previous cardiac surgery; and Group 4: idiopathic TR.

[a] $P < 0.001$ versus group 4.

[b] $P < 0.05$ versus group 4.

CI 1.39—4.08; $P = 0.002$), history of RHF (adjusted HR 2.62, 95% CI 1.43—4.79; $P = 0.002$), renal failure (adjusted HR 2.01, 95% CI 1.16—3.47; $P = 0.012$) and right atrial dilatation (adjusted HR 2.11, 95% CI 1.24—4.49; $P = 0.030$) remained independently associated with RHF decompensation requiring hospitalization.

Cardiovascular mortality and/or RHF

During follow-up, 79 patients (38%) experienced at least one episode of RHF decompensation requiring hospitalization ($n = 61$) and/or died of a cardiovascular cause ($n = 41$): 10 patients in group 1 (32.2%); 17 patients in group 2 (33.3%); 25 patients in group 3 (45.4%); and 27 patients in group 4 (38%) ($P = 0.34$). After pooling clinical, laboratory and echocardiographic variables, only baseline NYHA stage III or IV (adjusted HR 1.96, 95% CI 1.23—3.14; $P = 0.004$), history of RHF (adjusted HR 2.29, 95% CI 1.37—3.80; $P = 0.002$) and renal failure (adjusted HR 1.98, 95% CI 1.24—3.17; $P = 0.004$) remained independently associated with RHF decompensation requiring hospitalization and/or cardiovascular death.

Discussion

The results of this study show that the causes of significant TR are heterogeneous, but that all causes are associated with poor outcome, as 69 patients (33.2%) had died at a median follow-up of 18 months, resulting in a much lower survival rate than expected (1-year and 4-year observed survival rates of 74 ± 3% and 56 ± 4% versus expected survival rates of 93% and 74%, respectively). Moreover, 61 patients (29.3%) experienced at least one episode of RHF requiring hospitalization. In the multivariable analysis, male sex, NYHA stage ≥ III, renal failure and diuretic dose > 125 mg/day were associated with increased all-cause mortality. After adjustment, idiopathic TR was associated with a > 80% increase in the risk of all-cause mortality during follow-up compared with other causes of TR. Despite the fact that TR is associated with a dismal prognosis, it remains markedly undertreated compared with left-sided valvular heart disease, as tricuspid valve surgery was performed in only 5.3% of patients in our study.

Aetiology of TR

In agreement with previous studies [5,9,10,23], distribution patterns show that TR secondary to left heart disease (50.5%) was the leading cause of TR, and that primary TR (15.4%) was the rarest cause. Patients with TR secondary to left heart disease had dilated left ventricles, with more severely impaired LV and RV systolic function compared with the other groups. Valve prolapse was the leading cause of primary TR. Messika-Zeitoun et al. [15] showed that TR caused by valve prolapse is most often traumatic and severe, and can be treated successfully by surgery. Patients with primary TR were younger, with fewer comorbidities and a lower prevalence of atrial fibrillation, and less frequently required diuretics compared with the other groups.

In our study, idiopathic TR was defined by structurally normal tricuspid valves, no overt organic TR cause, no left-sided valvular or myocardial diseases or pulmonary disease, preserved LVEF and no previous valve surgery (tricuspid or left-sided valve surgery). This form was frequent (34.1%),

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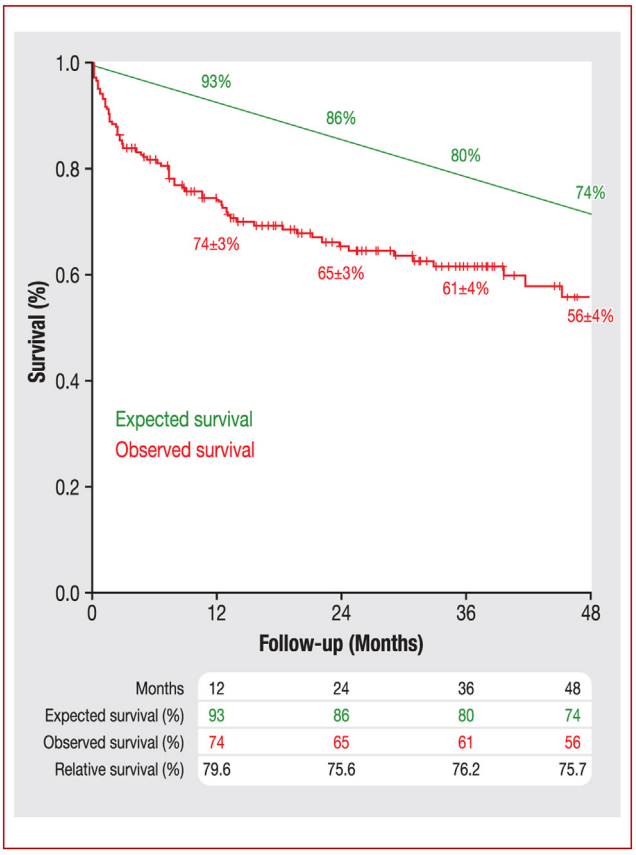

