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ORIGINAL RESEARCH

Donor Characteristics and Recipient Outcomes After Heart Transplantation in Adult Congenital Heart Disease

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BACKGROUND: Patients with adult congenital heart disease (ACHD) experience long waitlist times for heart transplantation (HTx) while a large proportion of donor hearts are refused. The goal of this study was to inform optimal donor selection for patients with ACHD listed for HTx by examining the impact of donor characteristics on post-HTx outcomes.

METHODS AND RESULTS: Using the Scientific Registry of Transplant Recipients, we conducted a retrospective analysis of patients aged ≥18 years listed for HTx in the United States between 2000 and 2016. We compared waitlist times between patients with ACHD and patients with noncongenital heart disease and constructed multivariate hazard models to identify donor characteristics associated with increased waitlist time. We then compared post-HTx survival between patients with ACHD and patients with noncongenital heart disease and constructed multivariate hazard models to identify donor characteristics associated with mortality. There were very few differences in donor characteristics between HTx recipients with ACHD and those with noncongenital heart disease. Status 1A–listed patients with ACHD experienced longer waitlist times compared with patients with noncongenital heart disease. Increased wait times were associated with some donor characteristics. Post-HTx outcomes varied over time, with patients with ACHD having inferior early mortality (0 to 30 days), similar intermediate mortality (31 days to 4 years), and superior late mortality (>4 years). We identified no donor characteristics associated with mortality to justify the observed differences in donor selection or waitlist time.

CONCLUSIONS: HTx candidates with ACHD wait longer for transplant but do not require unique donor selection criteria. HTx teams should consider liberalizing donor criteria and focusing only on evidence-based selection to improve waitlist outcomes and reduce the recipient–donor disparity.

Key Words: adult congenital heart disease ■ donor ■ transplantation

Because of the extraordinary advances in the fields of pediatric cardiology and cardiac surgery, the number of adults living with congenital heart disease has increased significantly in recent decades, and adults now represent the majority of the congenital heart disease population.[1] Despite advances in medical and surgical treatment, patients with adult congenital heart disease (ACHD) face a large burden of morbidity and mortality from heart failure. Among patients with ACHD with end-stage heart failure, heart transplantation (HTx) is a good therapeutic option. Given the increasing prevalence of ACHD, the volume and proportion of patients with ACHD undergoing HTx have been increasing rapidly.[2] There is a persistent shortage of cardiac allografts for patients with ACHD or noncongenital heart disease (NCHD) awaiting HTx.[3] Consequently, time spent on the waitlist is long, and registry analyses have shown that patients with ACHD experience longer waitlist times, a lower probability of high-priority listing status, and a lower likelihood of

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CLINICAL PERSPECTIVE

What Is New?

- It is not known whether donor characteristics affect waitlist times, priority listing status, and likelihood of transplantation in patients with adult congenital heart disease compared with patients with noncongenital heart disease.
- In the present study, awaiting donors with certain characteristics was associated with longer waitlist times for status 1A–listed patients with adult congenital heart disease, but these donor characteristics had no impact on mortality.
- No adult congenital heart disease donor characteristics were associated with early or intermediate mortality, and very few donor characteristics were associated with late mortality.

What Are the Clinical Implications?

- Based on these findings, heart transplantation candidates with adult congenital heart disease do not require separate and strict donor selection criteria, and heart transplantation teams should focus on liberalizing and further defining evidence-based donor criteria to improve waitlist outcomes and reduce the recipient–donor disparity.

Nonstandard Abbreviations and Acronyms

ACHD	adult congenital heart disease
HTx	heart transplantation
NCHD	noncongenital heart disease
SRTR	Scientific Registry of Transplant Recipients

transplantation compared with their NCHD counterparts.[4–6] This donor organ supply–demand mismatch is exacerbated by low donor heart acceptance rates for all patients.[7] At least half of all hearts available for donation are not recovered for transplantation, and the number of hearts that are recovered but ultimately do not get transplanted has been steadily rising during the past decade.[8] The increase in donor refusal overtime suggests an increasing avoidance of risk.[7]

Indeed, high waitlist mortality and donor heart shortage make donor allocation and acceptance one of the most important, but also most challenging, aspects of the HTx process. Overall, the goal of the transplanting team is to balance the risk of a longer wait time and associated possibility of clinical deterioration with that of suboptimal graft selection and risk of primary graft dysfunction or early adverse patient outcomes.[9] Many donor-specific factors need to be reviewed quickly and aligned with the awaiting recipient. In the United States, donor hearts are offered to individual transplant candidates based on geographic zone, medical urgency, ABO compatibility, and time spent on the waitlist. The accepting HTx team will review other demographic and clinical data about the donor heart and choose to accept or decline. Reasons for donor heart refusal are many; however, only a few are supported by evidence, including increasing age, ischemia time, history of stroke, diabetes mellitus, coronary artery disease, substance abuse, and in some cases age, sex, and weight mismatch.[7,10,11] Most stringent acceptance or refusal criteria have not been thoroughly tested in clinical or research settings. In addition, there are no specific guidelines on heart donor selection specific to patients with ACHD, and data on donor characteristics associated with increased recipient risk are scarce among the ACHD HTx population. There is anecdotal evidence, however, that ACHD HTx teams may await the "perfect" donor heart in younger patients or those considered higher risk.[12] There are consequences to being overly selective, that is, so called "cherry picking." Davies et al[12] demonstrated that among pediatric patients awaiting HTx, allograft refusal was actually associated with higher mortality rates, and other studies have shown a survival benefit associated with accepting high-risk donors.[13] It is currently not known if patients with ACHD have longer waitlist times due to HTx teams awaiting donors with certain characteristics.

We hypothesize that greater donor selectivity does not improve post-HTx outcomes for patients with ACHD awaiting HTx but, instead, may lengthen waitlist times and worsen post-HTx outcomes. To improve the evidence on which donor selection for patients with ACHD awaiting HTx is based, we used the Scientific Registry of Transplant Recipients (SRTR) to examine associations between donor characteristics and both waitlist times and post-HTx outcomes.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. This study used data from the SRTR. The SRTR data system includes data on all donor, waitlisted candidates, and transplant recipients in the United States submitted by the members of the Organ Procurement and Transplantation Network. The Health Resources and Services Administration, US Department of Health and Human Services provides oversight to the activities of the Organ Procurement and Transplantation Network and SRTR contractors. We obtained the SRTR database and approval from the University of Texas Southwestern Medical Center Institutional Review Board to conduct this research.

Informed consent was waived because of the minimal perceived risk to subjects and the deidentified nature of the database. We restricted analyses to adult recipients (aged ≥18 years) who underwent transplantation between 2000 and 2016.

