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Improved heart transplant survival for children with congenital heart disease and heterotaxy syndrome in the current era: An analysis from the pediatric heart transplant society

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BACKGROUND: Challenges exist with heterotaxy due to the complexity of heart disease, abnormal venous connections, and infection risks. This study aims to understand heart transplant outcomes for children with heterotaxy.

METHODS: All children with congenital heart disease listed for transplant from 1993 to 2018 were included. Those with and without heterotaxy were compared. Waitlist outcomes and survival post-listing and transplant were analyzed. Post-transplant risk factors were identified using multiphase parametric hazard modeling.

RESULTS: There were 4814 children listed, of whom 196 (4%) had heterotaxy. Heterotaxy candidates were older (5.8 ± 5.7 vs 4.2 ± 5.5 years, $p < 0.01$), listed at a lower urgency status (29.8% vs 18.4%, $p < 0.01$), more commonly single ventricle physiology (71.3% vs 59.2%, $p < 0.01$), and less often supported by mechanical ventilation (22% vs 29.1%, $p < 0.05$) or extracorporeal membrane oxygenation (3.6% vs 7.5%, $p < 0.05$). There were no differences in waitlist outcomes of transplant, death, or removal. Overall, post-transplant survival was worse for children with heterotaxy: one-year survival 77.2% vs 85.1%, with and without heterotaxy, respectively. Heterotaxy was an independent predictor for early mortality in the earliest era (1993-2004), HR 2.09, CI 1.16-3.75, $p = 0.014$. When stratified by era, survival improved with time. Heterotaxy patients had a lower freedom from infection and from severe rejection, but no difference in vasculopathy or malignancy.

CONCLUSIONS: Mortality risk associated with heterotaxy is mitigated in the recent transplant era. Early referral may improve waitlist outcomes for heterotaxy patients who otherwise have a lower status at listing. Lower freedom from both infection and severe rejection after transplant in heterotaxy highlights the challenges of balancing immune suppression.

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Congenital heart disease (CHD) remains an important indication for heart transplantation (HT) in children. Previous literature indicates worse outcomes after HT in those with CHD.[1-3] Most databases, however, lack details to

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describe the associations between outcomes after listing for HT in children and specific types of CHD, including those with other systemic anomalies or syndromes. The Pediatric Heart Transplant Society (PHTS) database provides detail to analyze CHD-specific outcomes and includes information related to other syndromes.

A distinct group of patients referred for HT is those with heterotaxy syndrome (HS). HS, or isomerism, is a constellation of developmental defects defined by abnormal laterality of thoracoabdominal viscera. These defects are often associated with complex cardiac anatomy and abnormalities of systemic and pulmonary venous connections. Patients with CHD and HS have been shown to experience worse outcomes after non-transplant cardiac surgery and transplant surgery.[4-11] This study aims to describe outcomes after listing and HT in CHD patients with HS (CHD-HS) when compared to non- HS (Other CHD) patients.

Methods

For the purpose of this analysis, we used data from the PHTS database. The PHTS is an international registry that collects data on pediatric HT candidates from the United States, Canada, Brazil, and Great Britain. Institutional review board approval was obtained when applicable by the study sites. The database contains de-identified data about candidates at the time of listing, through transplant, and annually post-transplant. Data is also submitted at the time of clinical events which include rejection, infection, post-transplant lymphoproliferative disorder (PTLD), cardiac allograft vasculopathy (CAV) and death.

All children (<18 years of age at listing) with a pre-transplant diagnosis of CHD in the database listed between January 1, 1993 to December 31, 2018 were included. Children listed for re-transplant or multi-organ transplant were excluded. Follow up was complete through December 31, 2019. Two cohorts were identified: (1) CHD-HS included all children with any code for heterotaxy and/or isomerism, asplenia, or polysplenia listed in their diagnosis or medical history; (2) other CHD included all children with CHD but without heterotaxy and/or isomerism, asplenia, or polysplenia. Single ventricle heart disease was denoted as such by the center submitting the data or determined by the diagnosis of tricuspid atresia, mitral atresia, double inlet left ventricle, or aortic atresia.

Primary outcomes measured were patient survival after listing for all candidates listed, irrespective of achieving HT, and survival after HT for those who underwent transplant. Secondary outcomes included freedom from rejection, infection, CAV, and PTLD. Rejection in PHTS is defined as any episode diagnosed by biopsy, echocardiography, or clinical findings that is treated with escalation of immune suppression. Rejection with hemodynamic compromise is determined by participating sites as previously reported and is based on hemodynamic, echocardiographic, or clinical features of heart failure or low cardiac output. [12,13] Data is reported to PHTS on infections requiring intravenous therapy or life-threatening infections requiring oral therapy. For this analysis, the presence of CAV is determined by the first detection of any angiographic disease.

Statistical analysis

Baseline characteristics at the time of listing and HT were collected. Data was examined using standard descriptive statistics, including mean and standard deviations for continuous variables and frequency (percentages) for categorical variables.

Baseline characteristics were compared between groups using the chi-square and the Fisher exact tests as appropriate for categorical variables and the *t*-test or ANOVA test for continuous variables.

Competing outcomes analysis was performed for the mutually exclusive outcomes after listing, including death while listed, HT, and remaining on the waitlist alive. Gray's test was used to compare cumulative incidence functions between these curves.

Standard Kaplan-Meier analysis was used for outcome analysis after listing and HT. Survival between groups was compared using the log-rank test. Freedom from rejection, infection, CAV and PTLD was also analyzed using Kaplan-Meier method.

Multiphase parametric hazard modeling was used to identify risk factors for post-transplant death. This method has been used extensively to identify the changing hazard profiles post-surgery and the association of risk factors with different phases of risk.[14] Up to three phases of risk (early declining phase, constant phase, and late phase) were evaluated. For our analysis, an early declining phase and constant phase best fit the shape of the hazard for post-transplant death. The early phase dominates the predictive model until it merges with the constant phase at about 1 year as seen in Supplemental Figure 1. Potential covariates were chosen *a priori*. A full list of all potential covariates are listed in Appendix I. Missing values were imputed to the mean. Stepwise selection was used to identify statistically significant risk factors for the final multivariable model, with a *p*-value of 0.05 for covariates to enter and remain in the model. Hazard ratios were expressed with 95% confidence intervals (CI). All analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC).

