Long-term outcomes of surgery for obstructive hypertrophic cardiomyopathy in a pediatric cohort

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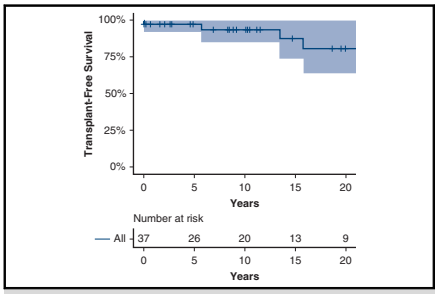
ABSTRACT

Background: Septal reduction therapy via septal myectomy or a modified Konno procedure is the mainstay of therapy for drug-refractory obstructive hypertrophic cardiomyopathy (HCM), although outcomes data on septal myectomy in pediatric patients are limited. We evaluated long-term outcomes following surgery for obstructive HCM in a pediatric cohort.

Methods: We retrospectively reviewed patients age ≤18 years with obstructive HCM who underwent a left and/or right ventricular septal myectomy at our institution between 1992 and 2022. Primary endpoints were transplantation-free survival, freedom from HCM-related death, and cumulative probability of HCM-related reintervention. We further evaluated outcomes in patients with and without Noonan syndrome or other RASopathies.

Results: Thirty-seven patients (median age, 7.4 years; interquartile range [IQR], 3.4-12.9 years) underwent transaortic septal myectomy. A combined modified Konno procedure was performed in 5 patients (13.9%). Sixteen patients (43.2%) had a RASopathy. A concomitant right ventricular outflow tract resection was performed in 9 patients (24.3%). There was 1 (2.7%) in-hospital death and 4 late deaths at a median follow-up of 10.5 years (IQR, 0.1-29.3). Twenty-year transplant-free survival and freedom from HCM-related death were 80.6% (95% confidence interval [CI], 64.2%-100%) and 87.1% (95% CI, 71.8%-100%), respectively. The 20-year cumulative probability of HCM-related reintervention was 34.2% (95% CI, 12.8%-57.1%). Seven patients required a septal reintervention. There was no difference in any primary endpoints between patients with and without a RASopathy.

Conclusions: Surgery for obstructive HCM, including septal myectomy with and without a modified Konno procedure, may be performed with low morbidity and good long-term outcomes in pediatric patients. Recurrent outflow tract obstruction is not uncommon. (JTCVS Open 2023;16:726-38)



Septal myectomy may be performed with acceptable long-term survival in pediatric patients.

CENTRAL MESSAGE

In pediatric patients with obstructive hypertrophic cardiomyopathy, transaortic septal myectomy is a safe and effective therapy that may be performed with low morbidity and acceptable long-term outcomes.

PERSPECTIVE

Septal myectomy is reserved for drug-refractory obstructive hypertrophic cardiomyopathy, though long-term data in a pediatric cohort are limited. We demonstrate the safety and efficacy of septal myectomy in pediatric patients with acceptable long-term survival and reintervention rates. Patients with Noonan syndrome or other RASopathies and complex, multilevel, or biventricular outflow obstruction remain challenging cohorts.

Hypertrophic cardiomyopathy (HCM) is a genetic disease of the myocardium characterized by pathologic ventricular septal thickening and left ventricular outflow tract (LVOT) obstruction. Histologic hallmarks include myocyte hypertrophy and disarray and interstitial fibrosis.[1] Clinically, HCM is a heterogeneous disorder with variability in

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Abbreviations and Acronyms

BSA = body surface area
CHB = complete heart block
HCM = hypertrophic cardiomyopathy
ICD = implantable cardioverter-defibrillator
LVMI = left ventricular mass index
LVOT = left ventricular outflow tract
MR = mitral regurgitation
NYHA = New York Heart Association
RVOT = right ventricular outflow tract
SAM = systolic anterior motion
TTE = transthoracic echocardiography

phenotypic expression, natural history, and symptomatology. Clinical features, ranging from complete absence of symptoms to severe heart failure or sudden cardiac death,[2] arise from dynamic obstruction secondary to asymmetric septal hypertrophy, systolic anterior motion (SAM)-mediated mitral regurgitation (MR), or arrhythmias. Compared to adults, pediatric patients are more likely to present with sudden cardiac death[3] and have more rapid progression of left ventricular hypertrophy.[4]

An extended left ventricular septal myectomy is the reference standard therapy for patients with obstructive HCM and severe, drug-refractory symptoms and has been shown to confer a survival benefit over medical management in adults.[5-7] To date, few published studies have evaluated outcomes of septal myectomy in a pediatric cohort,[2,8-13] and most of these are from a single center. We sought to strengthen the existing literature by reporting our 30-year institutional experience with septal myectomy in pediatric patients with obstructive HCM.

METHODS

Study Design and Patient Population

We retrospectively reviewed all patients with obstructive HCM who underwent left and/or right ventricular septal myectomy at age ≤18 years at New York-Presbyterian/Morgan Stanley Children's Hospital between January 1992 and December 2022. The diagnosis of obstructive HCM was established using 2-dimensional transthoracic echocardiography (TTE) and was defined as the presence of significant left ventricular hypertrophy with a maximal left ventricular wall thickness z-score ≥2 standard deviations above the body surface area (BSA)-corrected population mean.[14] The major indication for surgery was a resting or provoked maximal LVOT gradient ≥50 mm Hg with symptoms despite maximal medical therapy. Surgery was also recommended in asymptomatic or mildly symptomatic patients with a resting maximal LVOT gradient >75 mm Hg or severe SAM-mediated MR. Patients with biventricular outflow tract obstruction were included. All patients had at least 1 preoperative TTE and 2 postoperative imaging studies. We excluded patients who had septal hypertrophy and LVOT obstruction in the setting of other complex congenital cardiac disease (eg, Shone complex). Medical therapy was directed by the primary cardiologist. The Institutional Review Board at Columbia University Irving Medical Center approved this research with a waiver of informed consent (AAU3216; approved January 18, 2023).

