Long-term outcomes of heart transplantation in adults with congenital heart disease: The impact of single-ventricle versus biventricular physiology

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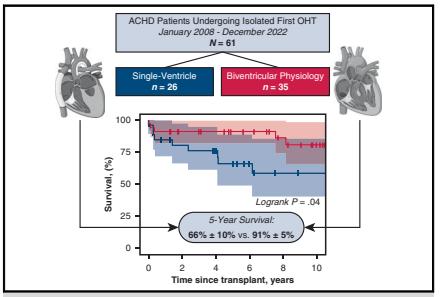
ABSTRACT

Objective: Congenital heart disease is a risk factor for mortality after orthotopic heart transplantation; however, the impact of preoperative circulation type and primary congenital heart disease diagnosis remains poorly delineated.

Methods: We retrospectively reviewed patients with adult congenital heart disease aged 16 years or more who underwent orthotopic heart transplantation at our institution between 2008 and 2022. Patients were categorized as having single-ventricle or biventricular circulation. The primary end point was 5-year post-transplant survival.

Results: Sixty-one patients with adult congenital heart disease (single-ventricle: n = 26 [42.6%], biventricular: n = 35 [57.4%]) underwent orthotopic heart transplantation at 33.7 [interquartile range, 19.1-48.7] years. The most common congenital heart disease diagnosis was hypoplastic left heart syndrome (n = 11, 42.3%) in the single-ventricle group and congenitally corrected transposition of the great arteries (n = 7, 20.0%) in the biventricular group. Twenty-four patients previously underwent Fontan palliation. At transplant, patients in the single-ventricle group were younger (18.5 [interquartile range, 17.6-32.3] years vs 45.0 [interquartile range, 33.0-52.2] years, $P < .001$) and more likely to have biopsy-proven cirrhosis (46.2% vs 14.3%, $P = .01$) and protein-losing enteropathy (42.3% vs 2.9%, $P < .001$). Patients in the single-ventricle group also had longer bypass times (223.4 ± 65.3 minutes vs 187.4 ± 59.5 minutes, $P = .03$) and longer durations of mechanical ventilatory support (3.5 [interquartile range, 2.0-6.0] days vs 1.0 [interquartile range, 1.0-2.0] days, $P < .001$). Operative mortality was comparable (11.5% vs 8.6%, $P = 1$). Median follow-up was 6.0 [interquartile range, 2.4-10.0] years. Five-year survival was worse in the single-ventricle group (66.0% ± 10.0% vs 91.3% ± 4.8%, $P = .03$), as was freedom from major rejection (58.3% ± 10.2% vs 84.0% ± 6.6%, $P = .02$). In univariable analysis, hypoplastic left heart syndrome and Fontan circulation were risk factors for post-transplant mortality (hypoplastic left heart syndrome: hazard ratio, 5.0, $P < .001$; Fontan: hazard ratio, 3.5, $P = .03$).

Conclusions: Adult patients with congenital heart disease undergoing heart transplant with single-ventricle physiology experienced a more complicated post-transplant course, with worse long-term survival and freedom from rejection. Multicenter studies are required to guide orthotopic heart transplantation decision-making in this complex cohort. (JTCVS Open 2024;19:257-74)



Single-ventricle ACHD heart transplant recipients have worse long-term survival.

CENTRAL MESSAGE

Patients with ACHD with single-ventricle physiology had a more complicated post-transplant course than the biventricular group, with worse long-term survival and freedom from significant rejection events.

PERSPECTIVE

Heart transplantation in adults with CHD may be performed with favorable contemporary outcomes; however, patients who undergo single-ventricle palliation remain a challenging cohort. Multicenter, prospective studies are required to guide decision-making for this growing patient population. The role of combined heart-liver transplantation should be further delineated.

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Institutional Review Board: AAAU2877 (approved 9/8/2023).

Read at the 104th Annual Meeting of The American Association for Thoracic Surgery, Toronto, Ontario, Canada, April 27-30, 2024.

Received for publication Jan 18, 2024; revisions received March 11, 2024; accepted for publication April 2, 2024; available ahead of print May 16, 2024.

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2666-2736

https://doi.org/10.1016/j.xjon.2024.04.006

Abbreviations and Acronyms

ACHD = adult congenital heart disease
CHD = congenital heart disease
HLHS = hypoplastic left heart syndrome
HR = hazard ratio
IQR = interquartile range
OHT = orthotopic heart transplant/transplantation

Congenital heart disease (CHD) is a known risk factor for mortality after heart transplantation in both the pediatric and adult population, although little is known about the impact of preoperative circulatory physiology and the fundamental CHD diagnosis on transplant outcomes.[1-5] It is generally believed that patients with single-ventricle physiology represent a high-risk cohort due to more complex anatomy, multiple prior sternotomies, high collateral burden, and multiorgan dysfunction.[6,7] A recent multiregistry analysis showed that single-ventricle physiology was associated with higher short-term mortality in adult congenital heart disease (ACHD) transplant recipients; however, 10-year conditional survival was similar between the univentricular and biventricular groups.[8] Overall, data on post-transplant outcomes by circulation type are limited and conflicting,[3,9-11] and larger studies using national databases lack granularity, often lacking specific CHD diagnoses and comprehensive procedural data in this heterogeneous population.[5]

Given the rising number of patients with CHD surviving into adulthood and parallel increase in the prevalence of advanced heart failure in this cohort,[12] it is important to determine contemporary post-transplant outcomes for recipients with ACHD. We sought to evaluate our institutional experience with heart transplantation for ACHD with a focus on whether circulation type (ie, single-ventricle or biventricular) impacts survival.

MATERIAL AND METHODS

Study Population

We retrospectively reviewed all patients 16 years or older with a CHD diagnosis who received a heart transplant at NewYork-Presbyterian/Columbia University Irving Medical Center between January 2008 and December 2022. Sixteen years of age was selected as the cutoff for inclusion as many become eligible to receive adult organs at this age. Patients who underwent a heart transplant before 2008 and received retransplantation during the study period were excluded, as were those who received a multiorgan transplant. Although not included in the primary analysis, all patients evaluated for heart transplantation during the study period were reviewed to assess decision-making patterns regarding transplant candidacy in patients with ACHD—a significantly heterogeneous cohort—as well as prognoses after decline for transplantation or delisting. The Institutional Review Board at Columbia University Irving Medical Center approved the study protocol and publication of data (AAAU2877, approved September 8, 2023). Patient written consent for the publication of study data was waived due to the retrospective nature of the study.

Data Collection and Definitions

All clinical data were retrospectively collected from the electronic medical record and institutional transplant databases. Patients were stratified by cardiac physiology at the time of transplant (ie, single-ventricle or biventricular circulation). No patients had 1.5-ventricle physiology. Patients were followed via routine clinical follow-up from the time of transplant until death, retransplantation, or loss to follow-up. As of December 31, 2022, follow-up was 93.4% complete; patients alive on this date were censored at the date of last known follow-up. Those who required a second heart transplant during the study period were censored at the time of retransplantation.

Vasoactive-inotropic scores were calculated as dopamine + dobutamine + 10 × milrinone + 100 × epinephrine + 100 × norepinephrine (all μg/kg/min) + 10,000 × vasopressin (U/kg/min).[13] Predicted heart mass mismatch was calculated as described in the International Society for Heart and Lung Transplantation Thoracic Organ Transplant Adult Heart Transplantation 2019 Report.[14] Postoperative infections included culture-confirmed bacteremia, deep sternal wound infections, mediastinitis, pneumonia, and sepsis. We collected longitudinal transthoracic echocardiography data to serially evaluate long-term cardiac function after hospital discharge. Ventricular systolic function was graded as normal or borderline reduced, mildly reduced, moderately reduced, or severely reduced. Significant ventricular dysfunction was defined as a moderate or greater reduction in either right (based on grade assigned in the report) or left (with a lower ejection fraction estimate of $\leq$35% considered significant) ventricular function on 2 serial examinations. For patients who had spontaneous improvement in the degree of dysfunction after a more severe grade was diagnosed, we selected the date of first appearance of at least moderate ventricular dysfunction for the calculation of time to event. Rejection events included (1) clinical rejection, defined as any rejection episode associated with new-onset heart failure prompting hospital admission and treatment; (2) acute cellular rejection (International Society for Heart and Lung Transplantation grade 2R or higher on protocol biopsy); and (3) grade pAMR2 or greater antibody-mediated rejection.

Study End Points

The primary end point was 5-year post-transplant survival. Secondary end points included operative mortality, major postoperative complications, 1-year survival, hospital readmissions, allograft rejection, and long-term graft function as determined by echocardiography.

Statistical Analysis

Continuous variables are expressed as median (interquartile range [IQR]) or mean ± SD, depending on distribution as determined by the Shapiro–Wilk test. Categorical variables are presented as proportions. Differences between groups were assessed using the Fisher exact or Pearson's chi-square test for categorical variables, the independent Student *t* test for normally distributed continuous variables, or the Mann–Whitney *U* test for non-normally distributed continuous variables. Given the limited number of events, only univariable logistic regression was performed to identify factors associated with in-hospital mortality. We used Kaplan–Meier survival analysis with log-rank tests to estimate time-dependent outcomes. Patients were censored at the time of last known follow-up or retransplantation. Risk factors for death were assessed using Cox proportional hazards modeling. Statistical analysis was performed using R statistical software, version 2023.06.2 + 561 (R Foundation for Statistical Computing).