Results

Among 9,204 children listed for HT, there were 4814 (52%) with CHD. HS was identified in 196 (4%) of the 4,814 with CHD. Figure 1 shows the study cohorts from all children listed for HT in the PHTS registry. Within the CHD-HS group, there were 33 (15%) children with polysplenia, 88 (45%) with asplenia, and 78 (40%) unknown. The remaining 4618 (96%) children with CHD did not have HS and were classified as other CHD. A similar proportion of children in each group underwent HT: (1) 130 of 196 (66%)

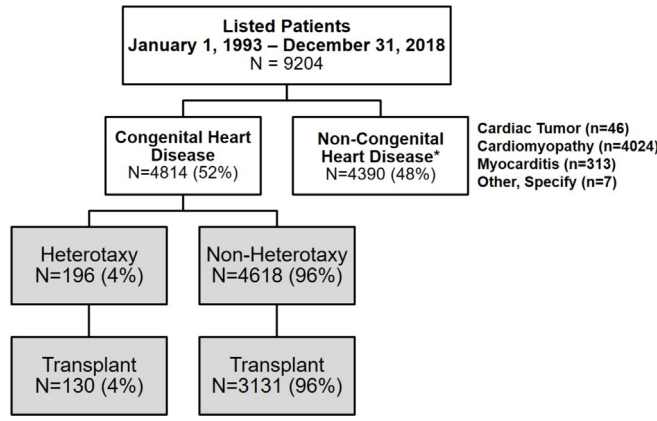

Figure 1 Patient cohort from all children listed for heart transplant, 1993 to 2018, in the PHTS registry. Among those listed with CHD, 4% had HS. Similarly, among all HT recipients in the cohort, 4% had HS.

with CHD-HS underwent HT, and (2) 3131 of 4618 (68%) with other CHD received a HT. CHD-HS comprised 4% of the total CHD HT recipients.

Patient characteristics

Patient characteristics between CHD-HS and other CHD were compared (Tables 1 and 2). At the time of listing, CHD-HS patients were older (5.8 ± 5.7 vs 4.2 ± 5.5 years, $p < 0.01$), more commonly listed at a lower urgency status 2 (29.8% vs 18.4%, $p < 0.01$), less often supported by mechanical ventilation (22% vs 29.1%, $p < 0.05$), and less frequently on extracorporeal membrane oxygenation (ECMO) support (3.6% vs 7.5%, $p < 0.05$) than the other CHD cohort. CHD-HS more often had single ventricle heart disease (71.3% vs 59.2%, $p < 0.01$) and differed by palliation stage compared to other CHD (Table 1). TAPVR was present in a significant proportion of CHD-HS, 33% vs 1.5%.

Characteristics at the time of transplant are shown in Table 2. CHD-HS were older age at HT, less commonly supported by ECMO, more often had TAPVR, and more often transplanted at the lower urgency status 2. There were no significant differences in history of prior surgery, mechanical ventilation, use of VAD support, donor ischemic times, use of induction therapy, or steroids at 30 days post-transplant between the 2 groups. Cardiopulmonary bypass time was longer in the CHD-HS group; the difference between the means was 28 minutes (Table 2).

Patient outcomes

Competing outcomes analysis found no difference in waitlist outcomes of transplant, death on waitlist, or removal

Table 1 Characteristics of CHD Patients With and Without Heterotaxy at Listing (PHTS 1993–2018)[a]

	CHD-HS $n = 196$	Other CHD $n = 4618$	p-value
Male	106 (54.1)	2813 (60.9)	0.06
White	132 (67.3)	3405 (73.7)	0.05
Age at listing (mean, SD)	5.8 ± 5.7 years	4.2 ± 5.5 years	<0.01
History of prior cardiac surgery	165 (84.2)	3618 (78.4)	0.05
Number of prior cardiac surgeries (mean, SD)	0.9 ± 0.5	0.9 ± 0.6	0.13
Ventilator at listing	38 (22.0)	1252 (29.1)	0.04
VAD at listing	1 (0.5)	94 (2.0)	0.13
ECMO at listing	7 (3.6)	348 (7.5)	0.04
Bilirubin at listing	1.0 ± 1.3	1.5 ± 3.4	0.09
Renal failure at listing (eGFR < 60 mL/min/1.73m^2)	23 (20.2)	687 (27.4)	0.09
MELD-XI score at listing	10.5 ± 2.1	11.0 ± 3.1	0.14
PRA >10%	17 (21.5)	635 (30.6)	0.08
Single ventricle heart disease	139 (71.3)	2734 (59.2)	<0.01
Palliation stage for single ventricle			<0.01
No prior surgery	39 (28.1)	747 (27.3)	
Stage 1 palliation	2 (1.4)	341 (12.5)	
Stage 2 palliation	39 (28.1)	740 (27.1)	
Fontan palliation	59 (42.4)	906 (33.1)	
TAPVR (All CHD)	61 (33.3)	58 (1.5)	<0.01
TAPVR (Single ventricle only)	43 (32.6)	44 (1.9)	<0.01
Splenic morphology, CHD-HS only		Not applicable	
Polysplenia	30 (15.3)		
Asplenia	88 (44.9)		
Not specified	78 (39.7)		
Status at listing: all centers			<0.01
Priority	136 (69.4)	3658 (79.2)	
Routine	60 (30.6)	959 (20.8)	
UNOS status at listing: US only			<0.01
1	19 (10.5)	557 (13.2)	
1A	87 (48.1)	2404 (56.9)	
1B	21 (11.6)	473 (11.2)	
2	54 (29.8)	777 (18.4)	
7		11 (0.3)	

CHD-HS, congenital heart disease with heterotaxy syndrome; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; PRA, panel reactive antibody; SD, standard deviation; TAPVR, total anomalous pulmonary venous return; UNOS, United Network for Organ Sharing; US, United States; VAD, ventricular assist device.