We identified all patients listed for HTx in the SRTR database and separated them based on their underlying heart disease as having ACHD or NCHD. These patients were then further subcategorized into candidates (those listed for transplant during the study period) and recipients (those who received a transplant during the study period). The primary outcome for candidates was waitlist time with censoring at the time of death, transplant, or delisting as a result of clinical worsening; the primary outcome for recipients was posttransplant survival with censoring at the time of death or repeat transplantation during the period between 2000 and 2016. In identifying characteristics associated with each of these outcomes we considered all candidate variables and all donor and recipient variables in the SRTR database.

Categorical donor, candidate, and recipient characteristics were expressed as frequencies, stratified by ACHD versus NCHD group, and compared using the chi-square test. Continuous donor, candidate, and recipient characteristics were expressed as mean±SD, and the results for ACHD and NCHD groups were compared using the Student *t* test. Variables with ≥50% of data missing were not reported and were excluded from analysis. Subgroup analysis was undertaken to compare the characteristics of ACHD and NCHD status 1A patients. Survival analysis was done using the Kaplan–Meier method, stratified by ACHD versus NCHD. When inspection revealed remarkably different patterns of survival, ACHD relative to NCHD, depending on time interval (0 to 30 days, 31 days to 4 years, and >4 years after transplant), Kaplan–Meier survival plots were produced for each of the time periods. Log-rank test was used to compare the survival rates of ACHD and NCHD overall and within each of the 3 time intervals. Except as specified in the proportional hazard and multivariable linear regression models, statistical significance was established at α=0.05.

To identify donor factors independently associated with survival posttransplant in each of the 3 time intervals, ACHD and NCHD groups were analyzed separately. Cox proportional hazard models were sought using candidate, donor, and recipient characteristics as independent variables and time to death as the dependent variable. Stepwise method modeling was done, specifying α for inclusion and α for retention in the models as 0.15. Models were similarly constructed in the status 1A subgroup.

No variable in which >50% of values were missing was included in the proportional hazards model–building process. A substantial minority of patients in the database had missing values for total bilirubin (n=18 762) and serum creatinine (n=19 279). Missingness of creatinine was significantly associated with both types of heart disease (43% missing in ACHD versus 34% in NCHD; $P<0.0001$) and mortality (43% missing among patients who ultimately died versus 29% among survivors; $P<0.0001$). Features of patients with missing bilirubin were almost identical. To exclude these cases from multivariable outcome model building was therefore likely to promote undesirable bias in the models. To address this, it was elected to retain these cases in the analysis by imputing the missing values for total bilirubin and creatinine using multiple linear regression from other patient characteristics available in the database. Missing data among most categorical variables also demonstrated potential for bias in the same way, being associated with both congenital heart disease and outcome, so excluding the cases with missing values was also considered a risk for bias. These variables were handled by creating, from each, 3 mutually exclusive dichotomous variables defined as present (yes, no), absent (yes, no), and unknown (yes, no). Although the proportion "unknown" was usually somewhat larger (again this was commonly a difference of ≈8%–10%) in the ACHD group, none of the "unknown" dichotomous variables were significant in any of our proportional hazards models once "present" or "absent" were accounted for.

Waitlist times in patients who were status 1A were compared between ACHD and NCHD groups using the Student *t* test. To identify factors independently associated with waitlist time, multivariable linear regression modeling was undertaken using the general linear model, incorporating candidate and donor characteristics as independent variables and waitlist time as the dependent variable. Stepwise modeling was done, specifying α for inclusion and α for retention in the models as 0.15. All statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

During the study period, there were 1649 patients with ACHD and 54 330 patients with NCHD listed for HTx. Of these, 903 patients with ACHD and 35 274 patients with NCHD underwent HTx. Baseline characteristics that were significantly different between HTx candidates with ACHD or NCHD and recipients are listed in Table 1. Notably, 45% of patients with ACHD were initially listed as status 1A compared with 52% of patients with NCHD ($P<0.001$), and patients with ACHD spent more time on the waitlist compared with patients with NCHD (253±391 versus 199±316 days; $P<0.001$).

Table 1. Differences in Candidate and Recipient Characteristics Between Patients With ACHD and Patients With NCHD

Characteristic	ACHD	NCHD	Absolute Mean Difference (95% CI)	*P* Value	% Missing (ACHD, NCHD)
Candidates, n=55 979	1649	54 330			
Age at listing, y, mean±SD	36.3±11.9	52.7±12.0	16.4 (15.8–17.0)	<0.001	0, 0
Female, n (%)	659 (40.0)	13 454 (24.8)		<0.001	0, 0
White, n (%)	1458 (88.4)	41 099 (75.6)		<0.001	0, 0
Black, n (%)	136 (8.2)	11 185 (20.6)		<0.001	0, 0
Multirace, n (%)	12 (0.7)	197 (0.4)		0.017	0, 0
BMI, kg/m^2, mean±SD	25.1±5.3	28.5±218.4	3.4 (1.5–5.3)	<0.001	0, 0
Height, cm, mean±SD	169.5±10.7	174.2±10.0	4.7 (4.2–5.2)	<0.001	0, 0
Weight, kg, mean±SD	72.5±18.8	83.9±18.4	11.3 (10.4–12.2)	<0.001	0, 0
Status 1A, n (%)	746 (45.2)	28 435 (52.3)		<0.001	0, 0
Status 2, n (%)	318 (19.3)	6994 (12.9)		<0.001	0, 0
Creatinine, mg/dL, mean±SD	1.18±0.8	1.41±1.0	0.23 (0.19–0.27)	<0.001	3, 2
Albumin, g/dL, mean±SD	3.8±0.8	3.7±0.7	0.21 (0.16–0.26)	<0.001	38, 34
Mean PA pressure, mm Hg, mean±SD	28.2±15.0	29.6±10.3	1.4 (0.54–2.2)	0.001	22, 8
Mean PCW pressure, mm Hg, mean±SD	17.4±8.2	19.9±8.8	2.4 (2.0–2.9)	<0.001	26, 11
History of cigarette use, n (%)	271 (20.1)	20 562 (48.4)		<0.001	18, 22
On medication for hypertension, n (%)	271 (24.9)	18 607 (48.6)		<0.001	36, 31
On medication for COPD, n (%)	19 (1.8)	1686 (4.5)		<0.001	37, 37
Diabetes mellitus, n (%)	16 (1.0)	2833 (5.2)		<0.001	0, 0
Dialysis, n (%)	38 (2.3)	1835 (3.4)		0.017	1, 0
Peptic ulcer disease, n (%)	32 (3.0)	2241 (7.1)		<0.001	37, 37
History of malignancy, n (%)	36 (2.2)	3719 (6.9)		<0.001	2, 2
Prior blood transfusions, n (%)	528 (50.0)	10 187 (27.6)		<0.001	49, 47
On amiodarone, n (%)	256 (24.1)	11 413 (30.7)		<0.001	37, 35
Implantable defibrillator, n (%)	723 (44.2)	36 092 (66.8)		<0.001	2, 2
Prior cardiac surgery, n (%)	1155 (70.6)	16 419 (30.4)		<0.001	19, 25
Prior HTx, n (%)	5 (0.30)	2197 (4.0)		<0.001	0, 0
On life support, n (%)	500 (30.6)	22 107 (40.9)		<0.001	1, 1
ECMO, n (%)	28 (1.7)	614 (1.1)		0.033	0, 0
IABP, n (%)	22 (1.3)	3016 (5.6)		<0.001	0, 0
Inotropes, n (%)	436 (26.4)	18 228 (33.6)		<0.001	0, 0
PGE, n (%)	5 (0.30)	38 (0.07)		<0.001	0, 0
Mechanical ventilation, n (%)	41 (2.5)	1915 (3.5)		0.024	0, 0
Recipients, n=36 177	903	35 274			
Age at HTx, y, mean±SD	37.3±12.3	53.2±12.0	16.0 (15.2–16.8)	<0.001	0, 0
Status 1A, n (%)	414 (45.9)	18 569 (52.6)		<0.001	0, 0
Status 1B, n (%)	336 (37.2)	12 649 (35.9)		<0.001	0, 0
Status 2, n (%)	153 (16.9)	4056 (11.5)		<0.001	0, 0
Waitlist time, d, mean±SD	253±391	199±316	54 (29–80)	<0.001	0, 0
Creatinine, mg/dL, mean±SD	1.25±0.9	1. 38±0.9	0.12 (0.06–0.18)	<0.001	3, 2
Mean PA pressure, mm Hg, mean±SD	25.4±10.8	27.8±10.0	2.4 (1.6–3.2)	<0.001	20, 9
Mean PCW pressure, mm Hg, mean±SD	16.9±7.6	18.4±8.8	1.4 (0.88, 2.0)	<0.001	22, 18
Previous HTx, n (%)	3 (0.3)	1139 (3.2)		<0.001	0, 0

