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Survival After Cardiac Transplantation in Adults With Single-Ventricle Congenital Heart Disease

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ABSTRACT

BACKGROUND Without large-scale analyses of adults with single-ventricle congenital heart disease (CHD) undergoing heart transplantation, little evidence exists to guide listing practices and patient counseling.

OBJECTIVES This study aims to evaluate survival after heart transplantation in adults with single and biventricular CHD and compare it to that of non-CHD transplant recipients.

METHODS In this 15-year (2005-2020) retrospective analysis, outcome-blinded investigators used probability-linkage to merge the National (Nationwide) Inpatient Sample and Organ Procurement and Transplantation Network data sets.

RESULTS Of 382 adult (≥18 years of age) heart transplant recipients with CHD, 185 (48%) had single-ventricle physiology. Compared to biventricular CHD, single-ventricle patients showed significantly reduced survival at 1 (80% vs 91%; HR: 2.50; 95% CI: 1.40-4.49; $P = 0.002$) and 10 years (54% vs 71%; HR: 2.10; 95% CI: 1.38-3.18; $P < 0.001$). Among patients who survived the first post-transplantation year, biventricular CHD patients exhibited similar 10-year survival as single-ventricle patients, except for those with hypoplastic left heart syndrome (79% vs 71%; HR: 1.58; 95% CI: 0.85-2.92; $P = 0.15$). Additionally, biventricular CHD transplant recipients showed significantly better 10-year conditional survival compared to their non-CHD counterparts (79% vs 68%; HR: 0.73; 95% CI: 0.59-0.90; $P = 0.003$).

CONCLUSIONS Among adult CHD transplant recipients, single-ventricle physiology correlated with higher short-term mortality. However, 10-year conditional survival was similar for biventricular and most single-ventricle CHD patients, and notably better for biventricular CHD patients compared to non-CHD heart transplant recipients. These findings have significant implications towards patient selection and listing strategies, easing concerns related to heart transplantation in adults with CHD and destigmatizing most subtypes of single-ventricle CHD.
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At present, there are 1.4 million adults living with congenital heart disease (CHD) in the United States.[1] With more than 40,000 infants born with CHD each year, 95% of whom are predicted to reach adulthood, the prevalence of adults with CHD is expected to steadily increase.[2] Although this is encouraging, approximately 20% of all CHD patients develop heart failure as a long-term consequence of palliative operations and ultimately require heart transplantation.[3] Compared to

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non-CHD adults undergoing heart transplantation, patients with CHD, particularly those with single-ventricle physiology, are thought to have the highest risk profile. This heightened risk is attributed to their complex baseline anatomy, prior surgical history, and, in the case of single-ventricle lesions, the sequelae of staged palliation and Fontan physiology.[4] These unique anatomical and physiological characteristics present a challenging clinical scenario for transplantation surgeons.

Despite the wide availability of transplantation data since 1987, outcomes of single-ventricle CHD patients remain largely unknown. Prior studies have faced significant methodologic constraints and limitations.[5] Specifically, transplantation outcomes across the spectrum of CHD have not been examined at the large scale due to the lack of granular diagnostic codes in national databases such as the Organ Procurement and Transplantation Network (OPTN) registry.[6,7] As such, only a handful of single-center reports are available to guide the management of single-ventricle CHD patients undergoing heart transplantation. However, these studies remain limited by small sample size and cannot accurately define generalizable prognostic indices for short- or long-term survival.[8,9] Identification of such benchmarks is crucial for more accurate risk stratification and could dramatically shape patient selection, listing practices, waitlist status decisions, and patient counseling in this heterogeneous group.[3]

In the present work, we used probability linkage to merge 2 national data sets and leverage their unique advantages to conduct the first large-scale analysis of post-transplantation outcomes in adults with single-ventricle CHD. We hypothesized that among various CHD types, single-ventricle patients would face higher mortality and significantly inferior outcomes after heart transplantation.

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METHODS

DATA SOURCE. This study used the OPTN database and the National/Nationwide Inpatient Sample (NIS). The OPTN data system includes data on all donors, wait-listed candidates, and transplant recipients in the United States submitted by the members of the OPTN. The Health Resources and Services Administration, U.S. Department of Health and Human Services, provides oversight of the activities of the OPTN contractor. Likewise, the National (Nationwide) Inpatient Sample (NIS) is the largest publicly available all-payer inpatient database in the United States and provides accurate estimates for 97% of all U.S. hospitalizations.[10]

Given the nature of comprehensive transplantation records within the OPTN registry and the extensively validated representativeness of the NIS, both databases contained sufficient variables and data points to allow simultaneous comparison and subsequent merging of individual records. Detailed information regarding the type of CHD was extracted from the NIS, and the OPTN database was used for analyzing recipient characteristics and post-transplantation outcomes. As both data sets contain de-identified information, the study was deemed exempt from full review by the Institutional Review Board at the University of California, Los Angeles.

STUDY POPULATION AND TIMEFRAME. All adult (≥18 years of age) CHD heart transplantation recipients between January 2005 and December 2020 with follow-up through June 2022 were included. In the OPTN database, patients with CHD were tabulated using the data dictionary. Within the NIS, heart transplant recipients with CHD were identified using International Classification of Diseases, 9th and 10th Revision codes (Supplemental Table 1). Patients undergoing multiorgan transplantation, cardiac retransplantation, or missing key clinical information were excluded. Those with a diagnosis of hypoplastic left heart syndrome (HLHS), tricuspid atresia, pulmonary atresia, double inlet ventricle, double outlet ventricle (except for tetralogy of Fallot and transposition of the great arteries), and Ebstein's anomaly were considered single-ventricle physiology, as described by the American Heart Association and the National Institutes of Health.[11,12] However, the type and extent of surgical palliation, as well as the decision between palliation and heart transplantation, have long been contentious topics for certain subtypes of CHD. Notably, double outlet right ventricles with noncommitted ventricular septal defects may be repaired using a single or biventricular approach in children.[13] Similarly, although severe cases of Ebstein's anomaly may warrant a Fontan procedure with right ventricle exclusion, most patients undergo biventricular repair or heart transplantation as children.[14] While incorporating the American Heart Association and National Institutes of Health definitions of single-ventricle CHD in our primary analysis for consistency, we also conducted individual examination of specific subtypes of single-ventricle lesions.

PROBABILITY LINKAGE. Three independent investigators linked records between the data sets using a probability linkage algorithm (**Figure 1**). Briefly,