MELD-XI score =5.11x ln(serum bilirubin)+ 11.76 x ln(serum creatinine) +9.44 . Patients on dialysis are assigned a creatinine of 4 mg/dL, patients with serum bilirubin <1 are assigned a bilirubin=1 mg/dL and patients with creatinine <1 are assigned a creatinine of 1 mg/dL. Priority=UNOS status 1, 1A, 1B or highest listing status in international, non-US centers; Routine=UNOS status 2 or non-urgent status for international, non-US centers.

[a]Numbers are reported as n (%), or mean ± standard deviation

Table 2 Characteristics of CHD Patients With and Without Heterotaxy at Transplant (PHTS 1993–2018) [a]

	CHD-HS n = 130	Other CHD n = 3131	p-value
Male	63 (48.5)	1905 (60.8)	<0.01
White	89 (68.5)	2341 (74.8)	0.11
Age at transplant (mean, SD)	6.4 ± 5.9 years	5.0 ± 5.8 years	<0.01
History of prior cardiac surgery	110 (84.6)	2461 (78.7)	0.10
Number of prior cardiac surgeries (mean, SD)	1.0 ± 0.6	0.9 ± 0.6	0.20
Ventilator at transplant	26 (21.3)	664 (22.9)	0.68
VAD at transplant	4 (3.2)	197 (6.7)	0.12
ECMO at transplant	2 (1.6)	217 (7.4)	0.01
Bilirubin at transplant	1.5 ± 3.2	1.2 ± 2.5	0.3
Renal failure at transplant (eGFR < 60 mL/min/1.73m^2)	31 (25.0)	755 (25.0)	0.10
MELD-XI at transplant	11.9 ± 4.4	10.8 ± 2.8	<0.01
Induction therapy	94 (72.3)	2337 (75.2)	0.46
Donor ischemic time, minutes (mean, SD)	245.4 ± 91.0	235.9 ± 77.8	0.18
Cardiopulmonary bypass time, minutes (mean, SD)[b]	228.6 ± 86.3	200.6 ± 88.1	<0.01
PRA at transplant >10%	17 (22.4)	615 (30.5)	0.13
Single ventricle heart disease	89 (68.5)	1876 (59.9)	0.05
Palliation stage for single ventricle			0.06
No prior surgery	29 (32.6)	506 (27.0)	
Stage 1 palliation	2 (2.2)	201 (10.7)	
Stage 2 palliation	22 (24.7)	497 (26.5)	
Fontan palliation	36 (40.4)	672 (35.8)	
History of TAPVR (All CHD)	38 (31.7)	37 (1.4)	<0.01
History of TAPVR (Single ventricle)	27 (32.1)	29 (1.9)	<0.01
Steroid use at 30 days	1 (3.7)	17 (2.4)	0.66
Status at transplant: all centers			<0.01
Priority	101 (77.7)	2712 (87.2)	
Routine	29 (22.3)	398 (12.8)	
UNOS status at transplant: US only			<0.01
1	10 (8.3)	361 (12.7)	
1A	70 (58.3)	1926 (67.6)	
1B	17 (14.2)	274 (9.6)	
2	23 (19.2)	289 (10.1)	
Months on waitlist, median (IQR)	1.72 (0.89-4.07)	1.81 (0.69-3.98)	0.59

CHD-HS, congenital heart disease with heterotaxy syndrome ; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; PRA, panel reactive antibody; SD, standard deviation; TAPVR, total anomalous pulmonary venous return; UNOS, United Network for Organ Sharing; US, United States; VAD, ventricular assist device.

MELD-XI score =5.11x ln(serum bilirubin)+ 11.76 x ln(serum creatinine) +9.44 . Patients on dialysis are assigned a creatinine of 4 mg/dL, patients with serum bilirubin <1 are assigned a bilirubin=1 mg/dL and patients with creatinine <1 are assigned a creatinine of 1 mg/dL. Priority=UNOS status 1, 1A, 1B or highest listing status in international, non-US centers; Routine=UNOS status 2 or non-urgent status for international, non-US centers.

[a]Numbers are reported as n (%), mean ± standard deviation, or median (interquartile range).

[b]Cardiopulmonary bypass time was only available for patients in the recent era (2005-2018).

due to deterioration between CHD-HS and other CHD (p = 0.7, 0.8, 0.3, respectively for the curves) (Figure 2). Survival after listing did not differ between the groups, p = 0.96 (Figure 3A). At 6 months post-listing, 76% of the CHD-HS and 74% of the other CHD were still alive while awaiting HT.

Across the entire study period, survival post-HT was significantly worse among those receiving a HT in the CHD-HS cohort compared to other CHD, p < 0.01 (Figure 3B). One year survival in the CHD-HS cohort was 77.2% (70% CI: 73.1%-80.7%) vs 85.1% (70% CI: 84.5%-85.8%), in other CHD, and 5 year survival was 66.4% vs 75.4%, respectively. However, survival shown by era demonstrated worse survival only in the earliest era for CHD-HS (Figure 4A). Survival was similar in the recent era between CHD-HS and other CHD, both of whom experienced improved survival over time (Figure 4B).

