

Original article

Delay of surgical treatment of severe tricuspid regurgitation and outcomes in patients with left-sided heart valve disease

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ABSTRACT

Introduction and objectives: The influence of the delay between diagnosis and surgery in severe tricuspid regurgitation (TR) remains controversial. We aimed to analyze the association between delay to surgery and operative and mid-term mortality in patients with severe TR concomitant to left-valve surgery.**Methods:** We conducted an observational retrospective study analyzing risk factors in patients undergoing left-valve surgery concomitant with severe TR. The clinical and demographic variables were prospectively collected. The time of first diagnosis of TR was retrospectively collected.**Results:** A total of 253 patients were analyzed. TR was functional in 82.6%. The median latency between diagnosis and surgery was 24 months. Operative mortality was 12.2%. On multivariate analysis, higher operative mortality was associated with older age, worse preoperative NYHA functional class, triple valve surgery, hyponatremia, and anemia. The median follow-up was 35 months. Survival at 1 and 5 years was 85.2% and 73.7%, respectively. Mortality during follow-up was associated with male sex, preoperative massive TR, and longer latency between diagnosis and surgery.**Conclusions:** The variables related to worse preoperative functional class were associated with increased operative mortality. Lower mid-term survival was associated with longer latency between diagnosis of severe TR and surgery, massive preoperative TR, and older age.

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Demora en el tratamiento quirúrgico de la insuficiencia tricuspídea grave y resultados en pacientes con valvulopatía izquierda

RESUMEN

Introducción y objetivos: La influencia de la demora entre diagnóstico y cirugía de la insuficiencia tricuspídea (IT) grave es controvertida. Analizamos la asociación entre demora quirúrgica y mortalidad, operatoria y a medio plazo, en pacientes con IT grave asociada a cirugía valvular izquierda.**Métodos:** Se hizo un estudio observacional retrospectivo de factores de riesgo en pacientes operados por valvulopatía izquierda asociada a IT grave. Las variables clínicas y demográficas se recogieron prospectivamente, y retrospectivamente el momento del primer diagnóstico de IT severa.**Resultados:** Se analizó a 253 pacientes. La insuficiencia tricuspídea fue funcional en el 82,6%. La mediana entre diagnóstico y cirugía fue de 24 meses. La mortalidad operatoria fue del 12,2%. En el análisis multivariante la mayor edad, peor clase funcional preoperatoria, triple cirugía valvular, hiponatremia y anemia se asociaron a mayor mortalidad operatoria. La mediana de seguimiento fue de 35 meses. La supervivencia a 1 y 5 años fue del 85,2% y 73,7%, respectivamente. El sexo masculino, la presencia de IT masiva preoperatoria y la demora entre diagnóstico de IT grave y cirugía se asociaron a mayor mortalidad durante el seguimiento.**Conclusiones:** Las variables relacionadas con una peor clase funcional se asociaron al incremento de la mortalidad operatoria. La mayor latencia entre el diagnóstico de insuficiencia tricuspídea grave y cirugía y el diagnóstico preoperatorio de insuficiencia tricuspídea masiva y la edad se asociaron con una disminución de la supervivencia a medio plazo.

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Palabras clave:

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Abbreviations

RH: right heart
TR: tricuspid regurgitation

INTRODUCTION

Severe tricuspid regurgitation (TR) may remain clinically silent for a prolonged period, as symptoms and signs of right ventricular dysfunction may be masked by diuretic therapy. Right heart (RH) dysfunction is an independent risk factor for operative mortality, postoperative complications, and TR recurrence after tricuspid valve repair.^{1,2} Delayed surgery is associated with poor results and decreased survival.¹ Some authors have suggested that avoiding surgical delay in severe TR might decrease operative mortality and the development of RH failure.^{1,3} However, the optimal timing of surgery is not clear. In patients undergoing left-sided surgery, the European (European Society of Cardiology)[ESC]/ European Association for Cardio-Thoracic Surgery [EACTS]) and American (American Heart Association [AHA]/American College of Cardiology [ACC]) guidelines recommend tricuspid valve surgery in symptomatic patients with severe primary TR (recommendation class I level C ESC/EACTS), in patients with severe secondary TR (recommendation class I level B ESC/EACTS) and in patients with mild or moderate secondary TR associated with tricuspid annular dilatation (≥ 40 mm or >21 mm/m²) and RH failure (recommendation class IIa level B ESC/EACTS).^{4,5}

In patients with concomitant left-sided surgery, severe TR is not the main surgical indication. We hypothesized that delayed intervention in severe TR might increase operative mortality, allowing the development of RH dysfunction. We aimed to analyze the influence of latency between diagnosis and surgery in operative and mid-term mortality and the factors associated with mortality during follow-up in patients with severe TR concomitant to left-valve surgery. As secondary objective, we aimed to identify the factors associated with postoperative RH failure.