(*Continued*)

Table 1. Continued

Characteristic	ACHD	NCHD	Absolute Mean Difference (95% CI)	*P* Value	% Missing (ACHD, NCHD)
Hepatitis C virus serology positive, n (%)	38 (4.3)	669 (1.9)		<0.001	4, 3
CMV serology positive, n (%)	435 (50.8)	20 187 (59.5)		<0.001	8, 8
EBV serology positive, n (%)	616 (70.4)	25 006 (72.4)		0.008	7, 5
On chronic steroids, n (%)	56 (6.3)	3396 (9.7)		0.001	4, 4
On immunosuppressive medications, n (%)	845 (95.1)	34 023 (97.5)		<0.001	2, 1
Hospitalization within past 90 d, n (%)	285 (58.5)	11 307 (62.9)		0.025	46, 49
Blood transfusion while on waitlist, n (%)	155 (17.5)	7713 (22.1)		0.003	6, 6
Implantable defibrillator, n (%)	58 (9.5)	3661 (15.8)		0.001	37, 37
On life support, n (%)	543 (60.1)	26 732 (75.8)		<0.001	0, 0
ECMO, n (%)	16 (1.8)	203 (0.58)		<0.001	0, 0
IABP, n (%)	24 (2.7)	2149 (6.1)		<0.001	0, 0
Inotropes, n (%)	449 (49.8)	14 251 (40.4)		<0.001	0, 0
Other life support, n (%)	29 (3.2)	2393 (6.8)		<0.001	0, 0
Time on inotropes, d, mean±SD	9.4±12.4	6.8±7.8	2.6 (1.3–3.9)	<0.001	0, 0
Post-HTx dialysis, n (%)	195 (22.0)	3644 (10.5)		<0.001	2, 1
Post-HTx cardiac reoperation, n (%)	140 (22.7)	2993 (12.6)		<0.001	37, 34
Post-HTx surgery, n (%)	144 (23.5)	4039 (17.2)		<0.001	32, 33
Post-HTx infection, n (%)	181 (29.4)	5790 (24.5)		0.017	34, 35
Post-HTx length of hospital stay, d, mean±SD	26.8±32.8	20.3±24.4	6.5 (4.3–8.8)	<0.001	9, 6
Acute rejection episode, n (%)	171 (20.7)	5311 (17.6)		0.022	8, 16
Low volume HTx center, n (%)	94 (10.4)	226 (0.6)		<0.001	0, 0
Moderate volume HTx center, n (%)	130 (14.4)	8222 (23.3)		<0.001	0, 0
Moderate volume ACHD HTx center, n (%)	130 (14.4)	11 038 (31.3)		<0.001	0, 0
High volume ACHD HTx center, n (%)	229 (25.4)	7083 (20.1)		<0.001	0, 0
Very high volume ACHD HTx center, n (%)	356 (39.4)	9285 (26.3)		<0.001	0, 0

ACHD indicates adult congenital heart disease; BMI, body mass index; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; EBV, Epstein-Barr virus; ECMO, extracorporeal membrane oxygenation; HTx, heart transplantation; IABP, intra-aortic balloon pump; NCHD, noncongenital heart disease; PA, pulmonary artery; PCW, pulmonary capillary wedge; and PGE, prostaglandin E.

Significant differences in donor characteristics between HTx recipients with ACHD or NCHD are shown in Table 2. Among all listed recipients, donors to recipients with ACHD were younger, shorter, weighed less, were more likely to be women, and had lower international normalized ratios. In addition, donors to all

Table 2. Differences in Donor Characteristics Among All Listed Recipients (N=36 177)

Characteristic	ACHD, n=903	NCHD, n=35 274	Absolute Mean Difference (95% CI)	*P* Value	Missing, % (ACHD, NCHD)
Age, y, mean±SD	28.9±11.2	31.9±11.8	2.9 (2.2–3.7)	<0.001	0, 0
Female, n (%)	333 (36.9)	10 268 (29.1)		<0.001	0, 0
Height, cm, mean±SD	171.4±10.5	174.2±9.6	2.8 (2.1–3.5)	<0.001	0, 0
Weight, kg, mean±SD	75.4±18.5	82.0±18.6	6.6 (5.3–7.8)	<0.001	0, 0
Ejection fraction, %, mean±SD	62.2±7.6	61.6±7.3	0.61 (0.13–1.1)	0.013	1, 2
INR, mean±SD	1.31±0.27	1.36±1.24	0.05 (0.03–0.07)	<0.001	20, 22

ACHD indicates adult congenital heart disease; INR, international normalized ratio; and NCHD, noncongenital heart disease.

listed recipients with ACHD had higher ejection fractions compared with recipients with NCHD.

