Increased mortality, morbidities, and costs after heart transplantation in heterotaxy syndrome and other complex situs arrangements

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ABSTRACT

Objectives: Identify pediatric heart transplant (HT) recipients with heterotaxy and other complex arrangements of cardiac situs (heterotaxy/situs anomaly) and compare mortality, morbidities, length of stay (LOS), and costs to recipients with congenital heart disease without heterotaxy/situs anomaly.

Methods: Using linked registry data (2001-2016), we identified 186 HT recipients with heterotaxy/situs anomaly and 1254 with congenital heart disease without heterotaxy/situs anomaly. We compared post-HT outcomes in univariable and multivariable time-to-event analyses. LOS and cost from HT to discharge were compared using Wilcoxon rank-sum tests. Sensitivity analyses were performed using stricter heterotaxy/situs anomaly group inclusion criteria and through propensity matching.

Results: HT recipients with heterotaxy/situs anomaly were older (median age, 5.1 vs 1.6 years; $P < .001$) and more often black, Asian, Hispanic, or “other” nonwhite (54% vs 32%; $P < .001$). Heterotaxy/situs anomaly was independently associated with increased mortality (hazard ratio, 1.58; 95% confidence interval, 1.19-2.09; $P = .002$), even among 6-month survivors (hazard ratio, 1.86; 95% confidence interval, 1.09-3.16; $P = .021$). Heterotaxy/situs anomaly recipients more commonly required dialysis (odds ratio, 2.58; 95% confidence interval, 1.51-4.42; $P = .001$) and cardiac reoperation (odds ratio, 1.91; 95% confidence interval, 1.17-3.11; $P = .010$) before discharge. They had longer ischemic times (19.2 additional minutes [range, 10.9-27.5 minutes]; $P < .001$), post-HT intensive care unit LOS (16 vs 13 days; $P = .012$), and hospital LOS (26 vs 23 days; $P = .005$). Post-HT hospitalization costs were also greater (\$447,604 vs \$379,357; $P = .001$).

Conclusions: Heterotaxy and other complex arrangements of cardiac situs are associated with increased mortality, postoperative complications, LOS, and costs after HT. Although increased surgical complexity can account for many of these differences, inferior late survival is not well explained and deserves further study. (J Thorac Cardiovasc Surg 2019;157:730-40)

Increased mortality, morbidities, and costs for heart transplant recipients with heterotaxy.

Central Message

Heart transplantation in patients with heterotaxy/cardiac situs anomalies is associated with increased mortality, early morbidities, and higher care costs compared with transplantation for other congenital heart diseases.

Perspective

Children with heterotaxy who undergo heart transplantation are understudied. We found they have increased mortality, early morbidities (including need for dialysis, cardiac reoperation, and vascular intervention), and care costs relative to nonheterotaxy transplant recipients. Anticipation of these features may aid decision making around transplant candidacy and during postoperative care.

See Editorial Commentary page 741.

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Abbreviations and Acronyms

CAV	= coronary allograft vasculopathy
CHD	= congenital heart disease
DSXM	= donor-specific cross-match
ECMO	= extracorporeal membrane oxygenation
eGFR	= estimated glomerular filtration rate
HT	= heart transplant
ICD	= International Classification of Diseases
ICU	= intensive care unit
LOS	= length of stay
OPO	= organ procurement organization
PHIS	= Pediatric Health Information System
PTLD	= posttransplant lymphoproliferative disease
SRTR	= Scientific Registry of Transplant Recipients
VAD	= ventricular assist device

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Heterotaxy is characterized by organ laterality defects and complex congenital heart disease (CHD).¹ Survival has historically been poor compared with other forms of CHD, particularly early after cardiac surgery due to technical difficulties posed by anomalies of situs.^{2,3} Heart transplantation (HT) has been reported for patients with heterotaxy in case reports⁴ and single center series.⁵ However, due to the lack of an indicator variable in transplant registries, there has been no large, multicenter analysis of outcomes and complications for recipient with heterotaxy; thus, limited information is available to guide providers and patients.

We used a novel linkage between the Scientific Registry of Transplant Recipients (SRTR) and the Pediatric Health Information System (PHIS) databases to describe survival, length of stay (LOS), hospitalization costs, and morbidities following HT for children and young adults with heterotaxy and other complex arrangements of cardiac situs (ie, heterotaxy/sinus anomaly). We hypothesized that HT recipients with heterotaxy/situs anomaly would have increased early post-HT mortality and greater LOS and hospital costs from HT to discharge compared with recipients with CHD in the absence of heterotaxy/situs anomaly. Following the early post-HT phase, we hypothesized that survival for heterotaxy/situs anomaly recipients would be similar to

nonheterotaxy/situs anomaly recipients. We did not specify hypothesis regarding morbidities given the multiple morbidities that were explored.

METHODS

Database Linkage and Patient Selection

Database linkage at the patient level used indirect identifiers and was performed and validated as previously described.⁶ SRTR includes data on all donors, wait-listed candidates, and recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network. The Health Resources and Services Administration of the US Department of Health and Human Services provides oversight to the activities of the Organ Procurement and Transplantation Network and SRTR contractors.⁷ PHIS is an administrative database of International Classification of Diseases ninth and 10th edition (ICD-9/10) codes, hospital charges, and resource use for hospital-based patient encounters across >45 US children's hospitals.⁸ We mapped ICD-10 to ICD-9 using the Agency for Healthcare Research and Quality MapIT Tool⁹ (Table E1).

The linked database contained 3062 records of transplant and follow-up data from November 2001 to November 2016. After exclusions for retransplantation (n = 189) and missing/non-CHD diagnosis (n = 1433), analysis was performed on patients who underwent primary HT for CHD (n = 1440 [47%]). Heterotaxy/situs anomaly (n = 186) was defined as any patient with an SRTR diagnosis of CHD plus ≥ 1 of the following ICD-9/10 codes within their entire PHIS record: 759.3/Q89.3 (situs inversus); 759.0/Q89.01, Q89.09 (polysplenia/asplenia); or 746.87/Q24.0 (dextrocardia). Primary HT recipients not meeting these criteria formed the comparison group of CHD recipients without heterotaxy/situs anomaly (n = 1254).

Data Sources and Collection

From SRTR we collected recipient sex, race, diagnosis (CHD/non-CHD), history of sternotomy and/or thoracic surgery for CHD, and HT date; age, waitlist urgency status, patient location (intensive care unit [ICU]/in-hospital/outside hospital), and use of inotropic support, mechanical ventilation, ventricular assist device (VAD), and extracorporeal membrane oxygenation (ECMO) at HT; dialysis while listed; pre-HT serum creatinine; donor-specific cross-match (DSXM); ischemic time; and donor and recipient organ procurement organizations (OPOs). The following were collected from SRTR: treatment for infection or acute rejection, cardiac reoperation, and posttransplant dialysis during the HT admission; latest vital status (ie, alive/deceased/retransplanted) with date; cause of death; infection or rejection requiring rehospitalization; and occurrence of post-transplant lymphoproliferative disease (PTLD) and coronary allograft vasculopathy (CAV).

