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Simultaneous Heart–Liver Transplantation for Congenital Heart Disease in the United States: Rapidly Increasing With Acceptable Outcomes

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BACKGROUND AND AIMS: There are more adults than children living with congenital heart disease (CHD) in the United States, with a growing proportion requiring heart–liver transplantation (HLT). Our aim was to ascertain the frequency, outcomes, and prognostic factors in this patient population.

APPROACH AND RESULTS: United Network for Organ Sharing data on adult patients who underwent heart transplantation (HT) from 2009 through March 2020 were analyzed. The primary study outcome was patient survival. Cox proportional-hazards modeling assessed for mortality associations. There were 1,084 HT recipients: 817 (75.4%) CHD HTs only, 74 (6.8%) CHD HLTs, 179 (16.5%) non-CHD HLTs, and 14 (1.3%) heart–liver–kidney transplants. The number of CHD HLTs increased from a prior rate of 4/year to 21/year in 2019. Among patients with CHD, the 5-year survival rates were 74.1% and 73.6% in HTs only and HLTs, respectively (P = 0.865). There was a higher rate of allograft failure attributable to rejection in CHD HTs only compared with CHD HLTs (3.2% versus 0.4%; P = 0.014). Only 25 out of 115 HT-performing hospitals undertook CHD HLTs. Higher-volume centers (averaging one CHD HLT per year) had a 5-year patient survival rate of 83.0% compared with 61.3% in lower-volume centers (P = 0.079). Among HLT recipients, total bilirubin (hazard ratio [HR], 1.06; 95% confidence interval [CI], 1.01-1.12) and diabetes (HR = 2.97, 95% CI = 1.21-7.31) were independently associated with increased mortality risk, whereas CHD and age were not.

CONCLUSIONS: The rate of HLT for adult CHD in the United States is rising dramatically. The survival outcomes between CHD HT only and CHD HLT groups are comparable; however, the HLT group had lower rates of acute rejection. Among HLT recipients, diabetes and elevated bilirubin are associated with increased posttransplant mortality risk. An average of one CHD HLT per year could be considered a minimum quality metric at transplant centers. (Hepatology 2021;73:1464-1477).

The first case of simultaneous heart–liver transplantation (HLT) was performed by Starzl and colleagues in a 6-year-old patient with homozygous familial hypercholesterolemia in 1984.[(1)] The role of the liver in this case was as a therapeutic intervention to address the inherent metabolic abnormality in order to optimize the longevity of the transplanted heart, which was successful with posttransplantation serum cholesterol decreasing to 270 mg/dL from a baseline of >1,000 mg/dL. Since this case, indications for HLT have expanded to include patients with cardiac cirrhosis; however, the operation continues to

Abbreviations: BMI, body mass index; CHD, congenital heart disease; CI, confidence interval; HLKT, heart–liver–kidney transplantation; HLT, heart–liver transplantation; HR, hazard ratio; HT, heart transplantation; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; OPTN, Organ Procurement and Transplantation Network; PRA, panel-reactive antibody; SD, standard deviation; UNOS, United Network for Organ Sharing.

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be performed infrequently, with only 159 HLTs performed between 1988 and 2014 in the United States.[2]

Over the past several decades, there has been a decline in mortality from congenital heart disease (CHD), attributable to improvements in both surgical and medical management.[3] An example is the Fontan procedure pioneered by Francis Fontan and Eugene Baudet in 1971[4] and further described in 1973 by Guillermo Kreutzer et al.,[5] which transformed the prognosis of children with only a single functional ventricle (e.g., tricuspid or mitral atresia, hypoplastic left [or right] heart syndrome). The Fontan circulation has been created by many methods but essentially obviates the need for the ventricle to pump blood to the lungs by creating a direct connection between the superior and inferior vena cava and pulmonary artery, with systemic venous pressure propagating blood flow through the lungs. Consequently, this translates to higher than normal caval and hepatic venous pressures given the absence of a pumping chamber prior to the pulmonary circulation, even under ideally functioning Fontan circumstances.[4,6] Thus, many post-Fontan patients with CHD develop advanced liver disease related to this chronic outflow impairment, coupled with the low cardiac output of the post-Fontan heart.[4,6] Compared to liver disease associated with long-standing congestive heart failure, hepatic changes in Fontan patients have been proven to be more severe with extensive fibrosis secondary to the fibroinflammatory response to functional outflow obstruction.[7,8] The Fontan operation is now firmly established as an effective treatment modality in suitable patients in the United States, with an average of 1,062 Fontan operations performed annually between 2001 and 2016.[9]

Adults with CHD continue to increase in age and number, with almost 1.4 million adults living with CHD in the United States in 2010, a 60% rate increase since 2000,[3] while the incidence of moderate and severe forms of CHD is about 0.6% of live births (1.9% of live births if the potentially serious bicuspid aortic valve is included).[10] Unfortunately, the Fontan procedure is palliative, not curative, with <50% of patients alive 30 years post-Fontan.[11] From the time of Fontan procedure, the patient enters a form of chronic heart failure and will face the possibility of heart transplantation (HT) at some point.[12] Studies have reported up to 21% of patients undergoing the Fontan procedure ultimately requiring HT at 20 years.[13] Evidently, the need for HT, as well as HLT in a sizeable subset, is expected to increase substantially. This anticipated increase has, however, not been observed as of yet, with the baseline rate of HLT for CHD remaining low at four to five cases annually as of 2015, with a minority of transplant centers performing HLT.[14] This may be due in part to the donor pool remaining relatively stagnant over the past decade. This particularly disadvantaged adults with CHD as they did not get elevation in United Network for Organ Sharing (UNOS) priority status, despite the established poor long-term prognosis, until the UNOS donor heart allocation system was updated in 2018.[15] It is expected that this system will increase the likelihood of patients with CHD being transplanted. In addition, improvements in operative techniques and postoperative care have helped patients with Fontan circulation to remain compensated longer, and thus, we likely have not yet observed the true surge of decompensated presentations.

Understanding the outcomes and prognostic factors is critical in the context of the inevitable substantial increase in demand for HLT in the coming years. The aim of our study was to ascertain current trends in frequencies and outcomes in HLT in the United States, particularly

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with regard to CHD, and to determine factors affecting outcomes, including center-specific transplant volume, in order to better inform clinical practice in the near future.

