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Tricuspid Valve Regurgitation After Heart Transplantation: A Single-Center 10-year Experience

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Abstract

Background: **Tricuspid valve regurgitation may affect the outcomes after heart transplantation. There is a paucity of data reporting the outcomes of heart transplants in our region. The objectives of this study were to report the occurrence of tricuspid regurgitation after heart transplantation, its course, and its effect on survival.**

Methods: **From 2009 to 2019, 30 patients had heart transplantation at our cardiac center. Their age was 36.73 ± 13.5 years, and 25 (83.33%) were males. Indications for transplantation were dilated cardiomyopathy (n = 21; 72.41%), ischemic cardiomyopathy (n = 8; 26.67%) and hypertrophic cardiomyopathy (n = 1; 3.45%). Cardiopulmonary bypass time was 157.24 ± 34.6 min, and ischemic time was 138 ± 73.56 min. All patients had orthotopic heart transplantation with a bi-caval technique.**

Results: **Eleven patients had severe tricuspid regurgitation postoperatively (37%). The degree of tricuspid regurgitation decreased significantly after 6 months (p = 0.011) and remained stationary during the follow-up. Pre-transplant dilated cardiomyopathy was significantly associated with severe tricuspid regurgitation post-transplant (p = 0.017). The mean follow-up was 39.43 ± 50.57 months. Survival at 10 years was 90% in patients with less than moderate tricuspid regurgitation postoperatively compared to 43% for patients with moderate and severe tricuspid regurgitation (log-rank p = 0.0498).**

Conclusion: **Tricuspid regurgitation is a common problem after heart transplantation. Despite the improvement of the degree of tricuspid regurgitation after 6 months, survival was negatively affected by postoperative moderate or severe tricuspid regurgitation. Patients with dilated cardiomyopathy may benefit from concomitant tricuspid valve repair at the time of heart transplantation. Further larger studies are warranted.**

Keywords: Heart transplantation, Tricuspid regurgitation, Bi-caval anastomosis

1. Introduction

The outcomes of heart transplantation had improved recently with the introduction of the new immunosuppressive agents [1]; however, several risk factors are still affecting the long-term outcomes. The problem of tricuspid regurgitation of the donor's heart is still debatable, and there is no consensus on the concomitant management of the tricuspid valve during a heart transplant [2]. Prophylactic tricuspid valve annuloplasty for all patients undergoing heart transplants may not be practical nor cost-effective, and high-risk patients

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who could benefit from this intervention are not known [3].

The outcome of heart transplantation may be affected by the center volume and the patients' characteristics, and the results of cardiac transplants are rarely reported from our region. We hypothesize that post-transplant tricuspid regurgitation may negatively affect the outcomes after heart transplant; therefore, the objectives of this study were to report the frequency of tricuspid regurgitation after heart transplantation, its course, management, and its effect on survival in our center.

2. Patients and Methods

2.1. Study Design and Patients

This research is a retrospective cohort study that included 30 patients who had orthotopic heart transplantation from 2009 to 2019 at a single cardiac center. The study included all patients who had heart transplants during the study period, and no patients were excluded. The study was approved by the Institutional Review Board (Reference number R19018), and the patients' consent was waived.

2.2. Data Collection

Electronic and paper chart review was conducted to collect the preoperative variables (age, gender, body mass index, associated comorbidities, and indication for heart transplantation). All patients had orthotopic heart transplantation with a bi-caval technique for right atrial anastomosis. Operative data recorded included aortic cross-clamp and cardiopulmonary bypass time. Postoperative data included the number of endocardial biopsies and acute rejection. The liver and renal functions were recorded postoperatively and during the follow-up. Postoperatively, all recipients' hearts were examined histologically, and the preoperative diagnosis was confirmed in all patients.

2.3. Echocardiography

All patients had regular clinical and echocardiographic assessment postoperatively. Evaluation of the tricuspid valve was conducted by a consultant echocardiographer before patients' discharge, after 6 months, then yearly up to 5 years of heart transplantation. Tricuspid regurgitation was graded as mild, moderate, and severe, according to the American Society of Echocardiography criteria [4]. Grading of tricuspid regurgitation was performed using the regurgitant jet area and vena contracta (Fig. 1). Jet area ˃ 10 cm^2 and vena contracta ˃ 7 mm presents severe TR. Right ventricular (RV) dilatation was assessed in the apical 4-chamber view, and severe dilatation was defined as a basal end-diastolic diameter >50 mm. RV function was assessed using tricuspid annular plane systolic excursion (TAPSE). The data reported in addition to the degree of tricuspid regurgitation include the ejection fraction, pulmonary artery systolic pressure, left ventricular end-diastolic, and end-systolic diameters.

