

Risk Analysis of the Long-Term Outcomes of the Surgical Closure of Secundum Atrial Septal Defects

Hong Rae Kim, M.D., Sung-Ho Jung, M.D., Ph.D., Jung Jun Park, M.D., Ph.D.,
Tae Jin Yun, M.D., Ph.D., Suk Jung Choo, M.D., Ph.D.,
Cheol Hyun Chung, M.D., Ph.D., Jae Won Lee, M.D., Ph.D.

Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, University of Ulsan College of Medicine

Background: Closure of a secundum atrial septal defect (ASD) is possible through surgical intervention or device placement. During surgical intervention, concomitant pathologies are corrected. The present study was conducted to investigate the outcomes of surgical ASD closure, to determine the risk factors of mortality, and establish the effects of concomitant disease correction. **Methods:** Between October 1989 and October 2009, 693 adults underwent surgery for secundum ASD. Their mean age was 40.9±13.1 years, and 199 (28.7%) were male. Preoperatively, atrial fibrillation was noted in 39 patients (5.6%) and significant tricuspid regurgitation (TR) in 137 patients (19.8%). The mean follow-up duration was 12.4±4.7 years. **Results:** There was no 30-day mortality. The 1-, 5-, 10-, and 20-year survival rates were 99.4%, 96.8%, 94.5%, and 81.6%, respectively. In multivariate analysis, significant preoperative TR (hazard ratio [HR], 1.95; 95% confidence interval [CI], 1.09 to 3.16; p=0.023) and preoperative age (HR, 1.04; 95% CI, 1.01 to 1.06; p=0.001) were independent risk factors for late mortality. The TR grade significantly decreased after ASD closure with tricuspid repair. However, in patients with more than mild TR, repair was not associated with improved long-term survival (p=0.518). **Conclusion:** Surgical ASD closure is safe. Significant preoperative TR and age showed a strong negative correlation with survival. Our data showed that tricuspid valve repair improved the TR grade effectively. However, no effect on long-term survival was found. Therefore, early surgery before the development of significant TR may be beneficial for improving postoperative survival.

Key words: 1. Survival
2. Heart septal defects, atrial
3. Tricuspid valve insufficiency

Introduction

Atrial septal defect (ASD) is one of the most common conditions known as grown-up congenital heart diseases. Excellent results after surgical correction have been well documented in long-term follow-up studies, especially in the young population [1,2]. Currently, percutaneous device closure is the method

of choice for secundum ASD closure, when applicable [3]. However, shunt remnants, migration of the device after intervention, and atrial tachyarrhythmias can occur [4]. Substantial tricuspid regurgitation (TR) and atrial fibrillation are common comorbidities with ASD; in these cases, it may be more beneficial to proceed with surgical closure, in order to correct these conditions simultaneously. Some studies have

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Corresponding author: Jae Won Lee, Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea (Tel) 82-2-3010-3584 (Fax) 82-2-3010-6966 (E-mail) jwlee@amc.seoul.kr

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addressed the effect of ASD closure on TR and have identified several risk factors for persistent TR after closure [5,6]. However, the effect of concomitant TR correction remains unknown. The aims of the present study were to investigate the outcomes of surgical ASD closure and to determine the risk factors for mortality, as well as to establish the effect of concomitant disease correction.

Methods

1) Patients

From the institutional prospective cardiac surgical database, we identified 715 consecutive adult patients (age >17 years) who underwent ASD closure from October 1989 to October 2009. Of these, we were able to retrieve the data of 693 patients with secundum ASD. We excluded patients with no follow-up echocardiographic data and those with other types of ASD, such as ostium primum and sinus venous ASD. Their mean age was 40.9±13.1 years (range, 18 to 76 years), and 199 patients (28.7%) were male. The mean follow-up duration was 12.4±4.70 years (range, 5 months to 25.5 years). For all patients, 12-lead electrocardiograms were reviewed to determine whether atrial fibrillation was present. All the patients were examined using 2-dimensional and Doppler transthoracic echocardiography. TR was evaluated using the apical 4-chamber view, and graded as none, trace, mild, moderate, and severe when the jet area occupied 0%, <10%, 10%-20%, 20%-33%, and >33% of the right atrial area, respectively. The regurgitation scoring was as follows: 0, no regurgitation; 1+, trivial; 2+, mild; 3+, moderate; 4+, severe. Significant TR was defined as moderate or severe TR. Pulmonary artery pressure was computed using the simplified Bernoulli equation with Doppler echocardiographic data. We defined severe pulmonary hypertension as a calculated systolic pulmonary artery pressure >45 mm Hg.

