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Clinical Research

Incidence of and Risk Factors for the Development of Significant Tricuspid Regurgitation after Isolated Aortic Valve Replacement

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Background: The late progression of tricuspid regurgitation (TR) after mitral valve surgery is well known. However, few reports have described the progression of TR after aortic valve surgery. We investigated the incidence of and risk factors for the development of significant TR after isolated aortic valve replacement (AVR).
Methods: This study analyzed patients with less than moderate TR who underwent isolated AVR at Seoul National University Hospital from January 1990 to December 2018. Significant TR was defined as moderate or higher. Echocardiographic follow-up was performed in all patients. The Fine-Gray model was used to identify clinical risk factors for the development of significant TR.
Results: In total, 583 patients (61.7±14.2 years old) were included. Operative mortality occurred in 9 patients (1.5%), and the overall survival rates at 10, 20, and 25 years were 91.1%, 83.2%, and 78.9%, respectively. Sixteen patients (2.7%) developed significant TR during the follow-up period (13 moderate; 3 severe). The cumulative incidence of significant TR at 10, 20, and 25 years was 0.77%, 3.83%, and 6.42%, respectively. No patients underwent reoperation or reintervention of the tricuspid valve. Hemodialysis or peritoneal dialysis for chronic kidney disease (hazard ratio [HR], 5.188; 95% confidence interval [CI], 1.154–23.322) and preoperative mild TR (HR, 5.919; 95% CI, 2.059–17.017) were associated with the development of significant TR in the multivariable analysis.
Conclusion: TR progression after isolated AVR in patients with less than moderate TR is rare. Preoperative mild TR and hemodialysis or peritoneal dialysis for chronic kidney disease were significant risk factors for the development of TR.

Keywords: Heart valve diseases, Aortic valve disease, Tricuspid valve, Tricuspid valve insufficiency

Introduction

Functional tricuspid regurgitation (TR) accompanied by left-sided valve disease is a common form of TR. In the past, left-sided valve surgery alone was considered sufficient to improve functional TR; however, numerous studies have reported that significant TR frequently develops after left-sided valve surgery [1-3]. Furthermore, the progression of TR is associated with higher rates of morbidity and mortality [3-8]. Current guidelines suggest that concomitant tricuspid valve surgery should be considered in patients with progressive TR and annular dilation at the time of surgery for left-sided valve lesions [9,10]. In addition, some studies reported that prophylactic tricuspid valve surgery could be beneficial for patients with less than moderate TR [11-14]. However, most of these studies investigated the natural course of the tricuspid valve after mitral valve surgery; hence, there are insufficient data about the progression of TR in patients with trivial or mild functional TR after aortic valve replacement (AVR).

This study aimed to investigate the incidence of significant TR after isolated AVR in patients with less than moderate TR and to identify the risk factors for TR progression during the follow-up period.

Methods

Ethics statement

The institutional review board of Seoul National University Hospital Biomedical Research Institute reviewed the study protocol and approved it as a minimal-risk retrospective study (approval no., H-2106-100-1228). Therefore, informed consent from the patients was not required.

Study population

Between January 1990 and December 2018, 2,275 patients underwent AVR at Seoul National University Hospital and were chosen for this study. The exclusion criteria were concomitant cardiac surgery other than the Cox-Maze procedure (n=1,562), patients with a history of cardiac surgery (n=78), active infective endocarditis (n=30), preoperative moderate or severe TR (n=1), and missing medical records (n=21). After applying the exclusion criteria, a total of 583 patients were enrolled in the present study. The median follow-up duration was 86.7 months (interquartile range, 43.0–167.3 months).

Echocardiographic evaluation

Preoperative transthoracic echocardiography was required for all patients, and the TR severity level was graded as none, trivial, mild, moderate, or severe. Significant TR was defined as moderate or higher. Regular echocardiographic evaluations, as part of the follow-up, were carried out at the operating surgeon's discretion. We did not consider an event as TR recurrence if it improved spontaneously without medical intervention. The last follow-up echocardiographic evaluation was performed at a median of 87.7 months (interquartile range, 15.2–125.8 months) after surgery.

Surgical procedures

All patients underwent aortic and bicaval cannulation, moderate-degree hypothermia, and cold cardioplegic arrest through median sternotomy. AVR was performed using an interrupted noneverting mattress suture reinforced with polytetrafluoroethylene as a tubule or pledget.