Abbreviations

OR	odds ratio
TR	tricuspid regurgitation

2.4. Study Outcomes

The outcomes of the study were long-term survival, postoperative tricuspid regurgitation and its progression, operative outcomes, and the need for diuretics or impairment of the renal and liver function.

2.5. Statistical Analysis

A descriptive analysis was used to present the data. Continuous data are presented as means and standard deviations and categorical data as

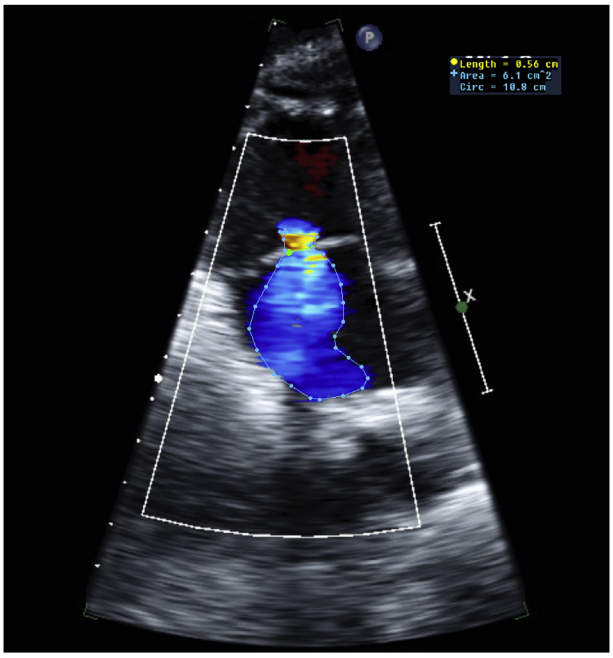

Fig. 1. Assessment of the grade of tricuspid regurgitation using the regurgitant jet area and vena contracta width.

numbers and percentages. The change of the degree of tricuspid regurgitation at 6 months compared to the discharge value was tested using the Skillings-Mack test. Kaplan-Meier curves were used to present the survival distribution, and the Log-rank test was used to compare survival between groups. The study has 80% power to detect survival differences between both groups with 2:1 patients allocation to TR vs. no TR groups. Logistic regression analysis was used to evaluate the association between postoperative severe and moderate tricuspid regurgitation and preoperative and operative variables. All analyses were performed using Stata 16 (Stata Corp-College Station- Texas- USA).

3. Results

3.1. Preoperative Data

Thirty patients had heart transplants during the study period. The mean age was 36.73 ± 13.5 years, and 25 (83.33%) were males. The main indication for transplantation was dilated cardiomyopathy (n = 21; 72.4%). Preoperative patients' data are presented in Table 1.

3.2. Operative Data

The mean cardiopulmonary bypass time was 157.24 ± 34.6 min, and the cross-clamp time was 138 ± 73.56 min. The acute cellular injury occurred in 3 patients (14.3%), and the average number of endocardial biopsies was 6.41 ± 4.8. Operative and postoperative data are presented in Table 2 and echocardiographic data in Table 3.

3.3. Tricuspid Regurgitation

Eleven patients (37%) had severe tricuspid valve regurgitation postoperatively; 3 of them regressed to mild or no regurgitation at 6 months follow-up. Nine patients (30%) had moderate TR; 7 of them regressed to mild or no regurgitation at 6 months. All patients with postoperative TR were managed medically with anti-failure treatment, and no surgical intervention was performed on those patients. The changes in the degree of TR, RV function, and dilatation over 5 years follow-up are shown in Fig. 2. The grade of TR decreased significantly at 6 months compared to the grade of TR at discharge (p-value 0.011). The mechanism of TR was functional in all patients due to right ventricular and annular dilatation.

Univariable logistic regression analysis showed a significant association between postoperative severe

Table 1. Patients' preoperative data. Continuous variables are presented as mean and standard deviation and categorical variables as number and percent. (LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; PASP: pulmonary artery systolic pressure).