To closely match the changing risk of mortality experienced in this cohort, a multiphase parametric model was used. This allowed for a rapidly declining early hazard and a constant hazard that, when combined, closely matched the observed hazard depicted in the Kaplan-Meier curves. This also allowed for the identification of factors associated with risk in each phase. Multivariate predictors of death after HT in all CHD (Model 1) and in CHD-HS only (Model 2) are shown in Table 3. Potential covariates evaluated in both early and constant phase are listed in Table 2. Independent predictors of higher mortality early after HT included level of support or multi-organ failure at the time of transplant. ECMO support, VAD support, mechanical ventilation, and renal failure at transplant were predictors of worse outcome. Single ventricle heart disease was a risk factor for early mortality in children with

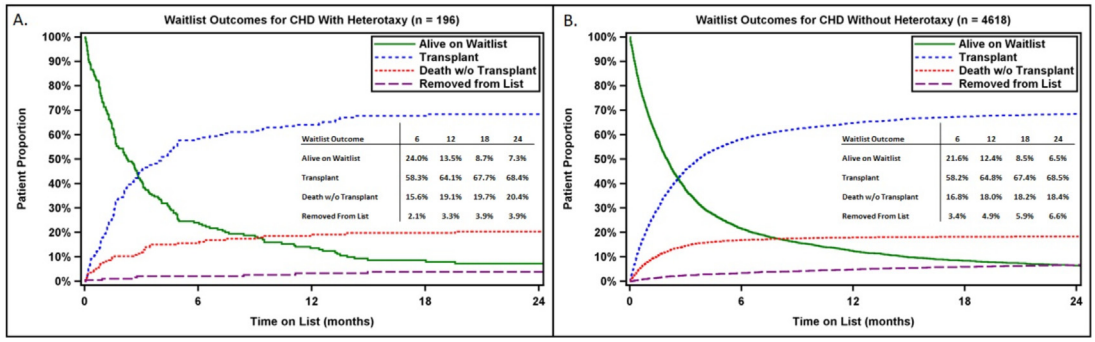

Figure 2 Competing risk analysis for wait list outcomes in CHD (A) with and (B) without Heterotaxy There was no statistical difference in the competing outcomes between CHD-HS and other CHD, *p*-value for transplant=0.7; *p*-value for death=0.8; *p*-value for removal from the waitlist=0.3. *p*-values calculated using Gray's test.

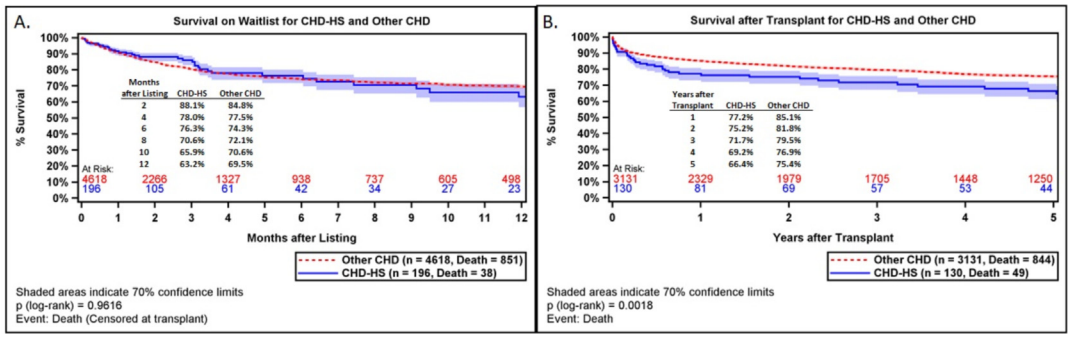

Figure 3 (A) Survival after listing for CHD with and without Heterotaxy and (B) survival post TX for CHD with and without Heterotaxy.

CHD. However, when the interaction between HS and single ventricle heart disease was assessed, there was no difference in risk related to HS with or without single ventricle disease. Earlier year of transplant was associated with higher early mortality risk. When the interaction between HS and era was assessed, only heterotaxy in the early era (1993-2004), not heterotaxy in the recent era, conferred early mortality risk (heterotaxy in era 1993-2004, HR 2.09, CI 1.16-3.75, $p = 0.01$, Table 3). Factors predicting constant phase mortality differed from those of early phase mortality and included recipient black race, history of prior surgery, and status 1 listing at transplant. HS was an independent risk factor for mortality in the constant phase (HR 1.59; 95% CI 1.02-2.48, $p = 0.04$). Earlier year of HT was also associated with greater mortality risk in the constant phase. Unlike the early hazard phase, there was no difference in the effect of heterotaxy on constant phase risk within the different eras.

Differences in secondary outcomes after HT were analyzed for CHD-HS and other CHD. While there was no difference in time to any rejection, the CHD-HS group had lower freedom from rejection with hemodynamic compromise ($p = 0.004$) (Figure 5A). There was also a difference in time to first infection (Figure 5B) with lower freedom from infection in the CHD-HS group ($p = 0.024$) (Figure 5B). There was no significant difference in freedom from CAV or PTLD.

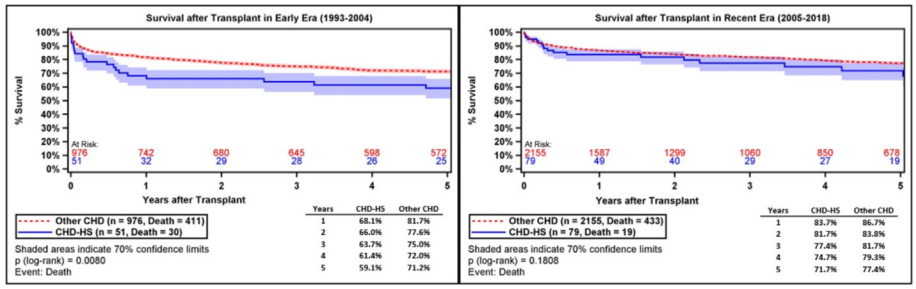

Figure 4 Patient survival after transplant for CHD with and without Heterotaxy by Era: (A) early Era 1 (1993-2004) and (B) recent Era 2 (2005−2018).

