Early and long-term outcomes following cardiac surgery for patients with heterotaxy syndrome

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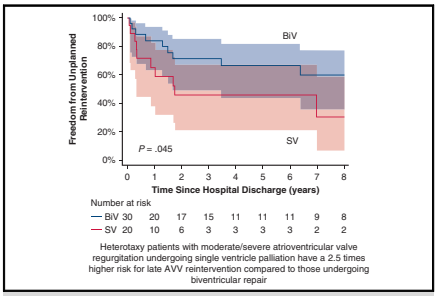
ABSTRACT

Objective: Heterotaxy syndrome is a complex multisystem abnormality historically associated with high morbidity and mortality. We sought to evaluate the early and long-term outcomes after cardiac surgery in heterotaxy syndrome.

Methods: This is a single-center retrospective review of patients with heterotaxy syndrome undergoing single-ventricle palliation or primary or staged biventricular repair from 1998 to 2018. Patients were stratified by single ventricle versus biventricular physiology, and the severity of atrioventricular valve regurgitation. Demographics, anatomic characteristics, and early and late outcomes, including the length of stay, mortality, and surgical or catheter reinterventions, were analyzed.

Results: Among 250 patients, 150 (60%) underwent biventricular repair. In-hospital mortality was 7.6% (n = 19). Median follow-up was 5.2 (range, 0-16) years. Among survivors to discharge, mortality was 19% (n = 44) and reintervention was 52% (n = 120). Patients with moderate/severe atrioventricular valve regurgitation were older (32 vs 16 months, $P = .02$), were more likely to experience adverse events during their index surgical admission (72% vs 46%, $P < .001$), and had longer in-hospital length of stay (20 vs 12 days, $P = .009$). Among patients with moderate to severe atrioventricular valve regurgitation, single-ventricle palliation is associated with a greater risk of unplanned reintervention compared with patients undergoing biventricular repair (hazard ratio, 2.13; CI, 1.10-4.12; $P = .025$).

Conclusions: There was no significant difference in early or late outcomes in single-ventricle versus biventricular repair strategies in heterotaxy. In the subgroup of patients with moderate/severe atrioventricular valve regurgitation, patients who underwent single-ventricle palliation were 2.5 times more likely to need a late reintervention compared with those undergoing biventricular repair. (JTCVS Open 2024;18:167-79)



Moderate or greater AVVR increases the risk for unplanned reintervention in SVP.

CENTRAL MESSAGE

Patients with HS and moderate or severe AVVR undergoing SVP were 2.5 times more likely to require late reintervention.

PERSPECTIVE

Among 250 patients with HS undergoing cardiac surgical intervention at a single center, patients undergoing SVP with preoperative moderate or severe AVVR were significantly more likely to undergo unplanned late reintervention when compared with patients undergoing BiV repair.

Heterotaxy syndrome (HS) is a complex abnormality where the normal right-left asymmetry of the human body is disrupted during early embryologic development. Patients with HS have abnormalities in the location and function of multiple organ systems, including the heart, spleen, lungs, liver, and gastrointestinal tract.[1,2] Of note, although HS is encountered in 0.4% to 2% of patients with congenital heart disease and 1 to 2/10,000 live births, the pathology is often among the most complex encountered in congenital cardiology.[3,4] Surgical technique and medical care for congenital heart disease have improved substantially over the last several decades; however, the prognosis for individuals with HS remains guarded.[5,6]

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Abbreviations and Acronyms

AVCD = atrioventricular canal defect
AVVR = atrioventricular valve regurgitation
BiV = biventricular
CICU = cardiac intensive care unit
DORV = double-outlet right ventricle
HS = heterotaxy syndrome
LOS = length of stay
OR = odds ratio
SVP = single-ventricle palliation

Historically, HS is divided into 2 groups: those with a tendency toward bilateral right-sidedness (asplenia or right atrial isomerism) and those with a tendency toward bilateral left-sidedness (polysplenia or left atrial isomerism).[7,8] The cardiac disease in asplenia tends to be more complex than encountered in polysplenia, and accordingly, outcomes tend to be worse.[9] These include unbalanced atrioventricular canal defects (AVCDs), double-outlet right ventricle (DORV), transposition of the great arteries, pulmonary stenosis, and total anomalous pulmonary venous return, which can be obstructed. Hypoplasia of the left or right ventricle is common in asplenia. Dual sinus and atrioventricular nodes also are common in asplenia and can form the substrate for important tachyarrhythmias.[10]

Common anomalies encountered in HS with polysplenia include interruption of the suprarenal inferior vena cava with azygos continuation to the superior vena cava, balanced AVCD, and systemic outflow obstruction. Sinus node dysfunction and high-grade atrioventricular block also can occur, with the latter potentially being lethal in utero.[5,11-13]

Many series describing cardiac surgical outcomes in HS are limited by a small sample size. A comprehensive understanding of anatomic and surgical risk factors and associated outcomes is further limited by the tremendous heterogeneity of cardiac disease encountered in HS. Therefore, we sought to identify anatomic, functional, and surgical variables associated with early and long-term outcomes in patients with HS. Of particular interest were the surgical strategy, specifically single-ventricle palliation (SVP) versus biventricular (BiV) repair and the effect of preoperative atrioventricular valve regurgitation (AVVR).

MATERIALS AND METHODS

Patient Characteristics

We conducted a retrospective review of all patients diagnosed with HS who underwent cardiac surgical intervention at our center between 1998 and 2018, Patients were identified by searching the Boston Children's Hospital Heart Center database for all instances of heterotaxy (IRB-P00011349, initially approved December 4, 2013, continuing review approval January 9, 2023, with a waiver of individual consent). All subjects met the definition of heterotaxy as outlined by Saba and colleagues.[14] Patients were stratified by SVP versus BiV repair and by the severity of AVVR (no/trivial/mild AVVR vs moderate or greater AVVR) based on preoperative echocardiographic reports.

Data Collection

Preoperative data included age, weight, prematurity, heterotaxy subtype (asplenia or polysplenia), prior surgical interventions, anatomic characteristics, and presence of AVVR (Figure E1). Postoperative data pertaining to early and late outcomes were also collected. Early outcomes included mortality, cardiac intensive care unit (CICU) length of stay (LOS), postoperative hospital LOS, total LOS, surgical and catheter interventions, and adverse events. Late outcomes of interest included planned or unplanned reinterventions at our institution (surgical or catheter-based) and late mortality. Patient follow-up was obtained exclusively from review of the electronic health records at Boston Children's Hospital and included clinic visits, inpatient care at Boston Children's Hospital, or scanned documentation with details of outside cardiology visits. For patients referred from outside institutions, efforts were made to obtain clinical information from their home institutions. All the diagnostic phenotypes were obtained from the fundamental diagnosis code(s) (diagnosis the patient was born with) of the patient. We selected this because this remains unchanged even if initial care was at an outside facility.