Figure 1. Survival of patients with significant tricuspid regurgitation compared with that in the age- and sex-matched general population. Relative survival was computed as the ratio of observed-to-expected survival (observed number of deaths in the study population/expected number of deaths in the general population).

and more frequent than in previous reports, such as those by Topilsky et al. [6], Mutlak et al. [9] and Kasai et al. [24], in which idiopathic TR rates of 12%, 9.5% and 21% were reported, respectively. This higher frequency could be explained by the selection of only patients with significant (at least moderate-to-severe) TR. In our study, patients with idiopathic TR were mostly women (63.4%), had a mean age of 77 years, and more frequently had a history of atrial fibrillation (88.7%), which is consistent with previous findings, suggesting a growing burden of idiopathic TR, therefore requiring better understanding of this entity in order to propose appropriate treatment. Our results showed marked tricuspid annular enlargement in the idiopathic TR group, similar to that observed in the other groups. We included only patients with moderate-to-severe and severe TR and, at this stage, regurgitation leads to right atrial and ventricular dilation, and consequently tricuspid annular enlargement, regardless of the cause. However, we are convinced that annular dilation precedes regurgitation in idiopathic TR, as suggested by the prevalence of atrial fibrillation in this group, leading to progressive right atrial enlargement that may contribute to annular dilation [6]. The mechanism of annular enlargement could also be linked to ageing, and may reflect annular degeneration [6,25]. Patients with idiopathic TR tended to be more symptomatic at baseline (25% in NYHA stage III–IV, 39% with a history of RHF), which may reflect late diagnosis because of poor knowledge of this entity.

TR outcome

Various studies have highlighted the poor outcome of severe TR [7,8], with a direct relationship between the grade of regurgitation and the risk of death [26]. In our study, 4-year survival was only 56 ± 4%, with an excess mortality of

Table 4 Univariate and multivariable Cox analysis of clinical and biological variables associated with all-cause mortality.

Variables	All-cause mortality			
	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (per year)	1.02(1.01–1.04)	0.021	1.02 (0.99–1.05)	NS
Male sex	1.74 (1.10–2.80)	0.023	1.94 (1.16–3.23)	0.011
Body surface area (per 0.1cm^2 decrease)	1.39 (0.48–4.06)	0.54	–	–
NYHA stage (III–IV vs. I–II)	1.88 (1.16–3.03)	0.010	1.69 (1.02–2.77)	0.040
Hypertension	0.98 (0.57–1.68)	0.95	–	–
Coronary artery disease	1.18 (0.66–2.01)	0.58	–	–
Diabetes	0.74 (0.44–1.24)	0.74	–	–
Atrial fibrillation	1.47 (0.10–5.2)	0.32	–	–
Right heart failure	1.68 (1.03–2.75)	0.038	1.44 (0.87–2.37)	NS
Cirrhosis	1.65 (0.70–3.80)	0.24	–	–
Charlson Comorbidity Index	1.10 (1.01–2.10)	0.050	1.07 (0.90–1.28)	NS
Renal failure	2.57 (1 60–4.12)	< 0.001	1.98 (1.20–3.27)	0.008
Haemoglobin (per g/dL)	0.88 (0.78–0.99)	0.030	0.91 (0.80–1.03)	NS
Diuretics dose > 125 mg/day	2.66 (1.65–4.28)	< 0.001	1.81 (1.08–3.03)	0.025
Tricuspid valve surgery	2.01 (0.72–5.59)	0.18	–	–
Previous left heart surgery	1.31 (0.75–2.29	0.31	–	–

CI: confidence interval; HR: hazard ratio; NYHA: New York Heart Association; NS: not significant.

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Table 5 Univariate and multivariable Cox analysis of echocardiographic variables associated with all-cause mortality.