Table 3 Risk Factors for Mortality after Transplant in all CHD Patients (Model 1) and in CHD-HS Only Patients (Model 2)

	Early hazard		Constant hazard	
Model 1: CHD-HS + Other CHD (n = 3261)	HR(95% CI)	p-value	HR(95% CI)	p-value
ECMO at transplant	3.26 (2.44-4.37)	<0.01		
VAD at transplant	1.87 (1.25-2.80)	<0.01		
Male gender	0.80 (0.65-0.98)	0.03		
Single ventricle CHD	1.24 (1.01 - 1.53)	0.04		
1 Year increase in year of transplant since 1993	0.98 (0.96-0.99)	<0.01		
Heterotaxy in Era 1993-2004	2.09 (1.16-3.75)	0.01		
Induction therapy at transplant	0.65 (0.51-0.81)	<0.01		
Renal failure at transplant (eGFR < 60)	1.58 (1.26-1.99)	<0.01		
Ventilator at transplant	1.47 (1.15-1.89)	<0.01		
Era 1993-2004			1.37 (1.10-1.70)	<0.01
Heterotaxy status			1.59 (1.02-2.48)	0.04
History of surgery at listing			1.79 (1.35-2.38)	<0.01
Recipient black race			2.0 (1.56-2.57)	<0.01
Status 1 at transplant (1,1A,1B)			0.63 (0.50-0.80)	<0.01
Model 2: CHD-HS (n = 130)				
Bilirubin at transplant (mg/dL)	1.18 (1.08-1.29)	<0.01		
Male Gender	0.26 (0.07-0.99)	0.03		
Polysplenia	2.6 (1.03-6.6)	0.04		

CHD, congenital heart disease; ECMO, extracorporeal membrane oxygenation; VAD, ventricular assist device.

Multiphase parametric hazard modeling was used to identify risk factors associated with early rapidly declining post-transplant risk (early phase, ≤1 year) as well as longer lasting risk factors (constant phase). Risk factors assessed in both hazard phases and models are listed in Appendix 1. Additionally, the following interactions were assessed: (1) heterotaxy and era; and (2) heterotaxy and single ventricle heart disease. Only the interaction between heterotaxy and era was significant.

Heterotaxy subgroup analysis: Single ventricle disease and polysplenia/asplenia

Single ventricle heart disease was further analyzed in the CHD-HS cohort. Within the listed CHD-HS cohort, 139 (71%) had single ventricle disease. Of the 139 single ventricle CHD-HS listed, 89 (64%) received a HT. There were 56 CHD-HS with biventricular heart disease, of whom 41 (73%) underwent HT. One patient was excluded from the sub-analysis because the detail of ventricular morphology could not be ascertained. There were no statistical differences found in survival after listing (Figure 6A) or after transplant (Figure 6B) when single ventricle CHD-HS outcomes were compared to biventricular CHD-HS.

Differences in patient characteristics and outcomes were also sought between CHD-HS with polysplenia and CHD-HS asplenia. CHD-HS asplenia more frequently had prior surgery at listing (88% vs 70%; $p < 0.05$), more often had single ventricle CHD (78% vs 50; $p < 0.05$), more often had TAPVR (42% vs 15%, $p = 0.01$), and less commonly received ventilator support (10.7% vs 32.1%; $p < 0.01$) than those with polysplenia (Table 4). Characteristics at HT were similar between groups except for history of TAPVR (Table 4). Waitlist survival was comparable (Figure 7A), but early post-transplant survival was significantly worse for CHD-HS with polysplenia. The association of polysplenia with post-transplant mortality was confirmed in multivariate analysis (HR 2.6; 95% CI 1.03-6.6, $p = 0.04$)

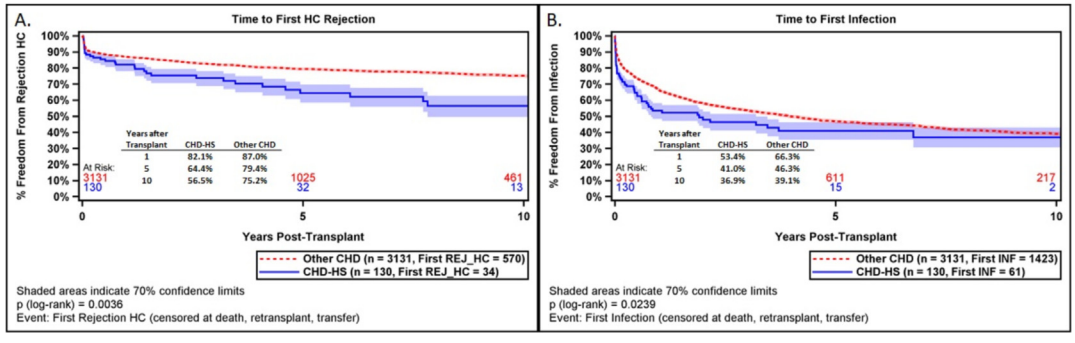

Figure 5 (A) Freedom from rejection with Hemodynamic compromise and (B) freedom from infection in CHD with and without Heterotaxy

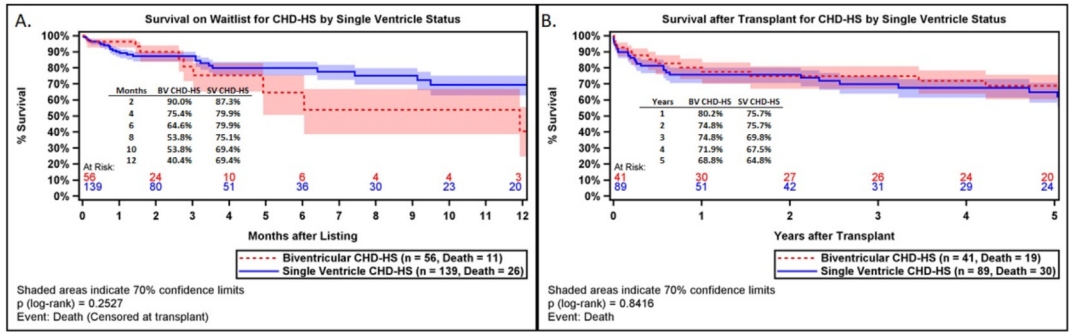

Figure 6 A. Survival after listing for CHD Heterotaxy with single ventricle heart disease and biventricular heart disease. B. survival after transplant for CHD Heterotaxy with single ventricle heart disease and biventricular heart disease.