METHODS

We conducted a retrospective and longitudinal study with a cohort design in patients older than 18 years with a diagnosis of severe TR concomitant to left-valve disease undergoing surgery. Clinical and demographic variables were prospectively collected. Time (in months) from first diagnosis of severe TR was retrospectively collected from echocardiographic patient information. The study was performed according to the strengthening the reporting of observational studies in epidemiology (STROBE) guidelines.⁶ The study protocol (identification number PI19-1435) received full approval by both the local Institutional research review committee and the clinical research ethics committee. The study period was from January 2012 to June 2020. We prospectively gathered data through follow-up of surviving patients. The patients were followed up either in person, by telephone, by contact with the cardiologist, and through medical records. No patients were lost to follow-up. All patients gave their written informed consent for analysis of their data.

Definitions

Operative mortality was defined as in-hospital mortality or mortality occurring within 30 days of operation. Surgical risk was

preoperatively estimated according to the European System for Cardiac Operative Risk (EuroSCORE) scales. Severity of tricuspid regurgitation was graded by echocardiography in 3 categories: severe TR was defined as an effective regurgitant orifice area (EROA) of ≥ 40 mm² and a regurgitant volume (R Vol) of ≥ 45 mL. Massive TR was defined by EROA 60 to 79 mm², R Vol 60 to 74 mL and vena contracta (VC) 14 to 20 mm and torrential TR was defined by EROA ≥ 80 mm², R Vol ≥ 75 mL, and VC ≥ 21 mm.⁷ In line with the World Health Organization (WHO), anemia was defined as hemoglobin level under 12 mg/dL in women and 13 mg/dL in men, or lower than 2 standard deviations with respect to mean levels in the reference population.⁸ Postoperative RH failure was defined as symptoms and signs of persistent right ventricular dysfunction [right atrial pressure (RAP) > 18 mmHg with a cardiac index < 2.0 L/min/m²] in the absence of elevated pulmonary capillary wedge pressure [(PCWP) (> 18 mmHg)], tamponade, ventricular arrhythmias or pneumothorax and RAP/PCWP ratio higher than 0.5 and/or tricuspid annular plane systolic excursion (TAPSE) < 17 mm on echocardiography⁹ after the surgical procedure and before hospital discharge.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 22.0, released in 2013 (IBM Corp, United States). Continuous variables are expressed as mean \pm standard deviation or as median and interquartile range [IQR], for nonnormal distributions. The Kolmogorov-Smirnov test was used to determine the normality of each variable. Categorical variables are expressed as absolute values and percentages. Association between variables was identified by the chi-square or Fisher exact test, when categorical, and by the Student *t*-test or Mann Whitney U-test, when continuous. The risk-adjusted mortality rate was calculated from the standardized mortality ratio. To obtain expected deaths, the logistic equation was adjusted according to the risk characteristics of the study population. The logistic equation for the EuroSCORE was obtained from Roques et al.¹⁰ To adjust time from severe TR diagnosis to surgery for confounding factors, logistic regression models were fitted with variables selected a priori. These were variables previously identified as independent predictors of mortality in patients undergoing concomitant tricuspid and left-sided valve surgery: age, time between diagnosis of severe TR and surgery, liver cirrhosis, New York Heart Association (NYHA) \geq III, preoperative anemia, triple valve surgery, and preoperative values of sodium and proteins. The association between analyzed variables and operative mortality in univariate analysis ($P < .2$) was entered in backward and forward stepwise logistic regression models. The risk factors associated with increased mortality during follow-up and actuarial survival were analyzed using a Cox model and Kaplan-Meier test. A Harrell *c*-statistic was calculated for the Cox model of mortality during follow-up and postoperative RH failure. A *P* value $< .05$ was considered significant.