PHIS data were used to characterize the underlying CHD phenotypes in the study population; characterize surgeries, procedures, and infections that occurred after HT during the HT hospitalization; and quantify inpatient costs and the durations of post-HT mechanical ventilation, ICU LOS, and hospital LOS. All costs were adjusted for inflation to 2016 US dollars using the medical component of the consumer price index and were calculated from charges using hospital and year-specific cost-to-charge ratios.

To characterize the spectrum of underlying CHD phenotypes we identified the following cardiovascular morphology ICD-9/10 diagnosis codes applied during the transplant hospitalization in PHIS: ICD-9 codes beginning with 745 (Bulbus cordis anomalies and anomalies of cardiac septal closure), 746 (Other congenital anomalies of the heart), and 747 (Other congenital anomalies of the circulatory system), and ICD-10 codes Q20-Q28 (Congenital malformations of the circulatory system). Similarly, cardiovascular surgeries and procedures that occurred after HT during the transplant hospitalization were assessed by identifying ICD-9 procedure codes that begin with 35, 36, 37, 38, and 39 (Operations on the cardiovascular system) and ICD-10 procedure codes beginning with 02 (Heart and great vessels). To explore differences in encapsulated bacterial infections,

we identified the relevant ICD-9/10 diagnosis codes assigned during the transplant admission (Table E2). Duplicated codes were only counted once per subject.

Statistical Analysis

Data are described as median (interquartile range) or count (%), as appropriate. Odds and hazard ratios are reported with 95% confidence intervals (CIs). Categorical data were compared using the χ^2 or Fisher exact test, as appropriate. Continuous data were compared using the Wilcoxon rank-sum test. Post-HT procedures were compared between the groups by calculating the odds ratio (OR) of procedure with Fisher exact 95% CI. Univariate survival was assessed with the Kaplan-Meier estimator and compared using the log-rank test. Survival curves were truncated when approximately 10% of patients were left at-risk. Because death competes with postdischarge infection, rejection, PTLTD, and CAV, each of these outcomes was analyzed by competing-risks regression¹⁰ in which the competing risk of death/retransplantation was considered. Significant differences in outcomes between the groups in univariate comparison were adjusted for covariates using multivariable Cox proportional hazards, logistic, and linear regression models, as appropriate. To build the models the following covariates were tested for a univariate effect on outcome: race, age, year of HT, prior sternotomy and/or prior CHD surgery, dialysis on waitlist, DSXM result, waitlist urgency status, patient location, inotropic support, mechanical ventilation, VAD, and ECMO at HT. For analysis of post-HT renal failure requiring dialysis, we included pre-HT dialysis, glomerular filtration rate (eGFR) <40 mL/min/1.73 m², and ischemic time >3.5 hours. eGFR was estimated using the modified Schwartz formula,¹¹ capped at 200 mL/min/1.73 m². Procurement distance was estimated by computing the geodesic distance between donor and recipient OPO ZIP codes,¹² and used as a covariate in linear regression analysis of ischemic time between the groups. Covariates with P values $\leq .1$ in univariate comparisons were included in the multivariable model with the main variable of interest. Covariates with Wald test $P > .1$ in the full multivariable models were then dropped from the analysis to produce final models. The proportional hazards assumption was assessed for Cox models by visualization of log-log survival plots and with regression of the scaled Schoenfeld residuals on the identity function of time.¹³ Covariates that violated the proportional hazards assumption were stratified in Cox models. Presence of significant interaction terms were assessed with the likelihood-ratio test.

Missing data were compared across groups (Table E3). For pre-HT VAD and dialysis, missing data were rare (<3%) and imputed as “no.” For DSXM, prior sternotomy and/or prior CHD repair, and prior univentricular CHD repair, missing data were assumed to be randomly missing and imputed using multiple imputation. Subjects with missing outcomes data were excluded for analysis of that outcome.

Sensitivity Analyses

To address potential misclassification based on the nonspecificity of the dextrocardia and situs inversus ICD codes, subjects were reclassified using stricter inclusion criteria of only polysplenia/asplenia ICD codes and survival analysis was repeated. To address possible misspecification of model variables, we modified all Cox models to include additional user-selected, clinically relevant covariates. Finally, to address the potential for bias from inadequate/incomplete selection of model covariates, we performed propensity score matching in which the probability of a subject being classified into the heterotaxy/situs anomaly group was determined by logistic regression on characteristics listed in Table E4. Missing data were coded as a categorical dummy variable for each covariate, allowing patients with missing data to be matched. Matching was 1:2 using a matching caliper of one-fifth the standard deviation of the logit of the propensity scores. Covariate balance was assessed through calculation of the standardized mean bias, with values > 0.2 considered significant.

All analyses were performed using Stata version 13 (StataCorp, College Station, Tex). This research was approved by the Vanderbilt University and

VIDEO 1. Senior author, Dr Brian Feingold, medical director, Heart Transplantation at UPMC Children’s Hospital of Pittsburgh, explains the importance and relevance of the article. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)32970-2/fulltext](https://www.jtcvs.org/article/S0022-5223(18)32970-2/fulltext).

University of Pittsburgh Institutional Review Boards, PHIS, and SRTR. See highlights of the study in Video 1.

RESULTS

Group Characteristics

Group characteristics at transplant are shown in Table 1. The heterotaxy/situs anomaly group was older (median age, 5.1 years vs 1.6 years; $P < .001$) and more often African American, Asian, Hispanic, or “other” nonwhite (54% vs 32%; $P < .001$). A lower proportion in the heterotaxy/situs anomaly group had reduced eGFR (3% vs 9%; $P = .004$). We found no other significant differences between groups, including proportion with prior sternotomy and/or surgery for CHD (76% vs 68%; $P = .196$). There were no significant differences in missing data between groups (Table E3).

ICD codes used to define the heterotaxy/situs anomaly group were distributed as follows: dextrocardia (71 out of 186 [38%]); polysplenia/asplenia (31 out of 186 [17%]); polysplenia/asplenia with dextrocardia (34 out of 186 [18%]); polysplenia/asplenia with situs inversus (17 out of 186 [9%]); polysplenia/asplenia, dextrocardia, and situs inversus (15 out of 186 [8%]); dextrocardia with situs inversus (12 out of 186 [6%]); and situs inversus alone (6 out of 186 [3%]). Table E5 demonstrates the spectrum of underlying CHD phenotypes described by ICD codes. The heterotaxy/situs anomaly group was enriched for codes for endocardial cushion defect, common ventricle, pulmonary outflow tract obstruction, disorders of pulmonary and systemic venous return, truncus abnormalities, and conduction abnormalities. The nonheterotaxy/situs anomaly CHD group was enriched for hypoplastic left heart syndrome, coronary artery anomalies, and secundum atrial septal defects. See Table E5 for full data.