Patients and Methods

STUDY POPULATION AND DATA ACQUISITION

Data were collected from the UNOS on adult patients (18 years of age or older) in the United States who underwent a primary HT from January 1, 2009, through March 17, 2020, including HLTs. Patients with simultaneous transplantation of other organs such as lungs, pancreas, intestine, and kidneys were excluded, apart from simultaneous heart–liver–kidney transplantations (HLKT). These data are prospectively collected by the Organ Procurement and Transplantation Network (OPTN) from transplant programs, organ procurement organizations, and histocompatibility laboratories, supplemented by the Centers for Medicare & Medicaid Services and the National Technical Information Service's Death Master File.[16] Clinical data acquired at the time of transplant included donor age, race, body mass index (BMI), UNOS region, and presence of diabetes, as well as recipient age, gender, race, transplant indication, UNOS region, transplant center, waitlist time, length of hospital stay, comorbidities, available laboratory parameters including Model for End-Stage Liver Disease (MELD) scores (in HLTs), panel-reactive antibody (PRA) activity levels closest to the time of transplant, the presence of ascites and hepatic encephalopathy, as well as pretransplant dialysis requirement. The validated MELD-IX score was also calculated on all patients using the formula 5.11 × ln (serum bilirubin in milligrams per deciliter) + 11.76 × ln (serum creatinine in milligrams per deciliter) + 9.44.[17]

Patients were assigned listing indications ascertained from the thoracic data set first from primary diagnosis (both coding and manual entries were analyzed) on the transplant recipient registration (TRR) form and next from the primary diagnosis (both coding and manual entries were analyzed) on the transplant candidate registration form, if no diagnosis had been assigned from the TRR. Sensitized patients were defined as recipients with a PRA level 25% or higher, consistent with prior studies on this subject.[18,19] Follow-up data included acute rejection episodes, posttransplant stroke, graft failure, and mortality. Per the OPTN, allograft failure was defined as the occurrence of either recipient death, removal of the transplanted organ, or a recipient being placed on a chronic allograft support system.

Data from both thoracic and liver data sets were analyzed separately and then merged as a means of cross-validation. There was 100% concordance in the HLT cases identified independently in the two data sets. Patient follow-up time was also compared between the two datafiles, with the most up-to-date time of follow-up in the final merged database. Data on the region of donor organ recovery were also queried from the deceased donor database and merged with the final data set. As a review of a publicly accessible de-identified database, IRB approval was exempted for this study.

STATISTICAL ANALYSIS

Continuous variables were summarized with medians and interquartile ranges (IQRs) or by means and standard deviations (SD), and frequencies and percentages were used for categorical variables. Comparative analysis of continuous variables was based on the two-sample Wilcoxon rank test for samples that failed the Shapiro-Wilk normality test; otherwise, it was based on the two-sample *t* test. Comparative analysis of categorical variables was based on the two-sided chi-squared test. All data (n = 1,084) were complete apart from the following:

- Missing categorical data: donor diabetes (n = 11), donor race (n = 2), recipient race (n = 7), recipient diabetes (n = 5), recipient dialysis (n = 14), posttransplant dialysis (n = 24), acute rejection (n = 20), and posttransplant stroke (n = 32). These missing data were imputed as "none present."
- Missing continuous data: recipient BMI (n = 1), recipient creatinine (n = 15), and recipient total bilirubin (n = 23). These missing data were ignored. The proportions of missing data in the HLT group were similar to the proportions observed in the entire cohort described above.

The groups of comparison were CHD HT only versus CHD HLT and non-CHD HLT versus CHD HLT. Kaplan-Meier survival analysis was used to estimate the primary study outcome of overall patient survival and secondary study outcomes of cardiac

allograft survival and liver allograft survival. Log-rank testing was used to conduct statistical comparison of survival rates. The survival analysis was deliberately not adjusted for technical deaths (i.e., deaths within 30 days of transplant) in order to better capture the true mortality associated with the complex surgery of patients with CHD. Cox proportional-hazards regression modeling was used to assess for variables associated with mortality among HLTs. Multiple iterations of the model were performed incorporating all available variables which have been shown to be associated with posttransplant mortality in the medical literature. The final model was assessed for proportional hazards assumptions by examination of Schoenfeld residuals. The following covariates were included in the model derivation: donor age, race, gender, BMI, diabetes, as well as recipient age, gender, BMI, waitlist time, operation type, listing indication, gender, race, diabetes, creatinine, total bilirubin, the presence of ascites (any severity), the presence of hepatic encephalopathy (any grade), dialysis requirement, MELD score, and MELD-IX score. These results are provided as hazard ratios (HRs) with confidence intervals (CIs). $P < 0.05$ was considered significant for all statistical methods. The statistical analyses were completed using the Stata statistical package (Stata Statistical Software: Release 16; StataCorp LLC, College Station, TX).

Results

FREQUENCY, LISTING INDICATIONS, AND PRACTICE SETTING

There were 1,084 adult HT recipients who met the study inclusion criteria, of whom 817 (75.4%) were CHD HT-only recipients, 74 (6.8%) were CHD HLT recipients, 179 (16.5%) were non-CHD HLT recipients, and 14 (1.3%) were HLKT recipients (Table 1). Of the 74 CHD HLT recipients, 70 (95%) had documentation of previous cardiac surgery (which was not HT given the study exclusion criteria). Among HLT recipients, the most common listing indication was CHD (74, 29.3%), the next most common was amyloidosis-related cardiomyopathy (59, 23.3%), followed by nonischemic dilated cardiomyopathy (55, 21.6%), while ischemic cardiomyopathy accounted for 30 (11.9%) of HLTs (Table 2).

While information on which organ was the "driving" organ for transplant among HLTs is not directly recorded in the OPTN database, we conclude, from the considerable evidence based on the following assessment, that the heart was the driving organ in the vast majority of cases. At the time of transplant, 241 (95.3%) were listed as status 1A or 1B (old HT priority criteria) or status 1-4 (updated 2018 HT priority criteria), while the remaining 12 (4,7%) were listed as status 2 (old heart criteria).[15] Sixty HLT patients had a MELD score between 20 and 29, of whom 58 (97%) were listed as heart status 1A or 1B (old heart criteria) or status 1-4 (new heart criteria). Only 3 patients had a MELD score at transplant of 30 or greater; of these, 2 were listed as status 1A (old heart criteria), while the other patient was listed as status 2 (new heart criteria), which is highly suggestive that the heart may still have been the driving organ. None of these 3 patients required a simultaneous kidney transplant. Moreover, 251 (99.2%) HLTs had a primary heart listing indication in the heart data set. About 70% of HLT recipients had a diagnosis of "cirrhosis, other" in the liver data set, suggestive of the large proportion of these patients with presumed cardiac cirrhosis.