RESULTS

A cohort of 253 consecutive patients with a diagnosis of severe TR concomitant to left-valve disease undergoing surgery were analyzed. The analyzed populations corresponded to 14.9% of patients who underwent valve surgery during the study period. The clinical and demographic variables are detailed in table 1. The etiology of severe TR was mostly functional (82.6%), although it could also be due to rheumatic heart disease (12.3%), infective endocarditis (2%), cardiac implantable devices (0.4%) and tricuspid valve repair failure (2.8%). The mean age of the patients was 69 ± 9.5 years, with a predominance of the female sex (68.8%). Preoperative TR grade was severe in 81% of the patients and massive in the remaining patients. All patients underwent concomitant left-

Table 1
Factors associated with operative mortality: univariate analysis

Variable	Nonsurvivors n = 31	Survivors n = 222	P
<i>Preoperative risk factors</i>			
Sex (female)	18 (58.1)	156 (70.3)	.170
Hypertension	21 (67.7)	121 (54.5)	.164
Smoke	1 (3.2)	20 (9)	.486
Diabetes mellitus	11 (35.5)	50 (22.5)	.114
Dyslipidemia	12 (38.7)	83 (37.4)	.887
Cirrhosis	3 (9.7)	5 (2.3)	.061
Peripheral vascular disease	4 (12.9)	23 (10.4)	.755
Cerebrovascular disease	0 (0)	3 (1.4)	1.000
Preoperative anemia	19 (61.3)	68 (30.6)	.001
Sinus rhythm	5 (16.1)	34 (15.3)	1.000
NYHA \geq III	26 (83.9)	126 (56.8)	.004
Age, y	71.8 \pm 7.5	68.6 \pm 9.7	.081
Weight, kg	67 \pm 10.4	68 \pm 12.4	.982
Height, cm	159.8 \pm 9.2	159.7 \pm 8.3	.949
BMI	26.5 \pm 4.1	26.5 \pm 4.3	.968
GFR, mL/min/1.73 m ²	56.8 \pm 24.3	68.4 \pm 42.4	.134
Preoperative Na, mMol/L	136.9 \pm 4.1	139.1 \pm 3.1	< .0001
Preoperative proteins, g/dL	6.9 \pm 0.8	7.2 \pm 0.6	.047
Time from diagnosis to surgery, mo	24 [79]	24 [47.75]	.007
<i>Preoperative treatment*</i>			
Loop diuretics	25 (80.6)	164 (73.9)	.417
Potassium-sparing diuretics	8 (25.8)	45 (20.3)	.478
Thiazides	1 (3.2)	13 (5.9)	1.000
Loop diuretics (furosemide mg)	40 [40]	40 [40]	.340
Potassium-sparing diuretics (spironolactone mg)	0 [25]	0 [0]	.777
Thiazides (hydrochlorothiazide mg)	0 [50]	0 [0]	.983
<i>Echocardiographic variables</i>			
Massive TR	9 (29)	39 (17.6)	.127
Secondary TR	4 (12.9)	40 (18)	.617
Concomitant tricuspid stenosis	5 (6.5)	5 (2.3)	.207
LVEF	62.1 \pm 10	59.7 \pm 8.5	.148
SPP, mmHg	59.7 \pm 14.5	57.9 \pm 15.9	.574
Tricuspid diameter, mm	42 \pm 3.2	40.8 \pm 5.3	.293
TAPSE, mm	17.3 \pm 3.7	17.6 \pm 4	.749
<i>Surgical variables</i>			
Redo surgery	9 (29)	41 (18.5)	.166
Triple valve operation	12 (38.7)	49 (22.1)	.043
Redo- tricuspid surgery	0 (0)	7 (3.2)	.602
Tricuspid valve replacement	4 (12.9)	18 (8.1)	.325
CPB time, min	172.1 \pm 57.4	137.4 \pm 42.3	< .0001
Aortic clamp time, min	122.3 \pm 37.6	102.9 \pm 30.3	.001
EuroSCORE logistic	14.1 \pm 10.2	9.8 \pm 8.2	.010
EuroSCORE II	13 \pm 10.3	6.7 \pm 6.1	< .0001
<i>Postoperative variables</i>			
Postoperative right heart failure	26 (83.9)	38 (17.1)	< .0001
ICU stay, d	5 [8]	4 [3]	.117
Intubation time, h	48 [160]	7 [8]	< .0001
In-hospital stay, d	9 [14.2]	12 [16]	.007

BMI, body mass index; CPB, cardiopulmonary bypass; GFR, glomerular filtration rate; ICU, intensive care unit; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SPP, systolic pulmonary pressure.