ABBREVIATIONS AND ACRONYMS

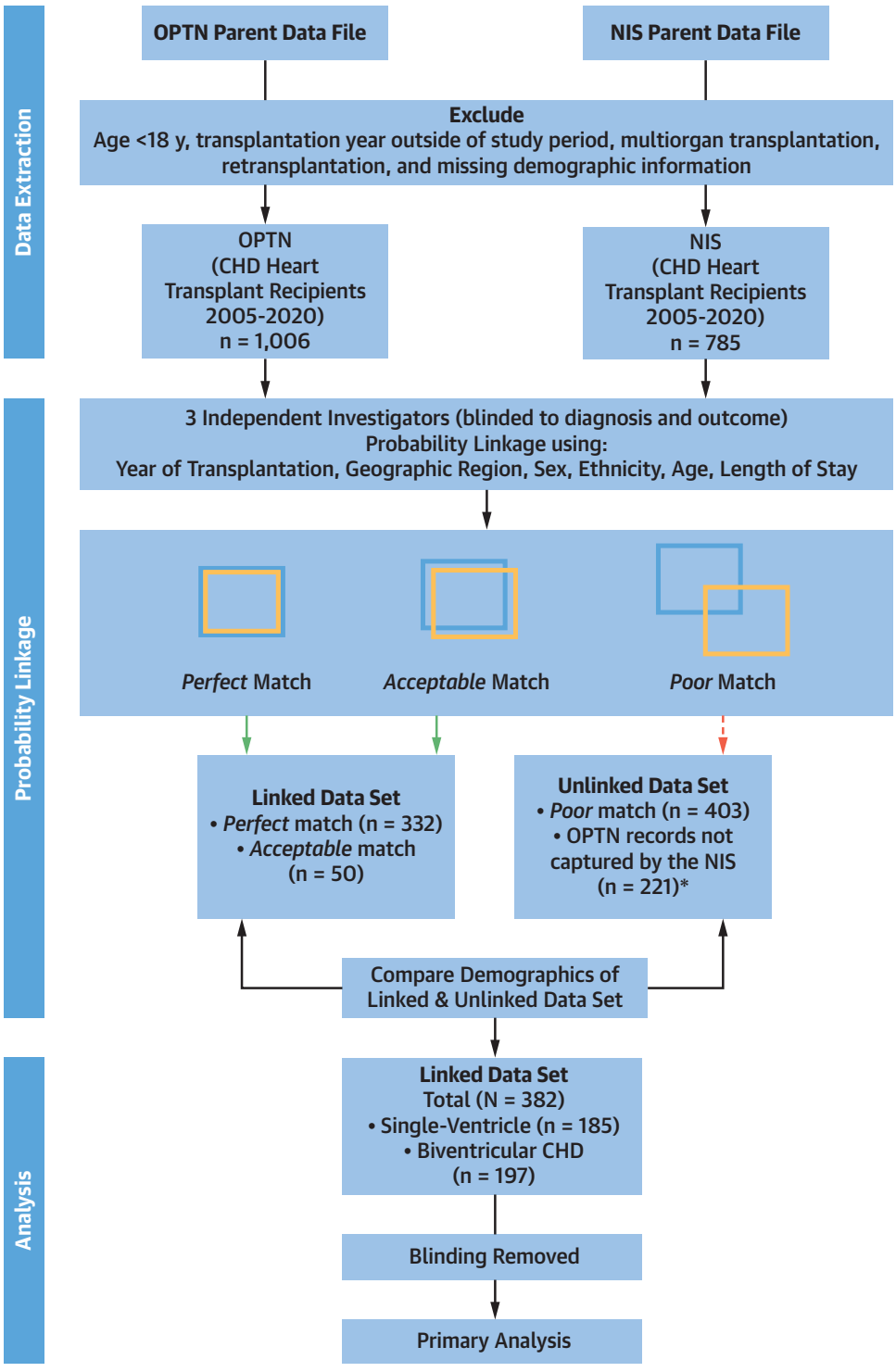
CHD = congenital heart disease

HLHS = hypoplastic left heart syndrome

NIS = national/nationwide inpatient sample

OPTN = Organ Procurement and Transplantation Network

FIGURE 1 **Probability Linkage Algorithm for Merging the OPTN and NIS Data Sets**



Data were extracted separately from the Organ Procurement and Transplantation Network (OPTN) and National (Nationwide) Inpatient Sample (NIS). Records with 6 of 6 ("perfect") and 5 of 6 ("acceptable") variables matching were linked. Records with <5 variables matching, multiple potential matches, or interinvestigator disagreement were considered a "poor" match and not linked. *Because of the sampling methodology of the NIS, the total volume of transplants captured by the NIS was expected to be fewer than the OPTN. CHD = congenital heart disease.

records were matched based on the degree of similarity between multiple predetermined variables and indirect patient identifiers.[15] Investigators were blinded to CHD subtype (NIS) and post-transplantation outcomes (OPTN) to reduce potential bias in the linkage process. In the first stage of linkage, individual records were compared using year of transplantation, geographic region, sex, ethnicity, age, and length of stay. Those with 6 of 6 matching variables were considered a "perfect" match and linked. The second stage of the linkage process accounted for differences in sampling and reporting methodologies between data sets and allowed inconsistencies in age and length of stay. Therefore, records with 5 of 6 matching variables were considered an "acceptable" match and linked. Those with fewer than 5 variables matching, multiple potential matches, or inter-investigator disagreement were considered a "poor" match and not linked. Records with a poor match were excluded from the primary analysis but included in our sampling validation and subsequent sensitivity analysis to evaluate for selection bias.

SAMPLING VALIDATION. Because of the sampling methodology of the NIS, the total volume of transplants captured by the NIS was expected to be fewer than the OPTN data set. However, before probability linkage, we evaluated the congruency in adult CHD transplantation trends between data sets. Further, we compared the baseline characteristics of our linked data set to unlinked records in the parent OPTN (Supplemental Table 2) and NIS (Supplemental Table 3) registries. Any differences between cohorts were then included in our sensitivity analysis, outlined below. Additionally, we compared survival outcomes of the linked cohort of adult CHD heart transplant recipients to unlinked records in the OPTN data set (Supplemental Figure 2).

STUDY OUTCOMES. The primary outcome was post-transplantation survival, defined as the interval from transplantation to death. Patients alive on June 30, 2022, were censored at the date of last known follow-up. Postoperative complications were secondarily assessed. Survival outcomes were compared between single and biventricular CHD patients as well as between CHD patients and non-CHD heart transplant recipients.

STATISTICAL ANALYSIS. Continuous variables are reported as mean ± SD if normally distributed, or median (IQR) if not. Categorical data are presented as n (%). Pearson's chi-square, Mann-Whitney U test, and 2-sided Student's *t*-tests were used to compare variables, as appropriate. The Healthcare Cost and Utilization Project prohibits reporting of NIS data relating to <11 observations. As such, results based solely on the NIS database with <11 observations have been masked.

To account for measured confounders, regression models adjusted for donor, recipient, and perioperative characteristics. All clinically relevant variables had 100% data completion; thus, multiple imputation was not used. Least absolute shrinkage and selection operator (LASSO) regularization was used to admit covariates into the models. LASSO offers penalized variable selection to increase out-of-sample validity and reduce overfitting.[16] Selected variables are reported in **Table 1**. Kaplan-Meier estimates were generated and graphically represented as survival curves for single and biventricular CHD as well as for non-CHD heart transplant recipients. Additionally, Cox proportional hazards models were used to calculate estimates of the risk-adjusted HRs for each group. Model reliability was assessed using Cox-Snell residuals (Supplemental Figure 1). We also performed restricted mean survival time (RMST) analysis to compare long-term outcomes between cohorts. Briefly, RMST is the average duration of freedom from death at 10 years, with mean absolute difference in survival time between the 2 groups considered the ΔRMST.[17]

We did not correct for multiplicity when evaluating associations. Therefore, results are presented as point estimates with 95% CIs unless specified, and generalizable conclusions should not be inferred from the widths of the intervals. For all analyses, $P < 0.05$ was considered statistically significant. All statistical tests were performed using Stata version 16.

SENSITIVITY ANALYSES. We repeated our analysis only among records with a perfect match to examine potential selection bias. Additionally, demographic and clinical variables that differed between the 2 data sets were then used to generate subgroups in our study population and included in our second sensitivity analysis. Subsequently, we estimated the HR associated with a diagnosis of single-ventricle CHD within each of these subgroups (Supplemental Table 4).

RESULTS

Overall, the number of adult CHD transplantations increased from 50 in 2005 to 119 in 2020 in the OPTN, and 34 in 2005 to 94 in 2020 in the NIS (P for trend <0.001). As shown in **Figure 2**, the transplantation trend between data sets was congruent.