There was an increase in annual transplant rate in all transplanted groups. The annual frequency of the CHD HT-only group more than doubled over the past decade, increasing from 43 in 2009 to 109 in 2019. The annual frequency of non-CHD HLT also more than doubled, from 10 in 2009 to 22 in 2019 (Fig. 1A). However, there was a noticeable disproportionate increase in annual frequency of the CHD HLT group, which increased >5-fold over the past decade, from a baseline rate of 4 transplants annually during 2010-2015 to 21 transplants in 2019 (Fig. 1A). The annual frequency of CHD HLTs is now similar to that of non-CHD HLTs. In fact, CHD HLTs have surpassed non-CHD HLTs in 2020 through the initial 3 months, with 6 CHD HLTs performed compared with 3 non-CHD HLTs.

There were 110/817 (13.5%) and 10/74 (13.5%) CHD HTs only and CHD HLTs performed at children's transplant centers, respectively. The median age of CHD HLT recipients at the time of transplant was 21 (IQR, 20-26) at children's transplant centers compared to a median age of 51 (IQR, 40-60) at adult transplant centers. There was no difference in survival outcomes for patients with CHD, with 1-year rates of

TABLE 1. Baseline Characteristics of HT and Simultaneous HLT Recipients in the United States, January 1, 2009-March 17, 2020 (n = 1,070 †)

	CHD (n = 891)			Statistical Comparison	
	CHD HT-only	CHD HLT	Non-CHD HLT	CHD HT-Only versus CHD HLT	Non-CHD HLT versus CHD HLT
Donor	n = 817	n = 74	n = 179		
Age (years)	27.0 (21.0-36.0)	26.5 (21.0-35.0)	29.0 (22.0-39.0)		
BMI (kg/m^2)	24.9 (22.0-29.1)	25.3 (23.6-27.1)	25.2 (23.1-28.0)		
Male gender	525 (64.3)	45 (60.8)	131 (73.2%)		*
Caucasian race	508 (62.2)	47 (63.5)	106 (59.2)		
Diabetes	23 (2.8)	1 (1.4)	7 (3.9)		
Recipient					
Age (years)	37.0 (25.0-48.0)	33.0 (28.0-40.0)	57.0 (48.0-62.0)		***
Male gender	493 (60.3)	40 (54.1)	135 (75.4)		***
Caucasian race	641 (78.5)	61 (82.4)	89 (49.7)		***
BMI (kg/m^2)	24.6 (21.1-28.9)	23.6 (20.8-26.7)	25.4 (22.5-29.5)		***
Post-transplant LOS (days)	19.0 (12.0-33.0)	26.5 (18.0-42.5)	21.5 (15.0-34.0)	***	*
Waiting list time (days)	139.0 (42.0-364.0)	142.0 (50.0-339.0)	91.0 (32.0-215.0)		**
Diabetes	71 (8.7)	4 (5.4)	30 (16.8)		*
Serum creatinine (mg/dL)	1.0 (0.8-1.3)	1.0 (0.8-1.2)	1.2 (0.9-1.5)		***
Serum total bilirubin (mg/dL)	0.8 (0.5-1.2)	0.9 (0.6-1.6)	0.9 (0.6-1.5)		
MELD score	n/a	15 (11.0-19.0)	15 (11.0-20.0)		
MELD-XI score	11 (9-15)	13 (10.0-15.0)	14 (10.5-17.0)		*
Dialysis requirement	23 (2.8)	4 (5.4)	8 (4.5)		
Ascites (mild or worse)	n/a	36 (49.7)	77 (43.0)		
Hepatic encephalopathy (grade 1 or worse)	n/a	13 (17.5)	28 (15.6)		

*0.01 < $P \leq 0.05$ (all other P values > 0.05).
†14 additional HLKT recipients are described separately in the article. Values are n (%) or median (IQR).
**0.001 < $P \leq 0.01$.
***$P < 0.001$.
Abbreviations: LOS, length of stay; n/a, not applicable.

83% and 87.5% and 5-year rates of 75.0% and 73.3% in the children and adult transplant centers, respectively ($P = 0.671$). All non-CHD HLTs were performed at adult transplant centers.

Overall, 545/1,070 (51%) donor organs came from the same UNOS region as the respective transplant recipient. Among HLTs, a larger proportion (147/253, 58.1%) received donors from the same UNOS region. The proportion of donor hearts being transplanted to recipients in the same UNOS region has decreased considerably over the study time period. Overall, 253/316 (80%) donors during the 2010-2013 period were given to recipients within the same UNOS region compared to 57/291 (20%) in the 2018-2019 period ($P < 0.001$). Among HLTs, 61/62 (98%) of donors in the 2010-2013 period were given to recipients within the same UNOS region compared to 20/81 (25%) in the 2018-2019 period ($P < 0.001$). The absolute frequency of transplant centers performing HTs increased to 87 in the 2018-2019 period from 83 in the 2010-2013 period. Although the absolute number of centers did not increase drastically, there was more diversity observed, with 24 "new" transplant centers in the 2018-2019 period. Given the complexity of CHD HLTs, the significant geographic variation among UNOS regions was observed, as expected, with regions 2, 5, and 7 accounting for almost 75% of all CHD HLTs in the United States (Fig. 1B).

COMPARATIVE DEMOGRAPHICS

The comparative demographics and characteristics between the study groups are summarized in Table 2.

TABLE 2. Indications for Simultaneous HLT in the United States, January 1, 2009-March 17, 2020 (n = 253)

Listing Indication	n (%)
CHD	74 (29.3)
ARVD	5 (2.0)
Alcohol-related DCM	2 (0.8)
Ischemic DCM	30 (11.9)
Non-ischemic DCM	55 (21.6)
HCM	12 (4.7)
Amyloidosis-related RCM	59 (23.3)
Sarcoidosis-related RCM	2 (0.8)
RCM (other)	9 (3.6)
VHD	2 (0.8)
Cancer	1 (0.4)
Other	2 (0.8)
Total	253 (100)

Abbreviations: ARVD, arrhythmogenic right ventricular dysplasia; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy; VHD, valvular heart disease.