RESULTS

Transplant Candidate Evaluation

Between January 2008 and December 2022, a total of 2035 unique patients were evaluated for heart transplantation at our institution. Of these, 93 patients (4.6%) with

ACHD underwent evaluation for an isolated first heart transplant. Three patients (3.2%) were determined not to be transplant candidates due to prohibitive surgical risk. Of the 90 patients with ACHD listed for heart transplant, 20 (22.2%) were delisted for various reasons, including a deterioration (n = 9) or improvement (n = 4) in clinical status, loss to follow-up (n = 3), patient preference (n = 2), or transfer of care (n = 2). The 2 transferred patients underwent successful transplantation at outside centers, as was 1 patient whom we declined due to surgical complexity. There were 7 (7.7%) waitlist mortalities at a median of 2.2 years [IQR, 0.3-3.4] after listing. Overall, 61 patients (67.8%) with ACHD underwent successful transplantation during the study period (Figure 1). Additionally, 6 combined heart-liver transplants were performed in patients with ACHD during this time.

After excluding patients undergoing transplantation at outside institutions, the rate of transplantation, delisting, and waitlist mortality at 1 year after listing was 54.1% ± 5.5%, 12.9% ± 3.7%, and 4.7% ± 2.3% (Figure 2, *A*), respectively (single-ventricle: 61.1% ± 8.3%, 11.1% ± 5.3%, 5.5% ± 3.9%; biventricular: 48.9% ± 7.3%, 16.3% ± 5.4%, 4.1% ± 2.9%, respectively). Kaplan–Meier modeling revealed a 1-year transplant-free survival of 67.1% ± 12.6% (Figure 2, *B*) after decline or delisting, with the highest mortality risk during the first 3 months thereafter; survival was not statistically different between the single-ventricle and biventricular groups (80.0% ± 17.9% vs 61.7% ± 15.8%, $P = .41$, Figure 2, *C*).

Patient Demographics and Baseline Characteristics

Preoperative patient characteristics are presented in Table 1. A total of 61 patients with ACHD (59.0% male) received a first-time heart transplant during the study period. Of these, 26 (42.6%) had single-ventricle physiology and 35 (57.4%) had biventricular circulation. The most common CHD diagnoses in the single-ventricle group were hypoplastic left heart syndrome (HLHS) (n = 11, 42.3%), double-inlet left ventricle (n = 4, 15.4%), and tricuspid atresia (n = 3, 11.5%). Twenty-four patients (92.3%) had undergone Fontan palliation by the time of transplant. Of the remaining 2 patients in the single-ventricle group, 1 had hemi-Fontan physiology and 1 had a fundamental diagnosis of dextro-transposition of the great arteries, double-outlet right ventricle, ventricular septal defect, and tricuspid atresia and had undergone a balloon septostomy as a neonate but no corrective surgery. The most common CHD diagnoses in the biventricular group were congenitally corrected transposition of the great arteries (n = 7, 20.0%), tetralogy of Fallot (n = 4, 11.4%), double-outlet right ventricle (n = 3, 8.6%), and partial atrioventricular septal defect (n = 3, 8.6%).

Patients in the single-ventricle group were significantly younger at the time of transplant (18.5 [IQR, 17.6-32.3] years vs 45.0 [IQR, 33.0-52.2] years, $P < .001$) and had more evidence of end-organ dysfunction, including biopsy-proven cirrhosis (46.2% vs 14.3%, $P = .01$), protein-losing enteropathy (42.3% vs 2.9%, $P < .001$), and lower albumin levels (3.6 [2.5-4.2] g/dL vs 4.1 [IQR, 3.9-4.4] g/dL, $P = .001$). The biventricular group had higher preoperative pulmonary capillary wedge pressures than the single-ventricle group (17.0 [IQR, 11.0-28.0] vs 10.0 [IQR, 8.5-12.0], $P < .01$) and, although not statistically significant, a higher rate of preoperative mechanical circulatory support (22.9% vs 3.8%, $P = .09$). There was no difference between groups in pretransplant sensitization, defined as a panel-reactive antibody titer of greater than 10% (3 [14.3%] vs 8 [27.6%], $P = .44$).

Intraoperative Data

Detailed procedural data are shown in Table 2. Total allograft ischemic times were similar between groups (single-ventricle: 229.5 ± 69.3 minutes vs biventricular: 212.8 ± 79.3 minutes, $P = .40$). Cardiopulmonary bypass (223.4 ± 65.3 minutes vs 187.4 ± 59.5 minutes, $P = .03$) and crossclamp (131.6 ± 39.0 minutes vs 99.1 ± 32.1 minutes, $P < .01$) times were both significantly longer in the single-ventricle group. Patients in the single-ventricle group were more likely to undergo a concomitant cardiac procedure (88.5% vs 45.7%, $P < .01$), with a pulmonary artery plasty required in 84.6% of the group. Except for a greater cryoprecipitate requirement in the single-ventricle group (4.0 [IQR, 1.0-10.0] units vs 0.0 units [IQR, 0.0-2.0], $P < .01$), there were no notable differences in intraoperative transfusion requirements.

Early Postoperative Data

In-hospital outcomes are summarized in Table 3. The single-ventricle group had a longer time to extubation (3.5 [IQR, 2.0-6.0] days vs 1.0 [IQR, 1.0-2.0] days, $P < .001$), as well as intensive care unit (15.5 [IQR, 7.0-28.0] days vs 8.0 [IQR, 5.5-14.0] days, $P = .045$) lengths of stay. Postoperative hospital stays were also longer, although this difference was not statistically significant (35.5 [IQR, 25.5-50.0] days vs 25.0 [IQR, 17.0-39.5] days, $P = .08$). There was no difference in the need for postoperative mechanical circulatory support between groups (single-ventricle: 19.2% vs biventricular: 17.1%, $P = 1.00$). Rates of postoperative complications assessed were similar. One patient in the biventricular group developed severe primary graft dysfunction and underwent retransplantation on postoperative day 6. There was no difference in operative mortality between groups (single-ventricle: n = 3 [11.5%] vs biventricular: n = 3 [8.6]%, $P = 1.00$). These 6 mortalities (9.8%) are detailed in Table E1. Univariable logistic regression revealed preoperative bilirubin and allograft ischemic

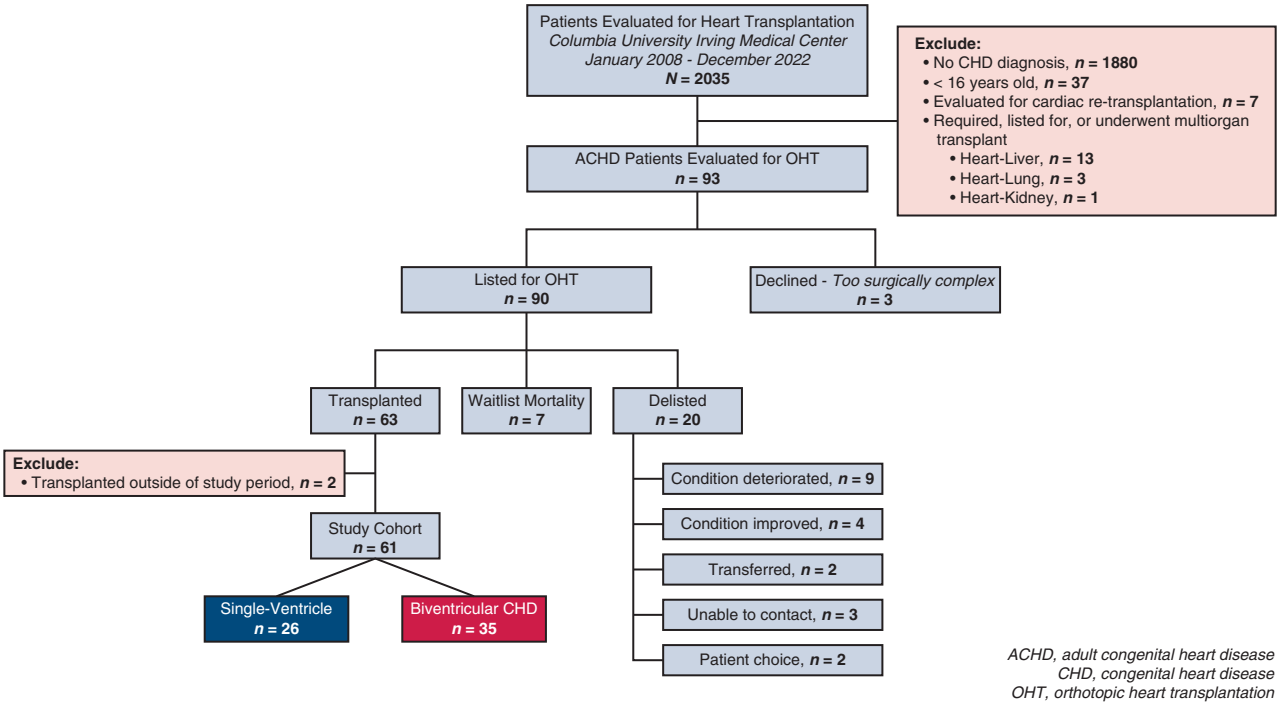

FIGURE 1. Consolidated Standards of Reporting Trials diagram depicting selection of the study cohort.

time to be independent predictors of in-hospital mortality (Table E2).