Evaluation of clinical outcomes

Operative mortality was defined as death within 30 days of surgery or during the same hospital admission. Postoperative low cardiac output syndrome was defined as the need for mechanical or inotropic support to maintain systolic blood pressure >90 mm Hg after correcting reversible factors. We defined respiratory complications as pneumonia or the need to perform tracheostomy, acute kidney injury as a serum creatinine >2× baseline or urine output <0.5 mL/kg/hr for >12 hours, stroke as neurological symptoms with infarct or hemorrhage identified on imaging studies, and mediastinitis as clinical symptoms with bacteria identified by culture studies. The patients underwent routine postoperative follow-up at 3- to 6-month intervals in the outpatient clinic. The survival data were obtained from death certificates in Statistics Korea. Clinical follow-up ended on December 31, 2021. The completeness of follow-up for survival was 100% and the echocardiographic follow-up was performed by 89.6%, 86.5%, 75.1%, 76.8%, and 44.0% of all available patients at 6 months and 1, 3, 5, and 10 years after surgery, respectively.

Statistical analysis

Statistical analyses were performed using IBM SPSS ver. 20.0 (IBM Corp., Armonk, NY, USA). Data were expressed as mean±standard deviation, median with range, or proportions. Survival rates were estimated using the Kaplan-Meier method. The cumulative incidence of significant TR was estimated with overall death as a competing risk factor for events, and the Fine-Gray model was used to investigate clinical risk factors for the development of significant TR. All preoperative characteristics were included in univariable analysis to identify risk factors for the development of significant TR. Variables with a p-value <0.05 in the univariable analysis were chosen for the multivariable analysis. Statistical significance was set at $p<0.05$.

Results

Preoperative characteristics and operative data

The preoperative patient characteristics are summarized in Table 1. The mean age was 61.7±14.2 years, and 359 patients (61.6%) were men. Regarding the preoperative TR grade, 367 patients (62.9%) had no TR, 175 patients (30.0%) had trivial TR, and 41 patients (7.0%) had mild TR. A total of 147 patients (36.2%) had a New York Heart Association (NYHA) functional class ≥3, and 176 patients (30.2%) had chronic renal failure, of whom 16 patients (2.7%) required hemodialysis or peritoneal dialysis. Forty-five patients (7.7%)

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Table 1. Preoperative characteristics of study patients who underwent aortic valve replacement (N=583)

Characteristic	Value
Age (yr)	61.7±14.2
Male	359 (61.6)
Tricuspid regurgitation grade	
None	367 (62.9)
Trivial	175 (30.0)
Mild	41 (7.0)
Risk factors	
NYHA functional class ≥3	147 (25.2)
Smoking	158 (27.1)
Overweight (BMI >25.0 kg/m^2)	195 (33.4)
Diabetes mellitus	84 (14.4)
Hypertension	249 (42.7)
History of stroke	27 (4.6)
Chronic renal failure (GFR <60 mL/min)	176 (30.2)
Hemodialysis or peritoneal dialysis	16 (2.7)
Atrial fibrillation	45 (7.7)
Coronary artery disease	65 (11.1)
Peripheral vascular disease	14 (2.4)
Pathophysiology	
Aortic stenosis	276 (47.3)
Aortic regurgitation	156 (26.8)
Aortic stenoinsufficiency	151 (25.9)
Preoperative echocardiography	
Left ventricular ejection fraction (%)	57.3±12.4
Left atrial size (mm)	44.0±7.7
Etiology of aortic valve pathology	
Rheumatic	140 (24.0)
Bicuspid	222 (38.0)
Degenerative	175 (30.0)
Endocarditis	12 (2.0)
Others	34 (5.8)

Values are presented as mean±standard deviation or number (%).
NYHA, New York Heart Association; BMI, body mass index; GFR, glomerular filtration rate.

had preoperative atrial fibrillation. The mean left ventricular ejection fraction and left atrial size were 57.3±12.4% and 44.0±7.7 mm, respectively. The etiology of the aortic valve pathology was bicuspid, degenerative, rheumatic, or endocarditis, for 222 (38.0%), 175 (30.0%), 140 (24.0%), and 12 (2.0%) patients, respectively.

The operative data are summarized in Table 2. Mechanical valves were used in 296 patients (50.8 %). Prosthesis-patient mismatch (effective orifice area index [EOAI] <0.85 cm^2/m^2) occurred in 31 patients (5.3%). The EOAI of implanted prostheses was calculated using data from a previous study [15]. The mean cardiopulmonary bypass and aortic cross-clamp times were 137.1±59.9 minutes and 88.0±33.3 minutes, respectively.