Data Collection and Definitions

We reviewed medical records to obtain preoperative, operative, and postoperative data. Follow-up data, including symptomatology or reintervention, were obtained from outpatient charts. For patients without routine surveillance at our institution, we obtained follow-up data by contacting their primary cardiologist. Follow-up beyond 1 year postoperatively was 86% complete. Longitudinal echocardiographic data (preoperative, intraoperative, discharge, 1 month, 3-5 years, and 8-12 years) were collected to serially evaluate ventricular function and mass, septal thickness, and valvulopathy. Maximal interventricular septal thickness was measured in end diastole and normalized to BSA using the Boston Children's Hospital z-score nomogram. Left ventricular mass index (LVMI) was calculated using echocardiographic data by indexing left ventricular mass to BSA. The location of septal hypertrophy was classified as LVOT, midventricular, or a combination of those levels. No patients had apical variant HCM. The degree of aortic regurgitation and MR was graded as none/trivial, mild, moderate, or severe. Syndromes caused by a mutation in the Ras/MAPK cell signaling pathway, such as Noonan syndrome and cardiofaciocutaneous syndrome, were grouped as RASopathies. The severity of heart failure symptoms was graded by the New York Heart Association (NYHA) heart failure classification or the modified Ross heart failure classification for infants.

We defined HCM-related reintervention as any surgical or catheter-based intervention on the interventricular septum or outflow tract. Causes of death related to HCM included sudden cardiac death and death secondary to heart failure. Sudden cardiac death was defined as an unexpected collapse occurring within 1 hour from the onset of symptoms in patients with a previously stable clinical course. Other potentially lethal cardiac events, including successful resuscitation from cardiac arrest or appropriate defibrillation of a malignant arrhythmia by an implantable cardioverter-defibrillator (ICD), were surrogates for sudden death. Death related to heart failure was defined as occurring in the setting of cardiac decompensation with limiting symptoms.

Study Endpoints

The primary endpoints were transplantation-free survival, freedom from HCM-related death, and HCM-related reintervention.

Operative Technique

We routinely perform extended septal myectomy via a transaortic approach. An oblique aortotomy is performed, and the aortic valve cusps are retracted to expose the hypertrophied septum. The myectomy is begun by incising the septum beneath the nadir of the right coronary cusp and extending leftward toward the anterior leaflet of the mitral valve. The second incision begins in the same area and is carried apically beyond the point of contact of the anterior mitral leaflet with the septum—marked by a fibrous contact lesion—and down to the base of the papillary muscles. The apical aspect of the resected area is widened by extending the incision rightward and resecting posterior septal myocardium. Any abnormal attachments between the papillary muscles and the septum are divided. In general, we do not perform any dedicated interventions on the mitral valve unless there is significant intrinsic dysfunction; an extended septal myectomy should lead to resolution of SAM of the mitral valve and MR.

Since 2010, in young patients with a small aortic annulus resulting in poor septal exposure—particularly when obstruction extends beyond the mid-cavitary level—or in patients with concomitant right ventricular outflow tract (RVOT) obstruction, we perform a ventriculoseptoplasty or a modified Konno procedure in addition to septal myectomy. An infundibulotomy is made, and a right-angled instrument is passed through the aortic valve to perforate the conal septum. This provides a landmark for the upper limit of the trans-septal incision, which is continued toward the apex. Additional myectomy may then be performed on both sides of the incision, with care taken to avoid conduction tissue. Anomalies of the mitral valve and the

subvalvular apparatus also may be addressed through the right ventriculotomy. The septal incision is closed with a ProxiCor patch (Aziyo Biologics), and the RVOT is reconstructed with a pericardial patch. In some cases, resection of obstructive right ventricular muscle bundles also may be performed via an oblique right atriotomy and through the tricuspid valve.

Statistical Analysis

Continuous variables were tested for normal distribution using the Shapiro-Wilk test. Normally distributed variables are expressed as mean ± standard deviation, and non-normally distributed variables are expressed as median (interquartile range [IQR] or range). Categorical variables are presented as proportions. Statistical significance was defined as $P < .05$. Kaplan-Meier survival analysis with the log-rank test was used to estimate time-dependent outcomes. Reintervention was assessed with death as a competing risk using the Fine-Gray subdistribution hazard. A subgroup analysis was performed to compare outcomes in patients with and without RASopathy. Statistical analysis was performed using R version 1.4.1106 (R Foundation for Statistical Computing).

RESULTS

Patient Characteristics

A total of 49 consecutive patients age <18 years with obstructive HCM underwent surgical intervention during the study period. Twelve patients (24.5%) underwent primary heart transplantation. Thirty-seven patients (63.4% male) underwent septal myectomy at a median age of 7.4 years (IQR, 3.4-12.9 years). Three patients (8.1%) were age <12 months, and 12 (32.4%) were age <5 years at the time of septal myectomy. Seven patients (18.9%) had a family history of HCM, and 3 (8.1%) had a family history of sudden cardiac death. Sixteen patients (43.2%) had a RASopathy, including 13 (35.1%) with Noonan syndrome, 2 (5.3%) with cardiofaciocutaneous syndrome, and 1 (2.6%) with Noonan syndrome with multiple lentigines (formerly called LEOPARD syndrome); these patients were grouped in the RASopathy cohort. Genetic testing on an HCM panel was performed in 6 of the 19 nonsyndromic patients (31.6%), and all were found to be genotype-positive for pathogenic or likely pathogenic mutations. Two patients (5.9%) had an intrinsic mitral valve anomaly. Five patients (13.9%) had a preoperative arrhythmia, and 5 (13.5%) had an existing transvenous ICD. There were 2 (5.9%) prior outflow tract interventions; 1 patient previously underwent balloon aortic valvuloplasty and 1 underwent a prior balloon pulmonary valvuloplasty. The majority of patients were in NYHA/Ross heart failure class I (n = 15; 44.1%) or class II (n = 13; 38.2%). Additional baseline characteristics are presented in Table 1.

Preoperative Echocardiographic Data

Preoperative TTE data are listed in Table 1. The mean maximal septal thickness z-score was 14.6 ± 9.2. The mean maximal LVOT gradient and median LVMI were 88.9 ± 30.1 mm Hg and 161.5 g/m^2 (range, 136.0-204.3 g/m^2), respectively. Twenty-nine patients (82.9%) had evidence of SAM, and 8 (22.9%) had at least moderate MR. Concomitant RVOT obstruction was present in 13 patients (36.1%), 9 (69.2%) of whom had a RASopathy.