Values are expressed as No. (%), mean \pm standard deviation, or median [interquartile range].

* Preoperative concomitant administration of double diuretics therapy (loop plus potassium-sparing or thiazide) was observed in 48 patients (19%). Triple therapy (potassium-sparing, loop and thiazide diuretics) was administered in 2 patients and monotherapy in the rest.

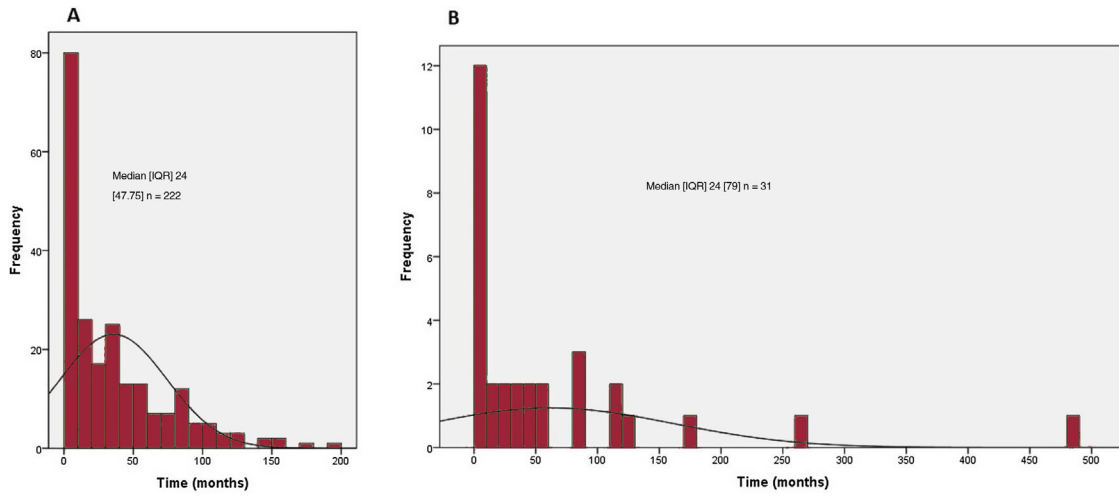


Figure 1. Mean latency between severe TR diagnosis and surgery in survivors (A) and nonsurvivors (B).

Table 2

Multivariate analysis: predictive variables for operative mortality

Variable	OR	95%CI	P
Age	1.06	1.006-1011	.028
NYHA ≥ III	3.69	1.2-10.5	.014
Preoperative anemia	2.91	1.2-6.7	.013
Preoperative Na (mmol/L)	0.85	0.7-0.9	.011
Triple valve surgery	2.69	1.1-6.2	.028
Delay severe TR diagnosis-surgery, mo	1.007	0.9-1.01	.101

AUC = 0.671; 95%CI, 0.573-0.770; P = .0001.

95%CI, 95% confidence interval; NYHA, New York Heart Association; OR, odds ratio; TR, tricuspid regurgitation.

Table 3

Multivariate analysis: predictive variables for postoperative right heart failure

Variable	HR	95%CI	P
NYHA ≥ III	3.46	1.69-7.06	.001
Age	1.04	1.01-1.08	.009
Preoperative anemia	2.81	1.50-5.28	.001
Preoperative Na, mmol/L	0.90	0.82-0.99	.037
Triple valve surgery	2.04	1.03-4.04	.039

95%CI, 95% confidence interval; HR, hazard ratio; NYHA, New York Heart Association.

C-index = 0.747; 95%CI, 0.680-0.814.

sided valve surgery: mitral in 64%, mitral and aortic in 24.1%, and aortic in 11.9%. The tricuspid valve interventions performed included 22 tricuspid valve replacements and 231 repairs. A total of 19.8% of patients had undergone at least 1 previous open-heart surgical intervention. TR after repair was moderate in 2 patients and none or mild the rest. Median latency between diagnosis of severe TR and surgery was 24 months, with an interquartile range (IQR) of 51 months.