Table 4 Comparison of Patient Characteristics at Listing and at Transplant for CHD-HS Based on Splenic Morphology (PHTS 1993-2018)[a,b]

Patient characteristics at listing	Asplenia $n = 88$	Polysplenia $n = 30$	p-value
Male	53 (60.2)	7 (23.3)	<0.01
White	59 (67.0)	19 (63.3)	0.71
Age at listing (mean, SD)	6.5 ± 5.7 years	4.1 ± 5.6 years	0.054
History of prior cardiac surgery	77 (87.5)	21 (70.0)	0.03
Number of prior cardiac surgeries (mean, SD)	1.0 ± 0.5	0.8 ± 0.7	0.29
Single ventricle CHD	69 (78.4)	15 (50.0)	<0.01
History of TAPVR	35 (41.7)	4 (14.8)	0.01
Ventilator at listing	8 (10.7)	9 (32.1)	<0.01
VAD at listing	1 (1.1)	0 (0.0)	0.56
ECMO at listing	1 (1.1)	1 (3.3)	0.42
Bilirubin at listing	0.9 ± 1.7	0.8 ± 1.2	0.79
Renal failure at transplant (eGFR < 60 mL/min/1.73m^2)	6 (12.8)	6 (30.0)	0.09
MELD-XI at listing	10.3 ± 2.3	10.3 ± 2.2	0.93
PRA > 10%	8 (32.0)	2 (14.3)	0.22
Status at transplant: all centers			0.29
Priority	55 (62.5)	22 (73.3)	
Routine	33 (37.5)	8 (26.7)	
UNOS status at transplant: US only			0.27
1	9 (11.5)	7 (25.9)	
1A	29 (37.2)	10 (37.0)	
1B	12 (15.4)	2 (7.4)	
2	28 (35.9)	8 (29.6)	

Patient characteristics at transplant	Asplenia $n = 53$	Polysplenia $n = 20$	p-value
Male	26 (49.1)	5 (25.0)	0.06
White	35 (66.0)	12 (60.0)	0.63
Age at transplant (mean, SD)	6.8 ± 5.8 years	5.5 ± 6.3 years	0.39
History of prior cardiac surgery	46 (86.8)	15 (75.0)	0.23
Number of prior cardiac surgeries (mean, SD)	0.9 ± 0.5	0.9 ± 0.6	0.50
Single ventricle CHD	38 (71.7)	10 (50.0)	0.08
History of TAPVR	21 (42.0)	3 (16.7)	0.05
Ventilator at transplant	7 (14.3)	7 (35.0)	0.052
VAD at transplant	2 (3.8)	0 (0.0)	0.37
ECMO at transplant	1 (1.9)	0 (0.0)	0.53
Bilirubin at transplant	2.2 ± 5.3	0.7 ± 0.7	0.40

(*continued on next page*)

Table 4 (*Continued*)

Patient characteristics at transplant	Asplenia $n = 53$	Polysplenia $n = 20$	p-value
Renal failure at transplant (eGFR < 60 mL/min/1.73m^2)	9 (18.4)	6 (30.0)	0.29
MELD-XI at transplant	11.6 ± 4.1	10.1 ± 1.5	0.27
Induction therapy	38 (71.7)	12 (60.0)	0.34
Cardiopulmonary bypass time, minutes (mean, SD) [c]	244.1 ± 92.4	247.9 ± 80.2	0.91
Donor ischemic time (mean, SD)	238.1 ± 96.6 minutes	246.8 ± 81.9 minutes	0.73
PRA at transplant >10%	8 (34.8)	2 (15.4)	0.21
Steroid use at 30 days	1 (7.7)	0 (0.0)	0.62
Status at transplant: all centers			0.38
Priority	37 (69.8)	16 (80.0)	
Routine	16 (30.2)	4 (20.0)	
UNOS status at transplant: US only			0.23
1	4 (8.7)	4 (22.2)	
1A	21 (45.7)	10 (55.6)	
1B	9 (19.6)	1 (5.6)	
2	12 (26.1)	3 (16.7)	

CHD-HS, congenital heart disease with heterotaxy syndrome; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; PRA, panel reactive antibody; SD, standard deviation; TAPVR, total anomalous pulmonary venous return; UNOS, United Network for Organ Sharing; US, United States; VAD, ventricular assist device.

MELD-XI score =5.11x ln(serum bilirubin)+ 11.76 x ln(serum creatinine) +9.44 . Patients on dialysis are assigned a creatinine of 4 mg/dL, patients with serum bilirubin <1 are assigned a bilirubin=1 mg/dL and patients with creatinine <1 are assigned a creatinine of 1 mg/dL. Priority=UNOS status 1, 1A, 1B or highest listing status in international, non-US centers; Routine=UNOS status 2 or non-urgent status for international, non-US centers.

There were 78 (40%) of the 196 listed CHD-HS without details to determine splenic morphology; these patients were excluded from the sub-analysis.

[a]There were 78 children listed with CHD-HS who were excluded from the sub-analysis because splenic morphology was not specified and could not be ascertained. There were 57 children transplanted with CHD-HS who were excluded from the sub-analysis because splenic morphology was not specified and could not be ascertained.

[b]Numbers are reported as n (%), or mean ± standard deviation

[c]Cardiopulmonary bypass time was only available for patients in the recent era (2005-2018).

(Table 3). Figure 7B depicts this early difference in survival but no significant difference overall between groups followed out to 5 years. There was markedly worse survival for CHD-HS polysplenia vs asplenia who underwent HT in the early era (Figure 8A, 1993-2004), but there was no difference in survival in the recent era (Figure 8B, 2005-2018).

Discussion

This large, international study from the PHTS provides a detailed analysis of listing and post-transplant outcomes in children with CHD and HS. Our study found similar waitlist mortality despite CHD-HS having a lower clinical acuity at listing. Consistent with previous literature in non-transplant cardiac surgery, we found higher post-transplant mortality for CHD-HS across the entire study period, but we report the novel finding of era differences.[4,5] When analyzing era differences, early mortality risk associated with HS was mitigated in the recent era of HT.