Intraoperative Data

Operative data are presented in Table 2. All septal myectomies were performed via a median sternotomy using a transaortic approach. The median cardiopulmonary bypass and cross-clamp times were 84 minutes (IQR, 63-103 minutes) and 47 minutes (IQR, 36-69 minutes), respectively. The predominant location of septal hypertrophy was at the LVOT in all patients, including 1 patient who had combined LVOT and midventricular obstruction. Four patients (10.8%) also had anomalous papillary muscle attachments to the septum causing LVOT obstruction. A concomitant RVOT resection was performed in 9 patients (24.3%), through the tricuspid valve in 6 patients, through the pulmonary artery in 2 patients, and via ventriculotomy in 1 patient. There were no iatrogenic ventricular septal defects or aortic or mitral valve injuries.

In 5 patients (13.5%), transaortic myectomy was inadequate for complete resection of mid-cavitary or apical obstruction, and a modified Konno operation was performed. The youngest patient was age 3.6 months (BSA, 0.35 m^2). Two patients had a RASopathy with concomitant RVOT obstruction, and all 5 patients had apical extension of the obstructive septal hypertrophy. One patient with a clinical diagnosis of HCM also had congenital aortic stenosis and underwent a Ross-Konno operation.

Early Postoperative Outcomes

In-hospital outcomes are summarized in Table 3. Six patients (16.2%) experienced at least 1 major postoperative complication, including new permanent pacemaker requirement in 5 (13.5%), prolonged mechanical ventilatory support in 2 (5.4%), and wound infection in 1 (2.7%). No patients required mechanical circulatory support. Of the 5 patients who required a permanent pacemaker, 4 had a RASopathy and 4 had undergone concomitant RVOT resection; none underwent a modified Konno procedure. There was 1 (2.7%) in-hospital mortality, secondary to acute respiratory failure in a 19-month-old tracheostomy-dependent patient.

The median postoperative hospital length of stay was 9 days (IQR, 7-15 days). The median maximal LVOT gradient was 18 mm Hg (IQR, 10-36 mm Hg) on predischarge TTE. The majority of patients were discharged in normal sinus rhythm (n = 24, 64.9%); 7 patients (18.9%) had a left bundle branch block. Nine patients (24.3%) underwent implantation of a new ICD prior to discharge, including 2 epicardial and 7 transvenous. There were 2 (5.4%) 30-day readmissions for a pericardial effusion and superficial infection of the ICD generator pocket.

TABLE 1. Preoperative patient characteristics and echocardiographic findings

Characteristic	Value
No. of patients	37
Male sex, n (%)	23 (62.2)
Age, y, median (IQR)	7.4 (3.4-12.9)
Weight, kg, median (IQR)	25 (14-44)
Body surface area, m^2, median (IQR)	0.92 (0.55-1.36)
Syndrome, n (%)	19 (51.4)
RASopathy	16 (43.2)
Kallmann	1 (2.7)
Simpson-Golabi-Behmel	1 (2.7)
HCM genetic testing performed, n (%)	6 (16.2)
MYH7	4 (10.8)
MYBPC3	2 (5.9)
CSRP3	1 (2.7)
Family history of HCM, n (%)	7 (18.9)
Family history of sudden cardiac death, n (%)	3 (8.1)
Arrhythmia, n (%)	5 (13.9)
Wolff-Parkinson-White	2 (5.9)
Ventricular tachycardia	1 (2.7)
Supraventricular tachycardia	1 (2.7)
Right bundle branch block	1 (2.7)
Existing implantable cardioverter defibrillator, n (%)	5 (13.5)
Medical therapy, n (%)	33 (89.2)
Beta blocker	29 (78.4)
Calcium channel blocker	7 (18.9)
Amiodarone	2 (5.4)
Other congenital heart defects, n (%)	13 (35.1)
Atrial septal defect	6 (16.2)
Pulmonary stenosis	3 (8.1)
Congenital aortic stenosis	2 (5.9)
Mitral valve anomaly	2 (5.9)
Ebstein anomaly	1 (2.7)
Ventricular septal defect	1 (2.7)
Prior outflow tract interventions, n (%)	2 (5.9)
Balloon aortic valvuloplasty	1 (2.7)
Balloon pulmonary valvuloplasty	1 (2.7)
NYHA class, n (%)	
I	15 (44.1)
II	13 (38.2)
III	2 (5.9)
IV	4 (11.8)
Left ventricular ejection fraction, %, mean ± SD	73.9 ± 8.8
Left ventricular mass index, g/m^2, median (IQR)	161.5 (136.0-204.3)
Maximal septal thickness, mm, median (IQR)	20 (11-27)
Maximal septal thickness *z*-score, mean ± SD	14.6 ± 9.2
LVOT peak gradient, mm Hg, mean ± SD	88.9 ± 30.1
At least moderate mitral regurgitation, n (%)	8 (22.9)
Systolic anterior motion of mitral valve, n (%)	29 (82.9)
Concomitant RVOT obstruction, n (%)	13 (36.1)

IQR, Interquartile range; *HCM*, hypertrophic cardiomyopathy; *NYHA*, New York Heart Association; *LVOT*, left ventricular outflow tract; *RVOT*, right ventricular outflow tract.

Late Outcomes

At a median follow-up of 10.5 years (range, 0.1-29.3 years), there were 3 late mortalities, all of which were HCM-related (heart failure, n = 2; embolic stroke from paroxysmal atrial fibrillation, n = 1). Two patients underwent heart transplantation for end-stage diastolic heart failure, one at 5.7 years after initial septal myectomy and the other at 18.0 years after a redo septal myectomy in a patient with a RASopathy. Overall transplantation-free survival was 93.6% (95% CI, 85.2%-100%) at 10 years and 80.6% (95% CI, 64.2%-100%) at 20 years (Figure 1, *A*). Freedom from HCM-related death was 100.0% (95% CI,

TABLE 2. Intraoperative data for transaortic septal myectomy

Parameter	Value
Cardiopulmonary bypass time, min, median (IQR)	84 (63-103)
Cross-clamp time, min, median (IQR)	47 (36-69)
Obstruction location, n (%)	
LVOT	36 (97.3)
LVOT + midventricular	1 (2.7)
Anomalous papillary muscle, n (%)	4 (10.8)
Concomitant RVOT resection, n (%)	9 (24.3)
RVOT obstruction location, n (%)	
Septal	3 (7.9)
Infundibular	7 (18.9)
Free wall	1 (2.6)
Modified Konno procedure, n (%)	5 (13.5)
Other concomitant procedures, n (%)	13 (35.1)
ICD implantation	5 (13.2)
ASD repair	3 (8.1)
Aortic valve repair	2 (5.3)
Subaortic fibromuscular ridge resection	2 (5.4)
Pulmonary valvotomy	1 (2.7)
Mitral valve repair	1 (2.7)
Ross-Konno	1 (2.7)
Iatrogenic ventricular septal defect	0 (0.0)
Iatrogenic aortic valve injury	0 (0.0)

IQR, Interquartile range; *LVOT*, left ventricular outflow tract; *RVOT*, right ventricular outflow tract; *ICD*, implantable cardioverter defibrillator; *ASD*, atrial septal defect.