The surgical correction methods and cardiopulmonary bypass strategy were left to the attending surgeon's discretion. In the tricuspid annuloplasty (TAP) group, 27 patients underwent TAP using prosthetic rings, 108 patients underwent De Vega suture annuloplasty, and 24 patients underwent Kay annuloplasty. The classic Carpentier-Edwards ring (Edwards Lifesciences Inc., Irvine, CA, USA) and the Duran ring

Table 1. Baseline characteristics

Characteristic	Value
No. of patients	693
Age (yr)	40.9±13.1
Male gender	199 (28.7)
Diabetes mellitus	21 (3.0)
Hypertension	73 (10.5)
History of cerebrovascular accident	1 (0.1)
Atrial fibrillation	39 (5.6)
Chronic renal failure	2 (0.3)
Chronic obstructive pulmonary disease	1 (0.1)
Echocardiographic data	
Left ventricular ejection fraction (%)	62.9±6.40
Size of atrial septal defect (mm)	24.3±7.80
Peak TR pressure gradient (mm Hg)	38.8±16.2
TR	
None-to-trace	26 (3.8)
Grade I	366 (52.8)
Grade II	164 (23.7)
Grade III	85 (12.3)
Grade IV	52 (7.5)
Pulmonary hypertension	162 (23.4)
Approach	
Sternotomy	439 (63.3)
Thoracotomy	254 (36.7)
AESOP	
Da Vinci	23 (3.3)
Tricuspid annuloplasty technique	
Ring annuloplasty	27
Carpentier-Edwards	13
Duran	14
De Vega	108
Kay	24
Maze procedure	35 (5.1)
Cardiopulmonary bypass time (min)	71.0±28.2
Aortic cross clamp time (min)	33.0±17.0

Values are presented as mean±standard deviation or number (%). The following instrument was used: AESOP (Automated Endoscope System for Optimal Positioning Computer Motion Inc., Santa Barbara, CA, USA), Da Vinci (Da Vinci Surgical System Intuitive Inc., Sunnydale, CA, USA).

TR, tricuspid regurgitation.

(Medtronic Inc., Minneapolis, MN, USA) were used in ring annuloplasty. In the subgroup analysis, patients with significant preoperative TR were divided into TAP (n=107) and non-TAP (n=30) groups.

Clinical follow-up examinations were performed at 2-week to 6-month intervals through the outpatient clinic. All data on mortality were obtained from the Korean National Registry of Vital Statistics (KNRB).

Table 2. Baseline characteristics of patients with significant TR

Characteristic	TR grade ≤2	TR grade >2	p-value
No. of patients	556	137	
Age (yr)	39.5±12.6	46.4±13.5	<0.001
Male gender	169 (30.4)	30 (21.9)	0.05
Diabetes mellitus	13 (2.3)	8 (5.8)	0.03
Hypertension	56 (10.1)	17 (12.4)	0.42
Atrial fibrillation	15 (2.7)	24 (17.5)	<0.001
Chronic renal failure	1 (0.2)	1 (0.7)	0.28
Echocardiographic data			
Left ventricular ejection fraction (%)	63.2±6.02	62.0±7.57	0.11
Size of atrial septal defect (mm)	23.7±7.28	26.9±9.08	<0.001
Peak TR pressure gradient (mm Hg)	35.8±12.9	49.7±21.2	<0.001
Pulmonary hypertension	93 (18.0)	69 (51.1)	<0.001
Maze procedure	15 (2.7)	20 (14.6)	<0.001
Cardiopulmonary bypass time (min)	68.1±26.6	82.9±31.2	<0.001
Aortic cross-clamp time (min)	30.4±15.0	42.5±20.4	<0.001

Values are presented as mean±standard deviation or number (%). TR, tricuspid regurgitation.

2) Statistical analysis

Categorical variables are presented as percentages or frequencies, and continuous variables are expressed as mean±standard deviation or median with range. The variables of the 2 groups were compared using the Student t-test. Kaplan-Meier curves were used to describe the overall survival and event-free survival rates, and the differences in these rates between the groups were assessed using the log-rank test. Cox proportional hazard models were used to identify predictors of mortality. Variables identified as significant in the univariate analysis ($p < 0.1$) were included in the multivariate analysis to determine the independent risk factors. All p -values < 0.05 were considered to indicate statistical significance. Statistical analysis was carried out using IBM SPSS ver. 21.0 (IBM Corp., Armonk, NY, USA).