Survival After Transplant

Median follow-up was 3.03 years (range, 1.00-6.91 years). The heterotaxy/situs anomaly group demonstrated inferior post-HT survival in unadjusted analysis ($P = .002$) (Figure 1, A). Univariable and multivariable Cox model specifications are shown in Tables E6 and E7. After adjustment for African-American race, calendar year of HT, and pre-HT ECMO, heterotaxy/situs anomaly was associated with an increased mortality compared with nonheterotaxy/situs anomaly CHD (hazard ratio [HR], 1.58; 95% CI, 1.19-2.09; $P = .002$). These findings

persisted amongst 6-month post-HT survivors in unadjusted ($P = .007$) (Figure 1, B) and adjusted analyses (HR, 1.86; 95% CI, 1.09-3.16; $P = .021$; adjusted for age and African-American race). There were no significant differences in cause of death between the groups (Table 2) or in the cumulative incidences of PTLT, CAV, admission for infection, or admission for rejection between the groups (Figure 2, A-D). Of note, 2 recipients (1%) in the heterotaxy/situs anomaly group and 30 (2%) in the nonheterotaxy/situs anomaly group underwent retransplantation during the observation period.

TABLE 1. Group characteristics at heart transplant

Characteristic	Nonheterotaxy CHD (n = 1254)	Heterotaxy (n = 186)	P value*
Age (y)	1.6 (0.3-9.0)	5.1 (0.8-11.5)	<.001
Female	509 (41)	80 (43)	.576
Weight (kg)†	9 (4.1-22.0)	15.2 (6.4-30.0)	<.001
Height (cm)†	76 (54-119)	98 (63-138)	<.001
Creatinine (mg/dL)†	0.4 (0.3-0.6)	0.4 (0.3-0.6)	.296
eGFR <40 mL/min/1.73 m ² †	111/1223 (9)	5/182 (3)	.004
Race			<.001‡
White	852 (68)	89 (46)	
African American	166 (13)	36 (19)	
Asian	20 (2)	10 (5)	
Hispanic	188 (15)	42 (23)	
Other	28 (2)	9 (5)	
Year of transplant	2011 (2007-2014)	2011 (2008-2014)	.267
Listing status			.261‡
1A	1023 (82)	146 (78)	
1B	156 (12)	31 (17)	
2	75 (6)	9 (5)	
Location			.357‡
ICU	637 (51)	85 (46)	
Hospitalized, non-ICU	209 (17)	37 (20)	
Not hospitalized	408 (33)	64 (34)	
Inotrope support	645 (51)	97 (52)	.875
VAD support†	86 (7)	13 (8)	.878
Pre-HT dialysis†	28 (2)	6 (3)	.434
ECMO	94 (7)	8 (5)	.206
Mechanical ventilation	276 (22)	36 (20)	.769
Positive DSXM†	203/1004 (20)	22/149 (15)	.207
Prior sternotomy and/or surgery for CHD†	512/826 (62)	94/137 (69)	.152
If prior sternotomy and/or surgery for CHD, underwent univentricular repair†	314/461 (68)	63/83 (76)	.196
Distance between donor and recipient OPO (miles)	494 (200-638)	328 (103-579)	.047
Total ischemic time (min)	230 (191-273)	240 (198-289)	.020

Data are presented as n (%) or median (interquartile range). CHD, Congenital heart disease; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; VAD, ventricular assist device; HT, heart transplant; ECMO, extracorporeal membrane oxygenation; DSXM, donor-specific crossmatch; OPO, organ procurement organization. *Continuous data compared with rank-sum test, binary outcomes compared using χ^2 test of proportions. †Missing data present; see Table E3 for number and proportion missing from each group for each of these variables. ‡Tested across all groups.

Risk Table

Non-Het:	1254	791	548	390	245	145
Het:	186	102	66	41	23	11

A

Risk Table

Non-Het:	1061	791	548	390	245	145
Het:	152	102	66	41	23	11

B

FIGURE 1. A, Survival after heart transplantation with heterotaxy/situs anomaly. Univariable Kaplan-Meier estimator showing that patients with heterotaxy/situs anomaly (Het) (red) have inferior survival after heart transplantation compared with other patients with congenital heart disease (CHD) in the absence of heterotaxy/situs anomalies (Non-Het) (blue). The curves sharply diverge early after transplant (approximately 6-12 mo) and continue to diverge more gradually thereafter, consistent with survival differences between the groups both early and later after transplantation. B, Survival after heart transplantation with Het, conditional upon survival to 6-months after transplantation. Univariable Kaplan-Meier estimator showing that among 6-month postheart transplant survivors, patients with Het (red) have decreased survival compared with patients with CHD in Non-Het (blue). This analysis confirms a survival difference between the groups occurring outside the perioperative phase.

Posttransplant Complications, LOS, and Cost

Perioperative complications analyzed from SRTR are shown in Table 3. Univariable and multivariable logistic model specifications are shown in Tables E8 and E9. Cardiac reoperation (adjusted OR, 1.91; $P = .010$) and renal failure requiring dialysis (adjusted OR, 2.58; $P = .001$) were increased among heterotaxy/situs anomaly recipients

prior to discharge following HT. Heterotaxy/situs anomaly recipients were more commonly treated for infection before discharge following HT (adjusted OR, 1.54; $P = .015$); however, we found no difference in PHIS-recorded encapsulated bacterial infection ICD codes between the groups (2.9% vs 2.3%; $P = .638$). There were similar proportions with acute rejection during the HT hospitalization (17% each; $P = .916$).

As shown in Table 4, data from PHIS support increased complications between HT and hospital discharge. ICD procedure codes for venous catheterization (OR, 1.65; $P = .010$), insertion of nondrug-eluting peripheral (non-coronary) vessel stent(s) (OR, 2.94; $P = .016$), and hemodialysis (OR, 2.67; $P = .013$) were more common among heterotaxy/situs anomaly recipients. We also found greater duration of mechanical ventilation after HT for heterotaxy/situs anomaly recipients (median 5 vs 4 days; $P = .039$) (Table 5), with a greater proportion of heterotaxy/situs anomaly recipients requiring mechanical ventilation for >1 week after HT (44 vs 36%; adjusted OR, 1.70; 95% CI, 1.20-2.40; $P = .003$) (Table 3).

Ischemic times were longer for the heterotaxy/situs anomaly group (median, 240 minutes [interquartile range, 198-289 minutes] vs 230 minutes [interquartile

TABLE 2. Cause of death

Cause	Nonheterotaxy congenital heart disease (n = 291)	Heterotaxy (n = 59)	P value*
Cardiovascular	70 (24)	12 (20)	.615
Cerebrovascular	21 (7)	6 (10)	1
Graft failure	83 (29)	16 (27)	.875
Hemorrhage	12 (4)	3 (5)	1
Infection	29 (10)	8 (14)	.725
Malignancy	6 (2)	3 (5)	.180
Pulmonary	28 (10)	10 (17)	.109
Other	48 (16)	8 (14)	.698
Unknown	26 (9)	4 (7)	.592

Values are presented as n (%). *Fisher exact test of proportions.