Table 2. Operative data of study patients who underwent aortic valve replacement (N=583)

Variable	Value
Mechanical valve	296 (50.8)
Bioprosthetic valve	287 (49.2)
Surgical ablation for atrial fibrillation	17 (2.9)
Valve size	
Small (17–21 mm)	204 (35.0)
Medium (22–24 mm)	205 (35.2)
Large (≥25 mm)	174 (29.8)
Prosthesis-patient mismatch (EOAI <0.85 cm^2/m^2)	31 (5.3)
Cardiopulmonary bypass time (min)	137.1±59.9
Aortic cross-clamp time (min)	88.0±33.3

Values are presented as number (%) or mean±standard deviation.
EOAI, effective orifice area index.

Table 3. Early clinical outcomes after aortic valve replacement (N=583)

Variable	No. (%)
Operative mortality	9 (1.5)
Postoperative complications	197 (33.7)
Low cardiac output syndrome	31 (5.3)
Bleeding reoperation	17 (2.9)
New-onset atrial fibrillation	116 (19.9)
Respiratory complications	22 (3.7)
Acute kidney injury	22 (3.7)
Stroke	8 (1.4)
Mediastinitis	4 (0.6)
Complete atrioventricular block	6 (1.0)

Clinical outcomes

The operative mortality rate was 1.5% (9 of 583 patients). Postoperative complications included low cardiac output syndrome (n=31, 5.3%), reoperation for bleeding (n=17, 2.9%), new-onset atrial fibrillation (n=116, 19.9%), respiratory complications (n=22, 3.7%), acute kidney injury (n=22, 3.7%), stroke (n=8, 1.4%), mediastinitis (n=4, 0.6%), and complete atrioventricular block (n=6, 1.0%) (Table 3). One patient underwent permanent pacemaker implantation among patients who were complicated by complete atrioventricular block postoperatively. Late death occurred in 200 patients, and the overall survival rates at 10, 20, and 25 years were 91.1%, 83.2%, and 78.9%, respectively.

Change in tricuspid regurgitation

The successive changes in TR are shown in Fig. 1. At discharge, 547 patients (93.8%) had no or trivial TR, 34 patients (5.8%) had mild TR, and 2 patients (0.3%) had significant TR (both had moderate TR). At the final follow-up,

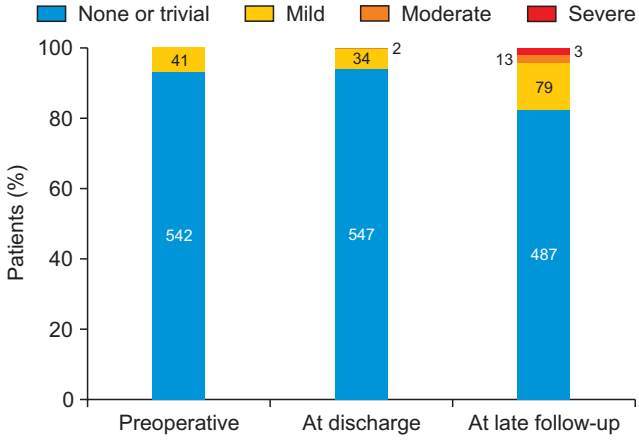

Fig. 1. Serial changes in tricuspid regurgitation following aortic valve replacement.

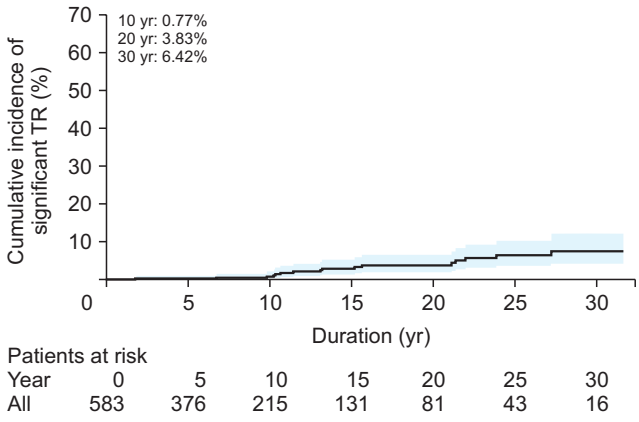

Fig. 2. Cumulative incidence curves for the development of significant tricuspid regurgitation (TR). Cumulative incidence rates are given for 10, 20, and 25 years postoperatively.

16 patients (2.7%) had developed significant TR, with 13 (2.2%) and 3 (0.5%) patients exhibiting moderate and severe TR, respectively. Eleven patients (2.0%) had progressed from none or trivial TR preoperatively to significant TR, and 5 patients (12.2%) from preoperative mild TR to significant TR.