The Figure depicts overall survival for patients with ACHD or NCHD after HTx. The survival curves (Figure [A]) suggest a time-dependent variability in mortality risk between groups. Although 30-day survival (Figure [B]) was worse for recipients with ACHD versus NCHD (P<0.001), among those surviving to 30 days (Figure [C]) survival rates were similar out to 4 years (P=0.31) and beyond 4 years were superior (Figure [D]) among survivors with ACHD compared with NCHD (P<0.001).

Next, we constructed multivariable models to identify donor characteristics associated with post-HTx mortality in each risk period including HTx recipients with ACHD or NCHD to identify donor characteristics that might influence donor-acceptance decision making regardless of recipient. These models included recipient waitlist time and site transplant volume as well as ACHD transplant volume as variables. Table 3 demonstrates hazard ratios (HRs) for risk factors that significantly predicted mortality in each risk period. We then investigated which of these factors were more common among patients with ACHD. There were no donor characteristics associated with early or intermediate mortality. Donor age was associated with late mortality (hazard ratio [HR], 1.009; 95% CI, 1.006–1.011; P<0.001), whereas donor ejection fraction was associated with late survival (HR, 0.996; 95% CI, 0.922–1.000; P=0.041). Neither center transplant volume nor waitlist time was associated with mortality in any time period. Panel reactive antibodies, ABO blood group, graft dysfunction, and an acute episode of rejection were not significant predictors of mortality, respectively.

To identify donor variables posing a specific risk to patients with ACHD, we constructed multivariable models of post-HTx mortality including only HTx

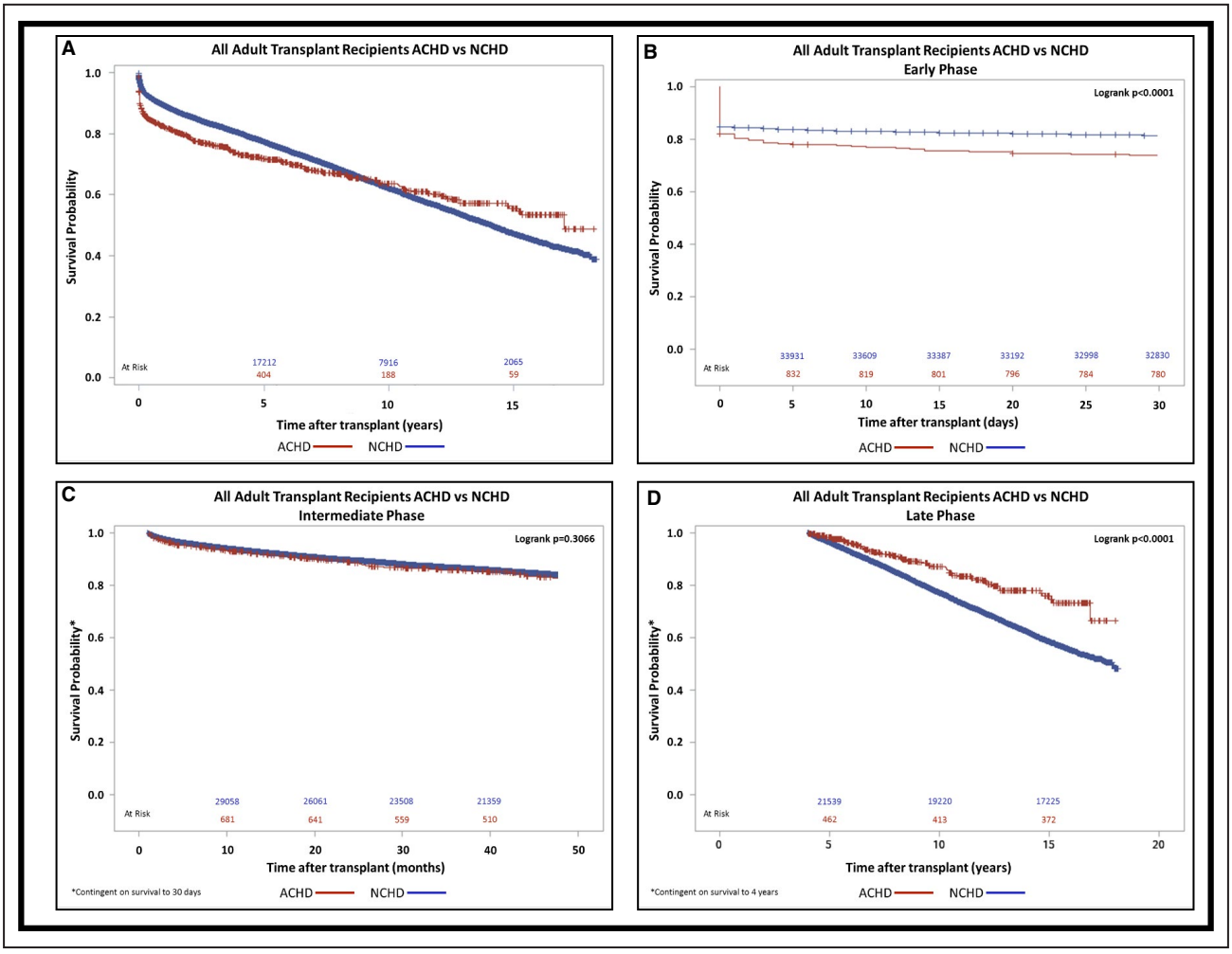

Figure 1. Survival curves for all listed HTx recipients.
A, Survival curves for all HTx recipients. ACHD vs NCHD data show that patients with ACHD experienced time-dependent survival variability such that (**B**) early survival to 30 days was inferior, (**C**) intermediate survival of 31 days to 4 years was similar, and (**D**) late survival after 4 years was superior. ACHD indicates adult congenital heart disease; and NCHD, noncongenital heart disease.