Listing criteria for organ allocation continues to be revised to decrease waitlist mortality in the sickest of patients. Prior studies in children and adults have shown that listing acuity does not necessarily correlate with risk of death while waiting or after HT.[15,16] In our study, CHD-HS were more commonly listed at a lower urgency status, fewer required mechanical ventilation, and fewer required ECMO support. Yet, death while listed was the same as

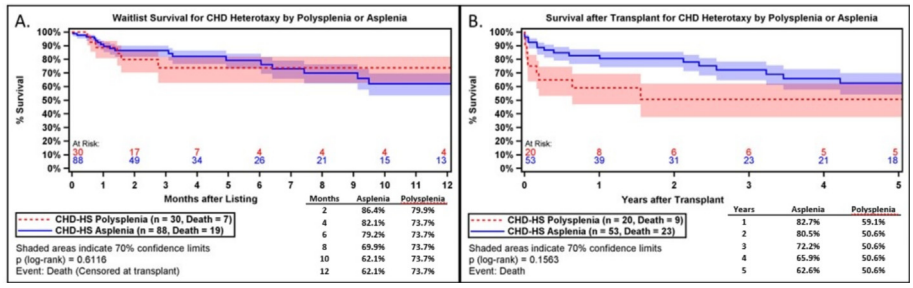

Figure 7 (A) Survival after listing censored at transplant for CHD Heterotaxy by Polysplenia or Asplenia and (B) survival after transplant for CHD Heterotaxy by Polysplenia or Asplenia.

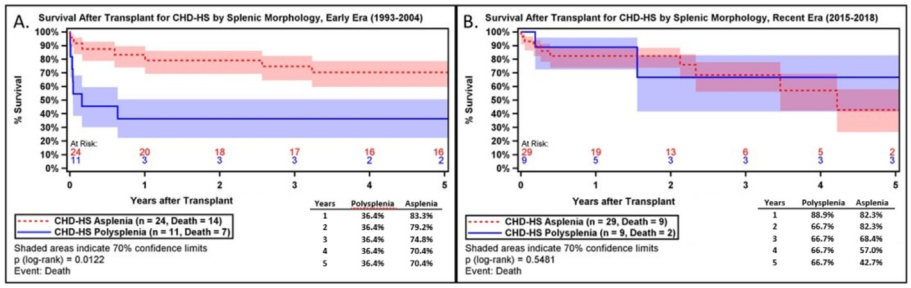

Figure 8 Survival after transplant for CHD Heterotaxy by Polysplenia or Asplenia. A: early Era 1 (1993−2004) and B. Recent Era 2 (2005−2018).

other CHD listed, and death after HT was greater in CHD-HS. One explanation is the greater proportion of CHD-HS with single ventricle heart disease. It is well known that children with heart failure due to single ventricle CHD have multiple mechanisms of failing physiology that are not amenable to advanced therapies linked to listing criteria such as inotropic support, VAD implantation, or mechanical ventilation.

We found worse survival after transplant surgery in CHD-HS compared to CHD without HS across the study period. This is consistent with other large series evaluating non-transplant cardiac surgery. The Society of Thoracic Surgeons (STS) national database found that in every STS −EACTS (European Association for Cardio-Thoracic Surgery) congenital heart surgery mortality category, discharge mortality is higher in CHD-HS compared to those without HS.[4] An analysis of the SRTR (Scientific Registry of Transplant Recipients) data reported increased post-operative complications, hospital length of stay, costs, and mortality after HT in children with HS.[11] While our results show worse survival across the entire study period, we demonstrate a novel era effect for HS with no difference in transplant survival between CHD with and without HS in the current era.

The finding of this era effect is important, especially given the aforementioned findings in non-transplant cardiac surgery and the recent transplant publication which linked the Pediatric Health Information System (PHIS) and the Scientific Registry of Transplant Recipients (SRTR) data to identify pediatric HT recipients with HS.[4] In the PHIS-SRTR analysis, the increased risk of mortality post HT for CHD-HS was 1.6 for HT performed between 2001 and 2016. This is identical to the overall risk we found of 1.6 for HS in the constant hazard phase for death after HT. This risk for death in the constant phase did not differ between eras in our study. However, there was an era difference in the risk for early death when this interaction was assessed. The effect of HS on early mortality risk was greatest in the early era of HT. For those with CHD-HS who underwent HT before 2005, the risk of early death was 2 fold greater referenced against children without HS and without early era of HT.

Our analysis also examined post-HT survival in CHD-HS with single ventricle vs biventricular heart disease. Single ventricle heart disease was a risk factor for early post-transplant mortality for the entire CHD cohort with and without HS, but single ventricle heart disease was not an independent risk factor for death in multi-variate analysis of the CHD-HS group. These results are notable when weighing the mortality risk of palliative surgery in single ventricle CHD-HS and the mortality risk of transplant. To add to this consideration, another study reported a higher rate of in-hospital death (27% vs 10%; $p = 0.02$) after first-stage palliation in single ventricle CHD-HS vs single ventricle CHD without HS. However, in survivors of first-stage palliation, later survival to Fontan was similar among those with and without heterotaxy.[5] Regarding Fontan palliation, a meta-analysis of 848 patients found higher early mortality after Fontan completion in HS patients but good long-term survival.[17] Likewise, the Australia-New Zealand Fontan Registry found no difference in late Fontan failure in 109 patients with vs 1,431 without HS.[18] Taken together, these results could suggest that higher risk un-operated infants with CHD-HS should be considered for primary HT while lower risk single ventricle CHD-HS can progress through staged palliation. However, the mean age of HT was 6.4 years and almost 90% of CHD-HS had prior cardiac surgery, including 40% of single ventricle CHD-HS completing Fontan palliation prior to HT. Thus, the favorable outcomes of Glenn and Fontan palliation in the prior studies and the transplant outcomes in our study are most applicable to children who have survived the initial neonatal period and first stage palliation.