Follow-up was censored at the date of last follow-up appointment at our institution or outside cardiology visit as indicated by scanned documentation available for that patient.

Analyses were based on a single index operation for each patient. The index operation was defined as the first operation that was performed at our center. Index operations included SVP or BiV repair. Index surgeries in the SVP group included neonatal palliations (eg, systemic-to-pulmonary artery shunt, pulmonary artery banding, Norwood procedure), superior cavopulmonary anastomoses (Glenn or Kawashima shunt), and total cavopulmonary connections (Fontan, hepatic vein inclusion, and hepatic-azygos shunt).

Early reintervention or mortality was defined as occurring during the postsurgical hospitalization or within 30 days of surgery if discharged home. Late reintervention or mortality was defined as those occurring after hospital discharge or 30 days or greater after surgery if discharged home within 30 days of index surgery date. Early and late unplanned surgical reinterventions included atrial septectomy, aortic valve repair or replacement, pulmonary vein stenosis repair, closure of residual atrial or ventricular septal defects, aortic surgery, or pacemaker insertion. Unplanned catheter reinterventions included angioplasty, aortic stent placement, atrial septal defect balloon occlusion, thrombectomy, and ventricular stent redilatation.

Staged SVP procedures were not considered unplanned late reinterventions. Likewise, chest exploration or closure, diagnostic catheterizations, and pulmonary arterioplasty at the site of prior pulmonary artery banding or shunt insertion were not included. Procedures concomitant with SVP such as aortic arch revision and atrioventricular valve plasty were considered unplanned.

Adverse events (during index hospitalization) included major bleeding, device malfunction, left or right heart failure, neurologic events, or infectious process, as defined by the Society of Thoracic Surgeons Congenital Heart Surgery Database data definitions.

Statistical Analysis

Categorical variables were summarized using frequencies and percentages, and continuous variables with medians and interquartile ranges (25th and 75th percentiles). Patients were sorted by index surgery approach, and cardiac characteristics and early outcomes were compared for patients with SVP versus BiV repair and for those presenting with no more than mild AVVR preoperatively versus moderate to severe AVVR using the Fisher exact test for categorical variables and the Wilcoxon

rank-sum test for continuous variables. For patients surviving to hospital discharge, times from discharge to late outcomes were compared using the log-rank test. Patients who did not experience the relevant outcome were censored at the time of last follow-up. Early and late outcomes were also compared for subgroups of patients with SVP versus BiV repair who were frequency matched on anatomic diagnosis. For the entire cohort, logistic regression models were used to investigate the relationships between surgical strategy and preoperative AVVR and early outcomes adjusting for age at surgery, asplenia versus polysplenia, and prior cardiac surgery. Odds ratios (ORs) are presented with 95% CIs. Cox regression was used to examine relationships between surgical strategy and preoperative AVVR and late outcomes, again adjusting for age at surgery, asplenia versus polysplenia, and prior cardiac surgery. Hazard ratios (HR) are presented with 95% CIs. In all models, interactions between surgical strategy and preoperative AVVR were assessed. Analyses were conducted in SAS version 9.4 (SAS Institute, Inc).

RESULTS

Overall Cohort

There were 250 patients identified with HS who underwent cardiac surgical intervention from 1998 to 2018 at our center. Of those 250 patients, 139 (56%) were male. BiV repair was performed in 150 patients (60%), and 100 patients (40%) underwent SVP. Polysplenia was present in 91 patients (36%), and asplenia was present in 99 patients (40%). The type of heterotaxy was indeterminate in 60 patients (24%).

TABLE 1. Patient characteristics and outcomes based on repair strategy: Single-ventricle palliation versus biventricular repair

Patient characteristics and outcomes	All (n = 250)	SVP (n = 100)	BiV repair (n = 150)	*P* value
Demographics				
Age at surgery (mo)	19 [5, 53]	27 [5, 77]	14 [5, 43]	.047
Age at surgery				
≤30 d	38 (15%)	17 (17%)	21 (14%)	.015
31 d to <1 y	67 (27%)	16 (16%)	51 (34%)	
1 to 17 y	133 (53%)	61 (61%)	72 (48%)	
≥18 y	12 (5%)	6 (6%)	6 (4%)	
Weight (kg)	9.8 [5.0, 15.1]	10.9 [5.6, 17.5]	8.1 [5.0, 13.1]	.072
Prematurity (n = 100,146)	8 (3.3%)	6 (6.0%)	2 (1.4%)	.065
Cardiac characteristics				
Splenia				.005
Polysplenia (left isomerism)	91 (36%)	29 (29%)	62 (41%)	
Asplenia (right isomerism)	99 (40%)	52 (52%)	47 (31%)	
Indeterminate	60 (24%)	19 (19%)	41 (27%)	
Prior cardiac surgery	160 (64%)	69 (69%)	91 (61%)	.23
AVVR				.64
None to mild	196 (78%)	80 (80%)	116 (77%)	
Moderate to severe	54 (22%)	20 (20%)	34 (23%)	
Era				.52
1998-2010	132 (53%)	50 (50%)	82 (55%)	
2011-2018	118 (47%)	50 (50%)	68 (45%)	
Early outcomes				
Any adverse event (n = 98,150)*	128 (52%)	56 (57%)	72 (48%)	.19
Reoperation	36 (14%)	17 (17%)	19 (13%)	.36
Mortality	19 (7.6%)	8 (8.0%)	11 (7.3%)	1.0
Postoperative hospital LOS (d)	13 [8, 26]	12 [8, 23]	13 [8, 27]	.56
Postoperative CICU LOS (d)	7 [3,15]	6 [3,14]	6 [3, 18]	.70
Total hospital LOS (d)	14 [9, 34]	13 [8, 31]	15 [9, 35]	.38
Late outcomes (if survived to discharge)	(n = 231)	(n = 92)	(n = 139)	
Any reintervention	120 (52%)	56 (61%)	64 (46%)	.082
Surgical reintervention	85 (37%)	38 (41%)	47 (34%)	.34
Catheter reintervention	81 (35%)	40 (43%)	41 (30%)	.082
Any unplanned reintervention	105 (45%)	45 (49%)	60 (43%)	.65
Unplanned surgical reintervention	75 (32%)	33 (36%)	42 (30%)	.54
Unplanned catheter reintervention	68 (29%)	29 (32%)	39 (28%)	.76
Mortality	44 (19%)	19 (21%)	25 (18%)	.80