Results

1) Baseline characteristics

The baseline characteristics of the patients are summarized in Table 1. The median size of the ASD was 24.3±7.80 mm. All operations were performed in an elective setting; 63.3% of the operations were performed through a sternotomy and 36.7% of the operations were performed via thoracotomy. The most common concomitant surgical procedures were

TAP ($n=159$, 22.9%) followed by the maze procedure ($n=35$, 5.1%). Table 2 describes the baseline characteristics of the patients with significant TR. The mean age of the significant TR group was older than that of the non-significant TR group. Atrial fibrillation and pulmonary hypertension were more frequent in patients with significant TR.

Table 3 shows the baseline characteristics of the TAP group and non-TAP group with significant TR. The mean age was older in the TAP group. No significant differences were found in preoperative ejection fraction or defect size. The TAP patients had atrial fibrillation and severe TR more frequently than the non-TAP group.

2) Outcomes

There were no early hospital deaths. The 1-year, 5-year, 10-year, and 20-year survival rates were 99.4%, 96.8%, 94.5%, and 81.6%, respectively (Fig. 1). There were 65 late deaths. However, it was not possible to determine the specific cause of death. There was one case of reoperation for a remnant shunt after ASD closure. Nine patients experienced post-operative bleeding. Temporary neurologic dysfunction occurred in 4 patients (Table 4).

Fig. 2 shows the effects of atrial fibrillation, pulmonary hypertension, and significant TR at the time of operation on long-term survival. Survival was decrea-

Table 3. Baseline characteristics compared between the TAP and non-TAP groups with significant TR

Characteristic	TAP	Non-TAP	p-value
No. of patients	107	30	
Age (yr)	47.7±13.4	42.0±13.2	0.04
Male gender	25 (23.4)	5 (16.7)	0.43
Diabetes mellitus	7 (6.5)	1 (3.3)	0.50
Hypertension	15 (14.0)	2 (10.0)	0.28
Atrial fibrillation	22 (20.6)	2 (6.7)	0.07
Chronic renal failure	1 (0.9)	0	0.59
Echocardiographic data			
Left ventricular ejection fraction (%)	61.8±7.70	63.0±7.05	0.49
Size of atrial septal defect (mm)	26.4±9.27	29.2±8.04	0.15
Peak TR pressure gradient (mm Hg)	48.9±21.3	53.2±21.2	0.38
TR			
Grade III	58 (54.2)	27 (90.0)	<0.001
Grade IV	49 (45.8)	3 (10.0)	<0.001
Pulmonary hypertension	52 (48.6)	17 (56.7)	0.49
Approach			
Sternotomy	89 (83.1)	24 (80.0)	
Thoracotomy	18 (16.9)	6 (20.0)	
AESOP	7 (6.5)	0	
Da Vinci	1 (0.9)	0	
Maze procedure	18 (16.8)	2 (6.7)	0.16
Cardiopulmonary bypass time (min)	87.4±31.7	66.9±23.9	0.001
Aortic cross-clamp time (min)	45.8±20.8	29.0±11.9	<0.001

Values are presented as mean±standard deviation or number (%). The following instrument was used: AESOP (Automated Endoscope System for Optimal Positioning Computer Motion Inc., Santa Barbara, CA, USA), Da Vinci (Da Vinci Surgical System Intuitive Inc., Sunnydale, CA, USA).

TAP, tricuspid annuloplasty; TR, tricuspid regurgitation.

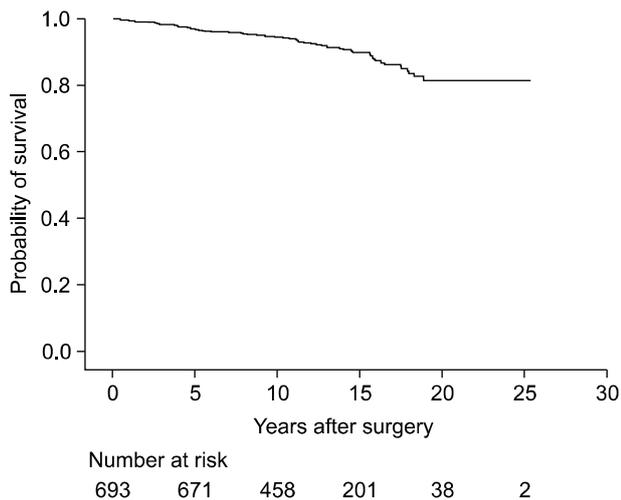


Fig. 1. Kaplan-Meier plots for overall survival, showing a 1-year survival rate of 99.4%, a 5-year survival rate of 96.8%, a 10-year survival rate of 94.5%, and a 20-year survival rate of 81.6%.