Variable	n = 30
Age (years)	36.73 ± 13.5
Male	25 (83.33%)
Body mass index (kg/m2)	24.56 ± 4.5
Body surface area (m2)	1.75 ± 0.20
Hemoglobin (mg/dl)	12.81 ± 1.9
Blood group	
O positive	20 (66.67%)
A positive	6 (20.00%)
B positive	4 (13.33%)
Hypertension (n = 29)	8 (27.59%)
Diabetes mellitus (n = 29)	10 (34.48%)
Stroke (n = 26)	2 (7.69%)
Indications	
Dilated cardiomyopathy	21 (72.41%)
Ischemic cardiomyopathy	8 (26.67%)
Hypertrophic cardiomyopathy	1 (3.45%)
Smokers (n = 29)	3 (10.34%)
Chronic obstructive lung disease (n = 27)	1 (3.70%)
Creatinine (μmol/L)	98.67 ± 39.59
Bilirubin (μmol/L)	38.10 ± 33.52
History of cardiac surgery	8 (29.63)
Preoperative PASP (mmHg)	46.46 ± 11.56
Preoperative LVESD (mm)	61.55 ± 11.53
Preoperative LVEDD (mm)	68.97 ± 11.23

Table 2. Operative and postoperative data. Continuous variables are presented as mean and standard deviation and categorical variables as number and percent. (AST: aspartate transaminase; ALT: alanine transaminase; PASP: pulmonary artery systolic pressure).

	n = 30
Cardiopulmonary bypass time (minutes)	157.24 ± 34.6
Cross-clamp time (minutes)	138 ± 73.56
Acute cellular injury (n = 21)	3 (14.29%)
Number of endomyocardial biopsies (total)	6.41 ± 4.8
Number of endomyocardial biopsies during the first hospitalization	1.39 ± 0.96
PVR at postoperative day 1 (dyn/s/cm^5)	189.36 ± 97.28
Indexed PVR (dyn/s/cm^5/m^2)	329.88 ± 159.18
postoperative ejection fraction (%)	54.83 ± 10.3
Postoperative PASP (mmHg)	41.30 ± 9.56
Postoperative LVEDD (mm)	40.96 ± 5.02
Postoperative LVESD (mm)	26.73 ± 5.85
Creatinine at last follow-up (n = 20) (μmol/L)	106.6 ± 41.7
ALT at last follow-up (n = 14)	39.86 ± 54.49
AST at the last follow-up (n = 7)	29.14 ± 25.38
Patients required diuretic therapy at follow-up (n = 18)	2 (11.11%)

Table 3. Postoperative data echocardiographic data. Continuous variables are presented as mean and standard deviation and categorical variables as number and percent. (LV: left ventricle; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter).

	n = 30
Postoperative LV ejection fraction (%)	54.83 ± 10.3
Postoperative PASP (mmHg)	41.30 ± 9.56
Postoperative LVEDD (mm)	40.96 ± 5.02
Postoperative LVESD (mm)	26.73 ± 5.85
Right ventricular dilatation	
Mild	6 (23.08%)
Moderate	13 (50%)
Severe	3 (11.54%)
Right ventricular dysfunction	
Mild	10 (35.71%)
Moderate	12 (42.86%)
Severe	1 (3.57%)

Table 4. Univariable logistic regression analysis for factors associated with postoperative moderate and severe tricuspid regurgitation (LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; PASP: pulmonary artery systolic pressure; PVR: pulmonary vascular resistance).

	Odds ratio (95% confidence interval)	p-value
Age	0.97 (0.88–1.07)	0.532
Body mass index	1.35 (0.88–2.08)	0.175
Recipient LVEDD	0.99 (0.89–1.11)	0.995
Recipient LVESD	0.99 (0.89–1.09)	0.900
Preoperative PASP	0.96 (0.88–1.04)	0.305
Dilated cardiomyopathy	8.5 (1.46–49.53)	0.017
Cross-clamp time	1 (0.99–1.03)	0.709
Cardiopulmonary bypass time	1 (0.96–1.05)	0.956
Postoperative PASP	0.999 (0.91–1.1)	0.984
PVR	1 (0.99–1.009)	0.738
Indexed PVR	0.53 (0.08–3.57)	0.513
Endocardial biopsy[a]	0.52 (0.17–1.57)	0.246

[a] Number of the endocardial biopsy was based on the number of procedures performed during the first hospitalization only.

and moderate TR with preoperative dilated cardiomyopathy (OR: 8.5; 95%CI: 1.46–49.53; p = 0.017) (Table 4).

3.4. Survival

The mean follow-up was 39.43 ± 50.57 months. Survival at one year was 71.5%, at 3 years 66.4%, at 5 and 10 years was 60.4% (Fig. 3). During the study period, mortality was reported in 10 patients, and the causes were sepsis (n = 4), rejection (n = 2), and unknown (n = 4).