SVP, Single-ventricle palliation; *BiV*, biventricular; *AVVR*, atrioventricular valve regurgitation; *LOS*, length of stay; *CICU*, cardiac intensive care unit. *Adverse events include 1 or more of the following: major bleeding, device malfunction, right heart failure, neurologic events, or infectious process: surgical reinterventions atrial septectomy, aortic valve repair or replacement, pulmonary vein stenosis repair, closure of atrial or ventricular septal defects, aortic surgery, or pacemaker insertion; catheter reinterventions include angioplasty, aortic stent placement, ASD balloon occlusion, thrombectomy, and ventricular stent redilatation.

At a median follow-up of 5.2 years (range, 0-16 years), overall mortality was 25%, and unplanned reinterventions occurred in 107 patients (45%). Of the 231 patients discharged alive, 24 (10%) had less than 1-month follow-up.

Early mortality was 7.6% (19 patients), and late mortality was 19% (44 patients). Adverse events during index hospitalization occurred in 52% of patients, and 36 patients (14%) had to undergo an early reoperation. The medians for postoperative CICU LOS, postoperative hospital LOS, and total hospital LOS were 7, 13, and 14 days, respectively (Table 1).

During the follow-up period, 32% of the patients (n = 75) underwent unplanned postdischarge surgical reintervention, and 29% (n = 68) underwent unplanned catheter intervention.

Surgical Strategy (Single-Ventricle Palliation Versus Biventricular Repair)

Patients who underwent SVP were older at the time of surgery when compared with patients who underwent BiV repair (median 27 months vs 14 months; $P = .047$) and were more likely to have asplenia (n = 52 [52%] vs n = 47 [31%]), whereas patients undergoing BiV repair were more likely to have polysplenia or to be indeterminate (n = 62 [41%] vs n = 29 [29%]; $P = .005$). Among patients who underwent SVP, common diagnoses were pulmonary outflow tract obstruction (n = 75, 75%), double-outlet right ventricle (DORV) (n = 63, 63%), and unbalanced atrioventricular canal defect (AVCD) (n = 55, 55%). Among the patients who underwent BiV repair, common diagnoses were balanced AVCD (n = 97, 65%), pulmonary outflow tract obstruction (n = 89, 59%), and DORV (n = 72, 48%). There was no statistically significant difference in overall mortality when comparing BiV 24% (n = 36) and SVP 27% (n = 27) (Figure 1). Likewise, there was no statistically significant difference when comparing BiV and SVP in the number of adverse events (48%, n = 72 vs 57%, n = 56), early unplanned reinterventions (13%, n = 19 vs 17%, n = 17), and late unplanned reinterventions (43%, n = 60% vs 49%, n = 45) (Table 1 and Figure 1).

Atrioventricular Valve Regurgitation

Patients with moderate or severe AVVR were older at the time of surgery compared with those with no or mild AVVR (32 vs 16 months, $P = .02$), weighed more (11.6 vs 8.8 kg $P = .05$), and were more likely to have had a prior cardiac surgical procedure (81% vs 59% $P = .002$). In univariate analysis, patients with moderate or severe AVVR at presentation were more likely to experience postoperative adverse events during their index surgical admission (72% vs 46%, OR, 2.96, CI, 1.53-5.72 $P = .001$) and had a longer postoperative hospital LOS (18 vs 12 days $P = .004$), postoperative CICU LOS (8 vs 5 days $P = .001$), and total hospital LOS (20 vs 12 days $P = .009$) compared with patients who had no or mild AVVR at presentation (Table 2). When comparing moderate or severe AVVR with no or mild AAVR, there was no statistical difference in late unplanned surgical reintervention (24%, n = 12 vs 35%, n = 63) and in early or late mortality (16%, n = 8 vs 20%, n = 36) (Table 2; Figures 2 and 3). Among patients with moderate to severe AVVR, SVP is associated with a greater risk of unplanned reintervention compared with patients who underwent BiV repair (HR, 2.13; CI, 1.10-4.12; $P = .025$).

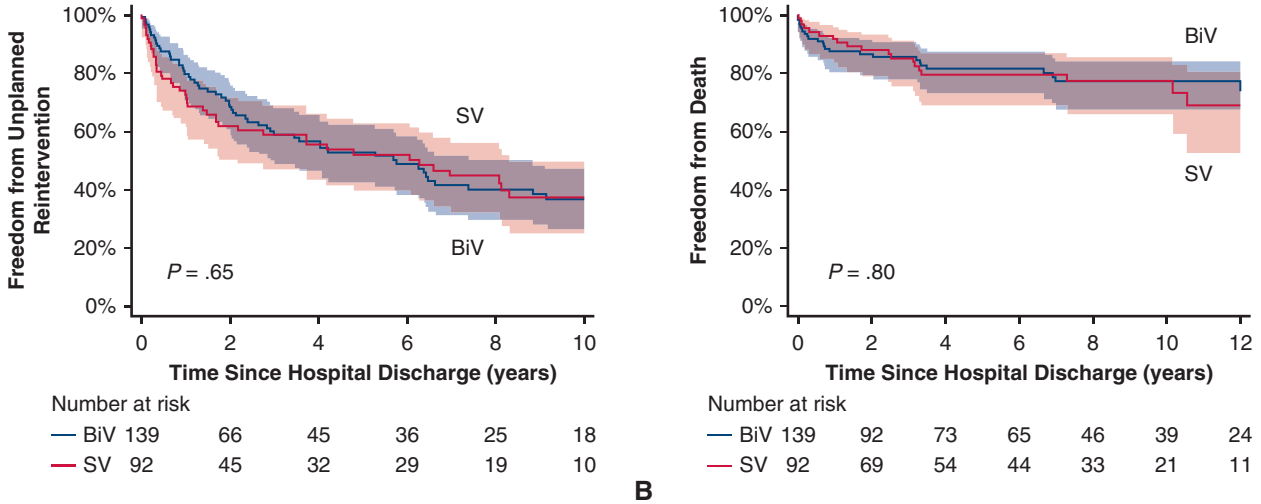

FIGURE 1. A, Time from hospital discharge to reintervention in patients undergoing SV palliation (*red*) versus BiV repair (*blue*). B, Time from hospital discharge to death in patients undergoing SV repair (*red*) versus BiV repair (*blue*). Estimates are shown with 95% confidence bands. *SV*, Single ventricle; *BiV*, biventricular.