Operative mortality was 12.2%. The mortality of concomitant tricuspid and left-sided valve surgery was 9.9% among patients undergoing mitral valve surgery, 10% among patients undergoing aortic valve surgery, and 19.7% among those undergoing concomitant mitral and aortic valve surgery (P = .128). No significant differences were found in crude and standardized mortality ratios. The standardized mortality ratio was 1.28, 95% confidence interval (95%CI, 0.59-2.15) for concomitant tricuspid and mitral valve surgery; 0.80, 95%CI, 0.00001-1.88 for concomitant tricuspid and aortic valve surgery, and 1.92, 95%CI, 0.82-13.10 for concomitant tricuspid, mitral and aortic valve surgery. Although the mean latency between severe TR diagnosis and surgery was similar, a higher IQR was observed in nonsurvivors (figure 1) (P = .007)

Age, triple valve surgery, worse functional status as assessed by NYHA functional class, and preoperative anemia and hyponatremia increased operative mortality (table 2). During the postoperative period, RH failure was diagnosed in 25.3% of all patients, which

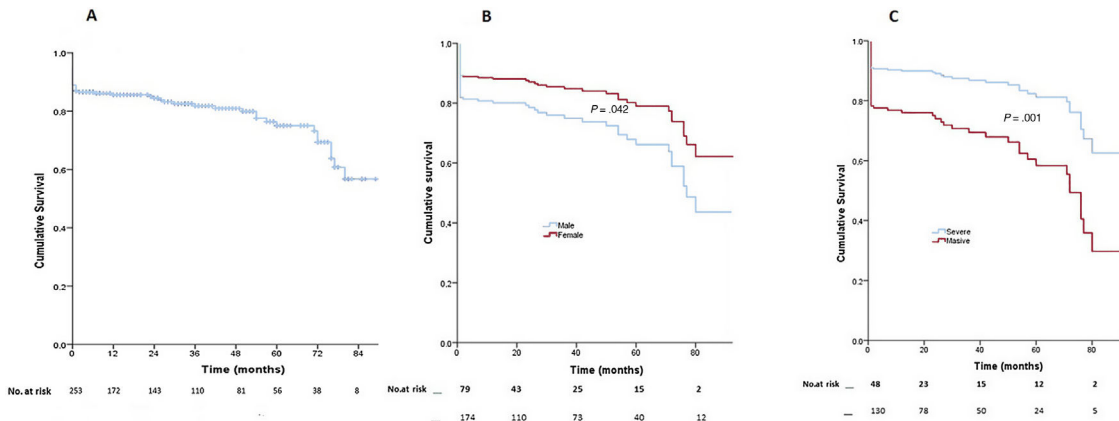


Figure 2. Kaplan-Meier curve showing the estimated survival function (A) survival time related to sex (B), and preoperative echocardiographic grade of TR (C).

Table 4
Cox regression: variables associated with higher mortality during follow-up

Variable	HR	95%CI	P
Age	1.04	1.01-1.07	.007
Sex (male)	1.85	1.08-3.22	.025
Masive preoperative TR	2.58	1.48-4.51	.001
Delay severe TR diagnosis-surgery (months)	2.11	1.002-1.008	.035

TR, tricuspid regurgitation.
C-index=0.687; 95%CI, 0.611-0.765.

was the immediate cause of death in 32.8% of them. In the remaining patients, the immediate cause of death was hemorrhagic complications (4 patients), neurological damage (1 patient), respiratory disease (1 patient), left heart failure (2 patients) and infection (2 patients). The risk factors for postoperative RH failure are detailed in [table 3](#).

We conducted the follow-up of patients, with a mean time of 33.7 ± 26.2 months, and median [IQR] of 35 [46.5] months. During this period, 11.3% of the patients died. Survival at 1 and 5 years was 85.2% and 73.7%, respectively ([figure 2A](#)). Male sex, latency from diagnosis of severe TR to surgery and preoperative diagnosis of massive TR were associated with higher mortality during follow-up, with c-index 0.687, 95%CI (0.611-0.765) ([table 4](#) and [figure 2B,C](#)).

DISCUSSION

In this research, we first aimed to analyze the influence on operative and mid-term mortality of delay between diagnosis of severe TR and surgery in patients with concomitant left-valve surgery. We observed that mid-term mortality increased in patients with left-valve surgery associated with long-standing severe TR. The etiology of severe TR was mostly functional and, not infrequently, there was a latency of years between the first echocardiographic diagnosis and surgery. Surgical treatment in functional severe TR used to be influenced by the indications for left-heart valve surgery, facilitating temporal progression of TR until surgical decision. The progression of tricuspid valve disease reduced the mid-term survival of patients, even after adequate surgical correction.