Late Outcomes

At a median follow-up of 6.0 years [IQR, 2.4-10.0], there was no difference in 1-year survival (single-ventricle: 84.6% ± 7.1% vs biventricular: 91.3% ± 4.8%, $P = .44$). Five-year and 10-year survivals were significantly worse in the single-ventricle group (5-year: single-ventricle: 66.0% ± 10.0% vs biventricular: 91.3% ± 4.8%, $P = .03$; 10-year: single-ventricle: 58.7% ± 11.4% vs biventricular: 80.8% ± 8.2%, $P = .04$) (Figure 3, *A*).

In the single-ventricle group, causes of late death included septic shock (n = 2) and chronic rejection (n = 1) (detailed below), as well as out-of-hospital cardiac arrest (n = 2) and gunshot trauma (n = 1). One patient (18.5-year-old male with HLHS status post-Fontan) whose postoperative course was complicated by respiratory failure requiring tracheostomy was readmitted 20 days after discharge to inpatient rehabilitation with profound metabolic acidosis and extensive bowel necrosis; the patient died 2 days later, 4 months post-transplant. Another patient (17.2-year-old male with HLHS status post-Fontan) whose postoperative course was complicated by recurrent antibody-mediated rejection and protein-losing enteropathy presented in cardiogenic shock 15.5 months post-transplant. He had cardiac arrest that same day and underwent emergency extracorporeal membrane oxygenation cannulation. The postarrest course was complicated by acute renal failure, fungemia, and bowel ischemia with perforation. He was given comfort care and died 1 month after readmission. Finally, a patient (18.1-year-old male with double-outlet right ventricle status post-Fontan) with a history of nonadherence to immunosuppression was readmitted 3 years post-transplant and found to have humoral rejection in the setting of mycophenolate mofetil discontinuation for 1 week, as well as active H1N1 infection and pneumococcal bacteremia. The hospital course was complicated by invasive aspergillosis, ventricular tachycardia, and seizure on hospital day 41 followed by intracranial hemorrhage; he died after withdrawal of care on hospital day 44. In the biventricular group, there were a total of 2 late deaths at 6.8 months and 8.0 years post-transplant, both due to sequelae of rejection. Two patients in the biventricular group underwent retransplantation at 1.7 and 10.5 years after their initial transplant due to graft failure following several rejection episodes.

Next, patients in the single-ventricle group had worse 1-year and 5-year freedom from major rejection events (single-ventricle: 58.3% ± 10.2% vs biventricular: 90.6% ± 5.2%, $P < .01$; single-ventricle: 58.3% ± 10.2% vs biventricular: 84.0% ± 6.6%, $P = .02$; Figure 3, *B*). However, freedom from significant ventricular dysfunction, as determined by follow-up echocardiography after hospital discharge, was similar at 1 year (single-ventricle: 87.0% ± 7.0% vs biventricular: 80.5% ± 7.2%, $P = .52$) and 5 years (single-ventricle: 72.5% ± 9.6% vs biventricular: 76.7% ± 7.8%, $P = .92$) post-transplant (Figure 3, *C*).

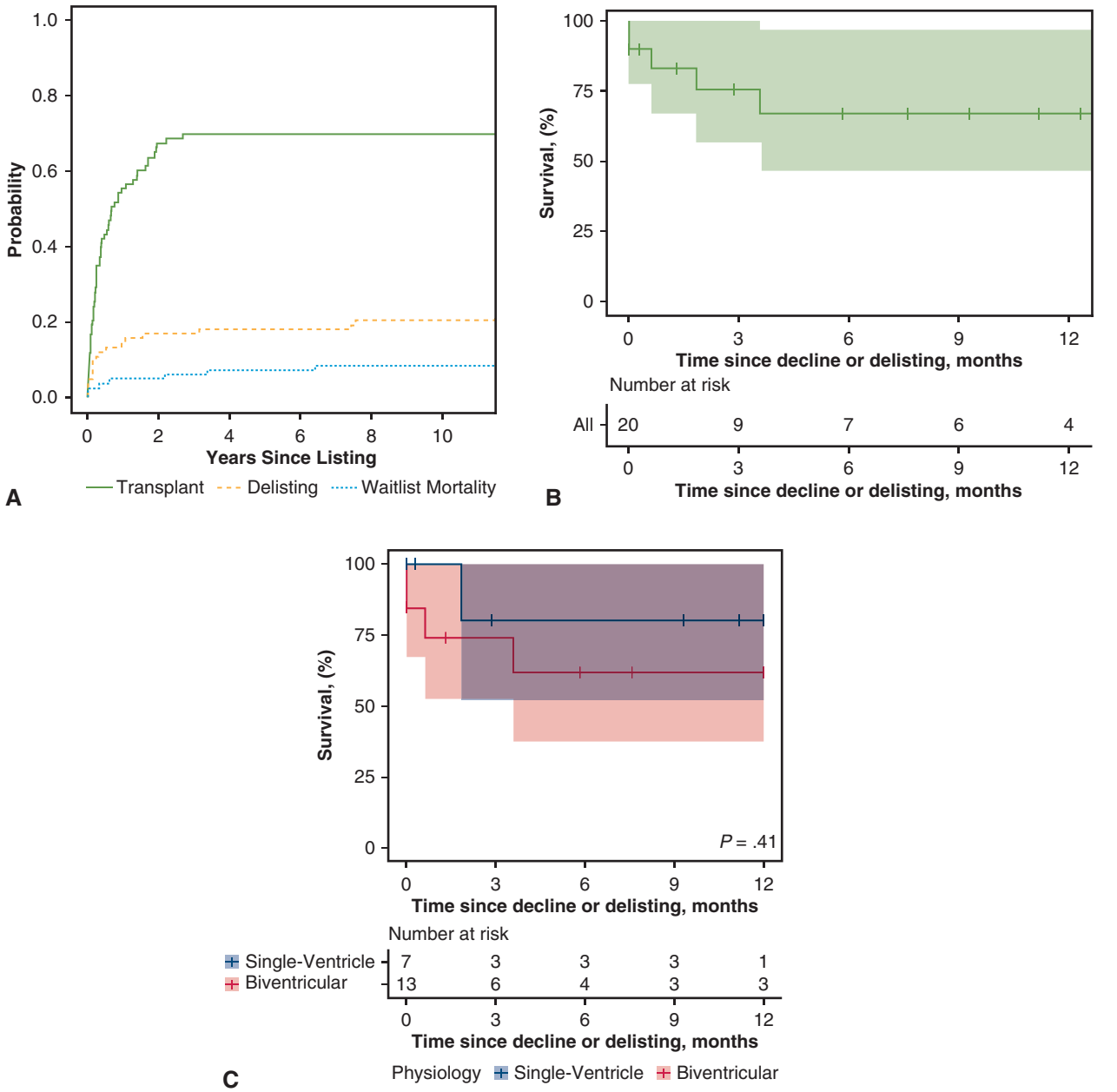

FIGURE 2. A, Cumulative incidence curve of cardiac transplantation (*solid line*), delisting (*dashed line*), or waitlist mortality (*dotted line*) after listing for isolated heart transplant. Kaplan–Meier plot showing (B) overall survival and (C) survival stratified by physiology after decline or delisting for transplant. Number of patients at risk is included in the lower panel. Shaded 95% CIs are shown.

Likewise, there was no difference in 1-year (single-ventricle: 34.8% ± 9.9% vs biventricular: 48.4% ± 9.0%, $P = .40$) or 3-year (single-ventricle: 17.4% ± 7.9% vs biventricular: 32.5% ± 8.9%, $P = .25$) freedom from unplanned hospital readmissions (Figure 3, *D*). At latest follow-up, the median number of unplanned readmissions was similar between groups (single-ventricle: 1.5 [IQR, 1.0-3.8] vs biventricular: 2.0 [IQR, 0.0-3.0], $P = .80$). In the single-ventricle group, the most common reasons for readmission were infection (n = 16), rejection (n = 13), and gastrointestinal concerns (n = 10); in the biventricular group, these were rejection (n = 21) and infection (n = 16).