TABLE 2. Patient characteristics and outcomes based on severity of atrioventricular valve regurgitation at presentation

Patient characteristics and outcomes	No to mild AVVR (n = 196)	Moderate to severe AVVR (n = 54)	*P* value
Demographics			
Age at surgery (mo)	16 [4, 45]	32 [7, 93]	.024
Age at surgery			
≤30 d	35 (18%)	3 (6%)	.078
31 d to <1 y	53 (27%)	14 (26%)	
1 to 17 y	100 (51%)	33 (61%)	
≥18 y	8 (4%)	4 (7%)	
Weight (kg)	8.8 [5.0, 14.5]	11.6 [5.1, 23.0]	.059
Prematurity (n = 192,54)	8 (4.2%)	0 (0.0%)	.21
Cardiac characteristics			
Splenia			.12
Polysplenia (left isomerism)	65 (33%)	26 (48%)	
Asplenia (right isomerism)	80 (41%)	19 (35%)	
Indeterminate	51 (26%)	9 (17%)	
Prior cardiac surgery	116 (59%)	44 (81%)	.002
SV palliation	80 (41%)	20 (37%)	.64
Era			.76
1998-2010	102 (52%)	30 (56%)	
2011-2018	94 (48%)	24 (44%)	
Early outcomes			
Any adverse event (n = 195,53)	90 (46%)	38 (72%)	.001
Reoperation	24 (12%)	12 (22%)	.080
Mortality	15 (7.7%)	4 (7.4%)	1.0
Postoperative hospital LOS (d)	12 [7, 25]	18 [10, 35]	.004
Postoperative CICU LOS (d)	5 [3, 13]	8 [6, 24]	.001
Total hospital LOS (d)	12 [8, 30]	20 [11, 41]	.009
Late outcomes (if survived to discharge)	(n = 181)	(n = 50)	
Any reintervention	96 (53%)	24 (48%)	.39
Surgical reintervention	72 (40%)	13 (26%)	.09
Catheter reintervention	64 (35%)	17 (34%)	.62
Any unplanned reintervention	85 (47%)	20 (40%)	.45
Unplanned surgical reintervention	63 (35%)	12 (24%)	.19
Unplanned catheter reintervention	56 (31%)	12 (24%)	.35
Mortality	36 (20%)	8 (16%)	.58

AVVR, Atrioventricular valve regurgitation; *SV*, single ventricle; *LOS*, length of stay; *CICU*, cardiac intensive care unit.

Subgroup Multivariable Analysis

After adjusting for the type of procedure, age, HS subtype, and prior cardiac surgery, patients with moderate or severe AVVR at presentation were more likely to experience postoperative adverse events during their index surgical admission (OR, 3.75, CI, 1.86-7.55, $P < .001$) and had greater odds of having a reoperation during the index hospitalization than those with no or mild AVVR (OR, 3.97, CI, 1.54-10.3, $P = .004$) (Table 3).

Among the entire cohort, patients with polysplenia had a greater risk of needing an unplanned late reintervention (HR, 0.45, CI, 0.27-0.74; $P = .002$). Age of 30 days or less at the time of surgery was associated with a late unplanned reintervention (HR, 2.63, CI, 1.35-5.15, $P = .005$) and with a late mortality rate (HR, 3.66; CI, 1.77-7.56, $P < .001$) (Table 4).

Subgroup Analyses of Matched Cardiac Phenotypes

In subgroup analysis matching patients by cardiac diagnoses, there were no significant differences in demographics, cardiac characteristics, early or late outcomes (Table 5).

Subgroup Analyses of Patients Restricted to First Surgery at Boston Children's Hospital

In subgroup analysis of patients who had no cardiac surgery before index operation at our institution, patients undergoing SVP were more likely to be premature at the time of index operation (13% vs 2%, $P = .046$) and were more likely to need late surgical (58% vs 40%, $P = .011$) or catheter reintervention (42% vs 23%, $P = .04$) (Table E1). In this subgroup, patients with moderate or severe AVVR were more likely to have adverse events

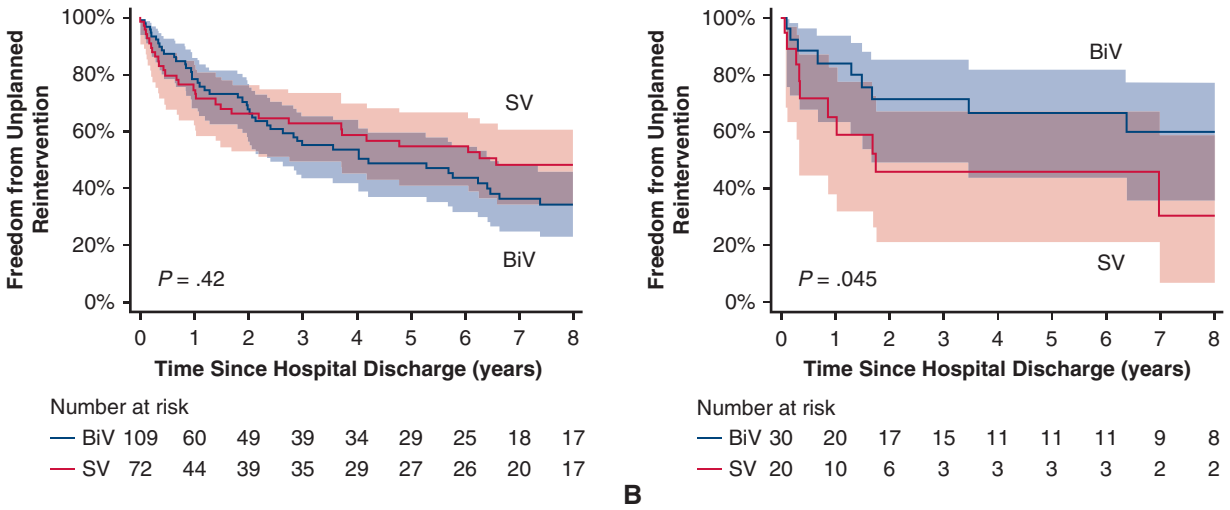

FIGURE 2. Freedom from reintervention in patients undergoing SV palliation (*red*) versus BiV repair (*blue*) in patients with no to mild AVVR at presentation (A) and moderate to severe AVVR at presentation (B). Estimates are shown with 95% confidence bands. *SV*, Single ventricle; *BiV*, biventricular.