Variables	All-cause mortality			
	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Left ventricular dilatation	0.93(0.54—1.60)	0.80	—	-—
LVEF < 50%	1.01 (0.60—1.68)	0.98	—	—
Left atrial dilatation	1.31 (0.67—2.55)	0.44	—	—
Cardiac output (L/min)	0.99 (0.83—1.17)	0.88	—	—
Significant left valvular disease	1.67 (1.02—2.75)	0.043	1.50 (0.90—2.49)	NS
RV enlargement	1.44 (0.89—2.32)	0.14	—	—
Right atrial enlargement	1.48 (0.82—2.67)	0.19	—	—
RV dysfunction	1.70 (1.06—2.73)	0.027	1.57 (1.15—2.40)	0.044
Tricuspid annulus dilatation	1.19 (0.63—2.24)	0.58	—	—
ERO of TR (per cm^2)	0.95 (0.40—2.19)	0.89	—	—
TR grade (moderate-to-severe versus severe)	0.79 (0.49—1.26)	0.32	—	—
Peak jet velocity of TR (per m/s)	1.01 (0.68—1.48	0.98	—	—

CI: confidence interval; ERO: effective regurgitant orifice; HR: hazard ratio; LVEF: left ventricular ejection fraction; NS: not significant; RV: right ventricular; TR: tricuspid regurgitation.

almost 20% by the first year compared with the expected survival in the age- and sex-matched general population. Clinical and laboratory variables independently associated with mortality were male sex, NYHA stage ≥ III, renal failure and diuretic dose > 125 mg/day. The only echocardiographic variable independently associated with mortality was the presence of RV systolic dysfunction, defined in accordance with current guidelines [21]. Sun et al. [27] studied the prognosis of 26 patients who underwent isolated tricuspid valve surgery for severe secondary TR, and reported an excess mortality in patients with TAPSE < 14 mm. However, TAPSE and S' should be interpreted with caution in patients with previous cardiac surgery, as they can remain altered even years after surgery without meaning RV dysfunction. Numerous studies [6,26—28] have shown that primary and secondary TR are associated with poor prognosis. However, only limited data are available concerning the prognosis of idiopathic TR. The results of the present study show that idiopathic TR is associated with a > 80% increased risk of all-cause mortality during follow-up compared with other causes of TR. Patients with severe idiopathic TR often present numerous co-morbidities, as illustrated by the high mean Charlson Comorbidity Index score of 3.6 in our study. It is therefore difficult to know whether TR affects the prognosis independently or whether mortality is mainly related to co-morbidities. However, in our study, although the Charlson Comorbidity Index score was associated with mortality in the univariate analysis, it was no longer associated in the multivariable analysis.

Severe TR leads to RHF in the absence of surgical management [29]. In our study, 61 patients (29.3%) experienced at least one episode of RHF requiring hospitalization during follow-up. Only baseline NYHA stage III or IV, history of RHF, renal failure and right atrial dilatation were independently associated with RHF decompensation requiring hospitalization. Worsening of TR leads to dilation of the right atrium and right ventricle, resulting in RV systolic dysfunction. These results suggest that patients should be referred for surgery at an earlier stage, before the onset of RV systolic dysfunction and RHF.

Tricuspid valve surgery

Only 11 patients in our study (5.3%) underwent tricuspid valve surgery during follow-up. Operative mortality is higher for tricuspid valve surgery than for other valves, probably as a result of RV dysfunction and co-morbidities [30], as an in-hospital mortality rate of 10% has been reported for isolated tricuspid valve surgery (ITVS) [6,31]. According to the study by Dreyfus et al. [32], based on a national administrative database, only 241 patients underwent ITVS in France during a 2-year period (2013—2014). ITVS was associated with high mortality (10%) and morbidity, with a 65% rate of complications, including a 19% rate of major complications [32]. The authors concluded that patients are often referred for surgery too late, and that earlier intervention may consequently improve immediate and possibly medium-term outcomes [32]. According to current European guidelines [1], ITVS should be performed (class I; level of evidence C) in the presence of severe symptomatic TR without RV dysfunction, and should be considered (class IIa; level of evidence C) in the presence of asymptomatic TR with progressive enlargement of the right ventricle, before the onset of systolic dysfunction. Unfortunately, these guidelines are rarely applied [12], and patients are operated on too late [32], while earlier treatment would probably improve their survival [26]. In our study, only 11 patients (5.3%) underwent tricuspid valve surgery during follow-up.