TABLE 3. Early postoperative outcomes following transaortic septal myectomy

Parameter	Value
Major postoperative complications, n (%)	6 (16.2)
New permanent pacemaker requirement, n (%)	5 (13.5)
Prolonged ventilator support, n (%)	2 (5.4)
Wound infection, n (%)	1 (2.7)
Maximal LVOT gradient at discharge, mm Hg, median (IQR)	18 (10-36)
Hospital length of stay, d, median (IQR)	9 (7-15)
Medications on discharge, n (%)	
Beta blocker	23 (62.2)
Calcium channel blocker	5 (13.5)
Amiodarone	7 (18.9)
Rhythm at discharge, n (%)	
Normal sinus	24 (64.9)
Complete heart block	5 (13.5)
Left bundle branch block	7 (18.9)
In-hospital mortality, n (%)	1 (2.7)
30-d readmission, n (%)	2 (5.4)

LVOT, Left ventricular outflow tract; *IQR*, interquartile range.

100%-100%) at 10 years and 87.1% (IQR, 71.8%-100%) at 20 years (Figure 1, *B*).

Seven patients underwent the following HCM-related reinterventions, including 3 patients with isolated septal myectomy and 1 patient each with septal myectomy with mitral valve repair, Ross-Konno and septal myectomy, bilateral septal myectomy with a transannular patch, and isolated RVOT resection with a transannular patch. There were no catheter-based reinterventions. The cumulative probability of HCM-related reinterventions at 5, 10, and 20 years was 6.7% (95% CI, 1.1%-19.6%) at 5 years, 19.2% (95% CI, 6.6%-36.6%) at 10 years, and 34.2% (95% CI, 12.8%-57.1%) at 20 years (Figure 1, *C*). Age at surgery, RASopathy, baseline echocardiographic data, and residual LVOT peak gradient at discharge were not found to be significant predictors of septal reintervention on univariate analysis (Table E1).

Serial echocardiographic data are shown in Table 4. Compared to baseline, the maximal LVOT gradient and the proportion of patients with SAM or at least moderate MR decreased at 1 month postoperatively and were maintained throughout the follow-up period. At the latest follow-up, 90.6% of patients were in NYHA class I, compared to 44.1% preoperatively (Figure 2).

Outcomes Following Septal Myectomy: RASopathy Versus No RASopathy

Given the known association between RASopathies and a severe HCM phenotype,[15] we compared outcomes following septal myectomy in 16 patients (43.2%) with a RASopathy and 21 patients (56.8%) without a RASopathy. Patients with a RASopathy had a lower BSA (0.6 m^2 [IQR, 0.5-0.9 m^2] vs 1.2 m^2 [IQR, 0.6-1.7 m^2]; $P = .008$) at the index septal myectomy and were more likely to undergo a concomitant RVOT intervention (n = 8 [50.0%] vs n = 1 [4.8%]; $P = .005$). Patients without a RASopathy were more likely to have a left bundle branch block at the time of discharge (RASopathy, n = 0 [0.0%] vs no RASopathy, n = 8 [40.0%]; $P = .009$); otherwise, there were no differences in early postoperative outcomes between the 2 cohorts (Table E2).

The median follow-up was 17.1 years (IQR, 6.9-22.4 years) for the RASopathy cohort and 10.1 years (IQR, 4.6-15.8 years) for the no RASopathy cohort. Transplantation-free survival at 10 years and 20 years was similar in the 2 cohorts (RASopathy: 100.0% [95% CI, 100%-100%] and 90.0% [95% CI, 73.2%-100%] vs no RASopathy: 88.4% [95% CI, 74.3%-100%] and 70.7% [95% CI, 44.2%-100%], respectively; $P = .48$) (Figure 3, *A*), as was freedom from HCM-related death at 10 and 20 years (RASopathy: 100.0% [95% CI, 100%-100%] and 90.0% [95% CI, 73.2%-100%] vs no RASopathy: 100.0% [95% CI, 100%-100%] and 83.3% [95% CI, 58.3%-100%]; $P = .78$) (Figure 3, *B*). The cumulative probability of HCM-related reintervention was 7.1% [95% CI, 0.4%-28.5%] at 5 years, 26.1% [95% CI, 5.2%-54.3%] at 10 years, and 47.2% [95% CI, 14.4%-74.8%] at 20 years in the RASopathy cohort, and 6.3% [95% CI, 0.4%-25.5%], 12.9% [95% CI, 1.9%- 34.7%], and 12.9% [95% CI, 1.9%-34.7%], respectively, in patients without a RASopathy ($P = .22$, Gray test) (Figure 3, *C*).

DISCUSSION

Our 30-year experience with transaortic septal myectomy in pediatric patients with obstructive HCM shows that septal myectomy may be performed with low morbidity and provides durable relief of LVOT obstruction, decreases MR, and improves functional capacity. For patients with complex obstruction, the modified Konno procedure may be performed with minimal risk of injury to the conduction system. Long-term survival in this challenging cohort is good, although recurrent outflow tract obstruction warrants close surveillance, particularly in patients with a RASopathy. A summary of the current study is shown in Figure 4.