(90% vs 50%, $P = .019$), had longer postoperative hospital LOS (median 24 days vs 12 days, $P = .052$) and postoperative CICU LOS (median 24 days vs 6 days, $P = .04$), and were less likely to need any late reintervention (25% vs 54%, $P = .049$) or surgical reintervention (12% vs 49% $P = .033$) (Table E2).

DISCUSSION

Heterotaxy syndrome comprises a highly heterogeneous anatomic and physiological group of patients. The complex cardiac pathology frequently encountered in HS has historically posed challenges from both medical and surgical standpoints. Identifying risk factors for poor outcomes

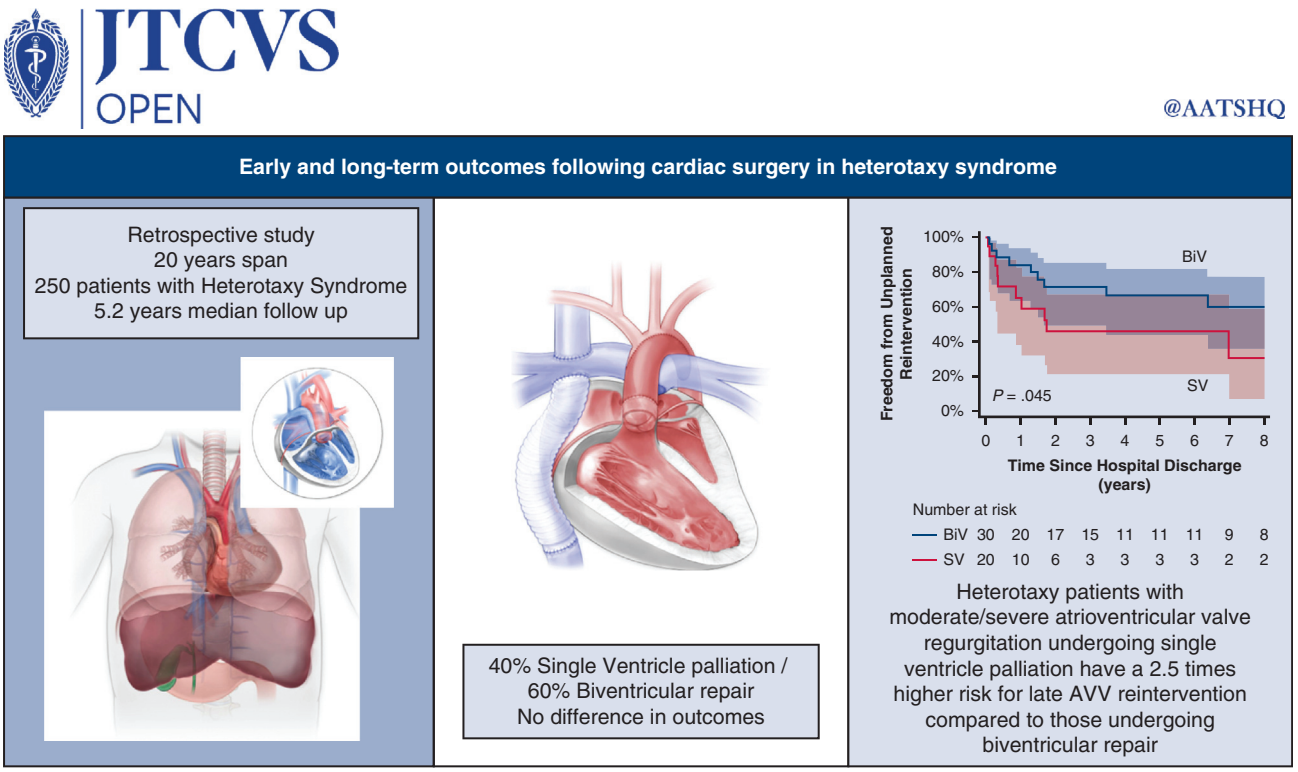

FIGURE 3. Early and long-term outcomes after cardiac surgery in 250 patients with heterotaxy syndrome with a median 5.2 years of follow-up. No significant difference in SV palliation versus BiV repair outcomes. Patients who presented with moderate or severe AVVR who underwent SV palliation have 2.5 times greater risk of late reintervention than those who underwent BiV repair. *BiV*, Biventricular; *SV*, single ventricle; *AVVR*, atrioventricular valve.

TABLE 3. Relationships between single-ventricle palliation and atrioventricular valve regurgitation and early outcomes in the entire cohort of patients with heterotaxy

Early outcomes	Univariate analysis			Multivariable analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Any adverse event						
SVP	1.44	0.87-2.41	.16	1.49	0.85-2.62	.16
Moderate to severe AVVR	2.96	1.53-5.72	.001	3.75	1.86-7.55	<.001
Age at surgery (vs ≥1 y)	–	–	–			
≤30 d				3.25	1.31-8.08	.011
31 d to <1 y				1.98	0.95-4.10	.067
Splenia (vs indeterminate)	–	–	–			
Polysplenia				0.93	0.46-1.88	.84
Asplenia				1.71	0.85-3.44	.13
Prior cardiac surgery	–	–	–	1.11	0.55-2.24	.78
Reoperation						
SVP	1.41	0.69-2.87	.34	2.02	0.88-4.66	.098
Moderate to severe AVVR	2.05	0.95-4.43	.065	3.97	1.54-10.3	.004
Age at surgery (vs ≥1 y)	–	–	–			
≤30 d				11.0	3.19-38.0	<.001
31 d to <1 y				4.09	1.35-12.4	.013
Splenia (vs indeterminate)	–	–	–			
Polysplenia				1.88	0.62-5.71	.26
Asplenia				1.52	0.51-4.56	.45
Prior cardiac surgery	–	–	–	0.65	0.24-1.79	.41
Mortality						
SVP	1.10	0.43-2.84	.85	1.50	0.54-4.18	.44
Moderate to severe AVVR	0.97	0.31-3.04	.95	1.48	0.43-5.07	.54
Age at surgery (vs ≥1 y)						
≤30 d				11.7	2.78-49.7	<.001
31 d to <1 y	–	–	–	8.34	2.10-33.2	.003

OR, Odds ratio; *CI*, confidence intervals; *SVP*, single-ventricle palliation; *AVVR*, atrioventricular valve regurgitation.

and areas for potential improvement in HS care remains an important goal.