Until now, the benefit of surgical correction of isolated functional TR compared with medical treatment has not been well established. Surgery should be considered early in selected symptomatic patients, but periprocedural morbidity and mortality is higher when patients present late and thresholds for severe RV dysfunction making intervention futile have not yet been defined.^{4,5} In this context, after diagnosis of nonsevere left-valve disease, aortic and/or mitral valve clinical and imaging studies prevail over evaluation of severe functional TR and usually determine the optimal surgical timing. Consecutively, the impact of the severity of tricuspid valve disease and right ventricular function remain underestimated. Since survival is affected, even

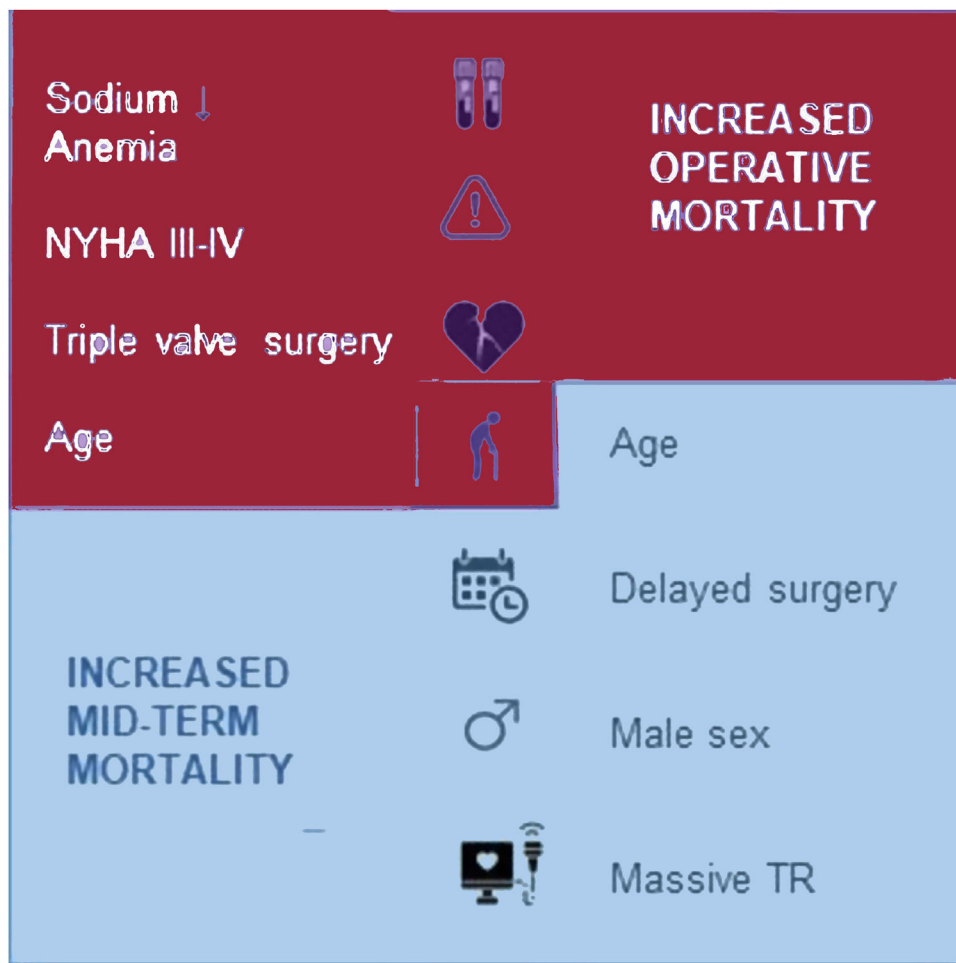


Figure 3. Central illustration. Risk factors associated with operative and mid-term mortality in patients with severe tricuspid regurgitation concomitant to left-valve surgery. NYHA, New York Heart Association; TR, tricuspid regurgitation.

after surgical correction of severe TR, a more exhaustive sequential echocardiographic study of the right ventricle and tricuspid valve would be advisable. In this setting, magnetic resonance imaging (MRI) can provide additional information that allows identification, over time, patients with higher surgical risk and lower mid-term survival.¹¹