Donor characteristics were similar among all three groups. The recipient characteristics among the CHD groups were also similar, apart from the CHD HLT group having a median of 7.5 more inpatient days posttransplant ($P < 0.001$). Finally, compared with the non-CHD HLT group, CHD HLT recipients were younger (median age, 33 versus 57 years) with more females (45.9%, versus 24.6%) and white race representation (82.4% versus 49.7%) and leaner (median BMI, 23.6 versus 25.4 kg/m^2) with reduced rates of diabetes (5.4% versus 16.8%) and lower median creatinine (1.0 versus 1.2 mg/dL) (all $P < 0.05$). Non-CHD HLT recipients had significantly reduced waitlist time compared with CHD HLT recipients (median, 91 versus 142 days; $P < 0.05$). Of note, non-CHD HLT recipients had higher MELD-XI scores compared with CHD HT-only recipients (median, 14 versus 11; $P < 0.05$). While CHD HLTs also had a higher median MELD-IX score compared with CHD HT-only recipients, this was not statistically significant ($P > 0.05$).

PATIENT SURVIVAL AND THE INFLUENCE OF TRANSPLANT CENTER VOLUME ON THE CHD PATIENT POPULATION

There were 21 patients who were not discharged since the time of transplant at the time of this analysis; therefore, these patients were excluded from the survival analysis and the Cox proportional hazards modeling, while all other patients were accounted for. The 1-year patient survival rates were 85.6%, 81.5%, and 88.3% for the CHD HT-only, CHD HLT, and non-CHD HLT groups, respectively (all $P > 0.05$)

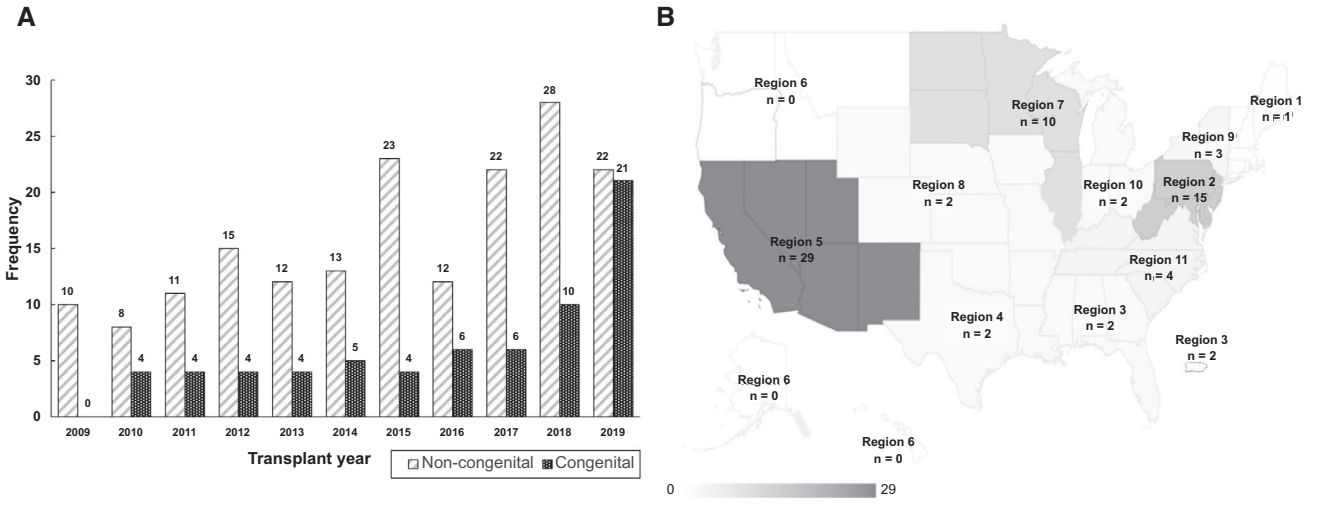

FIG. 1. (A) Annual trends of the frequency of simultaneous HLT in the United States from 2009 to 2019, stratified by CHD versus non-CHD. (B) Geographic variation in the frequency of simultaneous HLT performed for patients with CHD in the United States from 2009 to 2019. The total numbers of transplants in each UNOS geographic region are shown.

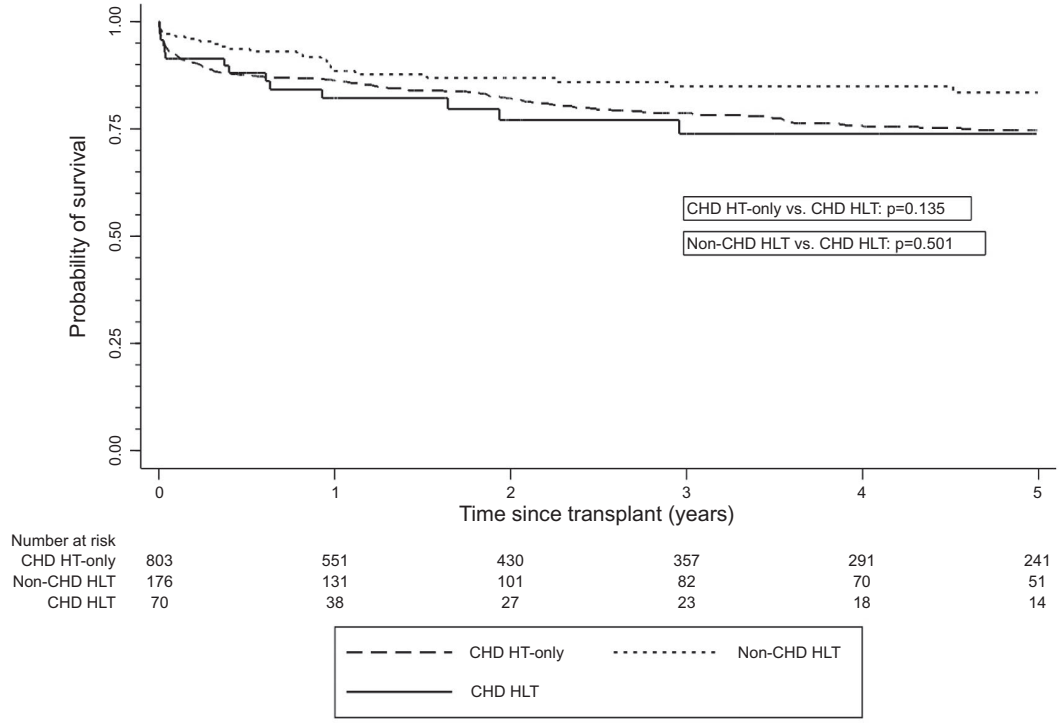

FIG. 2. Survival of patients with CHD who received HT-only or simultaneous HLT and of patients without CHD who received a simultaneous HLT in the United States from 2009 to 2019.