FIGURE 2. Cumulative incidences of development of common postheart transplant comorbidities. A, Posttransplant lymphoproliferative disease (PTLD). B, Coronary artery vasculopathy (CAV). C, First hospitalization for infection. D, First hospitalization for rejection. In each panel, patients with heterotaxy/situs anomaly (red) are compared with patients with congenital heart disease (CHD) in the absence of heterotaxy/situs anomalies (blue). All cumulative incidences depicted account for the competing outcome of death/retransplantation. E, Cumulative number of events at each time point are shown in the table below. There were no statistically significant differences observed for these outcomes. Dotted lines depict 95% confidence intervals and the numbers at risk in each group are shown at bottom of the panel.

TABLE 3. Perioperative outcomes

Outcome	Nonheterotaxy congenital heart disease	Heterotaxy	Unadjusted odds ratio (95% CI)	Unadjusted P value	Adjusted odds ratio (95% CI)	Adjusted P value
Infection during HT admission	294/974 (30)	57/145 (49)	1.50 (1.04-2.15)	.030	1.54 (1.06-2.25)*	.015*
Cardiac reoperation	97/979 (10)	27/143 (19)	2.12 (1.32-3.38)	.002	1.91 (1.17-3.11)†	.010†
Post-HT renal failure requiring dialysis	77/1253 (6)	23/186 (12)	2.16 (1.32-3.53)	.002	2.58 (1.51-4.42)‡	.001‡
Mechanically ventilated >1 wk	429/1202 (36)	78/177 (44)	1.42 (1.3-1.95)	.032	1.70 (1.20-2.40)§	.003§
Rejection during HT admission	187/1124 (17)	29/137 (17)	1.02 (0.67-1.57)	.916	—	—

Values are presented as n (%). CI, Confidence interval; HT, heart transplant. *Infection during HT admission adjusted for: year, pre-HT extracorporeal membrane oxygenation, pre-HT mechanical ventilation, home location at HT, positive donor-specific cross-match, and history of prior univentricular CHD repair. †Adjusted for patient race, ventricular assist device, and mechanical ventilation pre-HT. ‡Adjusted for pre-HT dialysis, estimated glomerular filtration rate <40 mL/min/1.73 m², ischemic time >3.5 hours, extracorporeal membrane oxygenation, ICU location at HT, and female race. §Adjusted for mechanical ventilation pre-HT, pre-HT extracorporeal membrane oxygenation, and age. Source data: Scientific Registry of Transplant Recipients.

range, 191-273 minutes]; $P = .020$), despite a shorter median distance between donor and recipient OPOs (328 miles [interquartile range, 103-579 miles] vs 494 miles [200-638 miles]; $P = .047$). After adjustment for significant covariates (distance, Hispanic race, outpatient location at HT, and history of prior univentricular CHD repair), heterotaxy/situs anomaly was associated with 19.2 (95% CI, 10.4-27.6; $P < .001$) additional minutes of ischemia. Table E10 shows model specifications.

As shown in Table 5, recipients with heterotaxy/situs anomaly had longer median post-HT ICU (16 days [interquartile range, 0-190 days] vs 13 days [interquartile range, 0-458 days]; $P = .012$) and total hospital LOS (26 days [interquartile range, 16-49 days] vs 23 days [interquartile range, 14-42 days]; $P = .005$), conditional on survival to discharge. Post-HT hospitalization costs were also greater for heterotaxy/situs anomaly recipients: median \$447,604 vs \$379,357; $P = .001$ amongst all recipients; \$421,040 versus \$360,211; $P = .001$ amongst those surviving to discharge. Across most subcategories, costs were

significantly greater for heterotaxy/situs anomaly recipients (Tables E11 and E12).

Sensitivity Analyses

After forcing clinically important variables of age and history of prior univentricular repair into the primary outcome Cox model, we still observed increased mortality among heterotaxy/situs anomaly recipients (HR, 1.52; 95% CI, 1.13-2.03; $P = .005$; adjusted for African-American race, year of HT, pre-HT ECMO, age, and history of prior univentricular repair). After reclassification of patients with heterotaxy based solely on ICD codes for polysplenia/asplenia, heterotaxy/situs anomaly remained an independent predictor of mortality (HR, 1.51; 95% CI, 1.04-2.21; $P = .032$) adjusted for African-American race, year of HT, and ECMO at HT (Figure E1). In propensity score-matched cohorts, 186 recipients with heterotaxy/situs anomaly were matched to 368 non-heterotaxy/situs anomaly CHD HT recipients (Table E4 and Figure E2). Heterotaxy/situs anomaly was associated with increased mortality (HR, 1.53; 95% CI, 1.09-2.16; $P = .015$).

TABLE 4. International Classification of Diseases ninth edition (ICD-9) procedure codes after heart transplant

ICD-9 description	ICD-9 code*	Heterotaxy (n = 177)	Nonheterotaxy congenital heart disease (n = 1199)	Odds ratio (95% confidence interval)†	P value‡
Other revision of vascular procedure	39.49	4 (2.3)	9 (0.8)	3.06 (0.99-9.47)	.074
Insertion of nondrug-eluting peripheral (noncoronary) vessel stent(s)	39.9	8 (4.5)	19 (1.6)	2.94 (1.29-6.68)	.016
Hemodialysis	39.95	11 (6.2)	29 (2.4)	2.67 (1.33-5.39)	.013
Venous cutdown	38.94	5 (2.8)	14 (1.2)	2.46 (0.91-6.66)	.086
Venous catheterization for renal dialysis	38.95	8 (4.5)	23 (1.9)	2.42 (1.09-5.39)	.050
Angioplasty of other noncoronary vessel(s)	39.5	18 (10.2)	79 (6.6)	1.60 (0.94-2.74)	.085
Venous catheterization, not elsewhere classified	38.93	47 (26.6)	215 (17.9)	1.65 (1.15-2.38)	.010
No posttransplant procedure performed	None	44 (24.9)	378 (31.5)	0.72 (0.50-1.03)	.081

Values for heterotaxy and nonheterotaxy congenital heart disease are presented as n (%). ICD-9, International Classification of Diseases ninth edition. *ICD-10 procedure codes were translated to ICD-9. †Fisher exact test. Source data: Pediatric Health Information System database.

TABLE 5. Resource use and length of stay (LOS) after heart transplant (HT)

Outcome	Nonheterotaxy congenital heart disease	Heterotaxy	P value*
Ventilation days	4 (1-14)	5 (2-21)	.039
iNO days	2 (0-5)	2 (0-5)	.176
ECMO post-HT	172/1030 (14)	22/177 (12)	.564
ICU LOS after HT (d)†	13 (0-458)	16 (0-190)	.012
Hospital LOS after HT (d)†	23 (14-42)	26 (16-49)	.005
Cost after HT (2016 \$, thousands)	\$379 (\$262-\$580)	\$448 (\$320-\$709)	.001
Cost after HT, if survived to discharge (2016 \$, thousands)†	\$360 (\$252-\$527)	\$421 (\$299-\$666)	.001

Values are presented as n (%) or median (interquartile range). *iNO*, Inhaled nitric oxide; *ECMO*, extra-corporeal membrane oxygenation; *ICU*, intensive care unit; *LOS*, length of stay; *HT*, heart transplant. *Binary data compared with Fisher exact test, continuous data with Wilcoxon rank-sum test. †Conditional upon survival to discharge. Source data: Pediatric Health Information System database.