TABLE 1 Demographic and Clinical Characteristics of Recipients and Donors

	Single-Ventricle CHD (n = 185, 48%)	Biventricular CHD (n = 197, 52%)	*P* Value
Recipient characteristics			
Days on the waitlist	100 (31-297)	100 (33-219)	0.67[a]
Age at listing, y[b]	36 (24-49)	38 (29-50)	0.09[a]
Sex[b]			
Female	80 (43)	66 (34)	0.05[c]
Male	105 (57)	131 (67)	0.05[c]
BMI, kg/m^2	25.97 ± 5.30	25.45 ± 4.95	0.33[d]
Race/ethnicity[b]			
Black	19 (10)	18 (9)	0.71[c]
Hispanic	20 (11)	17 (9)	0.47[c]
White	136 (74)	152 (77)	0.41[c]
Other	10 (5)	10 (5)	0.89[c]
Blood group			
A	69 (37)	83 (42)	0.34[c]
AB	9 (5)	9 (5)	0.89[c]
B	29 (16)	28 (14)	0.69[c]
O	78 (42)	77 (39)	0.54[c]
Functional status			
Complete dependence	0 (0)	0 (0)	NA
Partially independent (performs ≤30% work)	41 (22)	48 (24)	0.61[c]
Partially independent (performs 30%-70% work)	106 (57)	104 (53)	0.38[c]
Partially independent (performs 70%-90% work)	31 (17)	27 (14)	0.41[c]
Only requires supervision (performs ≥90% work)	1 (1)	1 (1)	0.96[c]
Complete independence	0 (0)	2 (1)	0.17[c]
Unknown	6 (3)	15 (7)	0.07[c]
UNOS status			
1A	16 (9)	22 (11)	0.41[c]
1B	46 (25)	56 (28)	0.43[c]
2	81 (44)	74 (38)	0.22[c]
Old 1	0 (0)	0 (0)	NA
Adult Status 1	1 (1)	0 (0)	0.30[c]
Adult Status 2	13 (7)	6 (3)	0.07[c]
Adult Status 3	7 (4)	8 (4)	0.89[c]
Adult Status 4	17 (9)	28 (14)	0.13[c]
Adult Status 5	0 (0)	0 (0)	NA
Adult Status 6	3 (2)	3 (2)	0.29[c]
History of cerebrovascular disease[b]	16 (9)	12 (6)	0.34[c]
Prior cardiac surgery[b]	160 (86)	169 (86)	0.84[c]
Diabetes	15 (8)	16 (8)	0.99[c]
Cigarette use	37 (20)	44 (22)	0.58[c]
Dialysis dependence[b]	4 (2)	4 (2)	0.93[c]
Ventilator dependence[b]	2 (1)	4 (2)	0.46[c]
Ventricular assist device[b]	64 (35)	75 (38)	0.48[c]
Extracorporeal membrane oxygenation[b]	2 (1)	3 (2)	0.70[c]
Intra-aortic balloon pump	14 (8)	13 (7)	0.71[c]
Implantable defibrillator	106 (57)	109 (55)	0.70[c]
Serum creatinine, mg/dL[b]	1.07 (0.80-1.35)	1.06 (0.89-1.28)	0.73[a]
Serum bilirubin, mg/dL[b]	0.80 (0.50-1.20)	0.80 (0.50-1.20)	0.73[a]
Pretransplantation status			
Admitted to nonmonitored unit	44 (24)	50 (25)	0.72[c]
Admitted to intensive care unit	70 (38)	72 (37)	0.79[c]

Continued on the next page

POPULATION CHARACTERISTICS. A total of 785 adult CHD heart transplant recipients were identified in the NIS, and 1,006 in the OPTN database. After probability linkage, 382 perfect and acceptable matches were pooled for primary analysis, of which 185 had single-ventricle physiology (Figure 1). Single and biventricular CHD groups were similar in age (36 years [IQR: 24-49 years] vs 38 years [IQR: 29-50 years]; $P = 0.09$), sex (43% vs 34% female, $P = 0.05$), and incidence of prior cardiac surgery (86% vs 85%, $P = 0.84$), respectively. A comprehensive report of demographics and clinical characteristics is shown in Table 1. The most common subtype of adults with single-ventricle CHD undergoing heart transplantation was HLHS (84 of 185, 45%) followed by doublet inlet ventricle (44 of 185, 24%) (Table 2).

SAMPLING VALIDATION. Of the 785 adult CHD patients in the NIS, 403 records with a poor match were excluded from the primary analysis. These records were similarly excluded from the 1,006 adult CHD patients in the OPTN. Further, 221 records within the OPTN were not captured by the NIS due to the nature of data sampling used by the NIS (Figure 1). Comparisons of baseline characteristics between linked and unlinked data are reported in Supplemental Tables 2 and 3.

Comparing survival outcomes between the linked and unlinked records showed no difference in 1-year unadjusted (86% vs 88%, log-rank $P = 0.30$) or adjusted (HR: 1.23; 95% CI: 0.86-1.76; $P = 0.26$) survival outcomes (Supplemental Figure 2A). Similarly, 10-year unadjusted (63% vs 68%, log-rank $P = 0.21$) and adjusted (HR: 1.17; 95% CI: 0.90-1.53; $P = 0.23$) survival was equivalent (Supplemental Figure 2B).

SHORT-TERM SURVIVAL. On unadjusted analysis, single-ventricle patients faced significantly lower 1-month (91% vs 95%), 6-month (82% vs 92%), and 1-year (80% vs 91%) survival, relative to biventricular CHD patients (log-rank $P = 0.003$) (Figure 3A). Following risk-adjustment, single-ventricle physiology was associated with increased hazard of 1-year mortality (HR: 2.50; 95% CI: 1.40-4.49; $P = 0.002$). Among all single-ventricle subtypes, HLHS was associated with the greatest hazard of mortality at 1-year (HR: 2.88; 95% CI: 1.40-5.90; $P = 0.004$) (Table 2). Factors associated with increased hazard of mortality included age at listing (HR: 1.04/year; 95% CI: 1.02-1.06; $P < 0.001$), dialysis dependence (HR: 4.10; 95% CI: 1.21-13.82; $P = 0.02$), history of cerebrovascular disease (HR: 3.08; 95% CI: 1.35-7.05; $P = 0.008$), serum bilirubin >2.4 mg/dL (HR: 2.68;

95% CI: 1.23-5.83; $P = 0.01$), and cold ischemia time >4 hours (HR: 2.71; 95% CI: 1.52-4.74; $P = 0.001$) (Figure 4A).

LONG-TERM SURVIVAL. Post-transplantation survival for single-ventricle patients was significantly lower at 3 (71% vs 87%), 5 (68% vs 83%), and 10 years (54% vs 71%) relative to biventricular CHD patients (log-rank $P < 0.001$) (Figure 3B). When followed for 10 years, single-ventricle patients, on average, survived 1.4 years less than the biventricular cohort (ΔRMST 1.40; 95% CI: 0.58-2.22; $P = 0.001$) (Figure 3C).

Following risk-adjustment, single-ventricle patients faced an increased overall hazard of 10-year mortality compared to biventricular CHD patients (HR: 2.10; 95% CI: 1.38-3.18; $P < 0.001$). Factors associated with this increased hazard of mortality included age at listing (HR: 1.02/year; 95% CI: 1.01-1.04; $P = 0.008$), history of cerebrovascular disease (HR: 2.56; 95% CI: 1.32-4.98; $P = 0.006$), prior cardiac surgery (HR: 2.70; 95% CI: 1.16-6.56; $P = 0.02$), serum bilirubin >2.4 mg/dL (HR: 2.85; 95% CI: 1.55-5.25; $P = 0.001$), and cold ischemia time >4 hours (HR: 2.04; 95% CI: 1.31-3.15; $P = 0.001$).

Overall, single-ventricle patients who survived the first year post-transplantation had equivalent hazard of 10-year mortality compared to the biventricular CHD cohort (HR: 1.58; 95% CI: 0.85-2.92; $P = 0.15$) (Figure 3D). However, among all single-ventricle subtypes, HLHS remained associated with an increased hazard of 10-year mortality (HR: 4.61; 95% CI: 1.79-11.86; $P = 0.002$) even after surviving the first year post-transplantation (Table 2). Factors associated with overall 10-year mortality were no longer statistically significant when we analyzed 10-year conditional survival (Figure 4B).

OUTCOMES COMPARED TO ADULTS WITHOUT CONGENITAL HEART DISEASE. Compared to 31,578 adults without CHD who underwent heart transplantation during the study period, patients with single-ventricle CHD faced significantly lower 1-year (91% vs 80%) and 10-year (62% vs 54%) survival (log-rank $P < 0.001$) (Figure 3). Following risk-adjustment, single-ventricle physiology was associated with increased hazard of mortality at 1 year (HR: 2.73; 95% CI: 1.95-3.82; $P < 0.001$) and 10 years (HR: 1.81; 95% CI: 1.40-2.35; $P < 0.001$) with non-CHD as reference.

Biventricular CHD patients faced similar 1-year (91% vs 91%; log-rank $P = 0.86$) and 3-year (87% vs 85%; log-rank $P = 0.14$), but improved 5-year (83% vs 79%; log-rank $P < 0.001$) and 10-year (71% vs 62%; log-rank $P < 0.001$) survival compared to adults without CHD (Figure 3). Following risk-adjustment, biventricular CHD was associated with similar hazard of mortality at 1 year (HR: 1.15; 95% CI: 0.72-1.84; $P = 0.55$) and 10 years (HR: 0.83; 95% CI: 0.61-1.15; $P = 0.27$).

On conditional survival analysis, biventricular CHD patients who survived the first year post-transplantation showed significantly reduced hazard of 10-year mortality compared to adults without CHD (HR: 0.73; 95% CI: 0.59-0.90; $P = 0.003$) (Figure 3D). In contrast, single-ventricle patients who survived the first year post-transplantation faced equivalent hazard of 10-year mortality compared to their non-CHD counterparts (HR: 1.24; 95% CI: 0.83-1.86; $P = 0.30$). Although other subtypes of single-ventricle CHD had equivalent conditional 10-year survival rates as non-CHD patients, patients with HLHS continued to show significantly higher risk of death at 10 years, even after surviving the first year post-transplantation (HR: 3.55; 95% CI: 1.55-8.14; $P = 0.003$) (Figure 5).