Most of the existing literature on septal myectomy is derived from a large single-center study. The Mayo Clinic has unparalleled experience with HCM[16-18] and was among the first to assess surgical outcomes in a strictly pediatric cohort in a 1996 study that validated the use of septal myectomy for HCM patients who have failed medical therapy.[18] The group has since published 3 follow-up studies, all of which demonstrated impressive

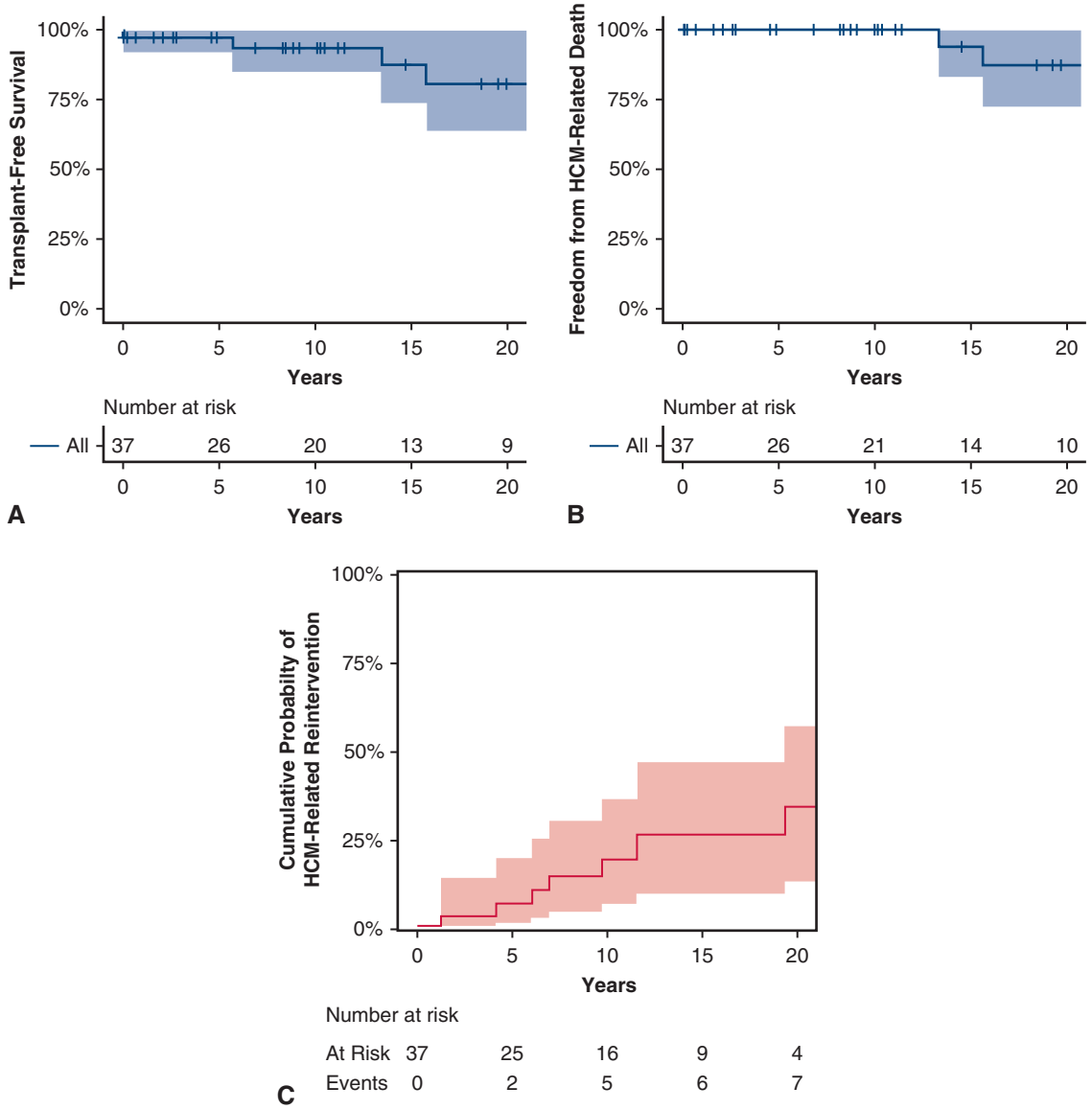

FIGURE 1. A and B, Kaplan-Meier plots of the primary endpoints of transplantation-free survival (A) and freedom from hypertrophic cardiomyopathy (*HCM*)-related death (B) after septal myectomy in the overall cohort. Survival at each time is shown with 95% confidence interval (*CI*) shaded. Numbers at risk are shown in the lower panel. C, Cumulative incidence curve (*solid line*) of HCM-related reintervention with death as a competing event. *Dashed lines* represent the 95% CI.

outcomes with low mortality, durable resolution of LVOT obstruction and MR, and improved functional capacity.[8-10] Compared to the most recent Mayo cohort, our patients were younger, with a median age of 7.4 years (vs 13 years) and 32.4% (n = 12) age <5 years at the time of surgery. This has important implications, because younger age is an established predictor of reintervention,[9] likely due to incomplete relief of LVOT obstruction due to limited visualization via the transaortic approach. Despite having one of the youngest cohorts in the septal myectomy literature, we demonstrate that the operation can be performed effectively and safely in experienced hands; we did not have any iatrogenic ventricular septal defects or valve injuries. All 5 patients (13.5%) who required a permanent pacemaker had a RASopathy and/or complex biventricular outflow tract obstruction. This is concordant with studies that identified biventricular obstruction as a risk factor for complete heart block (CHB) after septal myectomy, with a reported incidence of 18% to 20%.[11,19]

The Mayo group has extensive experience in addressing midventricular obstruction via an apical left ventriculotomy,[20-23] including in 18% of their most recent pediatric

TABLE 4. Longitudinal echocardiographic data before and after transaortic septal myectomy

Variable	Preoperative (N = 37)	1 month (N = 21)	3-5 years (N = 20)	8-12 years (N = 14)
LVEF, %, mean ± SD	74 ± 8.8	75 ± 16.1	66 ± 8.9	67 ± 9.0
Maximum LVOT gradient, mm Hg, mean ± SD/median (IQR)	89 ± 30	18 (11-37)	14 (6-39)	13 (5-37)
Maximum septal thickness, mm, median (IQR)/mean ± SD	20 (11-27)	13 (10-25)	16 (12-21)	24 ± 11
Maximum septal thickness z-score, mean ± SD/median (IQR)	14.6 ± 9.2	11.9 ± 7.9	9.0 (5.5-18.0)	13.5 ± 9.8
LVMI, g/m^2, median (IQR)/mean ± SD	161.5 (135.8-204.3)	148.1 ± 72.5	146 (109.4-173.0)	180.1 ± 74.5
Systolic anterior motion, n (%)	29 (82.9)	8 (40.0)	9 (45.0)	3 (23.1)
Moderate or greater MR, n (%)	8 (22.9)	3 (15.0)	4 (20.0)	1 (7.7)

LVEF, Left ventricular ejection fraction; *LVOT*, left ventricular outflow tract; *IQR*, interquartile range; *LVMI*, left ventricular mass index; *MR*, mitral regurgitation.

septal myectomy cohort.[10] They demonstrated the utility of this approach in relieving complex LVOT obstruction with or without a transaortic approach, with an estimated 10-year survival of 90% in adults.[23] We do not have experience with the transapical approach and instead perform a modified Konno operation as an adjunct to a transaortic septal myectomy when necessary. In our study, 5 patients with concomitant RVOT obstruction and/or apical extension of septal hypertrophy underwent a combination of the 2 approaches with no incidence of CHB and only 1 left-sided reintervention. This allows for relief of associated RVOT obstruction, a rare feature of HCM commonly present in patients with a RASopathy.