DISCUSSION

Significance of Main Findings

We provide the most extensive report of post-HT outcomes for children with heterotaxy/situs anomaly from a large sample of US pediatric HT centers (Figure 3). To date, knowledge about HT outcomes for heterotaxy patients has been limited to anecdotal experience, case reports, and single center series. Jacobs and colleagues¹⁴ reported sub-optimal outcomes in 5 HT recipients with heterotaxy, whereas Cohen and colleagues¹⁵ reported survival to 32 and 33 months for 2 HT recipients with heterotaxy. In the largest previous report, 29 pediatric HT recipients with heterotaxy at a single-center showed no difference in survival relative to controls with dilated cardiomyopathy.⁵ Our main findings are that patients with heterotaxy/situs anomaly have decreased survival after HT and accrue greater costs for care with longer LOS after HT relative to other recipients who underwent HT for CHD (Figure 3). We also observed increased early post-HT morbidities, including longer ischemic times, increased prevalences of cardiac reoperation, catheterization, peripheral vessel stenting, and renal failure among heterotaxy/situs anomaly recipients. Although associations do not imply causality, these increased morbidities could explain greater mortality and resource use among heterotaxy/situs anomaly recipients.

Not well explained is the late survival difference we observed. Although the heterotaxy/situs anomaly group was older and disproportionately non-white, both known risk factors for inferior survival after pediatric HT¹⁶ the late survival difference persisted after controlling for these. Potentially, greater medical/surgical complexity or accrued pre-HT comorbidities for heterotaxy/situs anomaly recipients persist after HT and influences late survival but was not captured in our analysis. Though we found no significant differences in prior sternotomies between the groups, these data do not convey number, timing, or complexity of cardiac surgeries prior to HT. Similarly, although we found no difference in time-to-event for common causes of late post-HT mortality (ie, rejection, infection, PTLN, and CAV), we lack details about severity of these events.

Rejection associated with hemodynamic compromise imparts significantly higher risk of death than rejection without hemodynamic compromise.^{17,18} Likewise, PTLN and CAV severity influence survival.^{19,20} The broad, multisystem involvement of heterotaxy syndrome,²¹ including the potential for overwhelming bacterial sepsis with asplenia/functional asplenia, may also contribute to the observed survival difference. In a recently reported neonatal heterotaxy syndrome cohort, extracardiac causes were implicated in 18% of deaths.²²

Perioperative Morbidities

The primary strength of our analysis is the ability to identify and analyze patients with heterotaxy and other complex arrangements of cardiac situs in a large, multi-center cohort, thereby providing novel insights into post-HT survival, perioperative complications, procedures, and resource utilization. We hypothesized that HT recipients with heterotaxy/situs anomaly have worse perioperative outcomes due to increased surgical complexity related to anomalies of cardiac position and venous return.^{4,23-26} Indeed, we have found evidence of this. Despite shorter procurement distances, adjusted ischemic time was 19 minutes more in the heterotaxy/situs anomaly group, suggesting greater surgical complexity and longer cardiopulmonary bypass durations. Increases in ischemic and bypass times in heterotaxy have been reported by others,⁵ and both are risk factors for mortality in children undergoing cardiac surgery.^{14,27} Also consistent with our hypothesized increased surgical complexity, we found that patients with heterotaxy/situs anomaly who were transplant recipients underwent cardiac reoperation about twice as frequently as nonheterotaxy/situs anomaly CHD recipients, and more commonly underwent cardiac catheterization and peripheral vascular stent placement before discharge from the HT hospitalization. Unfortunately, we do not know the indications for reoperations, catheterizations, or vascular stent placements to further characterize these events.

FIGURE 3. We leveraged 2 large, independent databases (Pediatric Health Information Systems [PHIS] and the Scientific Registry of Transplant Recipients [SRTR]) to identify pediatric heart transplant (HT) recipients with heterotaxy and other complex situs arrangements (a previously unstudied cohort across multiple centers), and compare posttransplant outcomes to patients with congenital heart disease (CHD) in the absence of heterotaxy. Dotted lines depict 95% confidence intervals and the numbers at risk in each group are shown beneath the graph. LOS, Length of stay.

Infection, renal failure requiring dialysis, and longer duration of mechanical ventilation were also more common postoperatively in heterotaxy/situs anomaly recipients. However, the occurrence of 1 may contribute to the need for another (eg, renal failure leading to volume overload contributing to prolonged mechanical ventilation.) Unfortunately, we cannot disentangle these associations in our dataset. Although asplenia predisposes to bacteremia/sepsis,²⁸ we found no differences in the presence of ICD-coded encapsulated bacterial infections between the groups. This may be due to relatively short observation, analysis of both asplenic and polysplenic patients in the heterotaxy/

situs anomaly group (which cannot be unbundled with ICD-9 coding), inability to identify causative organisms, or insufficient coding. Heterotaxy has been associated with prolonged mechanical ventilation and tracheostomy after cardiac surgery,²⁹ which has been attributed to increased prevalence of ciliary dyskinesia.³⁰ Although ciliary dyskinesia has been implicated in polycystic kidney disease,³¹ and heterotaxy syndrome is associated with genitourinary anomalies, we found no reports of predisposition toward renal failure in heterotaxy. Given that longer bypass times are independently associated with kidney injury in adults undergoing HT³² and children undergoing surgery

for CHD,³²⁻³⁴ a relationship between these in heterotaxy/situs anomaly recipients is feasible.

LOS and Costs

It is not surprising that post-HT LOS and costs were greater for heterotaxy/situs anomaly recipients given the increased complications observed. These increases are similar to what has been reported for pediatric HT recipients with other complicating features, such as requirement for mechanical circulatory support³⁵ or allosensitization,³⁶ and in whom HT is commonly performed. Therefore, on the basis of increased LOS and costs alone, children with heterotaxy/situs anomaly should not be excluded from transplant consideration.

Limitations

Our analysis has many limitations. Our definition of heterotaxy/situs anomaly relied on ICD codes, which can be ambiguous. Errors and incomplete coding may also exist. ICD codes do not allow us to distinguish between left- and right-isomerism, making our population clinically heterogeneous. Furthermore, heterotaxy can be difficult to categorize, even with access to more detailed anatomic information than was available.³⁷ However, the racial distribution of our heterotaxy/situs anomaly cohort mirrors other reports of increased prevalence in African-American, Asian, and Hispanic individuals.³⁸⁻⁴¹ Furthermore, our heterotaxy/situs anomaly cohort is enriched for diagnoses common in heterotaxy (eg, anomalous pulmonary and systemic venous return, pulmonary outflow anomalies, and congenital heart block). These observations support the validity of our cohort. Still, it is likely that some nonheterotaxy recipients in our primary analysis were misclassified, particularly those who met criteria based on having the ICD-9 diagnosis codes of dextrocardia and/or situs inversus without polysplenia. These codes may have been applied when the heart alone was malpositioned or in patients with situs inversus totalis. However, this would only diminish the differences between the groups. Also, when we included only patients with ICD codes for asplenia/polysplenia in sensitivity analysis, the survival difference remained.