Although single-ventricle physiology was not a risk factor for death after transplantation in the univariable analysis (hazard ratio [HR], 3.0, 95% CI, 1.0-8.9, $P = .05$), a diagnosis of HLHS (HR, 5.0, 95% CI, 1.7-15.0, $P < .01$), a prior systemic-to-pulmonary shunt (HR, 3.4, 95% CI, 1.1-10.1, $P = .03$), a prior Norwood operation (HR, 3.9, 95% CI, 1.3-11.9, $P = .01$), and a prior Fontan (HR, 3.5, 95% CI, 1.2-10.5, $P = .03$) were predictive of post-transplant

TABLE 1. Baseline characteristics

Variable	Single-ventricle (n = 26)	Biventricular (n = 35)	*P* value
Age at transplant (y)	18.5 [17.6, 32.3]	45.0 [33.1, 52.2]	**<.001**
Male	16 (61.5)	20 (57.1)	.94
Body mass index (kg/m^2)	24.1 [19.4, 27.1]	22.3 [20.0, 24.2]	.44
Comorbidities			
Cardiac arrhythmia	20 (76.9)	30 (85.7)	.59
Pacemaker or automated implantable cardiac defibrillator	13 (50.0)	26 (74.3)	.09
Atrial flutter or atrial fibrillation	7 (26.9)	17 (48.6)	.15
Ascites	9 (34.6)	10 (28.6)	.82
Biopsy-proven cirrhosis	12 (46.2)	5 (14.3)	**.01**
Stroke or transient ischemic attack	6 (23.1)	8 (22.9)	1.00
Protein-losing enteropathy	11 (42.3)	1 (2.9)	**<.001**
Hypertension	2 (7.7)	6 (17.1)	.49
Diabetes	0 (0.0)	3 (8.6)	.35
History of tobacco use	3 (11.5)	9 (25.7)	.29
Primary congenital heart disease diagnosis			**.002**
Hypoplastic left heart syndrome	11 (42.3)	0 (0.0)	
Congenitally corrected transposition of the great arteries	1 (3.8)	7 (20.0)	
Double-inlet left ventricle	4 (15.4)	0 (0.0)	
Dextro-transposition of the great arteries	2 (7.7)	2 (5.7)	
Double-outlet right ventricle	1 (3.8)	3 (8.6)	
Tetralogy of Fallot	0 (0.0)	4 (11.4)	
Ebstein's anomaly	1 (3.8)	2 (5.7)	
Tricuspid atresia	3 (11.5)	0 (0.0)	
Atrial septal defect	0 (0.0)	2 (5.7)	
Atrioventricular septal defect	0 (0.0)	3 (8.6)	
Congenital aortic stenosis	0 (0.0)	2 (5.7)	
Pulmonary atresia with intact ventricular septum	1 (3.8)	1 (2.9)	
Ventricular septal defect	0 (0.0)	2 (5.7)	
Aortic coarctation	0 (0.0)	1 (2.9)	
Congenital pulmonary stenosis	0 (0.0)	1 (2.9)	
Coronary artery anomaly	0 (0.0)	1 (2.9)	
Double-chambered right ventricle	0 (0.0)	1 (2.9)	
Hypertrophic cardiomyopathy (Noonan syndrome)	0 (0.0)	1 (2.9)	
Heterotaxy	1 (3.8)	0 (0.0)	
Truncus arteriosus	0 (0.0)	1 (2.9)	
Prior cardiac surgery	25 (96.2)	32 (91.4)	.83
Fontan	24 (92.3)	0 (0.0)	**<.001**
Shunt (Blalock-Taussig-Thomas, Waterson)	18 (69.2)	6 (17.1)	**<.001**
Bidirectional cavopulmonary shunt or Hemi-Fontan	21 (80.8)	0 (0.0)	**<.001**
Norwood or Damus-Kaye-Stansel procedure	13 (50.0)	0 (0.0)	**<.001**
Ventricular septal defect closure	0 (0.0)	11 (31.4)	**<.01**
Mitral valve repair or replacement	0 (0.0)	9 (25.7)	**.02**
Tricuspid valve repair or replacement	2 (7.7)	6 (17.1)	.49
Atrial septal defect closure	0 (0.0)	7 (20.0)	**.04**
Pulmonary artery banding	5 (19.2)	2 (5.7)	.22
Pulmonary valve replacement	0 (0.0)	7 (20.0)	**.04**
Aortic valve repair or replacement	2 (7.7)	4 (11.4)	.96
Aortic repair	2 (7.7)	4 (11.4)	.96
Right or left ventricle-to-pulmonary artery conduit	0 (0.0)	4 (11.4)	.21
Truncus or hemitruncus repair	0 (0.0)	2 (5.7)	.61
Other	4 (15.4)	13 (37.1)	.11

(Continued)

TABLE 1. Continued

Variable	Single-ventricle (n = 26)	Biventricular (n = 35)	*P* value
STAT category			**<.001**
0	1 (3.8)	3 (8.6)	
1	0 (0.0)	6 (17.1)	
2	5 (19.2)	9 (25.7)	
3	1 (3.8)	4 (11.4)	
4	6 (23.1)	13 (37.1)	
5	13 (50.0)	0 (0.0)	
No. of prior sternotomies	3.0 [3.0, 3.0]	2.0 [1.0, 3.5]	.08
Preoperatively intubated	1 (3.8)	1 (2.9)	1.00
Preoperative inotrope support	23 (88.5)	27 (77.1)	.42
Preoperative mechanical circulatory support	1 (3.8)	8 (22.9)	.09
Systemic ventricular assist device	1 (3.8)	4 (11.4)	.55
Intra-aortic balloon pump	0 (0.0)	3 (8.6)	.35
Extracorporeal membrane oxygenation	0 (0.0)	1 (2.9)	1.00
Preoperative hemodynamics			
Pulmonary capillary wedge pressure (mm Hg)	10.0 [8.5, 12.0]	17.0 [11.0, 28.0]	**<.01**
Pulmonary vascular resistance (Wood units)	1.9 [1.7, 3.5]	2.1 [1.4, 3.1]	.91
Baseline laboratory values			
Estimated glomerular filtration rate (mL/min/1.72 m^2)	60.0 [60.0, 60.0]	60.0 [57.0, 60.0]	.04
Creatinine (mg/dL)	0.8 [0.7, 0.9]	1.1 [0.9, 1.4]	**<.001**
Aspartate transaminase (U/L)	24.0 [19.0, 45.8]	22.0 [17.0, 29.5]	.08
Alanine transaminase (U/L)	22.0 [17.3, 31.5]	17.0 [14.0, 28.0]	.12
Alkaline phosphatase (U/L)	105.2 ± 75.2	78.0 ± 44.7	.08
Total bilirubin (mg/dL)	0.5 [0.2, 1.6]	0.5 [0.4, 1.1]	.67
Direct bilirubin (mg/dL)	0.2 [0.1, 0.7]	0.2 [0.1, 0.4]	.61
Albumin (g/dL)	3.6 [2.5, 4.2]	4.1 [3.9, 4.4]	**<.01**
Platelets ($\times 10^9$/L)	173.0 [133.0, 250.0]	185.0 [140.0, 218.0]	.86
Hemoglobin (g/dL)	12.3 ± 2.3	11.3 ± 2.2	.07
Functional status at listing			.84
Normal or good	8 (30.8)	9 (32.1)	
Moderately impaired	13 (50.0)	12 (42.9)	
Severely impaired	5 (19.2)	7 (25.0)	
Functional status at transplant			.57
Normal or good	3 (11.5)	2 (7.1)	
Moderately impaired	9 (34.6)	7 (25.0)	
Severely impaired	14 (53.8)	19 (67.9)	
Condition at transplant			.08
Hospitalized, in intensive care unit	9 (34.6)	22 (62.9)	
Hospitalized, not in intensive care unit	13 (50.0)	9 (25.7)	
Not hospitalized	4 (15.4)	4 (11.4)	
Predicted heart mass mismatch (%)	8.8 [–5.2, 35.5]	−1.7 [–10.5, 10.7]	.11
T-cell panel-reactive antibodies (%)	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	.52
B-cell panel-reactive antibodies (%)	0.0 [0.0, 8.0]	0.0 [0.0, 17.0]	.58
Panel-reactive antibodies >10% (%)	3 (14.3)	8 (27.6)	.44

Values in bold represent significant *P* values (<.05). *STAT,* Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery.

mortality (Table E3). These predictors remained independent risk factors in a multivariable model controlled for age at transplant (HLHS: HR, 12.1, 95% CI, 1.9-76.7, $P < .01$; prior systemic-to-pulmonary shunt: HR, 3.4, 95% CI, 1.1-10.5, $P = .03$; prior Norwood: HR, 8.0, 95% CI, 1.4-46.8, $P = .02$; Prior Fontan: HR, 4.4, 95% CI, 1.2-16.0, $P = .02$).

TABLE 2. Operative data

Variable	Single-ventricle (n = 26)	Biventricular (n = 35)	*P* value
Cardiopulmonary bypass time (min)	223.4 ± 65.3	187.4 ± 59.5	**.03**
Crossclamp time (min)	131.6 ± 39.0	99.1 ± 32.1	**<.01**
Allograft ischemic time (min)	229.5 ± 69.3	212.8 ± 79.3	.40
Concomitant procedure	23 (88.5)	16 (45.7)	**<.01**
Pulmonary artery plasty	22 (84.6)	6 (17.1)	**<.001**
Other arterial reconstruction	3 (11.5)	2 (5.7)	.73
Venous reconstruction	4 (15.4)	7 (20.0)	.90
Mechanical circulatory support insertion	0 (0.0)	3 (8.6)	.35
Mechanical circulatory support removal	1 (3.8)	5 (14.3)	.36
Tricuspid annuloplasty	0 (0.0)	3 (8.6)	.35
Xenograft closure of pericardium or peritoneum	0 (0.0)	3 (8.6)	.35
Intraoperative transfusion requirements			
Transfused packed red blood cells	15 (62.5)	27 (77.1)	.35
Packed red blood cells (U)	1.0 [0.0, 3.3]	2.0 [1.0, 4.0]	.18
Transfused fresh-frozen plasma	20 (80.0)	29 (82.9)	1.00
Fresh-frozen plasma (U)	2.0 [1.0, 4.0]	2.0 [1.0, 5.0]	.84
Transfused platelets	24 (96.0)	33 (94.3)	1.00
Platelets (U)	2.0 [1.0, 12.0]	3.0 [2.0, 6.0]	.96
Transfused cell saver	22 (91.7)	30 (85.7)	.78
Cell saver (mL)	725.0 [456.3, 1137.5]	500.0 [285.5, 750.0]	.19
Transfused cryoprecipitate	19 (79.2)	18 (51.4)	.06
Cryoprecipitate (U)	4.0 [1.0, 10.0]	0.0 [0.0, 2.0]	<.01

Values in bold represent significant *P* values (<.05).