There is a paucity of data on the management of biventricular obstruction in HCM, with the 2 largest experiences reporting different surgical approaches.[10,23] Quintana and colleagues[11] presented a series of 11 pediatric and young adult patients in which the RVOT obstruction was addressed via a limited subpulmonary longitudinal ventriculotomy and reported an 18% incidence of CHB. Laredo and colleagues[24] presented a series of 79 children, of whom 22 (28%) had biventricular outflow tract obstruction. Their preferred approach in all cases of obstructive HCM was to perform an isolated modified Konno procedure. They reported an 11% incidence of CHB, 6% operative mortality, and 82% transplantation-free survival at 20 years. No patients developed recurrent LVOT obstruction at 6-year follow-up.[24]

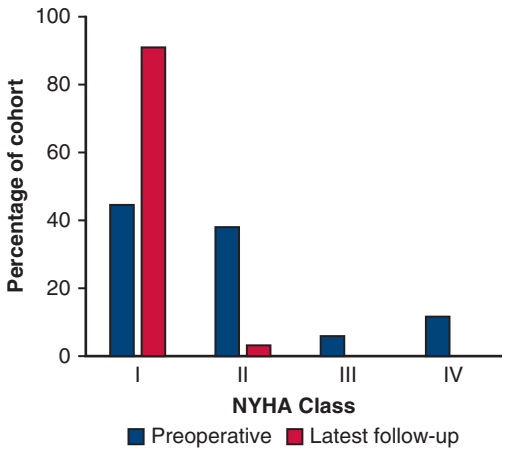

FIGURE 2. New York Heart Association Class (*NYHA*) preoperatively (*blue*) compared to at latest follow-up after septal myectomy (*red*).

These results demonstrate that the modified Konno procedure is an effective alternative to septal myectomy in selected patients with obstructive HCM. Our own results confirm this, and we have been more aggressive in recent years in switching to a modified Konno septoplasty approach in cases when an unsatisfactory result is predicted from a transaortic myomectomy alone. Even after septal reduction therapy, there remains a risk of recurrent obstruction—particularly during adolescence—related to rapid myocardial growth and adverse remodeling.[25] Therefore, replacement of the basal septum by a bioprosthetic patch theoretically would prohibit remodeling of the septum at this level. This may be particularly helpful in the youngest patients and in those with a RASopathy.

Interestingly, our cohort included a significant number of patients with a RASopathy (43.2%), who represented 5 of the 7 reinterventions for recurrent LVOT obstruction. Patients with a RASopathy had a lower BSA and were more likely to undergo concomitant right-sided resection. Although statistically insignificant and ultimately limited by power, patients with a RASopathy had a greater cumulative probability of HCM-related reintervention at 20 years compared to patients without RASopathy (47.2% [95% CI, 14.4%-74.8%] vs 12.9% [95% CI, 1.9%-34.7%]; $P = .22$). These findings parallel the results of Poterucha and colleagues,[26] who found that residual postoperative LVOT peak gradients were higher in patients with a RASopathy (n = 12) than in their matched nonsyndromic counterparts. Notably, our median follow-up for the RASopathy cohort was 17.1 years (range, 0.2-29.3 years), which