Table 3. Multivariable Analysis of Mortality Among Entire Cohort

Characteristic	Hazard Ratio (95% CI)	*P* Value
Early mortality (0 to 30 d)		
Candidate total bilirubin	1.016 (1.005–1.027)	0.006
Recipient on immunosuppressive medications	0.549 (0.475–0.635)	<0.001
Recipient on antiviral therapy	0.955 (0.909–1.002)	0.146
Recipient ECMO*	1.453 (1.109–1.904)	0.007
Recipient time receiving inotropes*	0.998 (0.996–1.001)	0.117
Post-HTx dialysis*	1.181 (1.111–1.273)	<0.001
Post-HTx surgery*	1.075 (1.020–1.132)	0.006
Post-HTx length of hospital stay*	0.996 (0.995–0.997)	<0.001
Intermediate mortality (31 d to 4 y)		
Candidate Black race	1.074 (1.023–1.128)	0.004
Candidate on dialysis	1.078 (0.933–1.237)	0.144
Candidate history of CABG	1.054 (1.003–1.107)	0.037
Recipient on immunosuppressive medications	0.628 (0.499–0.789)	<0.001
Recipient time receiving inotropes*	1.003 (1.001–1.005)	0.012
Post-HTx dialysis*	1.269 (1.179–1.366)	<0.001
Post-HTx surgery*	1.060 (1.003–1.120)	0.038
Post-HTx length of hospital stay*	1.002 (1.002–1.003)	<0.001
Donor age	1.001 (1.000–1.003)	0.134
Late mortality (>4 y)		
Candidate creatinine	1.033 (1.002–1.066)	0.038
Candidate height	0.995 (0.991–0.998)	0.005
Candidate weight	1.003 (1.001–1.005)	0.003
Candidate age	1.013 (1.010–1.016)	<0.001
Candidate Black race	1.252 (1.156–1.355)	<0.001
Candidate peripheral vascular disease	1.485 (1.290–1.710)	<0.001
Candidate diabetes mellitus	1.443 (1.320–1.577)	<0.001
Candidate 10 pack-y cigarette use	1.359 (1.262–1.464)	<0.001
Candidate history of cigarette use	1.286 (1.193–1.386)	<0.001
Candidate history of CABG	1.188 (1.076–1.311)	<0.001
Candidate history of heart valve surgery	0.781 (0.661–0.924)	0.004
Recipient on immunosuppressive medications	0.885 (0.822–1.011)	0.145
Recipient on intravenous medications for infection	1.110 (1.010–1.220)	0.030
Recipient on chronic steroids	1.183 (1.079–1.292)	<0.001
Recipient on antiviral therapy	1.037 (0.959–1.057)	0.141
Recipient 2 current HLA-DR mismatches	1.011 (0.941–1.044)	0.138
Recipient clinical infection	1.111 (1.032–1.196)	0.004
Post-HTx chest drain*	1.226 (1.021–1.472)	0.033
High volume ACHD center*	1.024 (0.953–1.055)	0.144
Donor age	1.009 (1.006–1.011)	<0.001
Donor ejection fraction*	0.996 (0.922–1.000)	0.041

ACHD indicates adult congenital heart disease; CABG, coronary artery bypass graft; ECMO, extracorporeal membrane oxygenation; HLA-DR, human leukocyte antigen–DR isotype; and HTx, heart transplantation.

*More common and/or higher among patients with ACHD compared with patients with noncongenital heart disease.

recipients with ACHD for each period of risk, as shown in Table 4. There were no donor characteristics associated with mortality in the early or intermediate periods. Donor prerecovery steroid use and meeting Centers for Disease Control and Prevention high-risk donor criteria were associated with late mortality (HR, 2.891 [95% CI, 1.189–7.029; *P*=0.006] and HR, 2.612 [95% CI, 1.327–5.142; *P*=0.006], respectively), whereas donor history of other drug use was associated with late survival (HR, 0.460; 95% CI, 0.248–0.850; *P*=0.013).

Next, we limited our analysis to patients with a final listing status of 1A given that patients with ACHD listed as 1A experience longer waitlist times and worse waitlist outcomes.[6] Table S1 depicts differences in candidate and recipient characteristics, and Table S2 depicts difference in donor characteristics. The candidate, recipient, and donor characteristics of patients listed as status 1A are largely similar to those of the total cohort. Figure S1 depicts overall survival for patients with ACHD or NCHD after HTx who were listed as 1A. The survival curves suggest a similar 3-period, time-dependent difference in mortality risk between groups as that seen for the total cohort. Table S3

Table 4. Multivariable Analyses of Mortality Among All Patients With ACHD

Characteristic	Hazard Ratio (95% CI)	*P* Value
Early mortality (0 to 30 d)		
Candidate total bilirubin	1.068 (1.025–1.112)	0.002
Intermediate mortality (31 d to 4 y)		
No variables associated		
Late mortality (>4 y)		
Candidate diabetes mellitus	3.621 (1.040–12.614)	0.043
Candidate pulmonary embolus	4.637 (0.600–35.855)	0.142
Candidate prior thoracic surgery	1.835 (1.044–3.227)	0.035
Donor history of other drug use	0.460 (0.248–0.850)	0.013
Donor prerecovery steroid use	2.891 (1.189–7.029)	0.006
CDC “high-risk donor”	2.612 (1.327–5.142)	0.006

ACHD indicates adult congenital heart disease; and CDC, Centers for Disease Control and Prevention.

depicts the multivariable models of post-HTx mortality in each period of risk. These models identified no donor-specific risk factors that were significantly associated with early, intermediate, or late mortality.

Because patients with ACHD spent more time on the waitlist compared with patients with NCHD, we investigated variables associated with waitlist times. After controlling for other factors, carrying a diagnosis of ACHD extended waitlist time by 69.5 days. Similarly, among patients listed as status 1A, patients with ACHD waited longer for a transplant compared with patients with NCHD and having ACHD extended waitlist time by 76.4 days after controlling for other factors. Finally, we investigated donor characteristics associated with waitlist times among patients with ACHD listed as status 1A because this group has been previously shown to have high rates of waitlist mortality or delisting attributed to worsening clinical status.[6] We identified awaiting an Epstein-Barr virus nuclear antigen negative donor (313±148 days; P=0.0355), a donor without an alcohol use disorder (199±66 days; P=0.003), and a cytomegalovirus (CMV) negative donor (122±43 days; P=0.005) as being associated with increased waitlist time. There were no differences in the numbers of Epstein-Barr virus–negative donors, CMV-negative donors, or donors with alcohol use disorders between recipients with ACHD or NCHD, respectively, and these variables were not significantly associated with mortality regardless of listing status. We also found that increased donor body weight (3±1 day per kg increase; P=0.011) and male donors (89±45 days; P=0.049) were associated with increased waitlist times, and donor height approached a significant association with increased waitlist time (4±2 days per cm increase, P=0.054). Panel reactive antibodies and ABO blood group were not significant predictors of waitlist time.

DISCUSSION

In this large, contemporary analysis of the SRTR HTx database, we aimed to inform donor selection for patients with ACHD by examining the impact of donor characteristics on post-HTx outcomes and waitlist time in patients with ACHD. We found posttransplant outcomes in ACHD vary over time, as has been demonstrated in other studies[4,14,15]; however, unlike in these studies, we identified 3 distinct periods of risk. Most important, we identified no donor characteristics associated with early or intermediate mortality, and very few donor characteristics associated with late mortality, which argues strongly against the need for unique donor selection criteria for ACHD. Moreover, we found evidence that donor selection may be impacting ACHD waitlist times, which may have implications for waitlist outcomes. The results presented in this article should reassure respective HTx teams, whether dedicated ACHD or conventional adult, that no change in the normal donor organ evaluation paradigm is necessary when considering grafts for patients.