Study limitations

This study has the limitations inherent to retrospective analysis of follow-up data. The study sample size was not very large ($n = 208$), but corresponds to all consecutive

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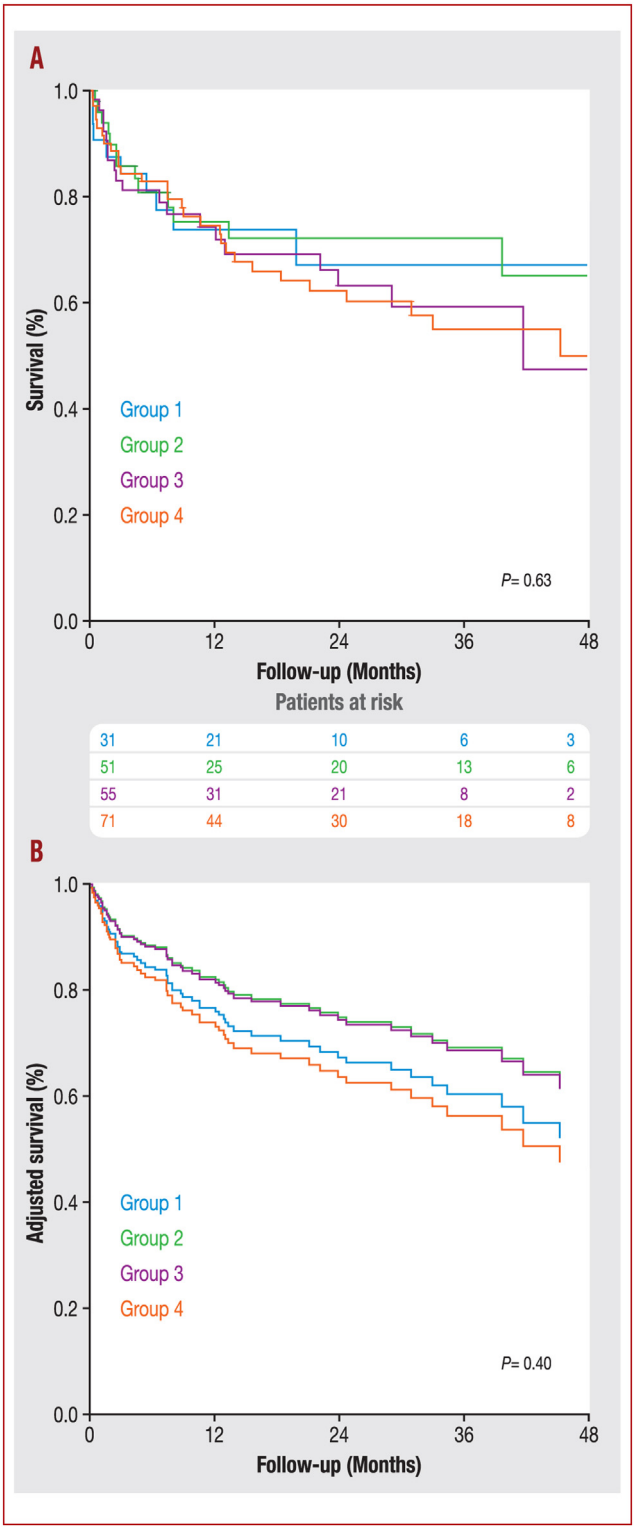

Figure 2. A. Kaplan-Meier survival curves for patients with tricuspid regurgitation (TR), according to aetiology. B. Adjusted Cox survival curves for patients with TR, according to aetiology. Group 1: primary TR; Group 2: TR secondary to left heart disease with previous left heart valve surgery; Group 3: TR secondary to left heart or pulmonary disease without previous cardiac surgery; and Group 4: idiopathic TR.