DISCUSSION

In this single-institution investigation of heart transplant outcomes in patients with ACHD over a 15-year period (Figure 4), recipients with initial single-ventricle physiology experienced a more complicated early postoperative course than the biventricular group. Despite no differences in early mortality, patients with single ventricles had worse survival at 5 years post-transplant and more clinically significant rejection events. In revealing favorable outcomes in adults with biventricular CHD and highlighting key challenges in patients who undergo single-ventricle palliation, this study has several important implications for patient selection, management, and counseling in this complex cohort.

To our knowledge, this is the first study to describe outcomes after listing for OHT in patients with ACHD with a focus on preoperative circulation type. We show that at our institution, patients in the single-ventricle group were just as likely, if not more, to undergo transplantation 1 year after listing (61.1% ± 8.3% vs 48.9% ± 7.3%) and less likely to be delisted (11.1% ± 5.3% vs 16.3% ± 5.4%), indicating a rather robust approach to transplanting single ventricles. We also report a highly acceptable 1-year waitlist mortality rate (<5%) in both groups and show that patients with single ventricles delisted or declined for OHT had numerically superior survival 1 year thereafter (80.0% ± 17.9% vs 61.7% ± 15.8%, $P = .41$). Such findings speak to the importance of not only carefully selecting single-ventricle candidates for transplant at experienced centers but also recognizing that many patients with single ventricles who do not undergo OHT shortly after initial evaluation may still have relatively favorable survival in the short term.

Post-Transplant Survival

Although post-transplant survival in patients with ACHD with biventricular physiology is similar to that of non-ACHD recipients,[6] several studies have documented an association between single-ventricle circulation and increased mortality.[6,15,16] Karamlou and colleagues[6] used the 1993-2007 Nationwide Inpatient Sample to assess the effect of anatomy on early mortality, which was significantly greater in the single-ventricle group (23% vs 8%, $P < .001$). Likewise, in a 2009 analysis that combined 2 national registries to yield a cohort of 367 pediatric and 121 adult CHD recipients, long-term survival in Fontan patients was considerably lower (77% and 70% at 1 and 5 years) compared with non-Fontan (88% and 81% at 1 and 5 years), further underscoring the mortality risk conferred by single-ventricle status.[1] Most recently, Bakhtiyar and colleagues[8] conducted the largest-scale analysis to date by merging the Nationwide Inpatient Sample and Organ Procurement and Transplantation Network datasets, which revealed significantly reduced survival in single-ventricle patients at 1 (80% vs 91%; HR, 2.50; 95% CI, 1.40-4.49; $P = .002$) and 10 years (54% vs 71%; HR, 2.10; 95%

TABLE 3. Postoperative outcomes

Variable	Single-ventricle (n = 26)	Biventricular (n = 35)	*P* value
Vasoactive-inotropic score at intensive care unit arrival	7.2 [5.1, 19.3]	15.6 [7.5, 29.0]	.14
Intensive care unit length of stay (d)	15.5 [7.0, 28.0]	8.0 [5.5, 14.0]	**.045**
Postoperative hospital length of stay (d)	35.5 [25.5, 50.0]	25.0 [17.0, 39.5]	.08
Total hospital length of stay (d)	82.5 [57.5, 144.0]	68.0 [35.5, 121.5]	.34
Days to extubation	3.5 [2.0, 6.0]	1.0 [1.0, 2.0]	**<.001**
Days on inotropes postoperatively	11.0 [6.0, 15.3]	6.0 [6.0, 11.0]	.12
Days on mechanical circulatory support postoperatively	2.7 ± 2.1	6.0 ± 3.1	.07
In-hospital mortality	3 (11.5)	3 (8.6)	1.00
Postoperative complications			
Bleeding requiring chest exploration	4 (15.4)	5 (14.3)	1.00
Other unplanned surgical intervention	2 (7.7)	10 (28.6)	.09
Mediastinitis	0 (0.0)	1 (2.9)	1.00
Infection	7 (26.9)	10 (28.6)	1.00
Stroke	1 (3.8)	0 (0.0)	.88
New dialysis requirement	6 (23.1)	8 (22.9)	1.00
Acute kidney injury	13 (50.0)	13 (37.1)	.46
Postoperative mechanical circulatory support	5 (19.2)	6 (17.1)	1.00
Extracorporeal membrane oxygenation	5 (19.2)	3 (8.6)	.40
Left ventricular assist device	0 (0.0)	1 (2.9)	1.00
Right ventricular assist device	0 (0.0)	1 (2.9)	1.00
Intra-aortic balloon pump	0 (0.0)	3 (8.6)	.35

Values in bold represent significant *P* values (<.05).

CI, 1.38-3.18; $P < .001$). These studies have been critical in highlighting an important trend, although national datasets—even when merged—provide limited information regarding various diagnostic CHD categories, surgical history, and longitudinal follow-up.[6,8,16-18]

Examining granular institutional data allowed us to report on specific CHD diagnoses, prior operations, and palliation stages, making for the largest contemporary single-center analysis on the subject. With a 1-year survival of 84.6% and 91.3% in the single-ventricle and biventricular groups, respectively, early survival closely paralleled what recent national database analyses have documented, although Bakhtiyar and colleagues[8] did find this difference to be statistically significant. Of note, 1-year survival in the biventricular group was equivalent to that of non-CHD recipients nationally and considerably better at 5 years (biventricular ACHD: 91.3%, non-ACHD nationally: 79%) and 10 years (biventricular ACHD: 80.8%, non-ACHD nationally: 62.1%).[8] Furthermore, in our cohort, 10-year survival was higher in the biventricular group (single-ventricle: 58.7% vs biventricular: 80.8%, $P = .04$). Such findings support the idea that an underlying diagnosis of CHD is not necessarily a risk factor for post-transplant mortality; rather, the disadvantage is likely due to outcomes in single-ventricle recipients.[4,6]

Indeed, we found several markers of single-ventricle physiology[19] to be predictors of post-transplant mortality, namely, a diagnosis of HLHS, a prior systemic-to-pulmonary artery shunt, a prior Norwood operation, and Fontan circulation. Previously, in a 2011 single-center study, Jacobs and colleagues[2] observed the highest operative mortality (33%) in patients undergoing transplantation after operations for HLHS or HLHS-related malformations.[2] Bakhtiyar and colleagues[8] also noted that patients with HLHS had the worst survival outcomes at 1 and 5 years and faced persistently increased hazards of death up to 10 years post-transplantation. Next, we discuss several risk factors for poor outcomes in patients with palliated HLHS, although these findings suggest that continued efforts at optimizing patient selection and identifying the proper timing for transplantation will be critical to minimizing mortality in ACHD recipients.[20] As was our experience, some patients with ACHD with heart failure or failing Fontan circulation may not be listed for transplantation, which speaks to the importance of early referral, before the onset of multiorgan dysfunction.[9] In children with CHD, post-transplant survival has been correlated with pre-transplant operative stage, leading some to suggest that listing for transplant with a cavopulmonary shunt in place, rather than proceeding to Fontan circulation, may result in better outcomes.[21,22] Such a strategy is less applicable in the adult population, making careful surveillance of organ function during the childhood years and experience with complex anatomic repair essential to optimizing outcomes.[9]