The current study reviews 20 years of surgical intervention among patients with HS at a single high-volume institution. As expected, the underlying anatomic diagnoses and surgical approaches were highly variable. On the whole, however, more patients underwent BiV repair than SVP, with no identifiable difference in short- or long-term outcomes. This would seem to indicate that, at a minimum, BiV repair is often feasible in HS. Furthermore, given the known challenges with a Fontan circulation in this setting, strategies other than SVP merit ongoing investigation. This is especially true as surgical technique continues to rapidly evolve and may increasingly offer more favorable outcomes after BiV reconstruction. Moderate or greater AVVR after Fontan operation is associated with a significantly increased risk of death or transplantation in patients with right ventricle dominance, and the cumulative incidence of moderate or greater AVVR or surgery for AVV failure was 56% among those with a common AVV and 46% with hypoplastic left heart syndrome (single tricuspid valve) at 25 years of age.[15] The Pediatric Heart Network's Single Ventricle Reconstruction trial demonstrated transplant-free survival and freedom from catheter interventions were similar in patients undergoing right ventricle-to-pulmonary artery shunt versus modified Blalock-Taussig shunt, although patients with total anomalous pulmonary venous return (likely representing HS) had worse outcomes.[16] Alternatives to SVP have been considered with acceptable results, including primary left ventricular rehabilitation with endocardial fibroelastosis resection and mitral and aortic valvuloplasty as part of a left ventricle recruitment strategy, allowing for BiV conversion in the future.[17,18]

Our study corroborates other work demonstrating that, as a group, reinterventions and mortality remain a critical area for improvement among patients with HS. Overall mortality in our group was 25%, and unplanned reinterventions occurred in approximately one-half of all patients. The high rate of unplanned catheter and surgical reintervention is likely to be a consequence of the anatomic complexity in these patients and progression of residual lesions particularly in those who had prior valve interventions. The morphological characteristics of valves in patients with HS often make them more difficult to repair, and it is our institutional policy to attempt repair always as a first step,

TABLE 4. Relationships between single-ventricle palliation and atrioventricular valve regurgitation and late outcomes in the entire cohort of patients with heterotaxy

Late (post discharge) outcomes	Univariate analysis			Multivariable analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Unplanned reintervention						
SVP	1.09	0.74-1.61	.65	–	–	–
Moderate to severe AVVR	0.83	0.51-1.35	.45	–	–	–
SVP and moderate to severe AVVR*	1.72	0.92-3.23	.089	2.13	1.10-4.12	.025
Age at surgery (vs ≥1 y)	–	–	–			
≤30 d				2.63	1.35-5.15	.005
31 d to <1 y				1.55	0.88-2.73	.13
Splenia (vs indeterminate)	–	–	–			
Polysplenia				0.45	0.27-0.74	.002
Asplenia				0.63	0.39-1.02	.061
Prior cardiac surgery	–	–	–	0.86	0.50-1.46	.57
Mortality						
SVP	1.08	0.60-1.97	.80	1.10	0.59-2.02	.77
Moderate to severe AVVR	0.81	0.37-1.73	.58	1.07	0.48-2.38	.87
Age at surgery (vs ≥1 y)	–	–	–			
≤30 d				3.66	1.77-7.56	<.001
31 d to <1 y				1.33	0.62-2.88	.47

HR, Hazard ratio; *CI*, confidence intervals; *SVP*, single-ventricle palliation; *AVVR*, atrioventricular valve regurgitation. *The relationship between procedure type and unplanned reintervention differs depending on AVVR status (interaction $P = .011$); SVP increases the risk of reintervention among patients with moderate to severe AVVR, but not among those with no to mild AVVR.

and if concerned about residual lesions, to intervene early, sometimes even before discharge from index surgery.[16,19,20]

In contrast to other studies, the heterotaxy phenotype (specifically asplenia) and TAPVC were not associated with increased mortality or adverse events; however, across all anatomic subtypes and operations, moderate to severe AVVR was identified as being associated with adverse events and hospital LOS. Future studies are needed to elucidate if these results are influenced by ventricular dominance.[15,21]

This effect was particularly notable among those undergoing SVP, which would seem to indicate that patients undergoing SVP with AVVR represent a particularly high-risk group meriting special attention and possibly novel surgical approaches.

Study Limitations

This study is limited by the fact that data were collected retrospectively by chart review, and the associated risk of missing and incomplete data, and loss to follow-up. Furthermore, given the referral pattern to our center, the index operation was often not the first operative intervention.

Given the highly varied cardiac diagnoses in this population, matching patients to perform an analysis of anatomic risk factors was difficult given the relatively small number of patients in any category. Furthermore, this study does not address noncardiac disease, which can be rather substantial, in HS. Detailed data pertaining to noncardiac disease (eg, pulmonary, immune, and gastrointestinal anomalies) would be exceptionally valuable in creating a more complete picture of patients with HS and shed light on how these anomalies interact to affect outcomes.

We were also unable to collect complete data on important contributors to long-term outcomes and quality of life, such as the burden of readmission, noncardiac operations, and developmental outcomes because ongoing care was often at a local institution. Furthermore, our study spanned 20 years, and the effect of changing imaging modalities, cardiac catheterization, and surgical strategies were not analyzed and beyond the scope of this study. Future studies that prospectively study these patients from fetal life are needed to identify risk factors and anatomic characteristics that can guide treatment strategies and may be best achieved through multi-institutional longitudinal registries. The ideal study would be a prospective study that compares heterotaxy outcomes with a matched cohort of patients without HS. Toward this goal, we have established a heterotaxy program to follow these patients through their lifetime.

CONCLUSIONS

During an average of 6 years follow-up postdischarge, there was no difference in early or late outcomes in SVP versus BiV repair strategies in patients with HS. In the subgroup of patients with moderate/severe AVVR, the patients who underwent SVP were more than 2.5 times more likely to need a late reintervention compared with those who underwent BiV repair.