(Fig. 2). The 5-year patient survival rates were 74.1%, 73.6%, and 83.6% for the CHD HT-only, CHD HLT, and non-CHD HLT groups, respectively (Fig. 2). Nevertheless, the observed differences in patient survival between groups were not statistically significant (all pairwise $P > 0.05$). A Cox analysis also showed no statistical difference in patient survival (all pairwise $P > 0.05$), adjusting for the covariates outlined in Patients and Methods.

The 25 transplant centers that performed all the CHD HLTs from 2009 to 2019 were divided into higher-volume and lower-volume transplant centers. The higher-volume centers consisted of four centers that performed an average of 9.5 (SD ± 3.7) CHD HLTs over the study period (an average rate of one CHD HLT per year). The lower-volume centers consisted of 21 centers that performed an average of 1.6 (SD ± 1.4) CHD HLTs over the study period (an average rate of 0.1 CHD HLTs per year). The 1-year patient survival rates were 87.9% and 73.6%, while the 5-year rates were 83.0% and 61.3% in the higher-volume and lower-volume transplant centers, respectively ($P = 0.079$) (Fig. 3).

HEART ALLOGRAFT SURVIVAL

There were four allograft failures attributed to liver failure in the HLT groups. One early graft failure (<30 days posttransplant) and three late graft failures (>30 days posttransplant). Of these 4 patients, 3 died; therefore, these patients were included as heart allograft failure, per the OPTN definition. One patient underwent a liver retransplantation 212 days after the primary transplant and thus was not included as a heart allograft failure case. Of note, there were three graft failures attributed to liver failure in the CHD HT-only group, and all of these patients died as a result. The first patient had graft failure at 75 days posttransplant, a total bilirubin of 0.7 mg/dL, and a MELD-XI score of 13; the second patient had graft failure at 982 days posttransplant, with a total bilirubin of 0.7 mg/dL and a MELD-XI score of 11; the third patient had graft failure at 3 days posttransplant, with a total bilirubin of 0.3 mg/dL and a MELD-XI score of 15.

The 1-year heart allograft survival rates were 84.7%, 86.2%, and 89.5% for the CHD HT-only, CHD HLT, and non-CHD HLT groups, respectively (all $P > 0.05$)

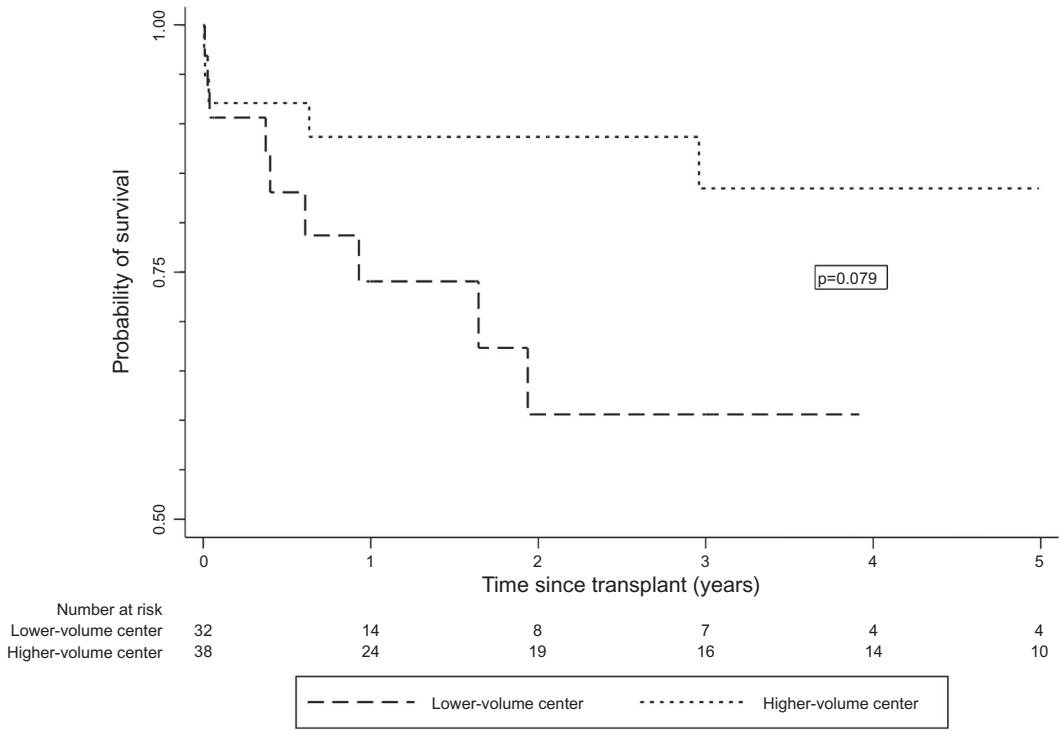

FIG. 3. Survival in patients with CHD who received simultaneous HLT in the United States from 2009 to 2019 stratified by volume of practice at transplant centers.

(Fig. 4A). The 5-year heart allograft survival rates were 72.6%, 77.7%, and 84.7% for the CHD HT-only, CHD HLT, and non-CHD HLT groups, respectively (Fig. 4A). Nevertheless, the observed differences in heart allograft survivals between groups were not statistically significant (all pairwise $P > 0.05$). A Cox analysis also showed no statistical difference in patient survival (all pairwise $P > 0.05$), adjusting for covariates.

LIVER ALLOGRAFT SURVIVAL IN SIMULTANEOUS HLT RECIPIENTS

The 1-year liver allograft survival rates were 84.6% and 89.4%, while the 5-year rates were 76.2% and 84.6% for the CHD HLT and non-CHD HLT groups, respectively ($P = 0.611$) (Fig. 4B). There were no statistically significant changes observed in adjusted liver allograft survival between the two groups ($P > 0.05$).