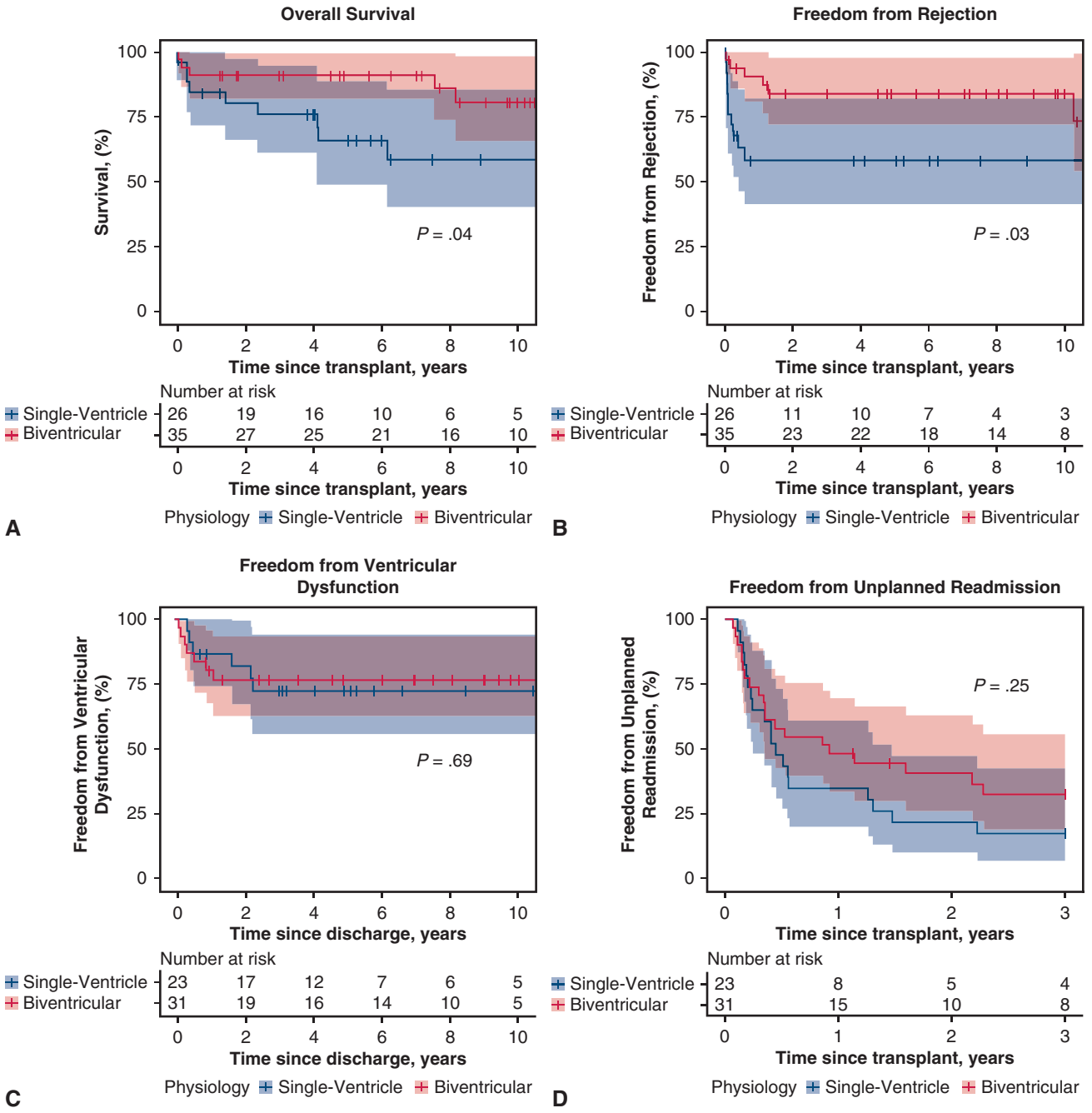

FIGURE 3. Kaplan–Meier plots of (A) overall survival, freedom from (B) rejection, (C) moderate or greater ventricular dysfunction, and (D) unplanned hospital readmission after heart transplantation stratified by physiology at time of transplant. Numbers of patients at risk are included in the lower panel. Shaded 95% CIs are shown.

Ultimately, though, overall patient status is likely a more significant predictor of outcomes than specific defect or stage of palliation.[5,23]

Secondary End Points

Secondary outcomes in this study included those in the immediate postoperative period, which are largely due to surgical risk.[4] Reassuringly, operative mortality was not significantly different between groups (single-ventricle: 11.5% vs biventricular: 8.6%, $P = 1.00$) and decreased over time, from 14.8% in the first 7 years of the study (2008-2014) to 5.9% in the years spanning 2015 through 2022. Still, single-ventricle patients had a more complicated post-transplant course, with more days on mechanical ventilatory support and longer stays in the intensive care unit.

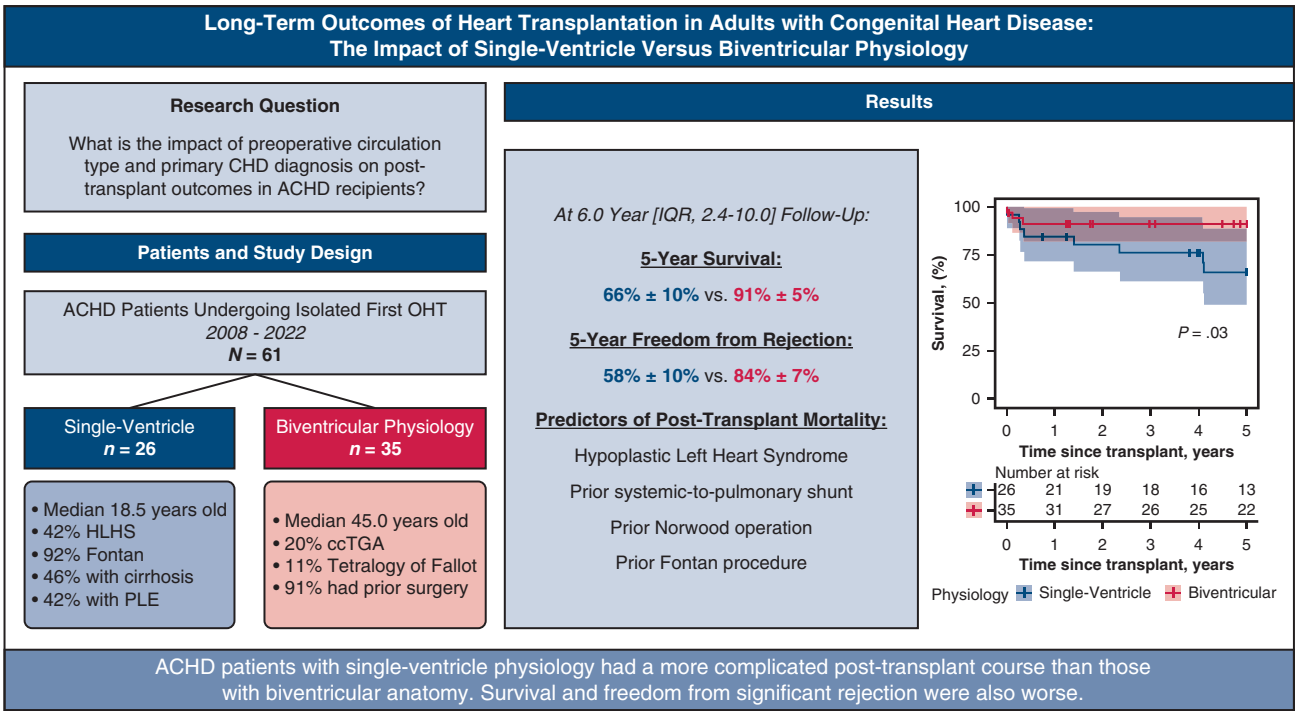

FIGURE 4. Visual summary of study design and key findings. *ACHD*, Adult congenital heart disease; *OHT*, orthotopic heart transplantation; *HLHS*, hypoplastic left heart syndrome; *PLE*, protein-losing enteropathy; *ccTGA*, congenitally corrected transposition of the great arteries; *IQR*, interquartile range.

Several factors contributed to an elevated perioperative risk profile in single-ventricle patients. First, end-organ dysfunction associated with failing Fontan circulation was present in nearly half of the group. Next, with more prior sternotomies (3 vs 2), the hazards of yet another redo sternotomy, adhesiolysis, and greater anatomic complexity increase.[5,6,8] Likewise, in our cohort, most patients (n = 24, 92.3%) in the single-ventricle group underwent a concomitant reconstructive procedure and consequently had longer cardiopulmonary bypass and crossclamp times, which not only are surrogates for a more complex operation that have independently been associated with inferior outcomes[3] but also increase the risk of infection and potentiate coagulopathy.[3,6] We did see a significantly greater cryoprecipitate transfusion requirement in the single-ventricle group (4 vs 0 units, $P < .01$), although it is difficult to attribute this finding to differences in baseline liver function or postbypass coagulopathy. Notably, we identified higher serum bilirubin levels to be a risk factor for operative mortality, which not only suggests some degree of hepatic involvement but also has been correlated with an increased risk of postoperative bleeding, surgical reexploration, and prolonged intensive care stays.[8,24] In select patients, a heart-liver transplant may be necessary and provide superior outcomes to heart-alone transplantation.[4,25]

Finally, previous studies have shown considerable allosensitization in patients with ACHD, which increases the risk of rejection, poor graft survival, and mortality.[3,26] Of all ACHD recipients, those with palliated HLHS are believed to be the most sensitized,[5,6] and this has been associated with prolonged waitlist times, higher waitlist mortality, and a higher incidence of rejection in this population.[5] In our study, single-ventricle patients similarly had considerably worse 1-year (58.3% ± 10.2% vs 90.6% ± 5.2%, $P < .01$) and 5-year freedom (58.3% ± 10.2% vs 84.0% ± 6.6%, $P = .02$) from major rejection events. Because there was no significant difference in pretransplant panel-reactive antibody titers or rates of sensitization between study groups, the factors driving the increased rate of rejection in the single-ventricle cohort warrant further investigation. Still, given the multiple surgeries that palliated HLHS patients undergo, this finding speaks to the importance of minimizing exposure to exogenous blood products and homograft tissue used for vascular reconstructions before transplantation, as well as to the critical need for proper immunosuppression post-transplant with perhaps a more aggressive approach in single-ventricle patients. At

our institution, heart transplant recipients are routinely discharged on a maintenance regimen of tacrolimus, mycophenolate mofetil, and prednisone. In cases of mycophenolate intolerance, azathioprine or everolimus is substituted. Prednisone is weaned 6 to 9 months post-transplant if there is no evidence of rejection or otherwise compromised graft function. When indicated, combined heart-liver transplantation may also improve graft tolerance.[27]