SECONDARY OUTCOMES. Both cohorts had similar incidence of post-transplantation stroke (4% vs 3%, $P = 0.34$), dialysis (25% vs 18%, $P = 0.09$), pacemaker implantation (1% vs 3%, $P = 0.18$), acute rejection during index hospitalization (9% vs 9%, $P = 0.99$), and rejection episodes during the first year of transplantation (19% vs 19%, $P = 0.98$).

CAUSE OF DEATH ANALYSIS. Of the 101 patients who died during the study period, 62 (61%) had single-ventricle physiology and 39 (39%) had biventricular CHD. Deaths among single-ventricle patients who died within 12 months of transplantation were

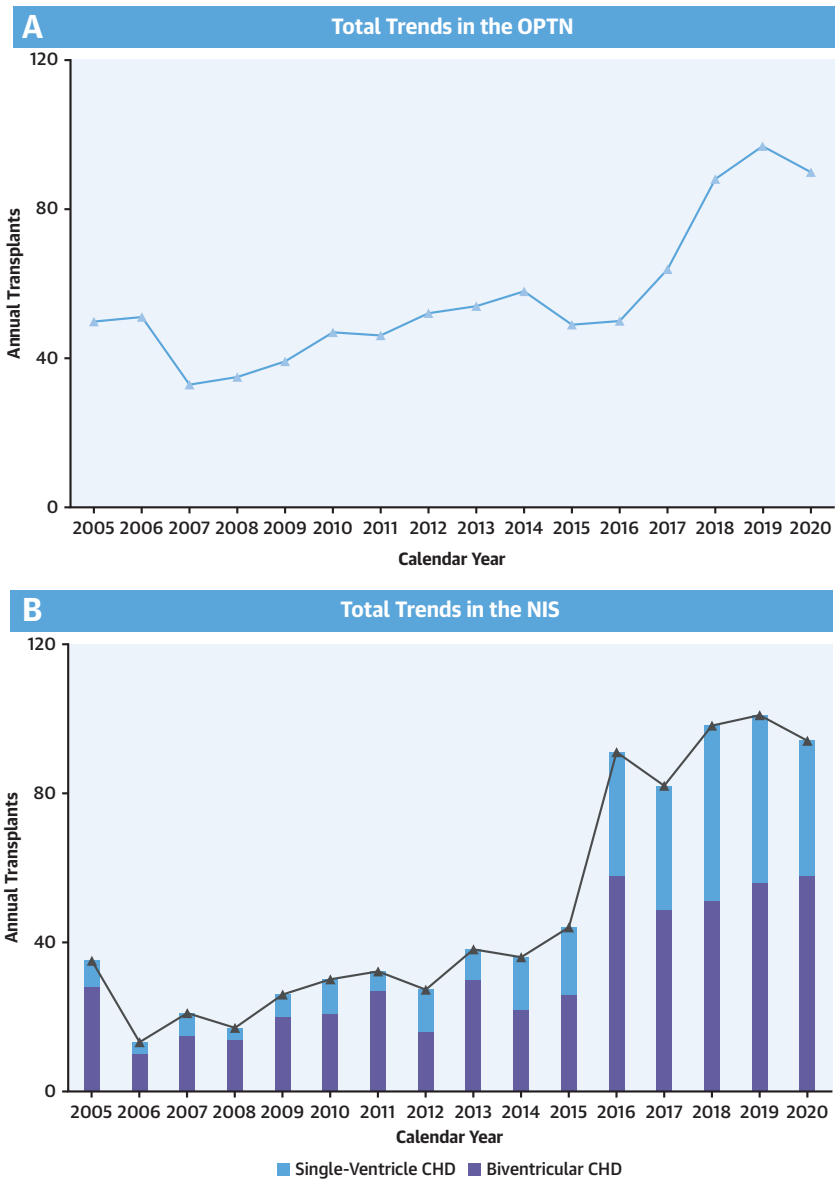
TABLE 1 Continued

	Single-Ventricle CHD (n = 185, 48%)	Biventricular CHD (n = 197, 52%)	*P* Value
Donor characteristics			
Age, y[b]	29 (22-37)	29 (23-36)	0.88[a]
BMI, kg/m^2	25.68 ± 5.16	26.23 ± 5.86	0.33[d]
Sex			
Female	58 (31)	63 (32)	0.90[c]
Male	127 (69)	134 (68)	0.90[c]
Race/ethnicity			
Black	37 (20)	31 (16)	0.28[c]
Hispanic	38 (21)	32 (16)	0.28[c]
White	106 (57)	129 (65)	0.10[c]
Other	4 (2)	5 (3)	0.81[c]
Cold ischemia time, h[b]	3.62 ± 1.22	3.37 ± 1.13	0.04[d]

Values are median (IQR), n (%), or mean ± SD. All values as reported by the Organ Procurement and Transplantation Network. Data completion 100% unless specified otherwise. [a]Mann Whitney U-test. [b]Student's *t*-test. [c]Pearson chi-square. [d]Included in multivariable regression analyses.

BMI = body mass index; CHD = congenital heart disease; NA = not available; UNOS United Network for Organ Sharing.

FIGURE 2 Annual Volume of Heart Transplantation in the OPTN and NIS



Annual volume of adults with CHD undergoing heart transplantation increased over the study period (*P* for trend <0.001). Trends were congruent between data sets. **(A)** Trends in the OPTN. **(B)** Trends in the NIS. Abbreviations as in Figure 1.

most commonly attributed to graft failure due to acute or chronic rejection (n = 8 of 38), systemic infection (n = 7 of 38), respiratory failure (n = 3 of 38), renal failure (n = 1 of 38), liver failure (n = 1 of 38), and cerebrovascular causes (n = 4 of 38) (Figure 4C). For patients surviving the first year post-transplantation, deaths among single-ventricle patients were most frequently attributed to cardiac arrest and cardiogenic shock (n = 6 of 24), multisystem organ failure (n = 4 of 24), and malignancy (n = 3 of 24) (Figure 4D).

SENSITIVITY ANALYSIS. When exclusively evaluating patients with a perfect match, overall 1-year (HR: 2.87; 95% CI: 1.54-5.33; $P = 0.001$) and 10-year (HR: 2.18; 95% CI: 1.40-3.38; $P = 0.001$) mortality remained higher for the single-ventricle cohort relative to biventricular CHD patients. Analyzing 1-year

TABLE 2 Adjusted Hazard of Mortality by Type of Single-Ventricle Lesion[a]

Diagnosis of SV	N	1-Year HR	95% CI	*P* Value	10-Year Conditional HR	95% CI	*P* Value
All SV	185	2.50	1.40-4.49	0.002	1.58	0.85-2.92	0.15
Doublet inlet							
Yes	44	2.51	1.06-5.91	0.04	2.26	0.95-5.36	0.06
No	141	2.72	1.45-5.09	0.002	1.44	0.71-2.92	0.32
Tricuspid atresia							
Yes	22	3.23	1.02-10.18	0.05	0.76	0.19-3.03	0.70
No	163	2.72	1.47-5.01	0.001	1.96	1.04-3.71	0.05
Double outlet[b]							
Yes	17	0.74	0.19-2.93	0.66	2.25	0.86-5.89	0.10
No	168	3.32	1.77-6.23	<0.001	1.52	0.77-2.97	0.23
Pulmonary atresia							
Yes	<11	NA	NA	NA	NA	NA	NA
No	<11	2.49	1.37-4.54	0.003	2.13	1.15-3.93	0.02
Ebstein's anomaly							
Yes	<11	NA	NA	NA	NA	NA	NA
No	<11	2.55	1.41-4.61	0.002	1.65	0.88-3.09	0.12
HLHS							
Yes	84	2.88	1.40-5.90	0.004	4.61	1.79-11.86	0.002
No	101	2.48	1.25-4.97	0.01	1.19	0.58-2.45	0.63

[a]Analysis showing the association between type of SV lesion and adjusted hazard of mortality at 1 year and 10 years conditional on surviving the first year post-transplantation. For all analyses, the reference group was biventricular congenital heart disease (HR: 1.00). Results with <11 records have been masked. [b]Double outlet right ventricle excluding Tetralogy of Fallot and transposition of the great arteries.