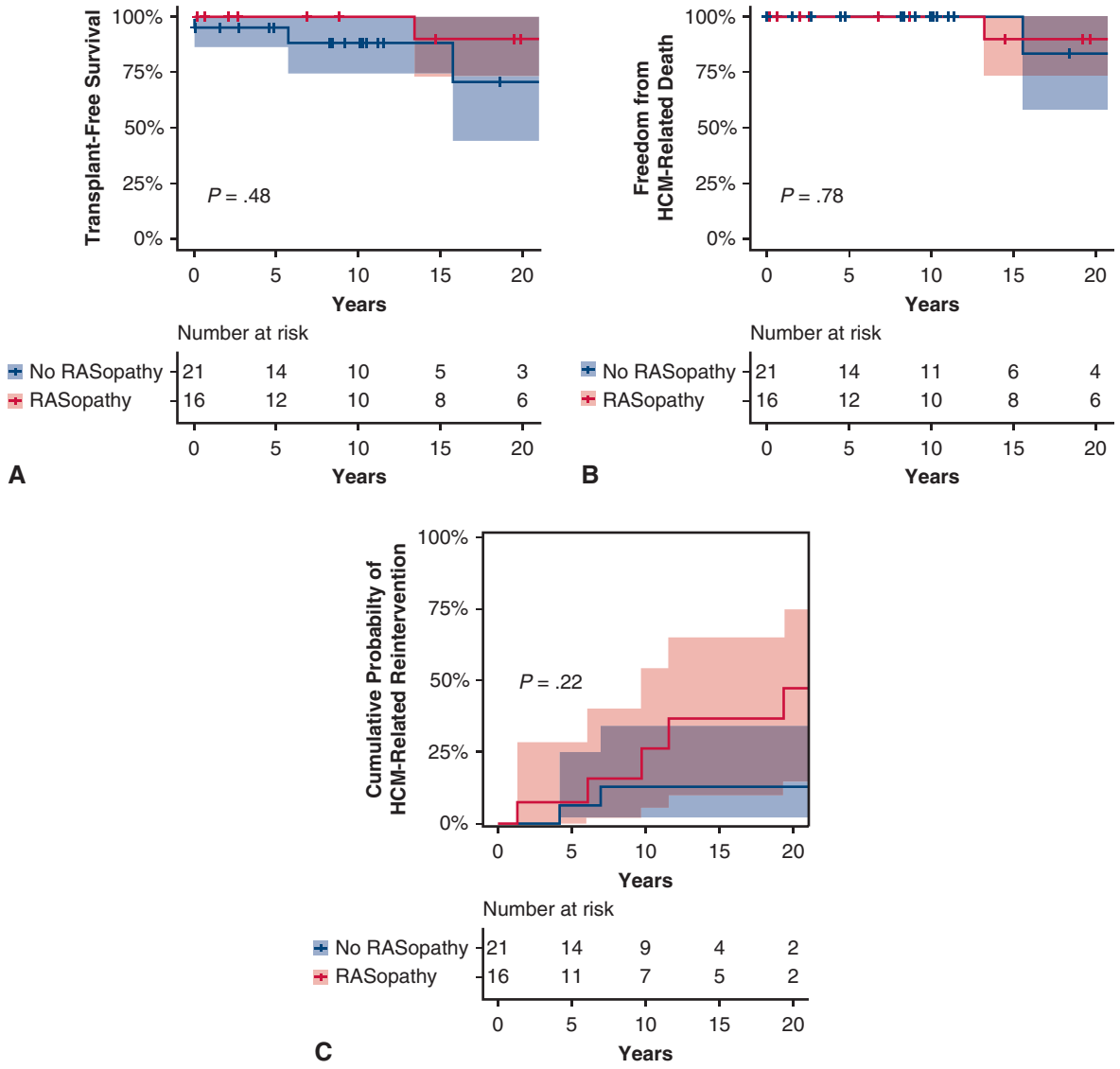

FIGURE 3. A and B, Kaplan-Meier plots of transplantation-free survival (A) and freedom from hypertrophic cardiomyopathy (*HCM*)-related death (B) after septal myectomy in patients with and without a RASopathy syndrome. Survival at each time point is shown with 95% confidence interval (*CI*) shaded. Numbers at risk are shown in the lower panel. C, Cumulative incidence curves (*solid lines*) of HCM-related reintervention with death as a competing event in patients with and without RASopathy. *Dashed lines* represent 95% CI.

represents the longest postmyectomy follow-up for patients with a RASopathy in the current literature. Continued follow-up will be essential to delineate the history of outflow tract obstruction after surgical intervention in this challenging cohort. Additionally, despite a higher reintervention rate, the RASopathy patients demonstrated a similar transplantation-free survival rate and freedom from HCM-related death rate as the non-RASopathy patients. This is particularly important because as some centers advocate for primary heart transplantation in young patients with RASopathies and severe obstructive disease.[26,27] Our 90.0% transplantation-free survival rate at 20 years in patients with RASopathies suggests that in carefully selected candidates, septal myectomy may be a reasonable alternative to primary transplantation.

Medical management of obstructive HCM historically has centered on symptom relief and risk reduction for sudden cardiac death with ICD implantation. Few therapies have had potential to ameliorate disease progression until the recent advent of inhibitory myosin modulators, such as mavacamten,[28] which has been shown to modulate disease expression in Phase III clinical trials by reducing the

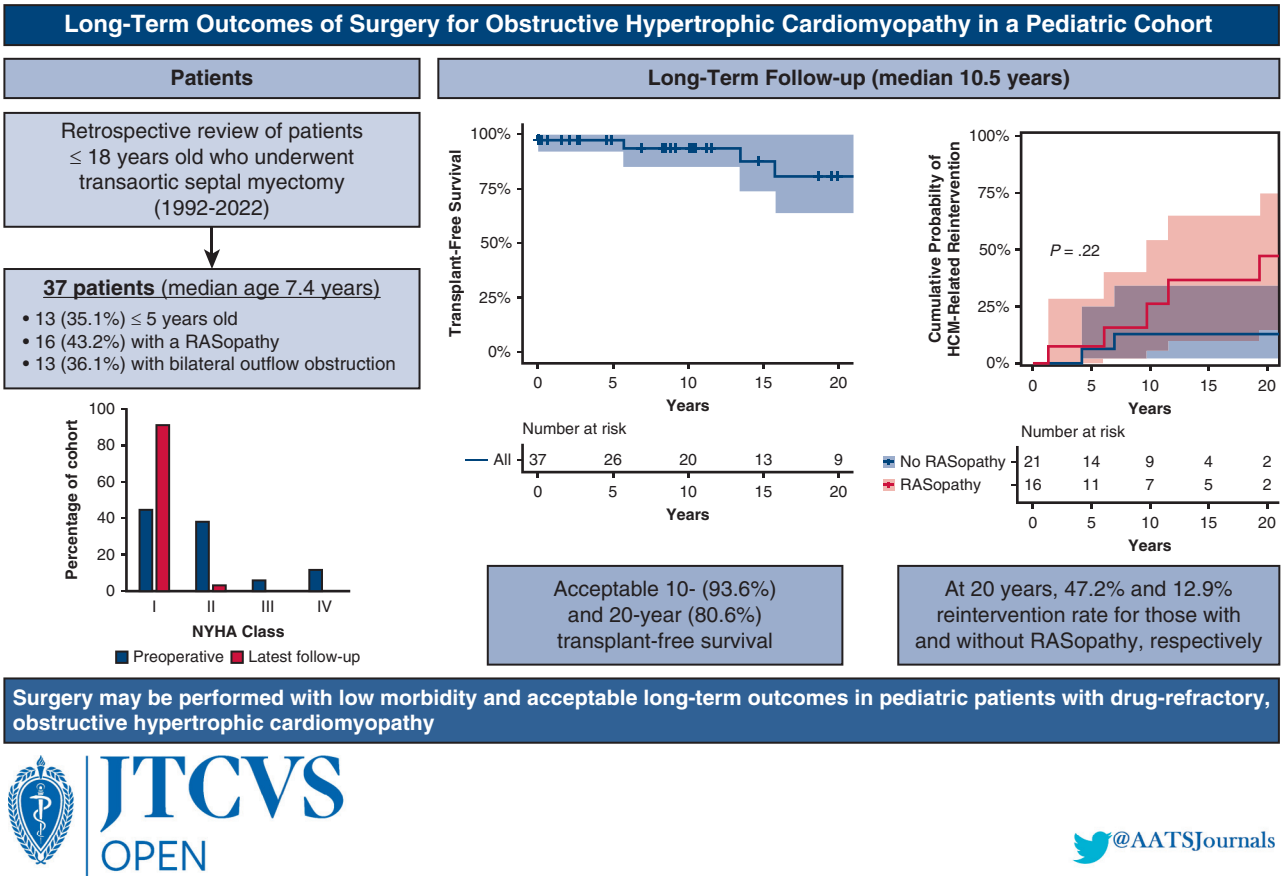

FIGURE 4. Long-term outcomes of septal myectomy in a pediatric cohort with obstructive hypertrophic cardiomyopathy (*HCM*). *NYHA*, New York Heart Association Class.