Other potential limitations are our model selection techniques and validity of the control group. Although we utilized data-driven model selection to identify relevant covariates for the regression models, some potentially important variables (eg, age and prior univentricular repair) did not meet inclusion criteria. However, when we locked these clinically relevant covariates into the multivariable model, we still observed increased mortality of heterotaxy/situs anomaly recipients. Further, when we controlled for possible selection bias through propensity score matching, the survival difference remained. These sensitivity

analyses suggest that our conclusions are robust, adding strength to our findings.

Because our sample is limited only to HT recipients at PHIS-member hospitals, primarily children and young adults, our findings should not be generalized to adults. Also, because PHIS does not capture outpatient encounters or track patients across hospitals, our analysis of postdischarge complications is limited to those reported at yearly intervals in the SRTR. The Pediatric Heart Transplant Study⁴² dataset collects greater detail on some of these events and thus may be a good choice for linkage to PHIS to further explore associations of postdischarge infection, rejection, PTLT, and CAV on late survival in heterotaxy syndrome. Ideally, a dataset that contains a more granular focus on heterotaxy could verify our findings, particularly some of the less-expected findings, such as prolonged mechanical ventilation or renal failure.

CONCLUSIONS

In a population-based analysis of administrative data on pediatric HT recipients with heterotaxy and other complex arrangements of cardiac situs we observed increased mortality, longer LOS, and greater costs of care from HT surgery to discharge relative to other nonheterotaxy/situs anomaly HT recipients with CHD (Figure 3). Early mortality and resource use differences could be explained by increased early postoperative complications, including more frequent cardiac reoperations and vascular stenting; however, the reason(s) for the difference in late survival is unclear. Further study is warranted.

Conflict of Interest Statement

Dr Brian Feingold participates in clinical trials funded by Novartis and receives research funding from Abbott Diagnostics. All other authors have nothing to disclose with regard to commercial support.

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Key Words: heterotaxy, heart transplantation, congenital abnormalities, dextrocardia, situs inversus, registries, reoperation

FIGURE E1. Sensitivity analysis of survival after heart transplant for patients meeting stricter inclusion criteria for heterotaxy. Univariable Kaplan-Meier analysis of survival after heart transplantation, using stricter inclusion criteria, defined as International Classification of Diseases code for polysplenia/asplenia only, to delineate heterotaxy recipients (*red*, poly-/asplenia) shows decreased survival compared with patients with congenital heart disease (CHD) in the absence of heterotaxy (*blue*, nonpoly-/asplenia CHD). This analysis shows a survival difference after transplant between the groups using this stricter definition of heterotaxy. Dotted lines depict 95% confidence intervals and the numbers at risk in each group are shown beneath the graph.

FIGURE E2. Sensitivity analysis of survival for patients with heterotaxy/situs anomaly compared with a propensity score-matched group of nonheterotaxy/situs anomaly patients with congenital heart disease (CHD). Univariable Kaplan-Meier estimator showing that patients with heterotaxy/situs anomaly (*red*) have inferior survival after heart transplantation compared with a propensity score-matched group of patients with CHD in the absence of heterotaxy (*blue*). There is a survival difference after transplant between the propensity score-matched groups. Propensity score matching was performed to address the potential for bias from inadequate/incomplete selection of regression model covariates in our primary survival analysis (Figure 1). Dotted lines depict 95% confidence intervals and the numbers at risk in each group are shown beneath the graph.

TABLE E1. International Classification of Disease 10th edition (ICD-10) mappings to International Classification of Diseases ninth edition (ICD-9) codes

ICD-10 code*	ICD-10 description	ICD-9 code	ICD-9 description
Q20.0	Common arterial trunk	745.0	Common truncus
Q20.1	Double outlet right ventricle	745.11	Double outlet right ventricle
Q20.3	Discordant ventriculoarterial connection	745.10	Complete transposition of great vessels
Q20.4	Double inlet ventricle	745.3	Common ventricle
Q20.5	Discordant atrioventricular connection	745.12	Corrected transposition of great vessels
Q21.0	Ventricular septal defect	745.4	Ventricular septal defect
Q21.1	Atrial septal defect	745.5	Ostium secundum type atrial septal defect
Q21.2	Atrioventricular septal defect	745.60	Endocardial cushion defect, unspecified type
Q22.0	Pulmonary valve atresia	746.01	Atresia of pulmonary valve, congenital
Q22.1	Congenital pulmonary valve stenosis	746.02	Stenosis of pulmonary valve, congenital
Q22.3	Other congenital malformations of pulmonary valve	746.00	Congenital pulmonary valve anomaly, unspecified
Q22.4	Congenital tricuspid stenosis	746.1	Tricuspid atresia and stenosis, congenital
Q22.5	Ebstein's anomaly	746.2	Ebstein's anomaly
Q22.6	Hypoplastic right heart syndrome	746.1	Tricuspid atresia and stenosis, congenital
Q22.8	Other congenital malformations of tricuspid valve	746.1	Tricuspid atresia and stenosis, congenital
Q23.0	Congenital stenosis of aortic valve	746.3	Congenital stenosis of aortic valve
Q23.1	Congenital insufficiency of aortic valve	746.4	Congenital insufficiency of aortic valve
Q23.2	Congenital mitral stenosis	746.5	Congenital mitral stenosis
Q23.3	Congenital mitral insufficiency	746.6	Congenital mitral insufficiency
Q23.4	Hypoplastic left heart syndrome	746.7	Hypoplastic left heart syndrome
Q24.0	Dextrocardia	746.87	Malposition of heart and cardiac apex
Q24.2	Cor triatriatum	746.82	Cor triatriatum
Q24.3	Pulmonary infundibular stenosis	746.83	Infundibular pulmonic stenosis
Q24.4	Congenital subaortic stenosis	746.81	Subaortic stenosis
Q24.5	Malformation of coronary vessels	746.85	Coronary artery anomaly
Q24.6	Congenital heart block	746.86	Congenital heart block
Q24.8	Other specified congenital malformations of heart	746.89	Other specified congenital anomalies of heart
Q24.9	Congenital malformation of heart, unspecified	746.9	Unspecified congenital anomaly of heart
Q25.0	Patent ductus arteriosus	747.0	Patent ductus arteriosus
Q25.1	Coarctation of aorta	747.10	Coarctation of aorta (preductal) (postductal)
Q25.2	Atresia of aorta	747.22	Atresia and stenosis of aorta
Q25.4	Other congenital malformations of aorta	747.20	Anomaly of aorta, unspecified
Q25.5	Atresia of pulmonary artery	747.31	Pulmonary artery coarctation and atresia
Q25.6	Stenosis of pulmonary artery	747.39	Other anomalies of pulmonary artery and pulmonary circulation
Q25.71	Coarctation of pulmonary artery	747.31	Pulmonary artery coarctation and atresia
Q25.72	Congenital pulmonary arteriovenous malformation	747.32	Pulmonary arteriovenous malformation
Q25.79	Other congenital malformations of pulmonary artery	747.39	Other anomalies of pulmonary artery and pulmonary circulation
Q25.8	Other congenital malformations of other great arteries	747.29	Other anomalies of aorta
Q26.1	Persistent left superior vena cava	747.49	Other anomalies of great veins
Q26.2	Total anomalous pulmonary venous connection	747.41	Total anomalous pulmonary venous connection
Q26.3	Partial anomalous pulmonary venous connection	747.42	Partial anomalous pulmonary venous connection
Q26.4	Anomalous pulmonary venous connection, unspecified	747.42	Partial anomalous pulmonary venous connection