SV = single-ventricle congenital heart disease; HLHS = hypoplastic left heart syndrome; NA = not available.

survivors revealed no significant difference in 10-year mortality between single-ventricle and biventricular CHD patients (HR: 1.52: 95% CI: 0.80-2.88; $P = 0.20$). The results were similar to those seen in our primary analysis. Additionally, on subgroup analyses, the association between single-ventricle physiology and increased hazard of mortality remained evident when the study cohort was stratified by sex, age, race, history of cerebrovascular disease, prior cardiac surgery, dialysis and ventilator dependence, extracorporeal membrane oxygenation, serum creatinine, serum bilirubin, donor age, and cold ischemia time (Supplemental Table 4).

DISCUSSION

In this national, outcome-blinded, retrospective cohort study of adults with CHD undergoing heart transplantation, single-ventricle physiology was associated with significantly greater short-term mortality. After surviving the first year post-transplantation, long-term outcomes were comparable between biventricular CHD and most subtypes of single-ventricle disease (**Central Illustration**). However, patients with HLHS faced persistently increased hazards of death up to 10 years post-transplantation. Unlike biventricular and other single-ventricle CHD subtypes, HLHS portended significantly reduced 10-year conditional survival when compared to patients without CHD. Moreover, we noted a higher number of deaths from respiratory failure, liver failure, and cerebrovascular events in single-ventricle CHD patients compared to their biventricular counterparts. Several of these findings warrant further discussion.

Single-ventricle CHD patients comprise a heterogeneous cohort. Ostensibly similar in their inability to support independent pulmonary and systemic circulations, these patients have varied surgical histories comprising pulmonary artery bands, ductal stents, shunts, and cavopulmonary anastomoses.[4] Given that anatomical complexity has been correlated with high perioperative and short-term mortality in CHD patients undergoing heart transplantation, it is not surprising that single-ventricle CHD patients exhibited worse short-term outcomes relative to patients with biventricular CHD.[18] However, after surviving the initial hazard period following transplantation, most of these patients showed improved survival outcomes. Our comparison of CHD patients to their non-CHD counterparts revealed that, in line with prior research, those with biventricular CHD had significantly better 10-year conditional survival than adults without CHD who underwent heart transplantation.[7,19] Similarly, most single-ventricle CHD subtypes showed improved 10-year survival