Study Limitations

This study is subject to the inherent limitations of a retrospective, single-center analysis. Patient referral, listing, and management strategies vary by institution, and although our practices are described in this study and in prior publications,[28] reporting on a relatively small sample size limits power and generalizability. Larger studies with numerically similar mortality rates have documented a significant difference in survival between the 2 groups, and our univariable Cox analysis revealed key markers of single-ventricle circulation to be predictive of postmortality; lack of a difference ($P \geq .5$) in long-term survival is likely the result of a type II error. Likewise, many patients in the biventricular cohort had relatively straightforward CHD lesions, with the majority falling into Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery Categories 0 through 3, which may explain why outcomes were similar to those of patients without CHD. Because the anatomic complexity of patients at each transplant center varies considerably, this may further limit the generalizability of our findings. Any prognostic indices must be interpreted in this context. Multicenter studies that can provide granular data and increase the power of such analyses are warranted.

CONCLUSIONS

Among ACHD heart transplant recipients, patients with single-ventricle physiology experienced a more complicated early postoperative course than those with biventricular circulation. Freedom from major rejection and 5-year post-transplant survival were worse in patients with single-ventricle physiology, and an original diagnosis of HLHS, a prior Norwood operation, a prior systemic-to-pulmonary shunt, and Fontan circulation were significant predictors of post-transplant mortality. Ultimately, our study highlights the favorable heart transplantation outcomes in adults with biventricular CHD and underscores several major challenges in patients who undergo Fontan palliation. Multicenter studies are required to guide clinical decision-making in this complex cohort. The role of combined heart-liver transplantation should be further delineated to improve outcomes in this subset of patients.

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: adult congenital heart disease, biventricular, Fontan palliation, heart transplantation, single-ventricle

TABLE E1. Clinical summary of early mortalities

Age at transplant	CHD details	Group	Previous cardiac surgeries	Concomitant procedures	Notable intraoperative details	Takebacks	Postoperative course
53.7 years	Heterotaxy with single ventricle dextrocardia, common atrioventricular valve, common atrium, bilateral SVC, TAPVR	Single-ventricle	• Left BTT shunt • Right cavopulmonary shunt • Fontan	Rerouting of TAPVR, PA plasty	Vasoplegia requiring methylene blue	Reexploration after arrest on POD 1	Cardiac tamponade Bedside chest reopening ECMO Disseminated intravascular coagulation **Death on POD 1**
54.8 years	Atrial septal defect	Biventricular	• Atrial septal defect closure, mitral valve repair	Xenograft pericardial closure	RA injury on entry requiring femoral CPB, profound coagulopathy	-	New dialysis requirement Liver failure Septic shock **Death on POD 6**
50.0 years	Double-outlet right ventricle, ventricular septal defect, pulmonary atresia	Biventricular	• Ventricular septal defect closure, RV-PA conduit • Conduit revision ×2	-	High shunt fraction, significant hypotension, lactic acidosis with high pressor and inotrope requirement	-	Liver failure due to hepatitis New dialysis requirement ECMO Sepsis **Death on POD 40**
46.3 years	Double-inlet left ventricle, mitral atresia	Single-ventricle	• PA band, BTT shunt • Fontan • Sub-AS resection • Bioprosthetic AVR	-	Significant bleeding	TVR on POD 42	Early graft dysfunction (flail tricuspid valve) New dialysis requirement Bacteremia, pneumonia Stroke Cardiogenic shock ECMO **Death on POD 96**
17.3 years	Hypoplastic left heart syndrome	Single-ventricle	• Norwood • Bidirectional Glenn • Fontan	PA plasty, coarctation and aortic arch aneurysm repair	Difficult dissection, significant bleeding, DHCA	Several chest reexplorations for bleeding and clotting	Pneumonia New dialysis requirement Multisystem organ failure **Death on POD 97**
55.9 years	Tetralogy of Fallot	Biventricular	• Ventricular septal defect repair ×2 • TVR × 2	Tricuspid valve annuloplasty, SVC reconstruction	LV dysfunction requiring ECMO	Reexploration POD 0 for mediastinal bleeding	Spinal cord infarction Pneumonia Gastrointestinal bleed New dialysis requirement ECMO **Death on POD 123**

SVC, Superior vena cava; *TAPVR*, total anomalous pulmonary venous return; *BTT*, Blalock-Taussig-Thomas; *PA*, pulmonary artery; *POD*, postoperative day; *ECMO*, extracorporeal membrane oxygenation; *RA*, right atrial; *CPB*, cardiopulmonary bypass; *RV*, right ventricle; *AS*, aortic stenosis; *AVR*, aortic valve replacement; *TVR*, tricuspid valve replacement; *DHCA*, deep hypothermic circulatory arrest; *LV*, left ventricular.

TABLE E2. Univariable logistic regression results

Univariable logistic regression				
Variable	Coefficient	Lower limit, 95% CI	Upper limit, 95% CI	*P* value
Age at transplant (y)	0.07	0.00	0.15	.06
Male	−1.17	−3.21	0.54	.20
Body mass index (kg/m^2)	−0.01	−0.19	0.13	.93
Aortic coarctation	−14.37	NA	474.30	1.00
Atrial septal defect	−15.39	NA	422.54	1.00
Atrioventricular septal defect	0.94	−2.13	3.10	.44
Congenital aortic stenosis	−15.39	NA	422.54	1.00
Congenital pulmonic stenosis	−14.37	NA	474.30	1.00
Coronary artery anomaly	−14.37	NA	474.30	1.00
Double-chambered right ventricle	−14.37	NA	474.30	1.00
Double-inlet left ventricle	1.24	−1.86	3.52	.32
Double-outlet right ventricle	1.24	−1.86	3.52	.32
Ebstein's anomaly	−15.41	NA	281.11	.99
Hypertrophic cardiomyopathy (Noonan syndrome)	−14.37	NA	474.30	1.00
Hypoplastic left heart syndrome	−0.11	−3.11	1.86	.93
Pulmonary atresia with intact ventricular septum	−15.39	NA	422.54	1.00
Dextro-transposition of the great arteries	−15.43	NA	209.53	.99
Congenitally corrected transposition of the great arteries	−16.51	NA	213.62	.99
Tetralogy of Fallot	1.24	−1.86	3.52	.32
Tricuspid atresia	−15.41	NA	281.11	.99
Truncus arteriosus	−14.37	NA	474.30	1.00
Ventricular septal defect	−15.39	NA	422.54	1.00
Prior cardiac surgery	15.43	−209.53	NA	.99
Systemic-pulmonary shunt	1.25	−0.47	3.29	.17
Norwood or Damus-Kaye-Stansel procedure	−0.33	−3.34	1.62	.77
Bidirectional cavopulmonary shunt or Hemi-Fontan	−0.05	−2.09	1.67	.95
Atrial septal defect closure	0.49	−2.55	2.54	.68
Ventricular septal defect closure	0.94	−1.14	2.73	.32
Pulmonary artery banding	0.49	−2.55	2.54	.68
Mitral valve repair or replacement	0.16	−2.86	2.16	.89
Tricuspid valve repair or replacement	0.32	−2.71	2.34	.79
Aortic valve repair or replacement	0.69	−2.36	2.79	.56
Aortic repair	−16.47	NA	190.19	1.00
Ventricle-to-pulmonary artery conduit	1.24	−1.86	3.52	.32
Truncus or Hemitruncus repair	−15.39	NA	422.54	1.00
Other prior cardiac surgery	−0.53	−3.53	1.40	.64
No. of prior sternotomies	0.31	−0.30	1.00	.33
Pulmonary valve replacement	0.49	−2.55	2.54	.68
Fontan	0.48	−1.28	2.25	.58
Single-ventricle	0.33	−1.43	2.09	.70
Hypertension	0.32	−2.71	2.34	.79
Diabetes	1.67	−1.50	4.19	.20
History of tobacco use	−16.60	NA	171.09	.99

(Continued)