We identified no donor characteristics associated with early or intermediate mortality and very few donor characteristics associated with late mortality when evaluating all patients with ACHD or NCHD who received a transplant. Increasing donor age was associated with late mortality, and increasing ejection fraction was associated with late survival, which is consistent with American Society of Transplantation recommendations to prioritize younger donor age and good graft function over other donor risk factors.[16] Notably, donor age was lower and ejection fraction was marginally greater among HTx recipients with ACHD compared with patients with NCHD. We hypothesize that the reason widely accepted donor risk factors such as ischemia time and predicted heart-size mismatch were not redemonstrated in the present analysis may be attributable to the fact that we limited the analysis to years after 2000. During this time period, these factors may largely have already been integrated into donor selection practice.

Among HTx recipients with ACHD considered in isolation, no donor characteristics were associated with early or intermediate mortality, but meeting Centers for Disease Control and Prevention high-risk donor criteria was associated with late mortality. To be considered a high-risk donor, one must meet certain criteria for behaviors associated with risk of infection with HIV and hepatitis C virus (although in the current era, hepatitis C virus is less of a concern).[17] This association with late mortality is difficult to interpret as the risk of infection is actually greatest early after HTx when immunosuppression is highest. However, high-risk donors may be more likely to harbor certain infections (HIV, CMV, and hepatitis C virus) that have been historically associated with late vasculopathy and malignancy, such as allograft coronary artery disease, Kaposi sarcoma, and non-Hodgkin lymphoma.[18,19] Some data suggest that patients with ACHD may be more likely to accept a high-risk donor as they are typically younger,[20] although we did not observe this in our study. To our knowledge, high-risk donors in patients with ACHD have not been thoroughly evaluated previously, but current literature in pediatric and adult HTx recipients suggest that carefully selected high-risk donor allografts can be used with equivalent survival rates.[21,22] Overall, the failure to identify novel donor characteristics associated with early mortality, a time when patients with ACHD have disproportionately worse waitlist outcomes, suggests that patients with ACHD should not require unique donor criteria, and teams should focus only on evidence-based donor selection.

Our study found that patients with ACHD were less likely to be initially listed as status 1A, had longer waitlist times when listed as status 1A, and were less likely to be transplanted compared with patients with NCHD. Other analyses have found the same, and even more concerning have demonstrated disproportionate waitlist mortality and delisting for clinical worsening among patients with ACHD listed as status 1A.[5,6] Importantly, we identified no novel donor characteristics associated with mortality at any time period posttransplant among patients with ACHD listed as status 1A. Although it remains to be seen how recent United Network for Organ Sharing (UNOS) changes in listing criteria and allocation will change waitlist outcomes in ACHD,[3] these data suggest that broadening donor selection criteria may improve these poor waitlist outcomes.

Anecdotally, HTx teams have been reported to "cherry pick" donors for patients with ACHD; however, the present study found only very limited evidence to support this. In fact, we found very few differences in donor characteristics between HTx recipients with ACHD and NCHD. ACHD donors were smaller in size and younger, likely reflecting the younger age and lower body mass index of patients with ACHD. Importantly, the present data do not suggest a systematic practice of oversizing donors for recipients with ACHD, although it may take place at certain individual institutions. The differences in donor characteristics we identified had no effect on mortality, and this should be further reassuring that the patients with ACHD do not require separate and strict donor selection criteria and to the contrary, may benefit from further liberalization.

In contrast, we found awaiting donors with certain characteristics were associated with longer waitlist times for patients with ACHD listed as status 1A. These included negative viral serologies, larger sizes, male sex, and no history of alcohol use disorders. Awaiting donors with these characteristics is largely based on historical, somewhat controversial, and evolving evidence. For example, although virology mismatch of CMV and Epstein-Barr virus (transplanting a positive serology donor into a negative recipient [D+/R–]) is not a formal donor selection criterion nor an absolute contraindication to transplantation, virology mismatch has been associated with worse post-HTx mortality, cardiac allograft vasculopathy, and posttransplant lymphoproliferative disease,[23,24] which may increase consideration of allograft rejection. However, recent studies and reviews have demonstrated that antivirals and tapering immunosuppressive regimens have been effective in preventing post-HTx complications attributed to CMV.[24] Treatment and preventive strategies for Epstein-Barr virus–related complications, although rare, are less robust and require further research.[25] With regard to donor body size, fear of undersizing has led some centers and publications to support empiric donor oversizing (maximizing the donor/recipient weight ratio) for patients with ACHD to negate the impact of potentially higher pulmonary vascular resistance.[26] However, recent analysis of the UNOS database found that oversizing does not improve survival in the ACHD population,[27] and the American Society of Transplantation has recommended against oversizing for recipients with pulmonary hypertension or for female to male transplantations.[16] Lastly, allografts from donors with alcohol use disorders might be avoided because of the risks of alcoholic cardiomyopathy, but evidence has shown that with careful screening and selection, allografts from donors with alcohol use disorders can be used with equivalent outcomes barring any pretransplant cardiac dysfunction.[28] The evidence behind the donor selection behaviors found in the present study are insufficient and poorly predictive of post-HTx outcomes, and limiting selection to donor characteristics with clear supportive evidence may decrease waitlist times and improve waitlist outcomes for patients listed as status 1A.

The present data confirm that recipients with ACHD have high early perioperative mortality (within 30 days) and decreased long-term mortality (>4 years). Previous registry studies have found the same.[14,15] In our study, early perioperative ACHD mortality was associated with higher recipient bilirubin and preoperative extracorporeal membrane oxygenation, and with post-HTx complications, such as requiring dialysis or cardiac reoperation. In contrast, superior late survival is likely attributable to a lower comorbidity burden in recipients with ACHD compared with recipients with NCHD. Given the high early mortality and the growing number of recipients with ACHD, alleviating perioperative risk should be a priority for the ACHD HTx population. We did not specifically address the impact of donor-specific factors on postoperative need for dialysis or cardiac reoperation in the present study; however, this should be pursued in future research aimed at improving early posttransplant outcomes in ACHD. Recent data from Menachem et al[29] and Nguyen et al[30] suggest that this early mortality gap can be improved through greater provider and center familiarity with the operative and perioperative management of this unique and complicated patient group. In contrast to these analyses, we found no association between center transplant volume and ACHD mortality. Differences in data source (SRTR in the present study versus UNOS) and division of patients by center volume (tertiles in the present study versus quartiles) and the larger number of patients in the present study because of the later inclusion date (2016 in the present study versus 2015) likely explain the disparate findings.