(Continued)

TABLE E1. Continued

ICD-10 code*	ICD-10 description	ICD-9 code	ICD-9 description
Q26.8	Other congenital malformations of great veins	747.49	Other anomalies of great veins
Q27.0	Congenital absence and hypoplasia of umbilical artery	747.5	Absence or hypoplasia of umbilical artery
Q27.39	Arteriovenous malformation, other site	747.69	Anomalies of other specified sites of peripheral vascular system
Q27.8	Other specified congenital malformations of peripheral vascular system	747.69	Anomalies of other specified sites of peripheral vascular system
Q20.8	Other congenital malformations of cardiac chambers and connections	745.8	Other bulbus cordis anomalies and anomalies of cardiac septal closure
Q27.9	Anomaly of the peripheral vascular system, unspecified site	747.60	Congenital malformation of peripheral vascular system, unspecified

*ICD-10 codes were mapped to the in-row ICD-9 codes for analysis.

TABLE E2. List of International Classification of Disease (ICD) codes related to encapsulated bacterial infection

ICD 9 or 10 code	Description
036.0	Meningococcal meningitis
036.1	Meningococcal encephalitis
036.2	Meningococcemia
036.3	Waterhouse-Friderichsen syndrome, meningococcal
036.40	Meningococcal carditis, unspecified
036.41	Meningococcal pericarditis
036.42	Meningococcal endocarditis
036.43	Meningococcal myocarditis
036.81	Meningococcal optic neuritis
036.82	Meningococcal arthropathy
036.89	Other specified meningococcal infections
036.9	Meningococcal infection, unspecified
038.2	Pneumococcal septicemia (<i>Streptococcus pneumoniae</i> septicemia)
038.41	Septicemia due to <i>Hemophilus influenzae</i>
041.2	Pneumococcus infection in conditions classified elsewhere and of unspecified site
041.5	<i>H influenzae</i> infection in conditions classified elsewhere and of unspecified site
320.1	Pneumococcal meningitis
481.	Pneumococcal pneumonia (<i>S pneumoniae</i> pneumonia)
482.2	Pneumonia due to <i>H influenzae</i>
567.1	Pneumococcal peritonitis
A39.0	Meningococcal meningitis
A39.81	Meningococcal encephalitis
A39.2	Acute meningococcemia
A39.3	Chronic meningococcemia
A39.4	Meningococcemia, unspecified
A39.1	Waterhouse-Friderichsen syndrome
A39.50	Meningococcal carditis, unspecified
A39.53	Meningococcal pericarditis
A39.51	Meningococcal endocarditis
A39.52	Meningococcal myocarditis
A39.82	Meningococcal retrobulbar neuritis
A39.83	Meningococcal arthritis
A39.84	Postmeningococcal arthritis
A39.89	Other meningococcal infections
A39.9	Meningococcal infection, unspecified
A40.3	Sepsis due to <i>S pneumoniae</i>
A40.3	Sepsis due to <i>S pneumoniae</i>
A41.3	Sepsis due to <i>H influenzae</i>
A41.3	Sepsis due to <i>H influenzae</i>

(Continued)

TABLE E2. Continued

ICD 9 or 10 code	Description
B95.3	<i>S pneumoniae</i> as the cause of diseases classified elsewhere
M00.111	Pneumococcal arthritis, right shoulder
M00.112	Pneumococcal arthritis, left shoulder
M00.119	Pneumococcal arthritis, unspecified shoulder
M00.121	Pneumococcal arthritis, right elbow
M00.122	Pneumococcal arthritis, left elbow
M00.129	Pneumococcal arthritis, unspecified elbow
M00.131	Pneumococcal arthritis, right wrist
M00.132	Pneumococcal arthritis, left wrist
M00.139	Pneumococcal arthritis, unspecified wrist
M00.141	Pneumococcal arthritis, right hand
M00.142	Pneumococcal arthritis, left hand
M00.149	Pneumococcal arthritis, unspecified hand
M00.151	Pneumococcal arthritis, right hip
M00.152	Pneumococcal arthritis, left hip
M00.159	Pneumococcal arthritis, unspecified hip
M00.161	Pneumococcal arthritis, right knee
M00.162	Pneumococcal arthritis, left knee
M00.169	Pneumococcal arthritis, unspecified knee
M00.171	Pneumococcal arthritis, right ankle and foot
M00.172	Pneumococcal arthritis, left ankle and foot
M00.179	Pneumococcal arthritis, unspecified ankle and foot
M00.18	Pneumococcal arthritis, vertebrae
M00.19	Pneumococcal polyarthritis
A49.2	<i>H influenzae</i> infection, unspecified site
B96.3	<i>H influenzae</i> as the cause of diseases classified elsewhere
J20.1	Acute bronchitis due to <i>H influenzae</i>
G00.1	Pneumococcal meningitis
J13.	Pneumonia due to <i>S pneumoniae</i>
J14.	Pneumonia due to <i>H influenzae</i>

TABLE E3. Comparison of proportions of missing characteristics and outcome data between primary study groups

	Nonheterotaxy CHD (n = 1254)	Heterotaxy/situs anomaly (n = 186)	P value*
Missing pre-HT characteristics			
Weight*	1 (0.1)	1 (1)	.242
Height*	23 (2)	3 (2)	1
Creatinine*	8 (1)	2 (1)	.377
eGFR*	31 (2)	4 (2)	1
VAD support	52 (4)	5 (3)	.424
Pre-HT dialysis*	4 (0.3)	0 (0)	1
Positive DSXM	250 (20)	37 (20)	1
Prior sternotomy and/or surgery for CHD	428 (34)	49 (26)	.037
If prior sternotomy and/or surgery for CHD, underwent univentricular repair*	51/512 (10)	114 (11)	.581
Heart- and great vessel-related ICD codes†	55 (4)	9 (5)	.706
Missing outcomes			
Infection during HT admission	280 (22)	41 (22)	1
Cardiac reoperation	275 (22)	43 (23)	.705
Post-HT dialysis*	1 (0.1)	0 (0)	1
Rejection during HT admission	130 (10)	15 (8)	.364
Mechanical ventilation post-HT	52 (4)	9 (5)	.695
Post-HT ICD procedure codes	52 (4)	9 (5)	.695
Post HT iNO days	52 (4)	9 (5)	.695
Post-HT ECMO	52 (4)	9 (5)	.695
Hospital LOS after HT	52 (4)	9 (5)	.695
Cost after HT	52 (4)	9 (5)	.695

Values are presented as n (%). Variables not listed in this table were completely recorded in both groups. CHD, Congenital heart disease; HT, heart transplant; eGFR, estimated glomerular filtration rate; VAD, ventricular assist device; DSXM, donor-specific cross-match; ICD, International Classification of Diseases; iNO, inhaled nitric oxide; ECMO, extracorporeal membrane oxygenation; LOS, length of stay. *Fisher exact test. †Not including dextrocardia ICD codes.