We also aimed to identify risk factors for mortality. Lower functional status was associated with increased operative mortality. We also found some preoperative biochemical markers related to an increase in operative mortality such as anemia and hyponatremia, which predicted a poor prognosis. The etiology of anemia in the study population was multifactorial: occult gastrointestinal bleeding secondary to chronic anticoagulant therapy, iron and vitamin B deficiencies, chronic disease (associated with an age-related inflammatory process)¹² and dilutional anemia, associated with hyponatremia. All patients received chronic diuretic therapy before surgery and a quarter was under polytherapy with 2 or more diuretics; however, preoperative hyponatremia was related to increased operative mortality, regardless of the type and doses of diuretic treatment.

Compared with data described by other authors, crude mortality after concomitant tricuspid and left-sided valve surgery was higher in our population, but these differences were not significant when the risk-adjusted mortality rate was calculated.^{13–15} Nevertheless, triple valve surgery is associated with higher postoperative mortality due to right ventricular dysfunction, not related to repair or tricuspid valve replacement procedures^{16,17} (figure 3).

We also aimed to identify risk factors for postoperative RH dysfunction. Postoperative RH failure was observed in a quarter of patients undergoing tricuspid surgery and was the immediate cause of death in a third of them. The etiology of the postoperative RH failure was multifactorial. On the one hand, right ventricular function is reduced during cardiac surgery, independent of procedural characteristics¹⁸; on the other hand, preoperative anemia is an independent risk factor for low postoperative cardiac output.¹⁹ We observed an increased probability of postoperative RH failure after triple valve surgery; however, no correlation between preoperative right ventricular dysfunction and postoperative RH failure was identified. An explanation is that, in these patients, left-sided valve disease is the main indication for cardiac surgery and right ventricular dysfunction was underdiagnosed. Therefore, we consider that exhaustive preoperative echocardiographic and MRI evaluation of tricuspid valve and right ventricular function might identify patients at higher risk of developing postoperative RH failure.

Limitations

This is a retrospective single-center study, with a long recruitment time and, therefore, the population might be not sufficiently representative. Obviously, the pathophysiology of TR with right ventricular impairment is a time-dependant and time-related aspect in which reversible patho-anatomical tissue changes in the right ventricle will slide into irreversible damage. Assessment of this pathophysiological process is preferably evaluated with sequential detailed echocardiography examinations. The clinical parameters (NYHA, RH failure, electrolyte abnormalities), as used in this study, are late signs and symptoms. Probably, the most appropriate follow-up after first diagnosis of severe functional TR in patients with concomitant left-valve disease will include specific sequential echocardiographic and MRI study protocols of tricuspid valve and right ventricular function. Both may help to identify markers related to higher risk of mortality, postoperative RH failure and decreased mid-term survival, advising early surgical treatment. In this study, patient

follow-up was carried out in the mid-term; consequently, there are no clear conclusions about the influence of delayed surgery on long-term mortality.

CONCLUSIONS

In conclusion, our study shows that, in patients with severe TR and concomitant left-valve disease, triple valve surgery and worse preoperative functional class increases operative mortality. Longer latency between diagnosis of severe TR and surgery decreased mid-term survival, even after adequate surgical correction. We consider that, after the first diagnosis of severe TR, sequential echocardiographic and MRI studies, focused on right ventricular and tricuspid valve function, may help to determine the most appropriate timing of surgery.

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AUTHORS' CONTRIBUTIONS

All authors contributed to the acquisition, analysis, or interpretation of the data for the work and final approval of the version to be published. B. Segura and Y. Carrascal also contributed to the conception, design, drafting and critically revision of the work for important intellectual content.

CONFLICTS OF INTEREST

None declared.

WHAT IS KNOWN ABOUT THE TOPIC?

- Delayed surgery of severe TR is associated with poor outcomes and decreased survival.
- Some authors suggest that avoiding surgical delay in severe TR might decrease operative mortality and the development of RH failure.
- However, the optimal timing of surgery remains controversial.

WHAT DOES THIS STUDY ADD?

In patients with severe TR and concomitant left-valve disease:

- Triple valve surgery increases operative mortality.
- Delays in surgery associated decreased mid-term survival.
- After the first diagnosis of severe TR, sequential echocardiographic and MRI studies, focused on right ventricular and tricuspid valve function, may help to determine the most appropriate timing of surgery.

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