Our findings are not without limitations. First, this study is subject to the inherent bias of retrospective studies including incomplete or inaccurate data entry from participating sites. Missing data can be a

substantial challenge in the analysis of large data sets, and we attempted to avoid problems with missing data by excluding ≥50% of data missing from models. This approach, however, may have omitted informative variables, and large numbers of exclusions can promote systematic bias when missingness is associated with outcomes and/or groups of special interest, as they are in this study. Imputing values for missing data, as was done here, was necessary to minimize bias but is a limitation in that it is inherently an approximation. Moreover, we are limited in the variables collected by the SRTR registry. In the case of congenital heart disease, this poses a unique challenge as the SRTR registry does not collect data on congenital anatomy or prior congenital operations. We therefore were unable to analyze outcomes according to specific congenital lesions. Given there is likely significant heterogeneity in risk depending on underlying anatomy, the risk of any individual patient with ACHD should be extrapolated from the present data only with caution.

In conclusion, HTx candidates with ACHD do not appear to require separate and strict donor selection criteria, and HTx teams should focus on liberalizing and further defining evidence-based donor criteria to improve waitlist outcomes and reduce the recipient–donor disparity.

ARTICLE INFORMATION

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Disclosures

J.M. is a consultant to Abbott Vascular. A.M.C. has worked as a consultant for Syncardia, Berlin Heart, and Medtronic. The remaining authors have no disclosures to report.

Supplementary Material

Tables S1–S3
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Differences in (A) Candidate and (B) Recipient Characteristics Among Status 1A Listed Patients.

(A) Candidates N=29181					
Characteristic	**ACHD N=746**	**NCHD N=28435**	**Absolute Mean Difference (95% CI)**	**p-value**	**% Missing (ACHD, NCHD)**
Age at listing, years ±SD	36.4 ± 12.0	52.2 ± 12.2	15.8 (14.9, 16.7)	<0.001	0, 0
Female, N (%)	267 (35.8)	6591 (23.2)		<0.001	0, 0
White, N (%)	657 (88.1)	21269 (74.8)		<0.001	0, 0
Black, N (%)	57 (7.6)	6068 (21.3)		<0.001	0, 0
Multi-race, N (%)	6 (0.8)	104 (0.37)		<0.001	0, 0
Height, cm ± SD	170.1 ± 10.7	174.5 ± 10.0	4.4 (3.7, 5.2)	<0.001	0, 0
Weight, kg ± SD	72.9 ± 18.9	84.2 ± 18.6	11.3 (10.0, 12.7)	<0.001	0, 0
Creatinine, mg/dL ± SD	1.19 ± 0.62	1.42 ± 0.95	0.22 (0.17, 0.27)	<0.001	2, 2
Albumin, g/dL ± SD	3.83 ± 0.83	3.57 ± 0.74	0.27 (0.19, 0.34)	<0.001	38, 36
Mean PCW pressure, mmHg ± SD	18.5 ± 8.6	20.5 ± 8.9	2.0 (1.2, 2.8)	<0.001	28, 14
History of cigarette use, N (%)	128 (20.3)	11122 (48.3)		<0.001	15, 19
On medication for hypertension, N (%)	118 (24.7)	9518 (48.9)		<0.001	38, 33
On medication for COPD, N (%)	9 (1.9)	867 (4.6)		0.013	39, 35
History of malignancy, N (%)	21 (2.8)	2003 (7.1)		<0.001	2, 2
On amiodarone, N (%)	110 (23.8)	6064 (23.2)		<0.001	40, 36
Implantable defibrillator, N (%)	339 (45.6)	18531 (65.5)		<0.001	2, 2
Prior cardiac surgery, N (%)	531 (71.4)	9089 (32.1)		<0.001	16, 19
Prior HTx, N (%)	3 (0.4)	1178 (4.1)		<0.001	0, 0
Life support, N (%)	286 (38.4)	13146 (46.4)		<0.001	0, 0
ECMO, N (%)	25 (3.4)	537 (1.9)		0.004	0, 0
IABP, N (%)	19 (2.6)	2412 (8.5)		<0.001	0, 0
Inotropes, N (%)	240 (32.2)	10380 (36.5)		0.015	0, 0
PGE, N (%)	3 (0.40)	31 (0.11)		0.021	0, 0

Received HTx, N (%)	414 (55.5)	18569 (65.3)		<0.001	0, 0
Removed from waitlist without HTx, N (%)	117 (15.8)	3440 (12.1)		0.003	0, 0
(B) Recipients N= 18983					
Characteristic	**ACHD N=414**	**NCHD N=18569**	**Absolute Mean Difference (95% CI)**	**p-value**	**% Missing (ACHD, NCHD)**
Waitlist time, days ± SD	297 ± 445	213 ± 351	84 (42, 126)	0.003	0, 0
Age at HTx, years ± SD	37.9 ± 12.5	52.7 ± 12.3	14.8 (13.6, 16.0)	<0.001	0, 0
Previous HTx, N (%)	3 (0.7)	556 (3.0)		0.007	0, 0
Prior cardiac surgery, N (%)	126 (31.1)	4496 (24.6)		0.009	11, 15
Hepatitis B surface antigen positive, N (%)	11 (2.8)	263 (1.5)		<0.001	8, 5
Hepatitis C serology positive, N (%)	18 (4.5)	370 (2.0)		<0.001	6, 3
CMV serology positive, N (%)	200 (51.0)	10532 (58.6)		0.027	8, 6
EBV serology positive, N (%)	276 (68.8)	13392 (73.8)		0.005	8, 5
On chronic steroids, N (%)	20 (4.9)	1726 (9.4)		0.008	4, 4
On immunosuppressive medications, N (%)	387 (95.6)	17856 (97.6)		0.011	2, 1
On life support, N (%)	334 (80.7)	16492 (88.8)		<0.001	0, 0
ECMO, N (%)	15 (3.6)	188 (1.0)		<0.001	0, 0
IABP, N (%)	22 (5.3)	1998 (10.8)		<0.001	0, 0
PGE, N (%)	3 (0.72)	39 (0.21)		0.027	0, 0
Inotropes, N (%)	263 (63.5)	7693 (41.5)		<0.001	0, 0
Other life support, N (%)	19 (4.6)	1679 (9.1)		0.002	0, 0
Total ischemic time, minutes ± SD	209.1 ± 70.7	191.8 ± 61.2	17.2 (10.2, 24.3)	<0.001	5, 4
Post-HTx surgery, N (%)	63 (26.8)	2266 (20.6)		0.004	43, 41
Post-HTx cardiac reoperation, N (%)	62 (26.2)	1637 (14.8)		<0.001	46, 41

Post-HTx dialysis, N (%)	101 (25)	2261 (12.4)		<0.001	2, 2
Post-HTx length of hospital stay, days ± SD	29.8 ± 37.3	22.0 ± 25.1	7.8 (4.0, 11.7)	<0.001	12, 7
Low volume HTx center, N (%)	41 (9.9)	94 (0.5)		<0.001	0, 0
Moderate volume HTx center, N (%)	54 (13.0)	4776 (25.7)		<0.001	0, 0
Low volume ACHD HTx center, N (%)	79 (19.1)	4482 (24.1)		0.017	0, 0
Moderate volume ACHD HTx center, N (%)	53 (12.8)	5805 (31.3)		<0.001	0, 0
High volume ACHD HTx center, N (%)	102 (24.6)	3375 (18.2)		<0.001	0, 0
Very high volume ACHD HTx center, N (%)	180 (43.4)	4907 (26.4)		<0.001	0, 0

ACHD, adult congenital heart disease; NCHD, non-congenital heart disease; SD, standard deviation; CI, confidence interval; PCW, pulmonary capillary wedge; COPD, chronic obstructive pulmonary disease; HTx, heart transplantation; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; PGE, prostaglandin E; CMV, cytomegalovirus; EBV, Epstein-Barr virus

Table S2. Differences in Donor Characteristics Among Status 1A Listed Recipients, N=18983.