FIGURE 3 Survival After Heart Transplantation: Adults With and Without CHD

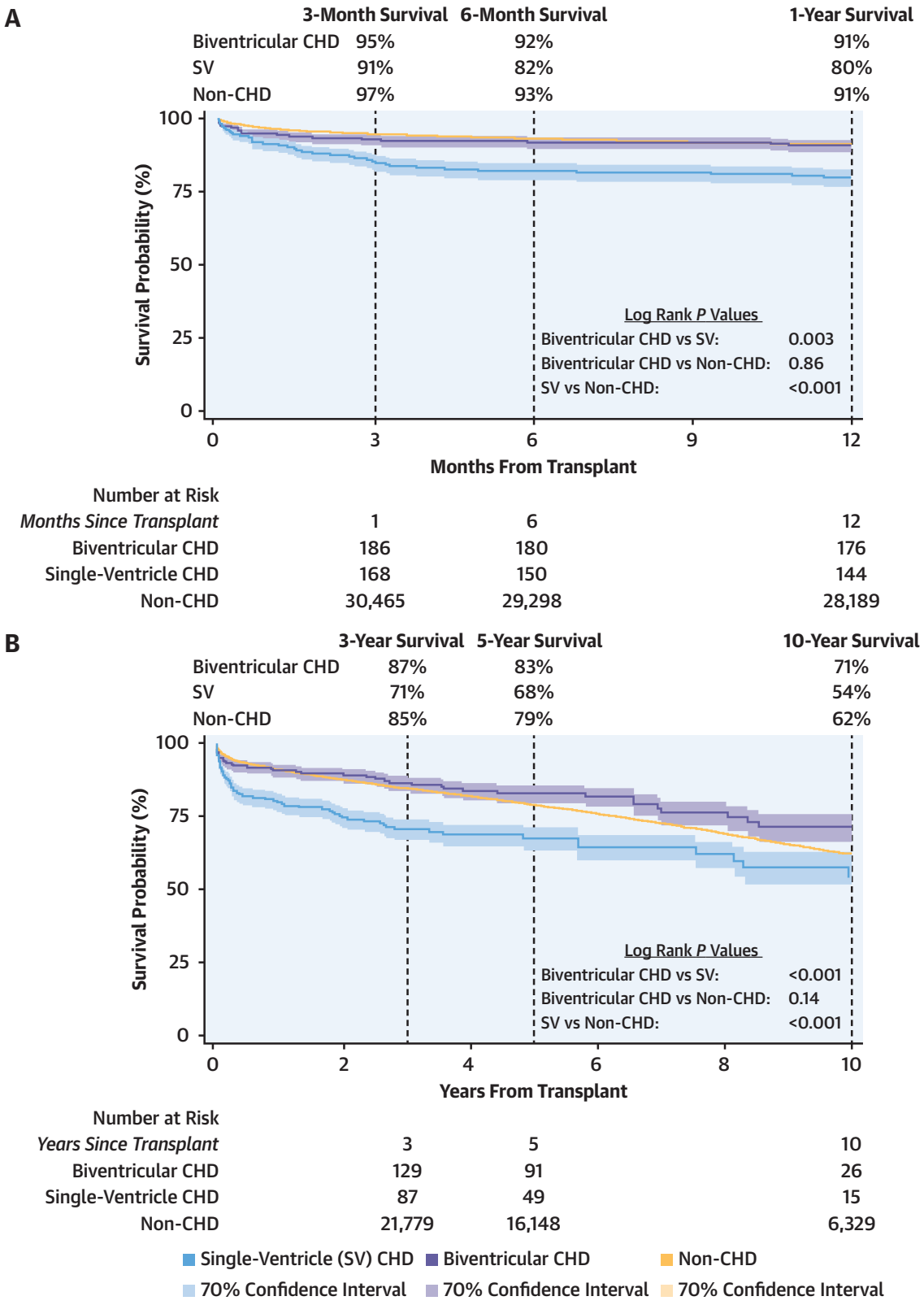


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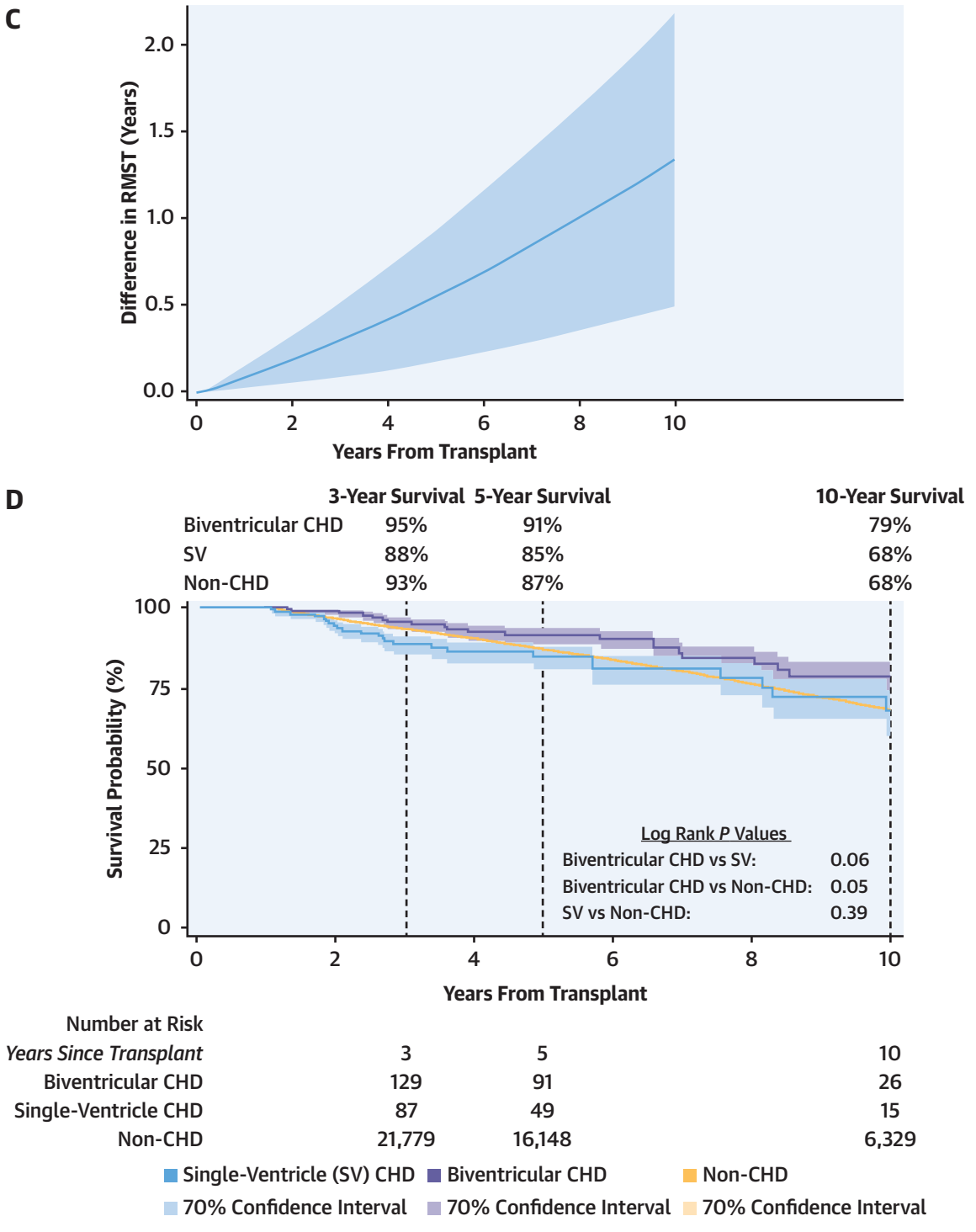
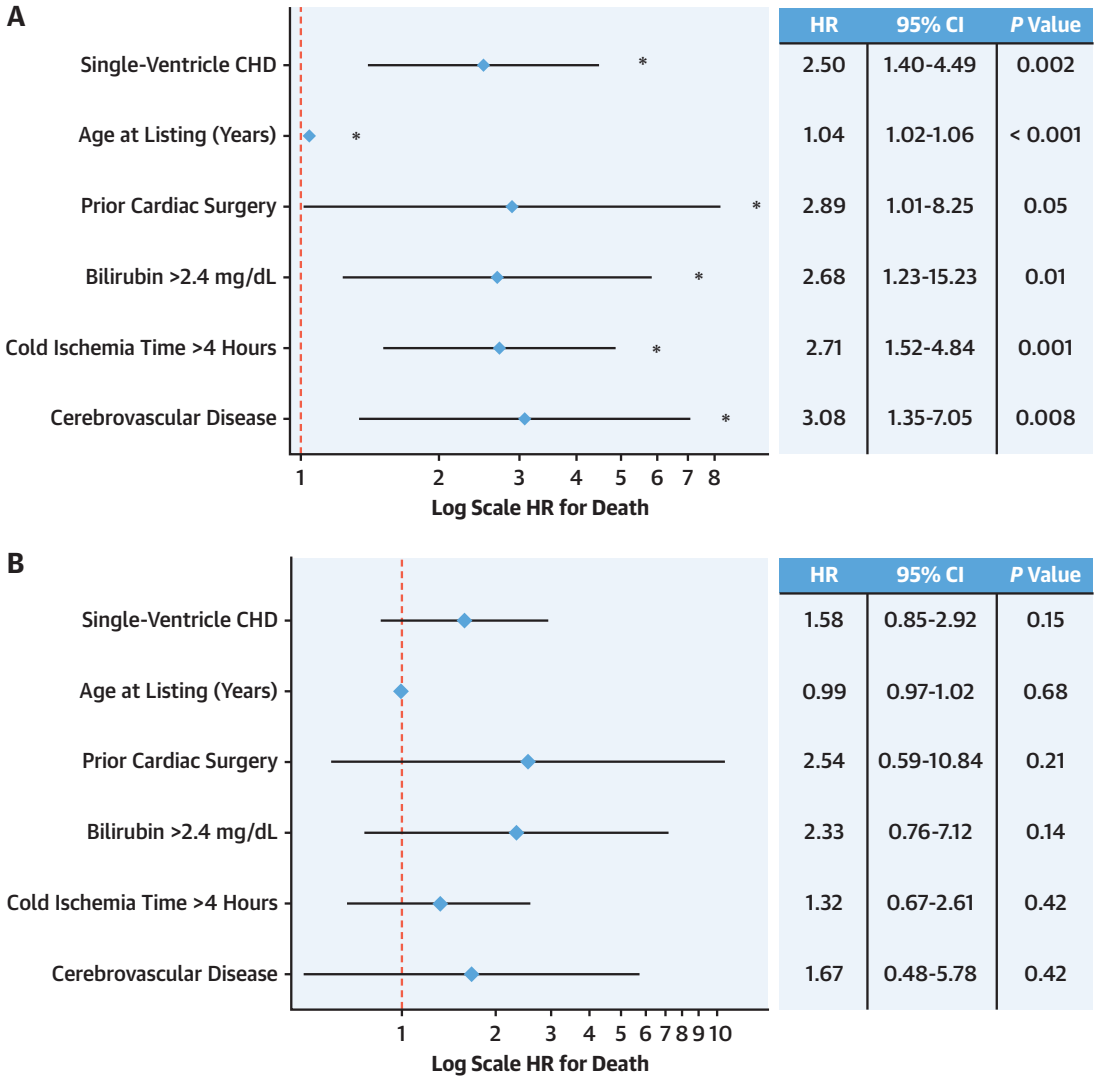
FIGURE 3 Continued



Kaplan-Meier post-transplantation survival curves for adults with single and biventricular CHD, and those without CHD. **(A)** Survival outcomes over 1 year of follow-up. **(B)** Survival outcomes over 10 years of follow-up. **(C)** Difference in restricted mean survival time (RMST) since heart transplantation between single and biventricular CHD patients over 10 years. **(D)** Conditional 10-year survival for patients who survived the first year post-transplantation. At-risk tables show actual number of patients at risk. SV = single ventricle; other abbreviation as in Figure 1.

FIGURE 4 Predictors of Death and Cause of Death Analysis



Forest plots show HRs for factors associated with all-cause mortality. **Diamonds** represent point estimates for the HR and horizontal lines indicate 95% CIs. **(A)** One-year hazard of mortality. **(B)** Ten-year hazard of mortality for 1-year survivors. Histograms show cause of death for CHD heart transplantation recipients. **(C)** One-year cause of death analysis. **(D)** Ten-year cause of death analysis for 1-year survivors. *Statistically significant HR. Abbreviation as in Figure 1.