Table 4. Postoperative complications

Variable	No. (%)
Cerebrovascular accident	4 (0.57)
Postoperative bleeding	9 (1.29)
Pericardial effusion	5 (0.72)
Wound dehiscence	6 (0.86)
Others	8 (1.15)
Total	32 (4.61)

sed to a statistically significant extent in the presence of pulmonary hypertension and significant TR.

In the univariate Cox proportional hazard models, age, atrial fibrillation, significant TR, and pulmonary hypertension were significant and independent predictors of the major adverse outcome (death). When multivariate Cox proportional analysis was performed using these significant variables, age (hazard ratio [HR], 1.03; 95% confidence interval [CI], 1.01 to 1.06; p=0.001) and significant TR (HR, 1.95; 95% CI,

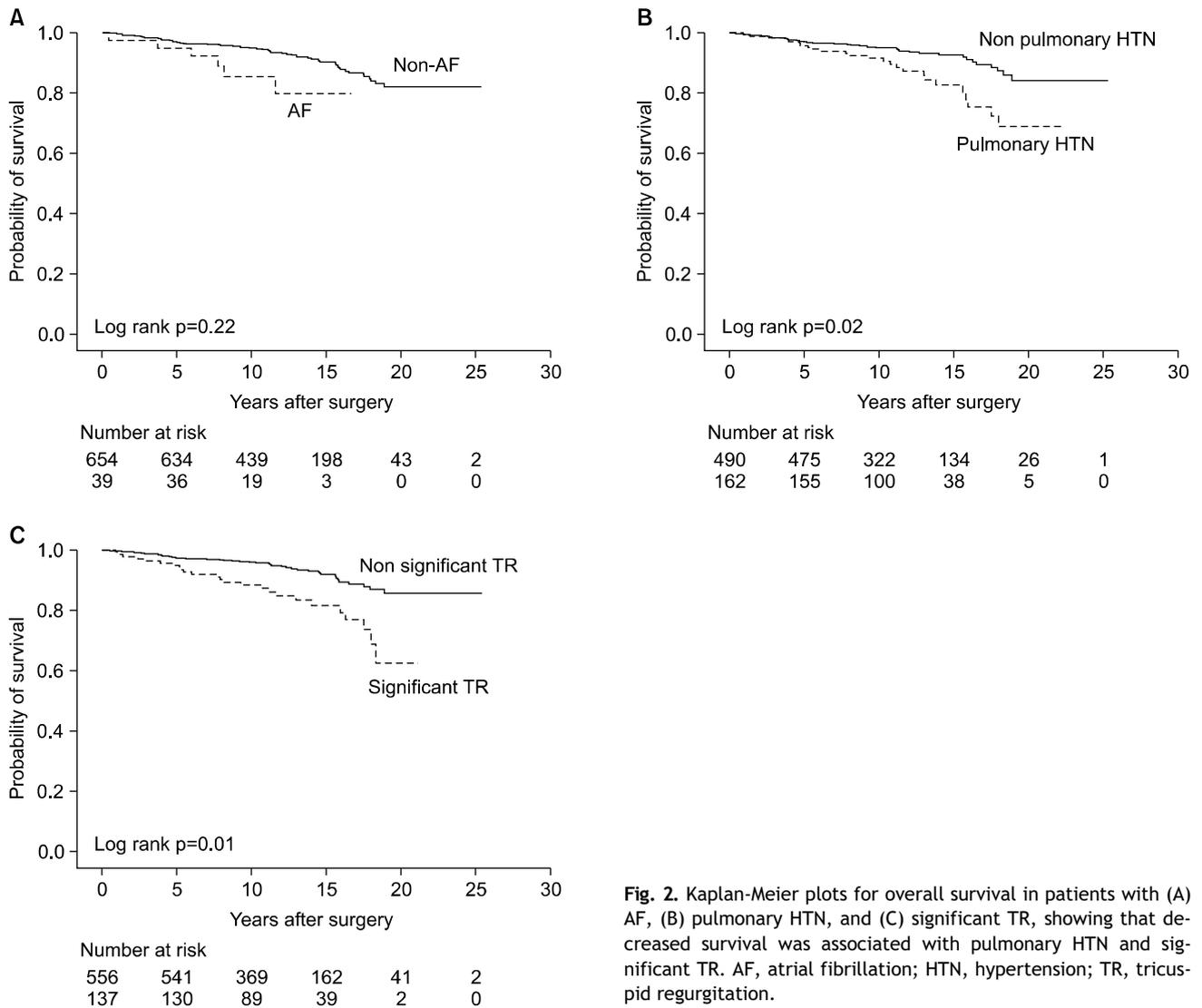


Fig. 2. Kaplan-Meier plots for overall survival in patients with (A) AF, (B) pulmonary HTN, and (C) significant TR, showing that decreased survival was associated with pulmonary HTN and significant TR. AF, atrial fibrillation; HTN, hypertension; TR, tricuspid regurgitation.

Table 5. Cox-regression analysis for preoperative characteristics predictive of mortality

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.04 (1.02–1.06)	0.001	1.03 (1.01–1.06)	0.001
Sex	1.04 (0.41–2.63)	0.930	-	-
Atrial fibrillation	2.59 (1.10–6.07)	0.028	1.08 (0.43–2.70)	0.878
Significant tricuspid regurgitation	2.80 (1.12–7.00)	0.027	1.95 (1.09–3.16)	0.023
Pulmonary hypertension	2.26 (1.34–3.70)	0.002	1.66 (0.94–2.94)	0.080
Diabetes mellitus	0.92 (0.21–3.97)	0.912	-	-
Size of atrial septal defect	1.02 (0.98–1.05)	0.310	-	-
Preoperative left ventricle ejection fraction	0.98 (0.94–1.03)	0.476	-	-

OR, odds ratio; CI, confidence interval.