TABLE 5. Patient characteristics and outcomes based on repair strategy: Subgroup analysis of a matched cohort of patients based on diagnosis

Patient characteristics and outcomes	SVP (n = 80)	Primary BiV repair (n = 80)	*P* value
Demographics			
Age at surgery (mo)	27 [6, 90]	16 [4, 52]	.18
Age at surgery			
≤30 d	13 (16%)	9 (11%)	.032
31 d to <1 y	12 (15%)	28 (35%)	
1 to 17 y	51 (64%)	40 (50%)	
≥18 y	4 (5%)	3 (4%)	
Weight (kg)	10.9 [6.2, 18.8]	9.5 [4.9, 15.5]	.25
Prematurity (n = 60,77)	4 (5.0%)	0 (0.0%)	.12
Cardiac characteristics			
Splenia			.64
Polysplenia	25 (31%)	27 (34%)	
Asplenia	37 (46%)	31 (39%)	
Indeterminate	18 (23%)	22 (27%)	
Prior cardiac surgery	55 (69%)	52 (65%)	.74
AVVR			.55
None/trivial/mild	66 (83%)	62 (78%)	
Moderate/severe	14 (17%)	18 (22%)	
Era			.63
1998-2010	39 (49%)	43 (54%)	
2011-2018	41 (51%)	37 (46%)	
Early outcomes			
Any adverse event	46 (58%)	41 (51%)	.43
Reoperation	13 (16%)	9 (11%)	.49
Mortality	7 (8.8%)	5 (6.3%)	.77
Postoperative hospital LOS (d)	12 [8, 21]	16 [8, 31]	.22
Postoperative CICU LOS (d)	6 [3,13]	7 [3, 19]	.54
Total hospital LOS (d)	12 [8, 24]	17 [9, 37]	.17
Late outcomes (if survived to discharge)	(n = 73)	(n = 75)	
Any reintervention	44 (60%)	39 (52%)	.23
Surgical reintervention	32 (44%)	26 (35%)	.14
Catheter reintervention	31 (42%)	27 (36%)	.45
Any unplanned reintervention	35 (48%)	37 (49%)	.96
Unplanned surgical reintervention	28 (38%)	24 (32%)	.29
Unplanned catheter reintervention	22 (30%)	26 (35%)	.63
Mortality	13 (18%)	17 (23%)	.54

SVP, Single-ventricle palliation; *BiV*, biventricular; *AVVR*, atrioventricular valve regurgitation; *LOS*, length of stay; *CICU*, cardiac intensive care unit.

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: asplenia, congenital heart disease, Fontan operation, heterotaxy syndrome, single ventricle