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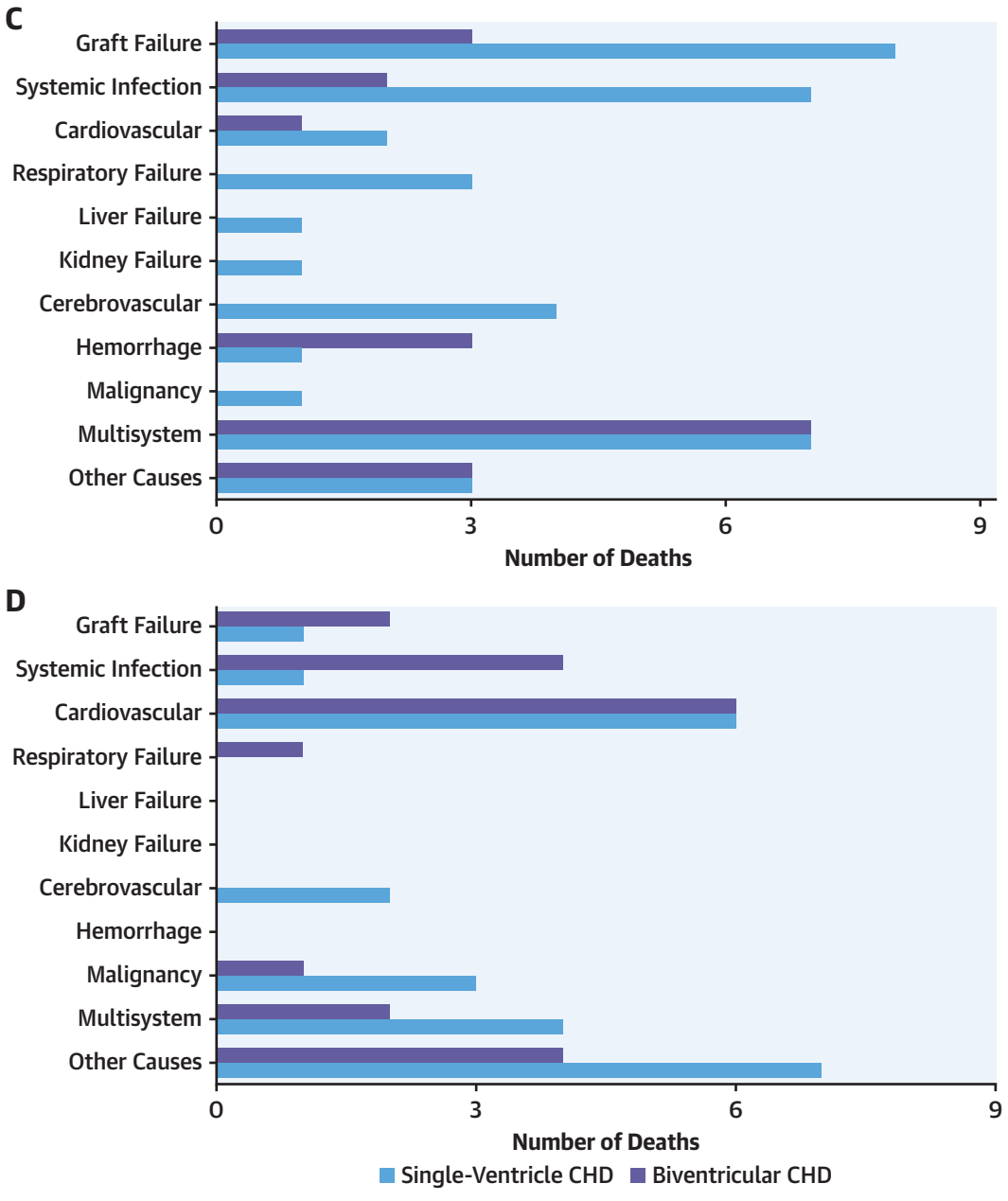
outcomes, except for patients with HLHS, who continued to exhibit reduced 10-year conditional survival compared to non-CHD patients. This finding has important implications. As survival outcomes are publicly reported quality metrics for transplant programs, equivalent long-term survival among most single-ventricle CHD subtypes should assuage concerns of centers that otherwise would be dissuaded from pursuing transplantation in these patients. Our findings will help inform expectations among patients, their families, and the transplantation community.

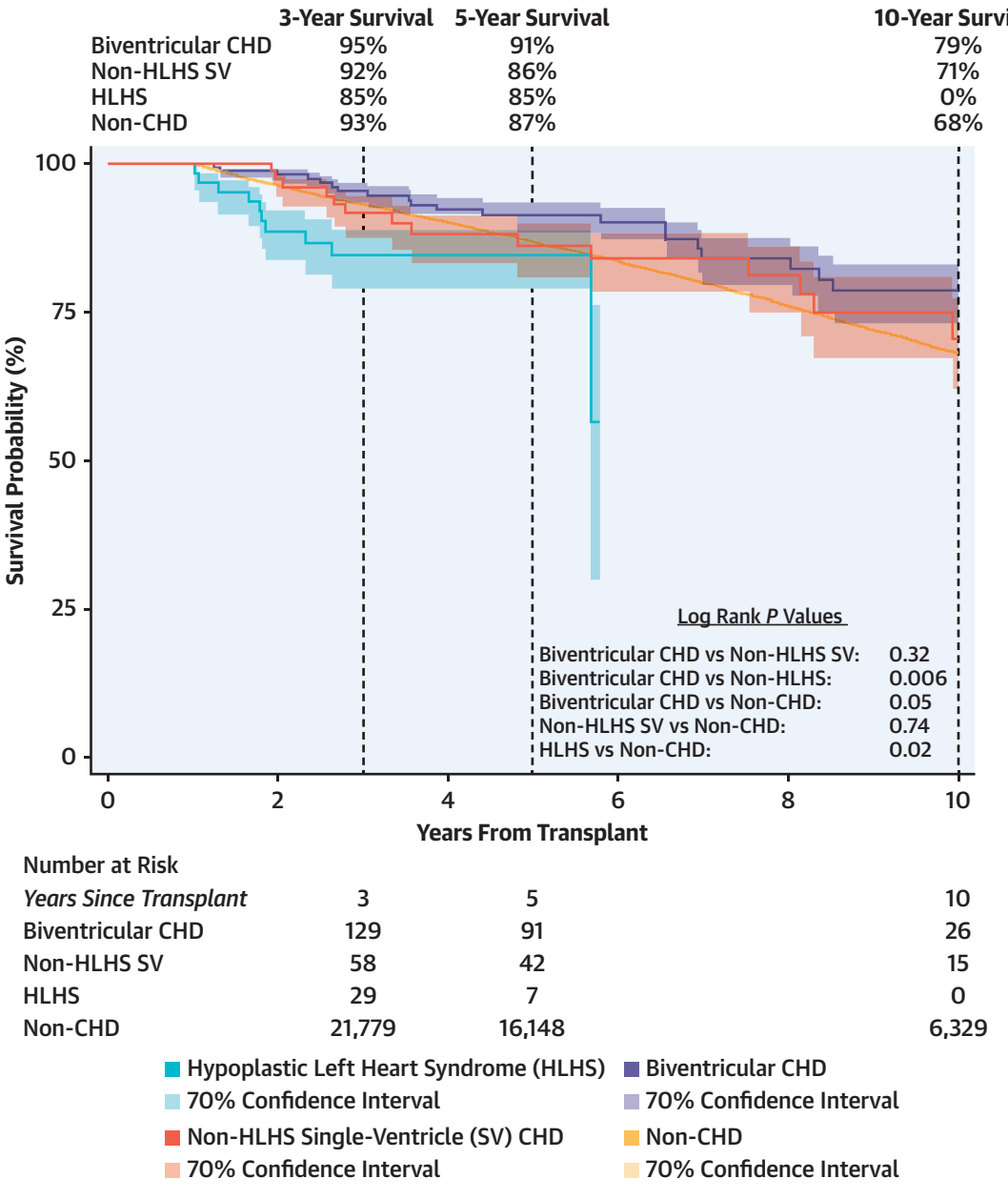
We report several perioperative factors that are associated with worse 1-year post-transplantation outcomes, including age at listing, dialysis dependence, prior cardiac surgery, elevated serum bilirubin, and cold ischemia time. Although some elements may be unmodifiable, our findings highlight the importance of mitigating the impact of these factors whenever possible. As established, single-

FIGURE 4 Continued



ventricle CHD recipients typically require extensive dissection and surgical reconstruction at transplantation. A comprehensive review of preoperative imaging and management at experienced transplantation centers could potentially reduce operative, cardiopulmonary bypass, and cold ischemia times. Further, by maintaining donor organs in a perfused state, modern donor allograft perfusion transport systems may reduce the impact of cold ischemia time on post-transplantation survival. Notably, identification of serum bilirubin as an independent risk factor for poor transplantation outcomes suggests some degree of hepatic involvement and subsequent coagulopathy. This may result in an increased risk of postoperative bleeding, surgical re-explorations, and prolonged intensive care stay.[20] Although recombinant factor VII has been used as a rescue therapy for patients with refractory

FIGURE 5 Conditional Survival After Stratifying Single-Ventricle Patients by Etiology