SIMULTANEOUS HLKT OUTCOMES

There were 14 patients who received HLKT, of whom 2 had a listing indication of CHD. The median age was 48.5 (43-54), with a median creatinine of 2.15 mg/dL (1.4-4.1); 7/14 (50.0%) were on dialysis. At an average follow-up time of 1,097 ± 1,342 days, 2/14 (14.2%) died within 1 year of transplant, while 1/14 (7.1%) had liver allograft failure secondary to hepatic artery thrombosis at 23 days posttransplant and underwent a successful retransplant.

ALLOGRAFT REJECTION AND SENSITIZED PATIENT OUTCOMES

There was a higher rate of allograft failure attributable to acute or chronic rejection in the CHD HT-only group compared with the HLT groups (3.2% versus 0.4%, $P = 0.014$). The rates of acute rejection were 23.4% in the CHD HT-only group compared with 5.5% in the HLT groups ($P < 0.001$). The rates of posttransplant stroke were 3.5% and 3.9% in the CHD HT-only group and HLT groups, respectively ($P = 0.765$). Of note, the posttransplant stroke rate was 4/74 (5.4%) in the CHD HLT group; however, there was no statistically significant difference observed

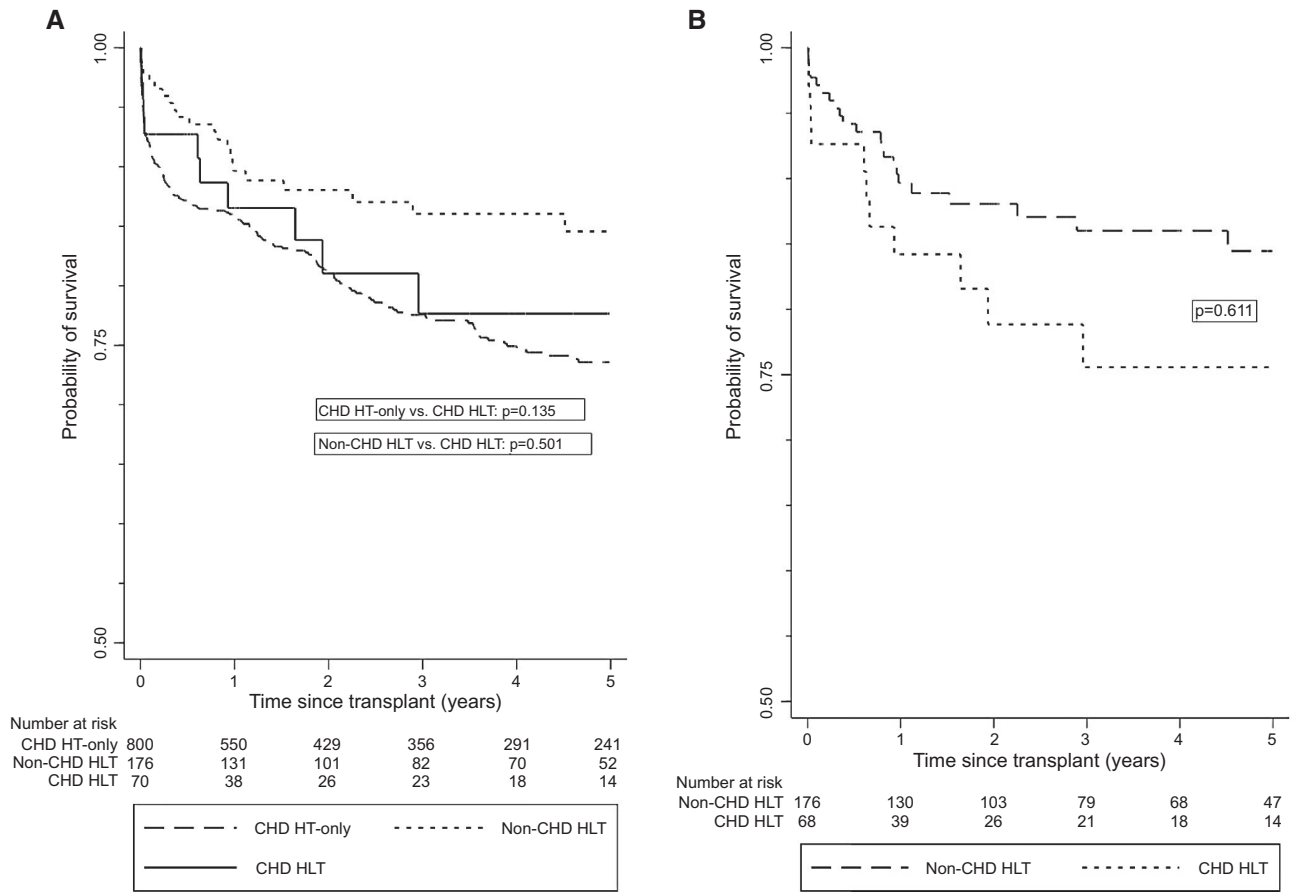

FIG. 4. (A) Heart allograft survival of patients with CHD who received HT or simultaneous HLT and of patients without CHD who received a simultaneous HLT in the United States from 2009 to 2019. (B) Liver allograft survival of simultaneous HLT in the United States from 2009 to 2019, stratified by CFD versus non-CHD.

compared to the CHD HT-only group (P = 0.418) or the non-CHD HLT group (P = 0.446).

There was a larger proportion of highly sensitized patients (i.e., PRA > 25%) in the CHD HLT group (47.3%) compared with the CHD HT-only group (31.3%, P = 0.005) and the non-CHD HLT group (29.7%, P = 0.003). The average follow-up time in the HLT group was 922 ± 1,014 days, while it was 1,209 ± 1,108 days in the HT-only group. Among the 341 highly sensitized patients, the rate of acute rejection was 58/256 (22.7%) in the CHD HT-only group compared with 6/85 (7.0%) in the HLT group (P = 0.020). However, the proportions were similar in the nonsensitized groups. Among sensitized patients, there was no difference in the rates of heart allograft failure in the CHD HT-only group compared with the HLT group (20% versus 17%, P = 0.698).

MORTALITY ASSOCIATIONS AMONG HLT RECIPIENTS

Among the HLT recipients (n = 245), the presence of CHD was not independently associated with increased mortality risk (HR = 1.00, 95% CI = 0.43-2.33) (Table 3). The only variables independently associated with increased mortality were recipient diabetes (HR, 2.97; 95% CI, 1.21-7.31) and total bilirubin (HR, 1.06; 95% CI, 1.01-1.12). Recipient age (HR, 0.97; 95% CI, 0.94-1.01) was not significant when associated with mortality. There were no violations of the proportional-hazards assumption indicated by the global test using Schoenfeld residuals (P = 0.785).