Patients were grouped according to the postoperative degree of TR, less than moderate in one group, and moderate and severe in one group. Survival at 10 years was 90% in patients with less than moderate tricuspid regurgitation postoperatively compared to 43% for patients with moderate and severe tricuspid regurgitation (log-rank p = 0.0498) (Fig. 4). During follow-up, two patients required diuretic therapy. Liver enzymes and creatinine levels were within the normal range; no patient had a renal or hepatic impairment (Table 2).

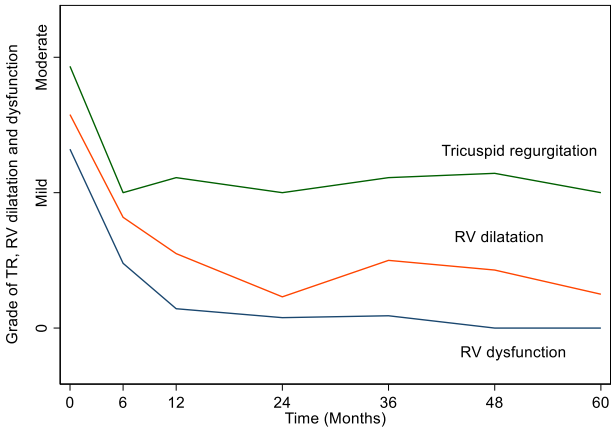

Fig. 2. Change in the degree of tricuspid regurgitation, right ventricular dilatation and dysfunction after cardiac transplantation: (RV: right ventricle, TR: tricuspid regurgitation).

4. Discussion

Tricuspid valve regurgitation after heart transplantation is the subject of ongoing research, and the optimal management of this problem continues to be debated. We studied postoperative TR in 30 patients who had orthotopic heart transplantation in a single-center in 10 years. We found that 37% had severe TR in the immediate postoperative period, and moderate and severe degrees of TR were associated with worse survival. Postoperative severe TR was significantly associated with dilated

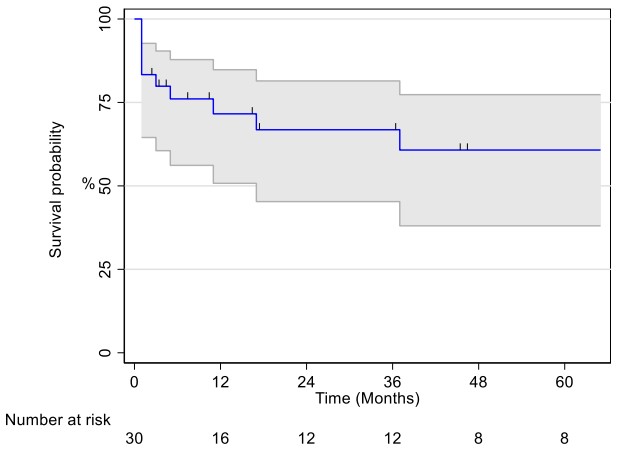

Fig. 3. Kaplan-Meier survival probability.

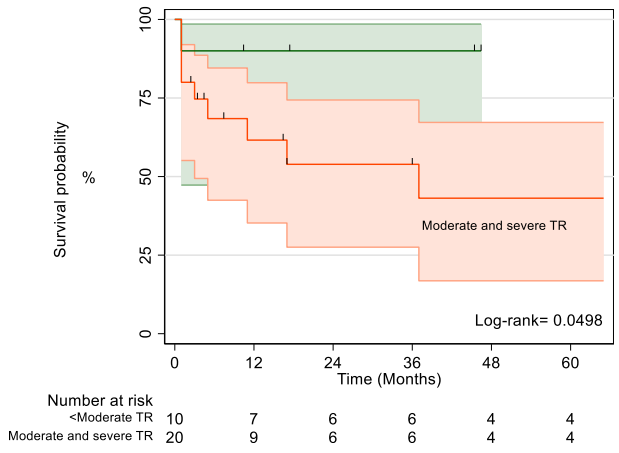

Fig. 4. Comparison of survival in patients with moderate and severe tricuspid regurgitation versus less than moderate regurgitation. (TR: tricuspid regurgitation).

cardiomyopathy. Kim and colleagues found that post-transplant tricuspid regurgitation did not affect long-term survival, and it was not related to the anastomosis technique, but the donor age was significantly associated with the occurrence of postoperative tricuspid regurgitation [5]. In an echocardiographic study comparing bi-caval versus atrial anastomosis technique, no effect of the technique on tricuspid regurgitation was found [6]. Several studies found that bi-caval technique decreased the post-transplant tricuspid regurgitation [7–10], and all patients in our study had bi-caval anastomosis.