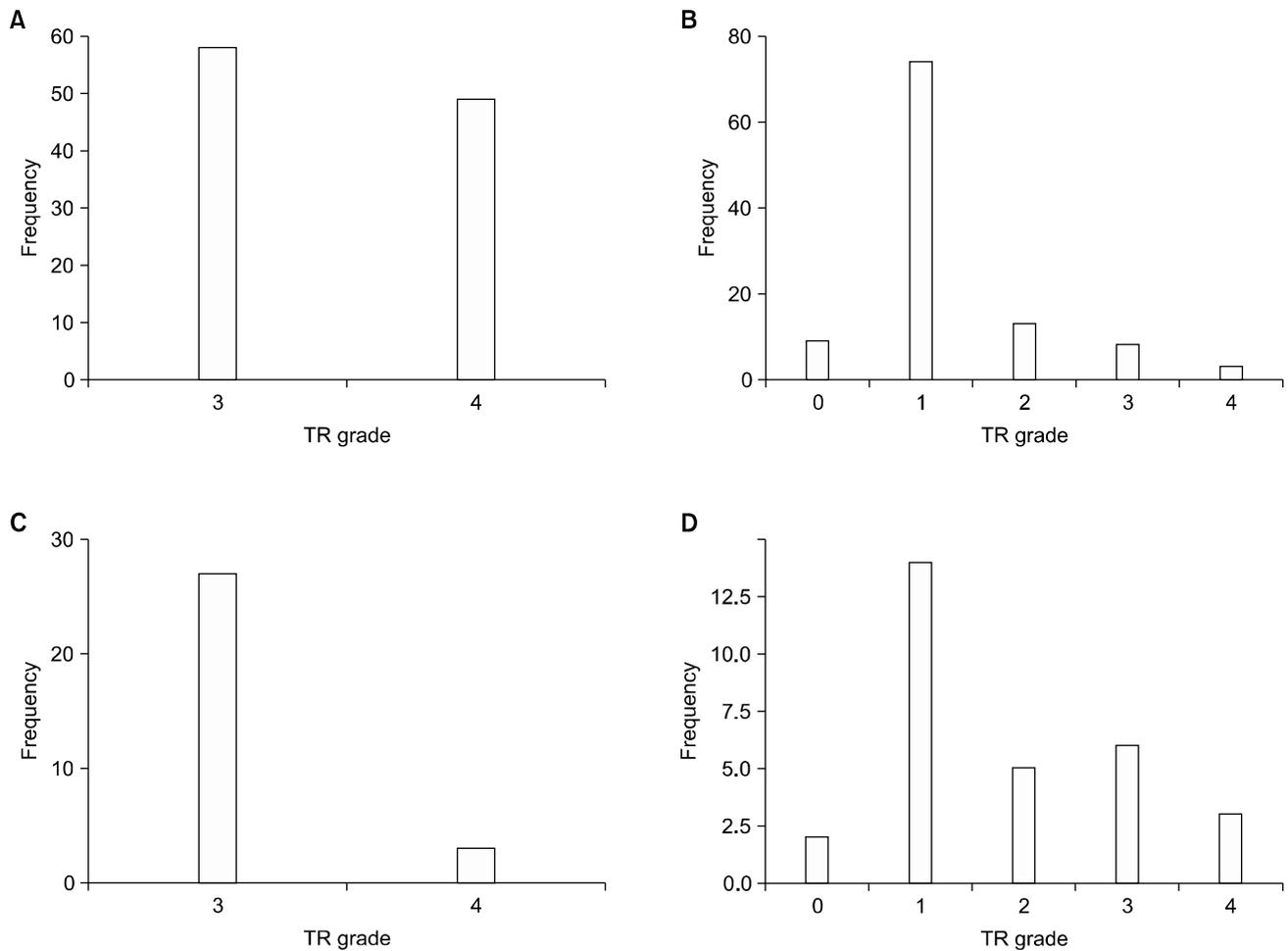


Fig. 3. The tricuspid regurgitation grade decreased in both TAP and non-TAP groups after surgery. (A) Preoperative TAP group; (B) Postoperative TAP group; (C) Preoperative non-TAP group; (D) Postoperative non-TAP group. TR, tricuspid regurgitation; TAP, tricuspid annuloplasty.

1.09 to 3.16; $p=0.023$) were significant and independent predictors of the major adverse outcome (Table 5).

In a subgroup analysis of patients with significant TR, the grade of tricuspid valve regurgitation decreased after ASD closure. In the TAP group, the TR grade improved more prominently (Fig. 3).

The Kaplan-Meier curves for estimated freedom from significant TR in the TAP and non-TAP groups showed a statistically significant difference between groups, in favor of the TAP group. However, no significant difference was found in the survival curves between the 2 groups (Fig. 4).

Discussion

In this study, we evaluated the outcomes of surgi-

cal ASD closure and the benefits of the concomitant correction of associated defects. The low mortality rate in our study confirms the safety of this surgical strategy, as has been demonstrated previously [1,2]. However, in this era, device closure has become the treatment of choice for secundum ASD when the morphology is suitable [3,4]. Therefore, in this study, we investigated the risk factors for poor outcomes in surgical ASD closure and the effect of correcting associated lesions.

In the risk factor analysis, our data showed that significant preoperative TR and age had a strong negative correlation with long-term survival. Atrial fibrillation was not correlated with survival. However, the total number of atrial fibrillation cases in our study population was only 39. Thus, we cannot come