Among patients with CHD receiving HLT (n = 70), age was not independently associated with

TABLE 3. Multivariate Cox Proportional Hazards Regression of Predictors of Mortality in Simultaneous Heart-Liver Transplant Recipients (n = 245)

Covariate	HR (95% CI)	*P* Value
Donor		
Age	0.98 (0.95-1.01)	0.264
Diabetes	0.66 (0.08-5.37)	0.699
Recipient		
Age	0.97 (0.94-1.01)	0.181
BMI	1.02 (0.95-1.09)	0.536
Congenital heart disease	1.00 (0.43-2.33)	0.991
Diabetes	2.97 (1.21-7.31)	0.024
Creatinine	0.92 (0.39-2.10)	0.838
Total bilirubin	1.06 (1.01-1.12)	0.028
MELD score	1.00 (0.94-1.07)	0.940

Abbreviations: BMI, body mass index; CI, confidence interval; HLT, simultaneous heart-liver transplant; HR, hazards ratio; MELD, model for end-stage liver disease.

mortality (HR, 0.97; 95% CI, 0.91-1.02). Similarly, when age was treated as a dichotomous variable (<40 years [n = 49] versus ≥40 years [n = 21]), there was no association with mortality risk (HR, 0.87; 95% CI, 0.27, 2.78). Similar results (i.e., $P > 0.05$) were observed when the dichotomous cutoff for age was increased to 50 years (<50 years [n = 65] versus ≥50 years [n = 5]).

Discussion

There are now more adults than children living with CHD in the United States.[3] As the size of the aging Fontan-palliated population grows, we are observing the long-term clinical consequences of a failing Fontan circulation including significant hepatic dysfunction. Heart transplantation remains the only definitive treatment for an increasing number of patients with heart failure after Fontan's procedure. A small but growing proportion requires consideration for simultaneous HLT (or even simultaneous HLKT[20]). Our study shows that CHD HLT has now increased >5-fold from the baseline rate and has surpassed non-CHD as the leading indication for HLT in the United States for the first 3 months of 2020. Outcomes are acceptable, with no statistically significant differences in mortality or allograft survival in patients undergoing CHD HT-only versus CHD HLT. Notably, there was a trend to reduced mortality in CHD HLT recipients associated with higher-volume centers that average one CHD HLT annually. Bilirubin and diabetes were independently associated with mortality among HLT recipients, while age was not found to be a significant factor affecting mortality. There were no increased rates of posttransplant stroke among HLT patients.

A prior analysis of the UNOS database from 1987 to 2015 showed that only 41 CHD HLTs were performed over three decades.[14] In our analysis from 2009 to March 2020, while an overall increase in HLTs is observed, the rate of CHD HLTs has disproportionately increased by >5-fold compared to a doubling of the CHD HT-only and non-CHD HLT groups. While this increase may be largely due to the growing number of the Fontan-palliated population presenting with decompensated heart failure, other factors may also have played a role, including organ allocation policy changes. Recent UNOS/OPTN policy changes in HT have been made, with one of the intents to widen distribution of transplantation for patients with CHD by giving them priority status.[21,22] Our results show that we may be seeing this policy having its desired effect. In addition, the 2015 revised UNOS/OPTN multiorgan policy mandated the second required organ to be allocated to the multiorgan candidate from the same donor, accommodating more HLTs.[23]

There have only been a few single-center and UNOS analyses of populations of patients with CHD published. Studies comparing outcomes of patients with CHD undergoing HT alone versus HLT have been conflicting, which may be explained by the small numbers involved.[14,24,25] This is an important issue as it has direct implications for transplant listing and selection. Our results show that the differences in 1-year and 5-year graft survival between the CHD HT-only and CHD HLT groups are not statistically significant and should provide reassurance to providers in proceeding with HLTs for select patients if deemed appropriate. Non-CHD HLT recipients did appear to have numerically better survival compared to CHD HLT recipients. However, this difference was not statistically significant. Within the constraints of the Cox multivariate analysis, a diagnosis of CHD did not confer additional mortality risk. We acknowledge that a type II error may be present given the relatively low CHD HLT sample size. Further research is needed

to confirm this hypothesis as CHD HLT sample size continues to increase. While the CHD HLT recipients were younger and leaner and had lower rates of diabetes compared to their non-CHD HLT recipient counterparts, these favorable characteristics do not evidently compensate for the additional morbidity that CHD afflicts upon patients.

Over the past decade, there has been a remarkable change in geographic allocation of organs. Now, only one in four donor hearts remain within the same region, a decrease from four in five at the start of this decade. Interestingly, almost all HLT donor organs were from the same region during the 2010-2013 period. This intuitively makes sense given the added logistics a dual-organ transplantation entail. We hypothesize that this change in allocation may be in part due to the increasing diversity of transplant centers performing HT, which is increasing interregion competition for organs and the aforementioned revised multiorgan policy.[23]

With the advancement of neonatal cardiac surgery and catheter-based techniques, the spectrum of cardiac surgery for adults with CHD has shifted from primary repair of the heart defect to treatment of residual defects from prior surgeries. Repeat sternotomy is common and a risk factor for severe morbidity following cardiac surgery.[26] The presence of donor-specific antibodies (DSAs) due to prior multiple blood transfusions imparts additional challenges in terms of donor availability and postoperative management. Furthermore, surgical risk factors such as marked adhesions, multiple collaterals, and longer time and expertise needed for reconstruction of an appropriate anatomy to accommodate the donor heart make HT in CHD a highly challenging procedure.[26,27] This requires surgeons with expertise in managing patients with prior surgeries in childhood. In fact, our results showed that 13.5% of young adult patients with CHD (median age 21) underwent their HT or HLT at children's transplant centers. This also highlights a potential challenge with transitioning of care as these young adults get older.