LVOT gradient, to improve symptoms in adult patients,[28] and possibly to induce reverse remodeling of the myocardium.[29] Although this therapy has not been investigated in pediatric patients, it raises the possibility of delaying surgical intervention until the infant or child is older, thus facilitating exposure for an extended septal myectomy and minimizing the risk of iatrogenic injury. In HCM patients with underlying RASopathy, identification of pathologic genetic mutations soon may have a pivotal role in pharmacologic intervention. MEK inhibitors target the MAPK pathway downstream from the Ras protein signal and have been approved as antineoplastic agents. Case reports of off-label use of MEK inhibitors in infants with Noonan syndrome have demonstrated regression of myocyte hypertrophy and LVOT obstruction with amelioration of symptoms.[30-32] These early reports suggest a potential avenue of medical management of obstructive HCM in patients with RASopathies.

Study Limitations

This study is limited by its single-center, retrospective methodology; our sample size and number of outcome events precluded multivariable analysis of predictors of reintervention or mortality. The most important limitation, however, is the lack of a direct comparison between septal myectomy and nonoperative management. Because we are a large tertiary center, many HCM patients are managed by local cardiologists outside of our hospital system, making it difficult to obtain granular data to form a robust comparison group. Although a recent study of patients who underwent septal myectomy between 1975 and 2003[9] overlaid their survival curve with that of patients managed medically between 1957 and the early 1980s,[33] ultimately demonstrating superior survival with myectomy, doing so might not have made for a fair comparison, given significant advancements in early screening, genetic testing, and medical therapy for HCM in recent decades. A contemporary

comparative analysis is needed to justify surgery earlier in the clinical course and in minimally symptomatic children.

CONCLUSIONS

Septal myectomy is safe and effective for symptomatic pediatric patients with obstructive HCM and may be performed with good long-term survival and acceptable reintervention rates. Complex, multilevel, or biventricular obstruction poses a clinical challenge that may be comprehensively addressed with low morbidity and mortality. Recurrent outflow tract obstruction is not uncommon and requires close surveillance.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: hypertrophic cardiomyopathy, RASopathy, Noonan syndrome, transaortic septal myectomy

TABLE E1. Univariate Cox regression for reintervention in all patients

Variable	HR	95% CI	*P* value
Age at surgery	0.81	0.65-1.00	**.046**
Sex	1.3	0.24-6.6	.78
RASopathy	2.9	0.58-15	.19
Preoperative maximum septal thickness *z*-score	0.94	0.84-1.00	.26
Preoperative max LVOT gradient	1.00	0.99-1.00	.22
Maximum LVOT gradient at discharge	1.00	0.97-1.00	.81
Concomitant RVOT obstruction	1.1	0.24-5.1	.89

Significant *P* values are in bold type. *HR*, Hazard ratio; *CI*, confidence interval; *LVOT*, left ventricular outflow tract; *RVOT*, right ventricular outflow tract.

TABLE E2. Intraoperative details and early postoperative outcomes in the subgroup analysis comparing septal myectomy in patients with and without RASopathy

Variable	RASopathy (N = 17)	No RASopathy (N = 21)	*P* value
Cardiopulmonary bypass time, min, median (IQR)	96.0 (77.3-117.2)	76.50 (62.75-98.25)	.17
Cross-clamp time, min, median (IQR)	60.0 (39.0-70.0)	46.00 (35.00-69.00)	.42
LVOT obstruction location, n (%)			
Basal	0 (0.0)	1 (4.8)	1.00
Midventricular	3 (17.6)	1 (4.8)	.45
Combined basal/midventricular	13 (76.5)	18 (85.7)	.76
Apical	15 (88.2)	10 (47.6)	**.02**
Anomalous papillary muscle	2 (11.8)	2 (9.5)	1.00
Concomitant RVOT resection, n (%)	9 (52.9)	1 (4.8)	<**.01**
RVOT obstruction location, n (%)			
Septal	3 (17.6)	0 (0.0)	.16
Infundibular	7 (41.2)	1 (4.8)	**.02**
Free wall	1 (5.9)	0 (0.0)	.92
Modified Konno procedure, n (%)	2 (11.8)	2 (9.5)	1.00
Other concomitant procedures, n (%)	7 (41.2)	10 (40.0)	1.00
ASD repair	4 (23.5)	0 (0.0)	.07
Mitral valve repair	0 (0.0)	1 (4.8)	1.00
Mitral valve replacement	1 (5.9)	0 (0.0)	.92
Aortic valve repair	2 (11.8)	0 (0.0)	.38
Pulmonary valvotomy	2 (11.8)	0 (0.0)	.38
ICD implantation	0 (0.0)	4 (19.0)	.17
Iatrogenic VSD, n (%)	0 (0.0)	0 (0.0)	1.00
Iatrogenic aortic valve injury, n (%)	0 (0.0)	0 (0.0)	1.00
Major postoperative complications, n (%)	4 (23.5)	2 (9.5)	.47
New permanent pacemaker requirement	4 (23.5)	1 (4.8)	.22
Prolonged ventilator support	1 (5.9)	1 (4.8)	1.00
Wound infection, n (%)	0 (0.0)	1 (4.8)	1.00
Hospital length of stay, d, median (IQR)	10 [8-17]	9 [7-14]	.59
Medical therapy on discharge, n (%)			
Beta blocker	9 (52.9)	15 (71.4)	.40
Calcium channel blocker	2 (11.8)	3 (14.3)	1.00
Amiodarone	3 (17.6)	4 (19.0)	1.00
Rhythm at discharge, n (%)			**.01**
Normal sinus	13 (76.5)	11 (55.0)	
Pacemaker-dependent	4 (23.5)	1 (5.0)	
Left bundle branch block	0 (0.0)	8 (40.0)	
Maximum LVOT gradient at discharge, mm Hg, median (IQR)	21.0 (10.0-30.0)	19.00 (9.50-53.70)	.61
In-hospital mortality, n (%)	0 (0.0)	1 (4.8)	1.00
30-d readmission, n (%)	1 (5.9)	1 (4.8)	1.00

Significant *P* values are in bold type. *IQR*, Interquartile range; *LVOT*, left ventricular outflow tract; *RVOT*, right ventricular outflow tract; *ASD*, atrial septal defect; *ICD*, implantable cardioverter defibrillator; *VSD*, ventricular septal defect.