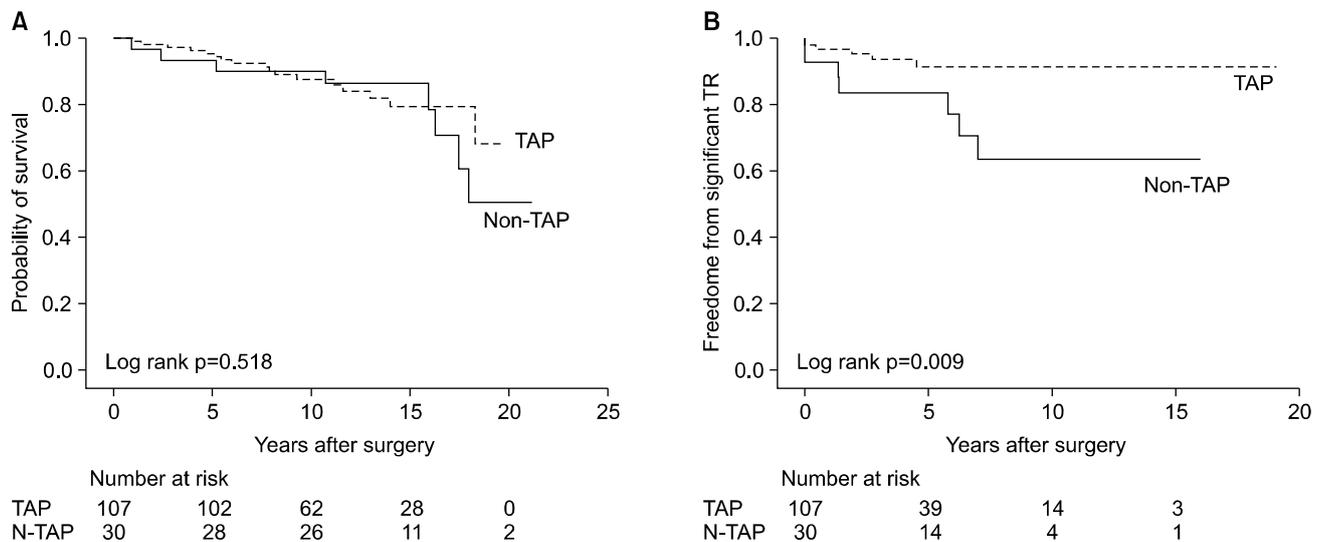


Fig. 4. Kaplan-Meier plots showed no significant difference in (A) overall survival, but a statistically significant difference in (B) freedom from TR between the TAP and non-TAP groups. TAP, tricuspid annuloplasty; TR, tricuspid regurgitation.

to a firm conclusion on the effect of correcting atrial fibrillation in surgical ASD closure based on the findings of this study.

Chronic left-to-right shunting induces right ventricular (RV) volume overloading, resulting in progressive RV dilatation. Change in the geometry of the ventricle accompanied with dilatation of the tricuspid valve annulus, which is possible in the anterior and posterior sides, results in tricuspid insufficiency. After shunt closure, annular dilatation and RV dilatation may improve. Our data also show that the TR grade improved after ASD closure. However, Toyono et al. [5] reported that persistent TR was observed in 50% of patients, although TR decreased after ASD closure. Furthermore, some patients in our study developed more severe TR after ASD closure. More than moderate TR is an indication for surgical treatment, and some reports have also argued that high pulmonary artery pressure is another indication for surgery [5-7].

In the subgroup analysis, the TAP group showed superior results in terms of TR grade improvement and duration of freedom from significant TR compared to the non-TAP group. However, no statistically significant differences in survival were found (log rank p=0.518). Several possible explanations exist for the lack of a benefit associated with survival found in our study. The first is that TR itself is an expression of deterioration of the RV, which is re-

modeled via irreversible fibrosis. Jones and Ferrans [8] found that histologic abnormalities increased progressively with age. Thus, relief of TR is not necessarily linked to improvement in ventricular function. Second, some of the baseline characteristics of the patients in the 2 groups were different, such as age and TR grade. In particular, the TAP group consisted of patients with more severe TR than those in the non-TAP group. Most of the non-TAP group had moderate TR. These are major risk factors affecting survival in the general population, meaning that these differences between the 2 groups may confound the effect of TAP on survival. Third, the retrospective nature of this study might have influenced the results. All data on mortality were obtained from the KNRB retrospectively. Detailed information regarding mortality is not included in the KNRB data. Furthermore, we were unable to show a direct causal relationship between TR and the endpoint (death). Thus, an additional study is needed to validate our results.

It is not clear in this study how significant TR changed the patients' subjective symptoms or quality of life. Therefore, it is difficult to conclude whether corrective tricuspid valve surgery should be performed jointly with ASD closure. It is known, however, that the development of increased pulmonary artery pressure is associated with poor long-term survival [9,10]. Therefore, we conclude that early intervention before the development of significant TR

might be beneficial for improving postoperative survival after ASD closure.

This study has limitations, specifically the retrospective nature of the analysis. Additionally, the data in this study were limited to a single high-volume tertiary academic center, and our results may not be generalizable.

Surgical ASD closure was confirmed to be safe. Significant preoperative TR and age were strongly correlated with long-term survival. In our data, tricuspid valve repair effectively improved the TR grade. However, we were not able to prove its effect on long-term survival. Therefore, early surgery before the development of significant TR may be beneficial for improving postoperative survival. Additional study is needed to further assess the effect of correcting associated lesions jointly with surgical ASD closure.

Conflict of interest

No potential conflicts of interest relevant to this article are reported.

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