TABLE E2. Continued

	Univariable logistic regression			
Variable	**Coefficient**	**Lower limit, 95% CI**	**Upper limit, 95% CI**	***P* value**
Cardiac arrhythmia	0.11	−1.86	3.11	.93
Atrial flutter or atrial fibrillation	0.48	−1.28	2.25	.58
Pacemaker or automated implantable cardiac defibrillator	−0.64	−2.41	1.13	.46
Stroke or transient ischemic attack	0.58	−1.48	2.34	.53
Biopsy-proven cirrhosis	1.07	−0.71	2.86	.22
Ascites	1.67	−0.06	3.72	.07
Protein-losing enteropathy	−0.22	−3.23	1.73	.85
Pulmonary capillary wedge pressure (mm Hg)	−0.06	−0.23	0.07	.43
Pulmonary vascular resistance (WU)	−1.17	−3.06	0.00	.12
Preoperative mechanical circulatory support	−16.53	NA	200.38	.99
Extracorporeal membrane oxygenation	−14.37	NA	474.30	1.00
Systemic ventricular assist device	−16.45	NA	282.28	1.00
Intra-aortic balloon pump	−15.41	NA	281.11	.99
Intubated preoperatively	−14.37	NA	474.30	1.00
Preoperative inotrope support	16.57	−179.52	NA	.99
Predicted heart mass mismatch (%)	−0.00	−0.05	0.04	.97
Estimated glomerular filtration rate (mL/min/1.72 m^2)	−0.01	−0.10	0.07	.81
Creatinine (mg/dL)	−0.76	−3.69	1.40	.55
Aspartate transaminase (U/L)	0.01	−0.00	0.03	.08
Alanine transaminase (U/L)	0.02	−0.04	0.07	.43
Alkaline phosphatase (U/L)	0.01	−0.01	0.02	.23
Total bilirubin (mg/dL)	0.72	0.06	1.45	**.03**
Direct bilirubin (mg/dL)	1.63	0.23	3.47	**.04**
Albumin (g/dL)	−0.05	−1.11	1.16	.92
Platelets ($\times 10^9$/L)	−0.02	−0.04	−0.00	.07
Hemoglobin (g/dL)	−0.00	−0.40	0.37	.99
T-cell panel-reactive antibodies (%)	−1.81	NA	51.92	1.00
B-cell panel-reactive antibodies (%)	−0.01	−0.15	0.06	.89
Panel-reactive antibodies >10% (%)	0.62	−2.51	3.06	.63
Cardiopulmonary bypass time (min)	0.01	−0.00	0.02	.09
Crossclamp time (min)	0.01	−0.01	0.03	.40
Allograft ischemic time (min)	0.01	0.00	0.03	**.04**
Concomitant procedure	0.13	−1.59	2.17	.88
Transplant in 2015-2022	0.13	−3.16	3.41	.93

Values in bold represent significant *P* values (<.05). *NA,* Not available; *WU,* wood units.

TABLE E3. Univariable Cox modeling results

Univariable Cox modeling					
Variable	Coefficient	Hazard ratio	Lower limit, 95% CI	Upper limit, 95% CI	*P* value
Age at transplant (y)	−0.01	0.99	0.95	1.03	.58
Male	0.16	1.17	0.39	3.49	.78
Body mass index (kg/m^2)	−0.08	0.92	0.81	1.04	.20
Aortic coarctation	1.30	3.67	0.47	28.45	.21
Atrial septal defect	−17.09	0.00	0.00	Inf	1.00
Atrioventricular septal defect	0.28	1.33	0.17	10.40	.79
Congenital aortic stenosis	−17.08	0.00	0.00	Inf	1.00
Congenital pulmonic stenosis	−17.04	0.00	0.00	Inf	1.00
Coronary artery anomaly	−16.04	0.00	0.00	Inf	1.00
Double-chambered right ventricle	−16.04	0.00	0.00	Inf	1.00
Double-inlet left ventricle	0.11	1.12	0.15	8.59	.91
Double-outlet right ventricle	0.91	2.47	0.55	11.09	.24
Ebstein's anomaly	−17.07	0.00	0.00	Inf	1.00
Hypertrophic cardiomyopathy (Noonan syndrome)	−17.04	0.00	0.00	Inf	1.00
Heterotaxy	NA	NA	NA	NA	NA
Hypoplastic left heart syndrome	1.61	5.01	1.67	15.04	**<.001**
Pulmonary atresia with intact ventricular septum	−17.09	0.00	0.00	Inf	1.00
Dextro-transposition of the great arteries	−18.16	0.00	0.00	Inf	1.00
Congenitally corrected transposition of the great arteries	−0.58	0.56	0.07	4.29	.58
Tetralogy of Fallot	−0.11	0.89	0.12	6.86	.91
Tricuspid atresia	−17.08	0.00	0.00	Inf	1.00
Truncus arteriosus	−17.04	0.00	0.00	Inf	1.00
Ventricular septal defect	−17.07	0.00	0.00	Inf	1.00
Prior cardiac surgery	18.11	7.34E7	0.00	Inf	1.00
Systemic-pulmonary shunt	1.22	3.37	1.12	10.11	**.03**
Norwood or Damus-Kaye-Stansel procedure	1.37	3.94	1.31	11.90	**.01**
Bidirectional cavopulmonary shunt or Hemi-Fontan	0.91	2.48	0.85	7.23	.10
Atrial septal defect closure	−0.36	0.70	0.09	5.34	.73
Ventricular septal defect closure	−0.43	0.65	0.15	2.92	.58
Pulmonary artery banding	0.27	1.31	0.29	5.86	.73
Mitral valve repair or replacement	−0.06	0.94	0.21	4.22	.94
Tricuspid valve repair or replacement	−0.61	0.54	0.07	4.16	.56
Aortic valve repair or replacement	−0.53	0.59	0.08	4.52	.61
Aortic repair	0.18	1.20	0.27	5.38	.81
Ventricle-to-pulmonary artery conduit	0.03	1.03	0.13	7.92	.97
Truncus or hemitruncus repair	−17.09	0.00	0.00	Inf	1.00
Other prior cardiac surgery	−0.97	0.38	0.08	1.69	.20
No. of prior sternotomies	0.16	1.17	0.81	1.69	.40
Pulmonary valve replacement	−0.82	0.44	0.06	3.40	.43
Fontan	1.24	3.47	1.15	10.49	**.03**
Single-ventricle	1.08	2.96	0.98	8.91	.05
Hypertension	−0.82	0.44	0.06	3.38	.43
Diabetes	0.54	1.71	0.22	13.11	.61

(Continued)

TABLE E3. Continued

Univariable Cox modeling					
Variable	**Coefficient**	**Hazard ratio**	**Lower limit, 95% CI**	**Upper limit, 95% CI**	***P* value**
History of tobacco use	−0.55	0.57	0.13	2.57	.47
Cardiac arrhythmia	−0.32	0.73	0.20	2.63	.63
Atrial flutter or atrial fibrillation	−1.01	0.37	0.10	1.32	.12
Pacemaker or automated implantable cardiac defibrillator	−1.13	0.32	0.11	0.94	**.04**
Stroke or transient ischemic attack	0.44	1.56	0.49	4.97	.45
Biopsy-proven cirrhosis	0.76	2.14	0.74	6.19	.16
Ascites	0.53	1.69	0.59	4.89	.33
Protein-losing enteropathy	0.87	2.39	0.80	7.15	.12
Pulmonary capillary wedge pressure (mm Hg)	−0.07	0.93	0.86	1.01	.09
Pulmonary vascular resistance (WU)	−0.94	0.39	0.13	1.18	.09
Preoperative mechanical circulatory support	−0.96	0.38	0.05	2.92	.35
Extracorporeal membrane oxygenation	−17.04	0.00	0.00	Inf	1.00
Systemic ventricular assist device	−0.39	0.68	0.09	5.20	.71
Intra-aortic balloon pump	−17.08	0.00	0.00	Inf	1.00
Intubated preoperatively	0.73	2.08	0.27	15.92	.48
Preoperative inotrope support	19.34	2.52E8	0.00	Inf	1.00
Predicted heart mass mismatch (%)	0.01	1.01	0.99	1.03	.21
Estimated glomerular filtration rate (mL/min/1.72 m^2)	0.01	1.01	0.95	1.07	.69
Creatinine (mg/dL)	−2.06	0.13	0.02	0.82	**.03**
Aspartate transaminase (U/L)	0.01	1.01	1.00	1.02	**.02**
Alanine transaminase (U/L)	0.03	1.03	1.00	1.06	.06
Alkaline phosphatase (U/L)	0.00	1.00	1.00	1.01	.37
Total bilirubin (mg/dL)	0.34	1.41	0.90	2.20	.13
Direct bilirubin (mg/dL)	0.92	2.52	1.03	6.17	**.04**
Albumin (g/dL)	−0.50	0.60	0.32	1.14	.12
Platelets ($\times 10^9$/L)	−0.00	1.00	0.99	1.01	.61
Hemoglobin (g/dL)	0.07	1.07	0.84	1.36	.60
T-cell panel-reactive antibodies (%)	−1.96	0.14	0.00	Inf	1.00
B-cell panel-reactive antibodies (%)	−0.00	1.00	0.96	1.03	.87
Panel-reactive antibodies >10% (%)	0.15	1.16	0.31	4.38	.83
Cardiopulmonary bypass time (min)	0.01	1.01	1.00	1.02	**.01**
Crossclamp time (min)	0.01	1.01	1.00	1.03	.13
Allograft ischemic time (min)	0.01	1.01	1.00	1.02	**<.001**
Concomitant procedure	0.76	2.13	0.59	7.64	.25
Transplant in 2015-2022	1.81	6.13	0.71	52.75	.10

Values in bold represent significant *P* values (<.05). *NA,* Not available; *WU,* wood units.