Characteristic	ACHD N=414	NCHD N=18569	Absolute Mean Difference (95% CI)	p-value	% Missing (ACHD, NCHD)
Age, years ± SD	29.2 ± 10.6	31.6 ± 11.4	2.4 (1.3, 3.5)	<0.001	0, 0
Female, N (%)	126 (30.4)	4786 (25.8)		0.033	0, 0
Height, cm ± SD	173.3 ± 9.4	174.9 ± 9.3	1.6 (0.7, 2.5)	<0.001	0, 0
Weight, kg ± SD	78.3 ± 18.1	83.3 ± 18.4	5.1 (3.3, 6.9)	<0.001	0, 0
AST, U/L ± SD	149 ± 465	102 ± 310	47 (1.5, 92)	0.043	0, 1
ALT, U/L ± SD	147 ± 446	100 ± 288	47 (3.4, 90)	0.035	0, 1
INR ± SD	1.30 ± 0.24	1.36 ± 1.31	0.06 (0.03, 0.10)	<0.001	14, 15

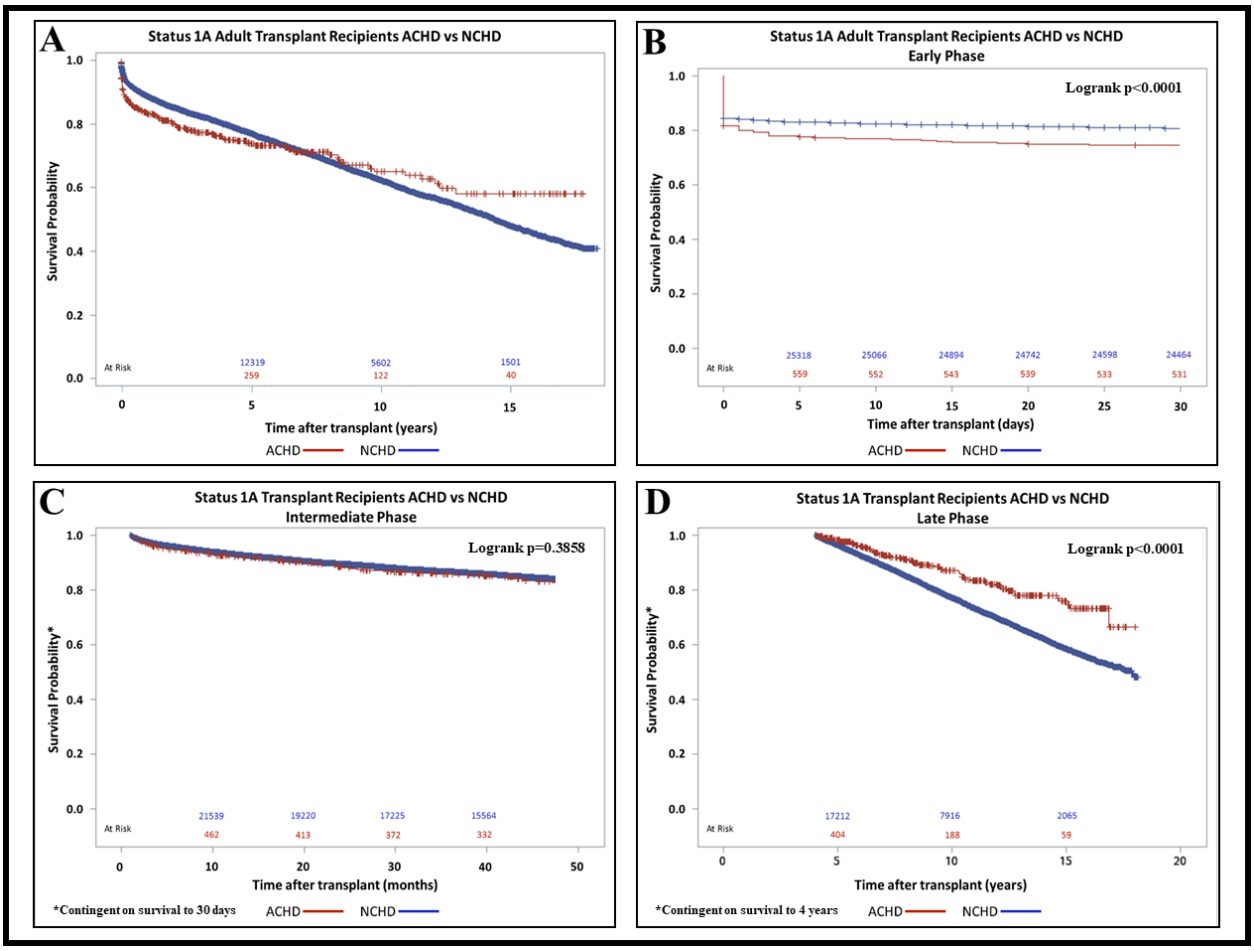
SD, standard deviation; CI, confidence interval; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, International Normalized Ratio

Table S3. Multivariable Analyses of Mortality Among Status 1A Listed ACHD Patients.

Characteristic	Hazard Ratio (95% CI)	p-value
Early Mortality (0 to 30 days)		
Candidate total bilirubin	1.078 (1.017-1.143)	0.012
Intermediate Mortality (31 days to 4 years)		
No variables associated		
Late Mortality (greater than 4 years)		
Candidate receiving amiodarone	4.913 (1.442-16.737)	0.011
Candidate with implantable defibrillator	0.236 (0.062-0.903)	0.035
Donor inotropic support	0.373 (0.124-1.126)	0.080
Donor ejection fraction	0.946 (0.878-1.019)	0.140
Donor history of other drug use	0.367 (0.102-1.319)	0.125

ACHD, adult congenital heart disease

Figure S1. Survival curves for all status 1A listed HTx recipients - Survival curves for all status 1A listed HTx recipients (2A), ACHD versus NCHD, again shows time-dependent variability similar to the entire cohort with inferior early survival (2B), similar intermediate survival (2C), and superior late survival (2D) for ACHD patients.



ACHD, adult congenital heart disease; NCHD, non-congenital heart disease