There was noticeable geographic variation among UNOS regions in the practice of performing HLT, with regions 2, 5, and 7 accounting for 75% of all CHD HLTs and only 25 transplant centers performing this procedure over the past decade. This presents a serious challenge to the health care system with the evident increased burden of CHD and disparity in access to care. Higher-volume centers performed an average rate of one CHD HLT per year, 10 times the annual rate for lower-volume centers, which on average performed one CHD HLT every 10 years. There was a trend for better patient survival rates at higher-volume centers, with a 1-year survival rate of 87.9% (versus 73.6%) and a 5-year survival rate of 83.0% (versus 61.3%); however, it fell short of statistical significance, presumably related to limited sample size. These results are compelling, with an early divergence of better outcomes observed in higher-volume centers. Thus, an average of one CHD HLT per year could be considered as a minimum quality metric at transplant centers in future guidelines in order to optimize the care of this complex patient population.

Our analysis also demonstrated that the rates of acute rejection were >4-fold higher in HT-only recipients compared to the HLT group (23.4% versus 5.5%; $P < 0.001$). This is likely due to the immunoprotective characteristics of the liver. This appears to influence the practice of transplant providers, with a significantly higher proportion of sensitized patients observed in the CHD HLT group compared to the CHD HT-only group (47.3% versus 31.3%; $P = 0.03$). The immune-tolerant property of the liver allograft was first described in liver transplants in pigs,[28,29] with researchers observing that the allograft could be accepted even when the donor and recipient were from widely different porcine breeds. The underlying mechanism is not well understood. The leading theory is that the human leukocyte antigen (HLA) class I expressed on the extensive sinusoidal endothelial surface and the soluble HLA class II of the donor liver act as a "sponge" to soak up circulating DSAs of the recipients, therefore reducing the risk of rejection.[30,31] The extension of the liver's immune-protective effect to other organs when transplanted simultaneously has been well described in the literature of simultaneous liver–kidney transplant as well as HLT.[32-35] In one single-center experience, 22 HLT recipients, when compared to 223 HT-only recipients, had lower incidence of T cell–mediated rejection, antibody-mediated rejection, and cardiac allograft vasculopathy. The presence of a simultaneously transplanted liver allograft was the most predictive factor for lower incidence of rejection.[32] While the harder endpoints such as reduced rates of graft failure attributable to rejection in sensitized CHD HLT recipients were not observed, the overall results are compelling

and suggest that sensitization levels should be considered as part of the overall selection process as to which CHD patients require HLT. Finally, the relatively longer operating times of HLT compared to HT alone did not appear to increase the risk of posttransplant stroke in patients, which is an important consideration.

One of the remaining substantial questions is when to perform HT only versus HLT in the setting of clear but incompletely defined chronic liver disease in the CHD population. There are two key aspects to this question. One is how best to assess fibrosis stage and liver function in patients with CHD and congestive hepatopathy, and another is the reversibility/risk of posttransplant decompensation in patients with evidence of more advanced disease. This analysis cannot directly address these important questions. Interestingly, the patients who experienced liver failure in the CHD HT-only group had favorable prognostic pretransplant parameters, with low bilirubin and MELD-IX scores, highlighting inadequate prediction of which patients require HLT using the existing prediction tools. As many patients with heart failure are on anticoagulation, we calculated the MELD-XI score of individual patients. The MELD-XI scores, calculated based on only bilirubin and creatinine, have been validated as a prognostic index in liver transplantation[17] as well as HT.[36-38] They are normalized to the same range and distribution as MELD scores and carry equivalent prognostic information. The MELD-IX did not appear to be a useful predictor of mortality in our cohort. In addition, other common measures of hepatic function including hepatic venous portal gradient and cross-sectional imaging have been reported to be substantially affected by chronic outflow obstruction.[7] Prospective studies of existing and potential biomarkers or predictive models are badly needed in order to optimize and standardize patient selection as the demand for transplant for CHD increases.

The associations with higher bilirubin conferring increased mortality risk in HLT recipients suggest that serum total bilirubin may be useful in highlighting which patients are at higher risk and require optimal posttransplant care. On average, every unit increase in total bilirubin conferred a 6% increased risk of death among HLT recipients. Recipient diabetes was also independently associated with mortality risk among the HLT recipients, conferring a 3-fold increase in hazard risk. Although the rate of diabetes is comparatively lower in patients with CHD, intense efforts should be made to improve glycemic control in patients with CHD and diabetes both pretransplant and posttransplant.

Our study has some limitations. It is important to acknowledge that the UNOS database lacks more granular data such as anatomical complexity and number of prior surgeries of the patients with CHD as well as pathologic degree of liver involvement, which could create bias in patient selection. It also limits our understanding of the phenotype of Fontan patients who received HT only versus HLT. This calls for future prospective studies investigating consensus among centers in selection criteria for Fontan patients. We do know that the vast majority (i.e., 95%) of CHD HLT recipients had prior cardiac surgery, supporting the hypothesis that many of these are post-Fontan. The UNOS database also contains missing data; however, as outlined in Patients and Methods, these missing data are minimal and unlikely to affect our results or conclusions. The MELD score was also not available for HT patients; however, we calculated the validated MELD-IX on all patients to mitigate this limitation. Finally, the small sample size (and ultimately low event rate) of our CHD HLT cohort precluded more extensive exploration of Cox proportional hazards modeling due to suboptimal power. However, we included the non-CHD HLT population in our model to increase our sample size and included the presence of congenital heart disease as a covariate. Thus, we were still able to derive meaningful outcomes with relevant clinical implications. That said, even with the addition of the non-CHD HLT recipients, we still acknowledge that the lack of statistical significance in some variables may be due to lack of power to detect the association. Future studies should assess for associations in the CHD HLT cohort as sample size increases in the near future.

Our results show that the rate of HLT for adults with CHD in the United States is rising quickly with a relatively small number of transplant centers with experience in managing these patients, highlighting the logistical barriers some patients face in order to acquire the appropriate care. Our results provide reassurance to providers who deem a patient with CHD requires HLT, with outcomes comparable to HT alone and reduced rejection rates observed without increased risk of stroke. Within the constraints of our analysis, age alone should not deter providers from considering

patients with CHD in their 40s or 50s for consideration of HLT. Patients with CHD require expert specialist care, which is further highlighted by the trend toward better outcomes at higher-volume centers. An average of one CHD HLT per year could be considered a minimum quality metric at transplant centers. Among HLT patients, diabetes and higher bilirubin levels predicted mortality and should be considered in future management and studies designed to optimize the care of this complex patient population. In summary, while long-term prospective studies are needed to evaluate the effects of medical therapy, listing priorities, timing, and risks of single-organ and multiorgan transplantations, our encouraging results support the listing of patients with CHD for HLT when indicated at transplant centers that regularly perform these operations.

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