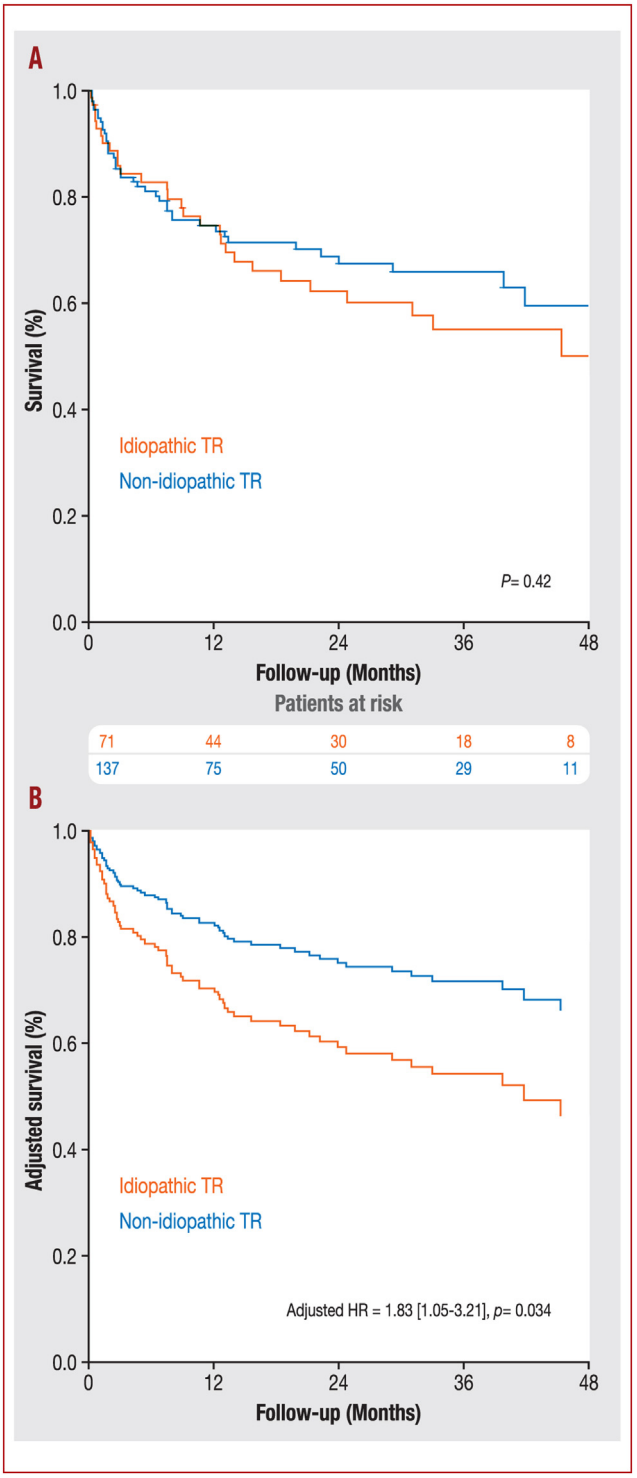

Figure 3. A. Kaplan-Meier survival curves for patients with significant tricuspid regurgitation (TR), according to aetiology. B. Adjusted Cox survival curves for patients with significant TR, according to aetiology. Curves are adjusted for age, sex, New York Heart Association class, right heart failure, Charlson Comorbidity Index, renal failure, haemoglobin, diuretic dose > 125 mg/day, significant left valvular disease and right ventricular dysfunction. HR: hazard ratio.

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patients diagnosed with significant TR in our echocardiography laboratory between 2013 and 2017. Further prospective multicentre studies are needed. Because right atrial volumes were not reported in our database, we defined right atrial dilatation using right atrial area. However, volumes are more robust and accurate than areas for right atrial size determination [21]. We used TAPSE and S' to define RV dysfunction. However, those variables should be interpreted with caution in patients with previous cardiac surgery, as they can remain altered even years after surgery without meaning RV dysfunction. Given the small number of patients who underwent tricuspid valve surgery during follow-up, we could not test its impact on survival.

Conclusions

The results of this study show that TR has various causes, but all forms of TR are associated with poor outcome. Secondary TR was the most common aetiology, and was mostly idiopathic, while primary TR was the rarest form. Patients with moderate-to-severe or severe TR have a markedly increased risk of mortality compared with the general population. Idiopathic TR, a new entity that has not yet been studied extensively, has a poorer prognosis than the other aetiologies. Prospective studies are needed to more reliably identify patients at risk of developing idiopathic TR, to prevent its onset or at least prevent deterioration. Despite the fact that TR is associated with a dismal prognosis, it remains markedly undertreated compared with left-sided valvular heart diseases, as only 5.3% of patients underwent tricuspid valve surgery in our study. The development of transcatheter therapies might represent an alternative treatment option to surgery in this high-risk population of patients with severe symptomatic TR [33].

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None.

Disclosure of interest

The authors declare that they have no competing interest.

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