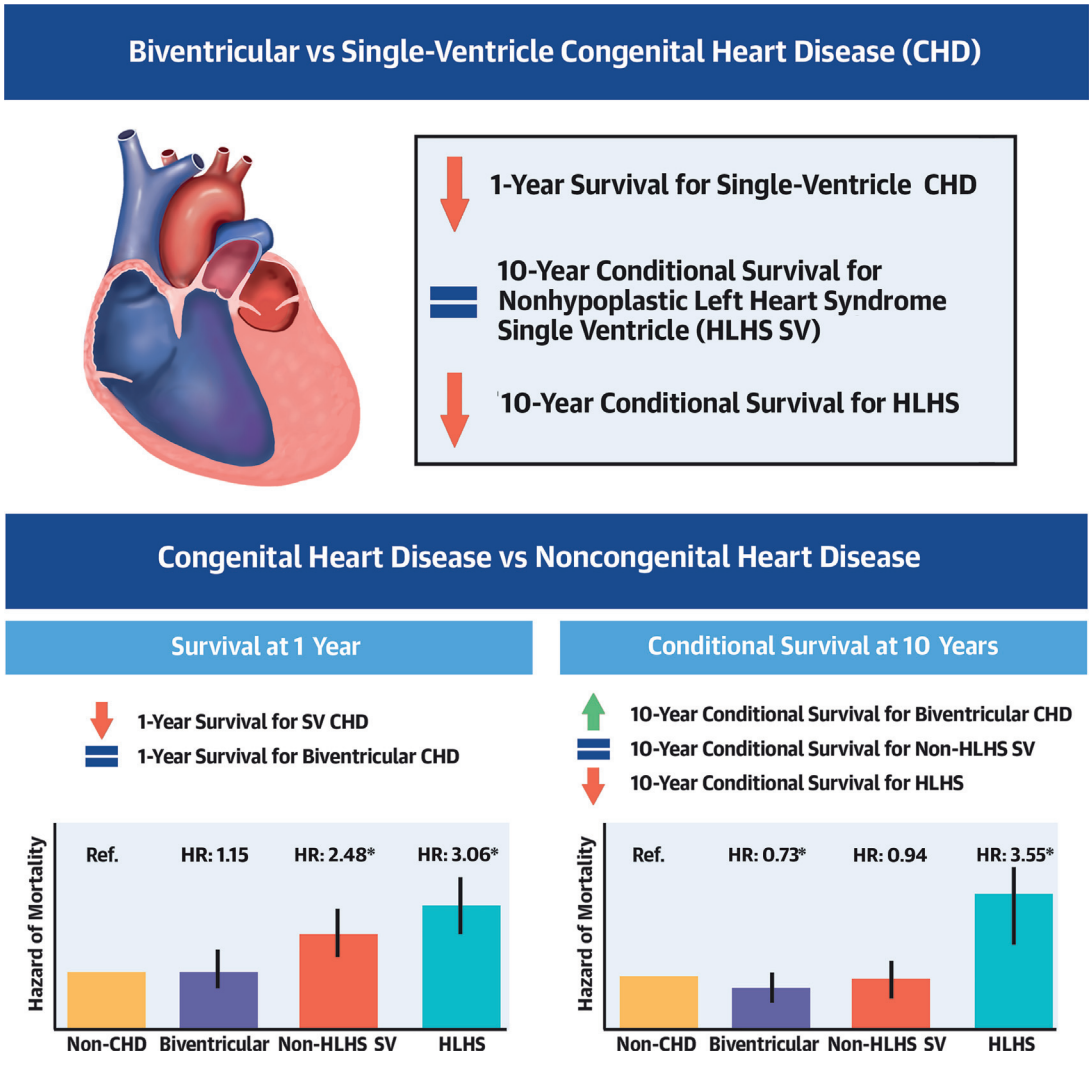


Conditional survival of adults with hypoplastic left heart syndrome (HLHS), non-HLHS single-ventricle CHD, biventricular CHD, and those without CHD. At-risk table shows actual number of patients at risk. Abbreviation as in Figure 1.

coagulopathy undergoing heart transplantation, its use in single-ventricle CHD patients warrants further risk-benefit analysis.[21] In addition, although we excluded patients undergoing multiorgan transplantation, future studies should aim to analyze outcomes in single-ventricle CHD patients undergoing a combined heart-liver transplantation.

Our 1-year cause of death analysis corroborated prior work that reported bleeding, systemic infections, and graft failure as the most frequent causes of death among CHD transplant recipients.[22] We found no difference in the incidence of such causes between single-ventricle and other CHD subtypes. We noted that 10% of patients with single-ventricle

CENTRAL ILLUSTRATION **Survival After Heart Transplantation in Adults With Congenital Heart Disease**



Bakhtiyar SS, et al. J Am Coll Cardiol. 2023;82(12):1226–1241.

Compared to adult heart transplant recipients with biventricular congenital heart disease (CHD), those with single-ventricle (SV) physiology showed a significantly higher risk-adjusted hazard of mortality at 1 year. After surviving the first year post-transplantation, hypoplastic left heart syndrome (HLHS) continued to face an elevated risk of mortality, but other subtypes of SV disease (non-HLHS SV) showed similar survival as their biventricular CHD counterparts. When comparing survival to adults without CHD, biventricular CHD patients showed notably better 10-year conditional survival, whereas patients with HLHS continued to experience significantly worse outcomes. *$P < 0.05$.

physiology died of cerebrovascular events, with no such deaths among other CHD subjects. We offer 2 potential explanations. First, studies have linked the hemodynamic fluctuations of single-ventricle patients to intrinsic vascular wall abnormalities, arterial stiffness and endothelial dysfunction, all of which are established risk factors of cerebrovascular events.[23-25] Given that these abnormalities are endogenous to the native vasculature, we postulate that these patients remain at increased risk for stroke following transplantation. Alternatively, acquired hypercoagulability may underlie this increased incidence of cerebrovascular events. Given their prolonged cyanosis, single-ventricle patients are known to have some degree of polycythemia.[26] Multiple studies have also reported decreased levels of protein C and protein S, and increased levels of factor VIII in single-ventricle patients—all of which suggest a

prothrombotic state.[27,28] This idea is further bolstered by a study by Hoffman et al[29] who reported a 10-fold increase in the prevalence of cerebrovascular events in patients with cyanotic CHD lesions. Mechanism aside, thromboembolic events in single-ventricle CHD patients carry a mortality rate of ~30%.[30] As such, a risk-benefit analysis of prolonged postoperative anticoagulation in this patient cohort is required. Future studies could aim to delineate the optimal timing of starting anticoagulation, presumably once perioperative bleeding risk has resolved.

STUDY LIMITATIONS. This study has certain limitations inherent to its retrospective design. Although the OPTN and NIS databases provide larger sample sizes compared to single-center studies, they lack adequate granularity to analyze all aspects of transplantation. We were unable to specifically identify or analyze outcomes in patients who had undergone a Fontan procedure, as surgical history was not available. However, we were able to stratify by subtype of single-ventricle CHD and, similar to prior studies, found HLHS to be most common.[31] In our analysis, this group had the worst survival outcomes at 1 year (80%) and 5 years (85%) among all CHD patients. For context, in a 2009 study of 121 adult and 367 pediatric heart transplant recipients with CHD, 22% underwent a Fontan repair and showed a 1-year survival of 71% and a 5-year survival of 60%.[32] Further, the sampling algorithm of the NIS database is not designed to capture certain pediatric inpatient hospitalizations, thereby limiting our probability linkage only to adults with CHD.[10] As such, we could not compare outcomes between pediatric and adult CHD patients undergoing heart transplantation and could not comment on the possibility that earlier transplantation could improve survival. Another limitation is the analytic constraint of linking 2 separate data sets. Without a common patient identifier, we relied on probability linkage to match records across databases. Nonetheless, we tested the adequacy of this linkage across multiple analytic approaches and performed vigorous sensitivity analyses to mitigate any potential selection bias. Although our rigorous outcome-blinded probability-linkage algorithm reduced the number of records available for primary analysis, this methodological stringency increased the validity of our results while ensuring sufficient statistical power.

CONCLUSIONS

In the absence of large retrospective studies analyzing post-transplantation survival in single-ventricle CHD patients, clinicians and care providers have operated within an umbra of ignorance regarding expectations following heart transplantation in this unique patient population. Because of this dearth of information on survival outcomes, along with the scarcity of donor organs and the need to maximize the benefit yielded by heart transplantation, some transplantation centers have been hesitant to pursue transplantation for these patients. Analyzing the largest population of single-ventricle CHD transplant recipients, this study shows that single-ventricle physiology was associated with significantly greater short-term mortality. However, after surviving the first year post-transplantation, long-term outcomes were comparable between biventricular and most single-ventricle CHD patients. Further, 10-year survival conditional on surviving the first year post-transplantation was significantly better for biventricular CHD patients compared to non-CHD heart transplant recipients. These findings carry significant implications towards patient selection and listing strategies, as they not only alleviate concerns associated with heart transplantation in adults with CHD, but also work towards destigmatizing most subtypes of single-ventricle CHD. We hope to provide a foundation for future multicenter studies to define prognostic indices for short- and long-term survival, as well as help guide the management of this complex patient cohort.

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The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Among adults with single-ventricle congenital cardiac defects undergoing heart transplantation, mortality is highest in the first year, following which long-term survival is similar to that for other forms of congenital heart disease.

TRANSLATIONAL OUTLOOK: Additional studies are needed to determine the optimal timing and duration of postoperative anticoagulation to reduce the risk of cerebrovascular events in single-ventricle CHD patients undergoing heart transplantation.

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KEY WORDS congenital heart disease, heart transplantation, single ventricle

APPENDIX For supplemental tables and figures, please see the online version of this paper.