Long-term outcomes for the development of significant tricuspid regurgitation

The cumulative incidence of significant TR development at 10, 20, and 25 years was 0.77%, 3.83%, and 6.42%, respectively (Fig. 2). In the univariate analyses, an NYHA functional class ≥3, history of stroke, hemodialysis or peritoneal dialysis, and preoperative mild TR were significant factors for the development of significant TR. In the multivariable analysis, hemodialysis or peritoneal dialysis (hazard ratio [HR], 5.188; 95% confidence interval [CI], 1.154–23.322) and preoperative mild TR (HR, 5.919; 95% CI, 2.059–17.017) were significant risk factors (Table 4). When the patients were divided into 2 groups according to risk factors (hemodialysis or peritoneal dialysis and preoperative mild TR), there was a significant difference between the groups in the cumulative incidence of significant TR ($p<0.001$) (Fig. 3).

Discussion

This study had 2 main findings. First, TR progression after isolated AVR in patients with less than moderate TR seldom occurred, with a 20-year cumulative incidence of 3.83%. Second, the risk of TR progression after isolated AVR increased in patients with chronic renal failure undergoing renal replacement therapy and in patients with preexisting mild TR.

The development of late TR is a common and clinically significant event after left-sided valve surgery and is known to adversely affect cardiac morbidity and mortality [1-8]. The management of TR has become more aggressive in recent years. Tricuspid valve surgery is currently recommended for patients with significant TR during left-sided valve surgery [9,10]. In addition, prophylactic tricuspid valve surgery during mitral valve surgery has also been recommended in several studies [11-14]. However, TR management is still debated because most studies were limited to investigating TR associated with mitral valve disease. Only a few studies have reported the prognosis of functional TR accompanied by aortic valve disease.

Jeong et al. [16] examined changes in TR after AVR for aortic stenosis (AS) and found that the incidence of significant TR after AVR was 17.2% (61 of 354) and that functional TR did not improve in half of the patients with mild or moderate preoperative TR. Dumont et al. [17] reported that moderate-to-severe TR was present in 30 patients (25.8%) at the 1-year follow-up after surgical AVR or transcatheter aortic valve implantation for AS, and that the TR was unchanged or worsened in 99 patients (85.3%). Similarly, Yajima et al. [18] evaluated patients who underwent isolated AVR for severe AS by dividing them into 2 groups: those with or without preoperative TR. They found that 12 patients (8.8%) in the non-TR group and 21 patients (35%) in the TR group presented with significant TR during the follow-up. In the present study, 16 patients (2.7%) developed late significant TR after isolated AVR. The cumulative incidence of significant TR development at 10, 20, and 25 years was 0.77%, 3.83%, and 6.42%, respectively. In our

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Table 4. Risk factor analysis for the development of significant TR after isolated aortic valve replacement in patients with less than moderate TR

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-value[a]	HR (95% CI)	p-value[a]
Age	1.018 (0.997–1.040)	0.090		
Sex	0.489 (0.186–1.290)	0.148		
Body surface area	0.119 (0.011–1.311)	0.082		
Body mass index >25.0 kg/m^2	0.380 (0.087–1.660)	0.198		
NYHA functional class ≥3	2.908 (1.096–7.714)	0.032	2.712 (0.966–7.610)	0.058
Smoking	1.437 (0.534–3.864)	0.472		
Diabetes mellitus	1.253 (0.303–5.189)	0.755		
Hypertension	1.697 (0.644–4.473)	0.285		
History of stroke	4.621 (1.205–17.717)	0.025	3.852 (0.968–15.331)	0.055
Chronic renal failure	1.649 (0.571–4.758)	0.355		
Hemodialysis or peritoneal dialysis	5.751 (1.374–24.068)	0.016	5.188 (1.154–23.322)	0.031
Coronary artery disease	0.840 (0.110–6.395)	0.866		
Preoperative atrial fibrillation	2.760 (0.811–9.393)	0.104		
New onset postoperative atrial fibrillation	2.592 (0.713–9.428)	0.148		
Rheumatic etiology	0.788 (0.290–2.143)	0.641		
Bicuspid etiology	0.840 (0.269–2.621)	0.764		
Degenerative etiology	2.921 (0.782–10.907)	0.111		
Mechanical valve	1.645 (0.628–4.308)	0.311		
Prosthesis-patient mismatch	5.448 (0.667–44.533)	0.114		
Left ventricular dysfunction (<50%)	1.135 (0.374–3.445)	0.823		
Left atrial size	1.025 (0.949–1.106)	0.534		
Preoperative mild TR	6.168 (2.158–17.624)	<0.001	5.919 (2.059–17.017)	0.001

TR, tricuspid regurgitation; HR, hazard ratio; CI, confidence interval; NYHA, New York Heart Association.
[a]p-value <0.05 indicates statistical significance.