Most deaths occurred in the first 3 months after HT. The etiology for early post-HT deaths in CHD-HS is likely multi-factorial, including the surgical risk of complex CHD and other co-morbidities. Regarding surgical risks, the CHD-HS cohort more often had single ventricle disease and over 80% had cardiac surgery prior to listing. However, in unadjusted Kaplan-Meier analysis, there was no association between waitlist or post-transplant survival with single ventricle status within the HS cohort. Additionally, HS remained an independent predictor of poor post-transplant survival in multivariate analysis after adjusting for single ventricle status, indicating that the higher incidence of single ventricle disease alone does not explain the increased post-transplant mortality in this group. With respect to other co-morbidities seen in HS, children with HS have been shown to have more respiratory complications.[19] This has been hypothesized to be linked to ciliary dysfunction, like that seen in primary ciliary dyskinesia; thus,

leading to an increased predisposition to respiratory complications. Moreover, functionally asplenic patients, as in HS, are more susceptible to infections with encapsulated organisms, which can be a life-threatening complication in immunosuppressed patients. Both factors could contribute to worse outcomes in CHD-HS. Our finding of shorter time to first infection in CHD-HS vs other CHD supports this concern.

When weighing the balance of immune suppression and infection risk, the outcomes of rejection, CAV, and PTLD become important. While time to first rejection was similar between the CHD-HS and other CHD groups, patients with CHD-HS had lower freedom from rejection with hemodynamic compromise. This is a key finding because prior PHTS analyses have shown poor survival after an episode of rejection with hemodynamic compromise.[12,13] Other events that may be surrogates for the degree of immune suppression or the patient's inherent immunologic risk, namely CAV and PTLD, were not different between groups. Because infection and rejection tend to be early events, the details of early immune suppression after HT becomes pertinent. There was no difference in use of induction or maintenance steroids at 30 days between the CHD-HS and the other CHD groups. It is unclear if increased surveillance for events or tailoring immunosuppression would balance the risk of infection and rejection in CHD-HS. This balance remains a challenge in all HT recipients, and perhaps, a greater challenge in CHD-HS.

The finding of worse survival after HT in polysplenia merits discussion. Reasons for this finding are not entirely clear, but this survival difference was negated in the current era. One possible explanation is the unique challenges of the interrupted inferior vena cava and the unpredictability of the hepatic venous drainage at time of HT. Complex transplant procedures and caval reconstructions can contribute to early graft failure after HT in CHD-HS with polysplenia. Imaging of the venous anatomy for complex surgical reconstruction has certainly improved over time. In CHD-HS asplenia, anomalies in pulmonary venous return are more common, and in non-transplant cardiac surgery, HS with total anomalous pulmonary venous return (TAPVR) repair have worse surgical outcomes, with increased re-operations for pulmonary vein stenosis[6] and worse survival.[7,8] In fact, concomitant TAPVR repair was an independent risk factor for mortality in the series of infants with HS undergoing staged palliation.[5] In our study, the mean age at HT for CHD-HS asplenia was 6.8 years, and 80% of these patients had prior cardiac surgery. Thus, while 42% of the asplenic patients had TAPVR, the morbidity and mortality associated with repair likely occurred in the early stages of palliative surgery, and significant or recurrent stenosis of the pulmonary veins would have been a contraindication to listing for isolated HT in those patients. None of the children in our study had combined heart-lung transplant. It is plausible that advancements in surgical techniques and pre-operative imaging for candidate selection and surgical planning have contributed to the dramatic improvement in early HT survival seen in CHD-polysplenia.

Limitations

Our analysis has several limitations inherent to the retrospective design. There is heterogeneity within HS and a wide spectrum of associated defects. We were able to perform detailed analysis regarding single ventricle physiology, and surgical palliation, but details of vascular anomalies, collateral vessels, and technical issues related to transplant surgery or graft function are not available. We found interesting results in the subanalysis of asplenia vs polysplenia, but conclusions are limited by the high number of unspecfied heterotaxy (40%).

Lastly, the database only contains children who are deemed acceptable HT candidates. Thus, we could not analyze factors related to candidate referral and selection practices that can impact waitlist and post-transplant survival.

Conclusions

In conclusion, we found similar waitlist survival but lower transplant survival in children with CHD and HS across the entire study period. However, HS conferred the greatest risk for early transplant mortality in the earlier era. This risk was mitigated over time such that transplant survival was similar between those with and without HS in the recent era. Early referral may improve waitlist survival for CHD-HS who otherwise have lower listing status but similar waitlist outcomes compared to other CHD candidates. The shorter time to first infection and shorter time to first rejection with hemodynamic compromise in CHD-HS highlight the need to balance immune suppression to improve outcome. Our findings are most applicable to older children after prior surgical palliation, and the results show favorable outcomes for children with HS in the current era of HT.

Authors' contribution

All authors participated sufficiently in the work and take public responsibility for the content. Khan: concept and/or design, data interpretation, critical revision of article, approval of article. Pahl: concept and/or design, data interpretation, critical revision of article, approval of article. Koehl: statistics, data analysis, approval of article. Cantor: data analysis, data interpretation, critical revision of article, approval of article. Kirklin: design, data interpretation, critical revision of article, approval of article. Rusconi: data interpretation, critical revision of article, approval of article. Barnes: data interpretation, critical revision of article, approval of article. Azeka: data interpretation, critical revision of article, approval of article. Everitt: design, data interpretation, critical revision of article, approval of article

Disclosure statement

There are no relevant financial conflicts to disclose.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.healun.2021.07.008.

Appendix 1

Potential covariates for Multivariate Risk Model. Except bilirubin and MELD-XI, all variables listed had <20% missing values and were imputed to the mean.

PHTS: January 1, 1993-December 31, 2018
TAPVR
Surgery Count
Bilirubin at Transplant (37% missing values)
MELD-XI Score at Transplant (37% missing values due to missing bilirubin)
ECMO at Transplant
VAD at Transplant
Sex
Single Ventricle Status
Era (1993-2004, 2005-Current)
Years Since 1993
Heterotaxy and Era Interaction Term
Heterotaxy and Single Ventricle Status Interaction Term
History of Renal Insufficiency
Donor Ischemic Time
Cardiopulmonary Bypass Time
Age at Transplant
Induction Therapy
Heterotaxy Status
Renal Impairment (eGFR < 60)
History of Surgery
Ventilator at Transplant
Race
Status 1 at Transplant
Inotropes at Transplant

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