In a large recent study about tricuspid regurgitation after heart transplantation, Bishawi and colleagues found that independent predictors of moderate and severe tricuspid regurgitation were high donor creatinine, the male recipient and sex mismatch [2]. We found that dilated cardiomyopathy was significantly associated with moderate or severe postoperative tricuspid regurgitation, which could be attributed to the size mismatch between donor and recipient hearts. Donor related criteria were not available for assessment in our cohort.

We observed a significant improvement in the degree of tricuspid regurgitation after 6 months postoperatively, and it remained stationary throughout the follow-up. However, moderate and severe tricuspid regurgitation negatively affected long-term survival. The result from our study is consistent with other series. Veen and associates in their larger series found that 33% of the patients had moderate to severe TR after transplant, and it declined to 15% after 5 years; however, mortality was significantly higher in patients with moderate to severe TR [11]. Bishawi and coworkers found that survival is significantly decreased in patients with moderate and severe tricuspid regurgitation after adjusting for recipient pulmonary vascular resistance, donor and recipient creatinine, ischemia time, donor age, sex mismatch, and body mass index [2]. Another study found that more than mild tricuspid regurgitation was an independent predictor of mortality [12].

Whether a tricuspid regurgitation is per se harmful and independently associated with increased mortality after heart transplantation or is merely a surrogate for other factors such as right ventricular failure is unclear from our small study, and it requires further investigation. In our series, the mechanism of TR was functional in all patients, and there was a high prevalence of right ventricular dilatation and dysfunction in the early postoperative period, which improved gradually simultaneously with the improvement of the degree of TR.

A randomized trial compared prophylactic DeVega annuloplasty of the donor's heart to those who had bi-caval anastomosis without annuloplasty. Patients with DeVega had a better right ventricular function and lower incidence of tricuspid regurgitation during long-term follow-up [3,13]. On the other hand, Greenberg and associates found that concomitant donor's tricuspid valve repair was not associated with a reduction of mortality, postoperative tricuspid valve regurgitation, or dialysis [14].

The benefits of prophylactic donor's tricuspid valve annuloplasty during heart transplantation is controversial, and its use in all patients may not be applicable. Repairing a normal valve may lead to postoperative stenosis and increase the risk of heart block and infective endocarditis. We recommend identification of the risk factors for tricuspid regurgitation in each institution, which may be center-specific and affected by the volume of the center, and recipient and donor's characteristics then perform prophylactic annuloplasty to those high-risk patients to improve the long-term outcomes. An alternative approach is to tackle the tricuspid regurgitation early in the postoperative period by transcutaneous techniques to preserve the right ventricular function and improve the long-term outcome.

4.1. Study Limitations

We reported the results from a single-center with relatively low volume (3 transplants/year). There are

several limitations of the study, including the retrospective nature of the design with its inherent biases and the small patients' number. Moreover, we did not have sufficient donor-related variables; therefore, we could not examine the association of donor-related variables with post-heart transplant tricuspid regurgitation. The study is retrospective, and data were collected from the medical charts; therefore, inter or intra-observational variability were not calculated. However, the study showed the negative effect of post-transplant moderate and severe tricuspid regurgitation on long-term survival. Additionally, it showed its association with dilated cardiomyopathy, which needs further investigation in a larger study.

5. Conclusion

Tricuspid regurgitation is a frequent finding after heart transplantation. Despite the improvement of the degree of tricuspid regurgitation after 6 months, survival is negatively affected by postoperative moderate or severe tricuspid regurgitation. In the present study, dilated cardiomyopathy was associated with postoperative moderate or severe tricuspid regurgitation, and this group of patients may benefit from concomitant tricuspid valve repair at the time of heart transplantation. However, more studies are required to investigate such speculations further.

Author Contribution

Khaled D. Algarni: Conception, Design, Supervision, Analysis And/Or Interpretation, Literature Review, Writer. **Amr A. Arafat**: Design, Data Collection And/Or Processing, Analysis And/Or Interpretation, Literature Review, Writer. **Claudio Pragliola**; Conception, Design, Supervision, Analysis And/Or Interpretation, Literature Review, Writer. **Yahya S. Alhebaishi**: Supervision, Materials, Critical Review. **Latifa A. AlFayez**: Data Collection And/Or Processing, Critical Review. **Khaled AlOtaibi**: Data Collection And/Or Processing, Critical Review. **Abeer M. Bakhsh**: Supervision, Materials, Critical Review. **Ahmed A. Amro**: Supervision , Materials, Critical Review. **Adam I. Adam**: Supervision, Data Collection And/Or Processing, Critical Review

Declaration of Competing Interest

None.

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