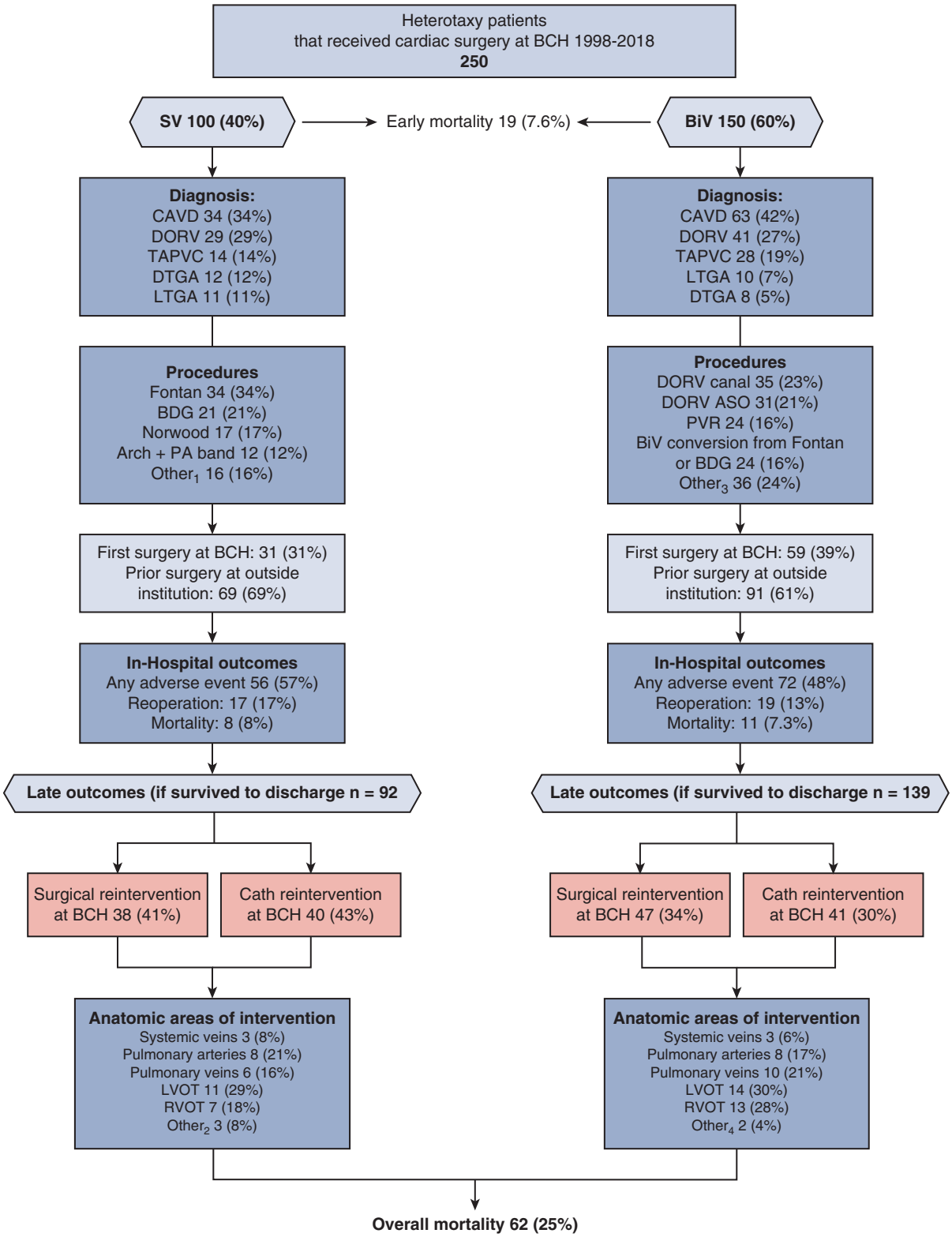

FIGURE E1. Flow chart detailing clinical characteristics and outcomes based on the management strategy of patients with HS included in this study. Diagnosis, procedures, and interventions listed are mutually exclusive and based on primary diagnosis, procedure, and first intervention, respectively. $Other_1$: SV group other procedures: orthotopic heart transplant, aortic valve repair. $Other_2$: aortic arch, aorta, pacemaker leads. $Other_3$: orthotopic heart transplant, aortic valve repair, RVOT or LVOT intervention. *BCH*, Boston Children's Hospital; *SV*, single ventricle; *BiV*, biventricular; *CAVD*, complete atrio ventricular canal defect; *DORV*, double-outlet right ventricle; *TAPVC*, total anomalous pulmonary venous connection; *DTGA*, dextro transposition of great arteries; *LTGA*, levo transposition of great arteries; *BDG*, bidirectional Glenn; *ASO*, arterial switch operation; *PVR*, pulmonray valve replacement; *LVOT*, left ventricular outflow tract; *RVOT*, right ventricular outflow tract.

TABLE E1. Patient characteristics and outcomes based on repair strategy (single-ventricle palliation vs biventricular repair) in patients with no cardiac surgery before index cardiac surgical intervention at our center

Patient characteristics and outcomes	All (n = 90)	SVP (n = 31)	BiV repair (n = 59)	*P* value
Demographics				
Age at surgery (mo)	4 [7 d, 9]	1 [6 d, 8]	5 [19 d, 10]	.27
Age at surgery				
≤30 d	31 (34%)	15 (48%)	16 (27%)	.10
31 d to <1 y	42 (47%)	10 (32%)	32 (54%)	
1 to 17 y	17 (19%)	6 (19%)	11 (19%)	
Weight (kg)	5.3 [3.3, 7.4]	4.2 [3.0, 7.4]	5.6 [3.5, 7.4]	.21
Prematurity	5 (5.6%)	4 (13%)	1 (2%)	.046
Cardiac characteristics				
Splenia				.062
Polysplenia (left isomerism)	29 (32%)	5 (16%)	24 (41%)	
Asplenia (right isomerism)	32 (36%)	14 (45%)	18 (31%)	
Indeterminate	29 (32%)	12 (39%)	17 (29%)	
AVVR				.16
None to mild	80 (89%)	30 (97%)	50 (85%)	
Moderate to severe	10 (11%)	1 (3%)	9 (15%)	
Era				.025
1998-2010	42 (47%)	9 (29%)	33 (56%)	
2011-2018	48 (53%)	22 (71%)	26 (44%)	
Early outcomes				
Any adverse event	49 (54%)	19 (61%)	30 (51%)	.38
Reoperation	21 (23%)	11 (35%)	10 (17%)	.067
Mortality	11 (12.2%)	5 (16.1%)	6 (10.2%)	.50
Postoperative hospital LOS (d)	14 [7, 34]	15 [8, 41]	14 [7, 34]	.50
Postoperative CICU LOS (d)	7 [3, 26]	16 [5,31]	6 [3, 24]	.34
Total hospital LOS (d)	17 [9, 37]	20 [8, 45]	16 [9, 36]	.57
Late outcomes (if survived to discharge)	(n = 79)	(n = 26)	(n = 53)	
Any reintervention	40 (51%)	15 (58%)	25 (47%)	.091
Surgical reintervention	36 (46%)	15 (58%)	21 (40%)	.011
Catheter reintervention	23 (29%)	11 (42%)	12 (23%)	.040
Any unplanned reintervention	39 (49%)	15 (58%)	24 (45%)	.16
Unplanned surgical reintervention	31 (39%)	12 (46%)	19 (36%)	.27
Unplanned catheter reintervention	22 (28%)	10 (38%)	12 (23%)	.10
Mortality	15 (19%)	6 (23%)	9 (17%)	.64

SVP, Single-ventricle palliation; *BiV*, biventricular; *AVVR*, atrioventricular valve regurgitation; *LOS*, length of stay; *CICU*, cardiac intensive care unit.

TABLE E2. Patient characteristics and outcomes based on severity of atrioventricular valve regurgitation at presentation in patients with no cardiac surgery before index cardiac surgical intervention at our center

Patient characteristics and outcomes	No to mild AVVR (n = 80)	Moderate to severe AVVR (n = 10)	*P* value
Demographics			
Age at surgery (mo)	4 [7d, 9]	5 [1, 18]	.48
Age at surgery			
≤30 d	29 (36%)	2 (20%)	.50
31 d to <1 y	37 (46%)	5 (50%)	
1 to 17 y	14 (18%)	3 (30%)	
≥18 y	0 (0%)	0 (0%)	
Weight (kg)	5.4 [3.3, 7.3]	5.0 [3.4, 11.4]	.70
Prematurity	5 (6.3%)	0 (0.0%)	1.0
Cardiac characteristics			
Splenia			.92
Polysplenia (left isomerism)	26 (33%)	3 (30%)	
Asplenia (right isomerism)	29 (36%)	3 (30%)	
Indeterminate	25 (31%)	4 (40%)	
SV repair	30 (38%)	1 (10%)	.16
Era			.75
1998-2010	38 (48%)	4 (40%)	
2011-2018	42 (52%)	6 (60%)	
Early outcomes			
Any adverse event	40 (50%)	9 (90%)	.019
Reoperation	18 (23%)	3 (30%)	.69
Mortality	9 (11.3%)	2 (20.0%)	.35
Postoperative hospital LOS (d)	12 [7, 33]	24 [16, 59]	.052
Postoperative CICU LOS (d)	6 [3, 21]	24 [19, 53]	.040
Total hospital LOS (d)	15 [8, 36]	26 [16, 66]	.080
Late outcomes (if survived to discharge)	(n = 71)	(n = 8)	
Any reintervention	38 (54%)	2 (25%)	.049
Surgical reintervention	35 (49%)	1 (12%)	.033
Catheter reintervention	22 (31%)	1 (12%)	.18
Any unplanned reintervention	37 (52%)	2 (25%)	.062
Unplanned surgical reintervention	30 (42%)	1 (12%)	.077
Unplanned catheter reintervention	21 (30%)	1 (12%)	.21
Mortality	14 (20%)	1 (12%)	.52

AVVR, Atrioventricular valve regurgitation; *SV*, single ventricle; *LOS*, length of stay; *CICU*, cardiac intensive care unit.