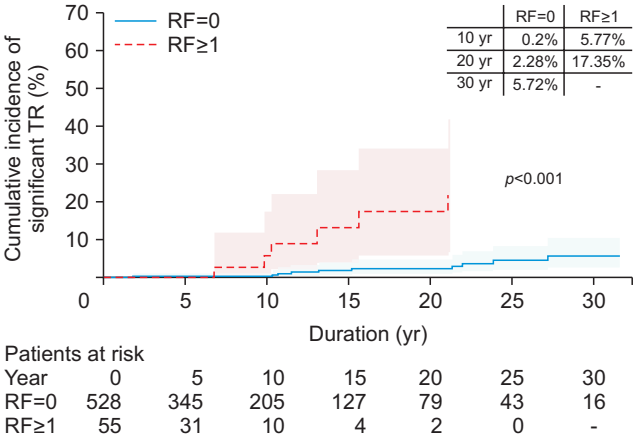

Fig. 3. Cumulative incidence curves for the development of significant tricuspid regurgitation (TR) according to the presence of risk factors (chronic kidney disease with hemodialysis or peritoneal dialysis, preoperative mild TR). RF, risk factor.

study, the incidence of late significant TR after AVR was relatively low compared with that in other studies. A possible explanation for this is that TR progression is known to be related to the preoperative TR grade. We only included patients with less than moderate TR, which may have led to the low incidence rate. In addition, unlike previous studies, death was considered a competing risk when analyzing the incidence of significant TR in this study. Since we considered patients who died during a long follow-up period when analyzing patient data, the incidence could be low. Taking these factors into account, our result may more accurately represent an actual clinical setting.

In our study, multivariable analysis revealed that chronic kidney disease with renal replacement therapy and preoperative mild TR were significant risk factors for TR progression. Although several studies have found a correlation between the degree of preoperative TR and postoperative TR progression [4,16,18,19], the fact that mild TR was related to progressive TR compared to no or trivial TR is a notable finding, given that a mild degree can be neglected by surgeons during left-sided valve surgery. Chronic kidney disease with renal replacement therapy is also a known factor associated with significant TR [20]. The pathophysiological consequences of renal impairment, such as uremia, inflammation, microvascular dysfunction, and accelerated atherosclerosis can manifest in cardiological

complications. This includes progressive myocardial stiffening, hypertrophy, and interstitial fibrosis, which in turn can give rise to right ventricular (RV) dysfunction and TR progression [21,22].

This study also showed the relationship between the cumulative incidence of significant TR and the presence or absence of risk factors. In particular, the cumulative incidence of significant TR development at 10 and 20 years in patients with risk factors increased up to 5% and 17%, respectively. Given that corrective surgery for late TR is associated with high operative mortality and morbidity [23-25], concomitant prophylactic tricuspid valve surgery should be considered when there is a high risk of TR progression in young patients.

The present study had certain limitations. First, it was a single-center, retrospective, observational study. Second, echocardiographic follow-up was not regularly performed. Third, the echocardiographic data were incomplete in some cases. For example, the parameters of RV function such as tricuspid annular diameter and RV dimension or volume, which could have a significant impact on TR, were not included because these parameters were not routinely measured in patients undergoing AVR at our hospital.

In conclusion, progression of TR after isolated AVR in patients with less than moderate TR rarely occurs. Preoperative mild TR and hemodialysis or peritoneal dialysis for chronic kidney disease were significant risk factors for the development of TR. Thus, a concomitant tricuspid valve procedure should be considered as a prophylactic measure when performing AVR in young patients with mild TR or chronic renal failure undergoing renal replacement therapy.

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Conceptualization: JWC. Data curation: MSK, JWC, SHS, HYH, KHK. Formal analysis: MSK, JWC. Methodology: JWC. Project administration: JWC. Visualization: MSK. Writing–original draft: MSK. Writing–review and editing: JWC. Final approval of the manuscript: MSK, JWC, SHS, HYH, KHK.

Conflict of interest

Jae Woong Choi is an editorial board member of the journal but was not involve in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflict of interest relevant to this article was reported.

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