TABLE E4. Propensity score-matched group characteristics at heart transplant (HT)

	Nonheterotaxy CHD (n = 368)	Heterotaxy/situs anomaly (n = 186)	Standardized mean bias	P value [‡]
Age (y)				.656
0-2	132 (36)	62 (33)	−0.053	
2-12	159 (43)	88 (47)	0.083	
> 12	77 (21)	36 (19)	−0.039	
Female	143 (38)	80 (43)	0.085	.347
Race				.943 [‡]
White	180 (49)	89 (48)	−0.021	
African American	67 (18)	36 (19)	0.029	
Other	121 (33)	61 (33)	−0.002	
Year of transplant	2011 (2008-2014)	2010 (2008-2014)	−0.033	.665
Listing status				.758 [‡]
1A	293 (80)	146 (78)	−0.028	
1B	62 (17)	31 (17)	−0.005	
2	13 (4)	9 (5)	0.065	
Location				.849 [‡]
ICU	176 (48)	85 (46)	−0.043	
Hospitalized, non-ICU	74 (20)	37 (20)	−0.005	
Not hospitalized	118 (32)	64 (34)	0.050	
Inotrope support	201 (55)	97 (52)	−0.050	.582
VAD support	29 (8)	13 (7)	−0.034	.708
Mechanical ventilation	84 (23)	39 (21)	−0.045	.619
ECMO	20 (5)	10 (5)	−0.003	.977
Positive DSXM*	44 (12)	22 (12)	−0.004	.997 [‡]
Missing DSXM	74 (20)	37 (20)	−0.005	
Prior sternotomy/CHD repair*	177 (48)	94 (51)	0.049	.707 [‡]
Missing prior sternotomy/CHD repair	94 (26)	49 (26)	0.018	
Prior univentricular repair surgery*	117 (32)	63 (34)	0.044	.552 [‡]
Missing univentricular repair	109 (25)	60 (32)	0.057	

Data are presented as n (%) or median (interquartile range). CHD, Congenital heart disease; ICU, intensive care unit; VAD, ventricular assist device; ECMO, extracorporeal membrane oxygenation; DSXM, donor-specific cross-match. *Missing data present. †Continuous data compared with rank-sum test, binary outcomes compared using χ^2 test of proportions. ‡Tested across all groups.

TABLE E5. Heart- and great vessel-related International Classification of Diseases (ICD) codes

ICD-9 code*	ICD description	Nonheterotaxy CHD (n = 1199)†	Heterotaxy/situs anomaly (n = 177)†	Absolute risk difference	P value‡
745.69	Other endocardial cushion defects	60 (5)	61 (34)	0.295	<.001
745.3	Common ventricle	108 (9)	57 (32)	0.232	<.001
745.11	Double outlet right ventricle	101 (8)	48 (27)	0.187	<.001
747.41	Total anomalous pulmonary venous return	8 (1)	30 (17)	0.163	<.001
747.49	Other anomalies of the great veins	29 (2)	27 (15)	0.128	<.001
746.89	Other specified congenital anomalies of heart	209 (17)	46 (26)	0.086	.006
745.10	Complete transposition of great vessels	61 (5)	23 (13)	0.079	<.001
74.73	Pulmonary artery anomaly	100 (8)	26 (15)	0.063	.006
746.02	Stenosis of pulmonary valve, congenital	30 (3)	15 (8)	0.060	<.001
747.21	Anomalies of aortic arch	9 (1)	10 (6)	0.049	<.001
745.6	Endocardial cushion defect, unspecified type	7 (1)	8 (5)	0.039	<.001
746.01	Atresia of pulmonary valve, congenital	69 (6)	17 (10)	0.038	.048
747.31	Pulmonary artery coarctation and atresia	77 (6)	18 (10)	0.037	.066
746.86	Congenital heart block	17 (1)	9 (5)	0.037	.001
746.83	Infundibular pulmonic stenosis	5 (0)	7 (4)	0.035	.001
745.12	Corrected transposition of great vessels	23 (2)	9 (5)	0.032	.009
745.19	Other transposition of great vessels	14 (1)	5 (3)	0.017	.078
746.3	Congenital stenosis of aortic valve	59 (5)	3 (2)	−0.032	.052
746.1	Tricuspid atresia and stenosis, congenital	90 (8)	5 (3)	−0.047	.017
747.1	Coarctation of aorta	139 (12)	12 (7)	−0.048	.056
747.0	Patent ductus arteriosus	192 (16)	19 (11)	−0.053	.069
746.85	Coronary artery anomaly	94 (8)	3 (2)	−0.061	.001
745.5	Ostium secundum type atrial septal defect	235 (20)	19 (11)	−0.089	.005
746.7	Hypoplastic left heart syndrome	535 (45)	35 (20)	−0.248	<.001

Values are presented as n (%). Ordered from greatest to least absolute risk difference. Positive absolute risk difference favors heterotaxy group, negative favors nonheterotaxy CHD. Only ICD codes with P value <.1 are shown. ICD, International Classification of Diseases; CHD, congenital heart disease. *ICD-10 codes were translated to ICD-9 per Table E1. †ICD codes only available for 1199 of 1254 patients in the nonheterotaxy CHD group, 177 of 186 in the heterotaxy group. ‡Fisher exact test.

TABLE E6. Univariate Cox model for survival estimates

	Survival		6-mo conditional survival	
	Univariate HR	P value	Univariate HR	P value
Heterotaxy	1.54	.002	1.66	.008
Age (y)	1.00	.723	1.02	.051
Female	1.03	.787	0.93	.596
Race				
White	Ref		Ref	
African American	1.73	<.001	2.47	<.001
Asian	1.65	.14	2.07	.111
Hispanic	1.13	.426	1.45	.07
Other	1.40	.294	2.22	.042
Year of transplant	0.96	.01	0.97	.241
Listing status				
1A	Ref			
1B	0.84	.314	1.00	.986
2	0.94	.785	1.02	.949
Location				
ICU	Ref		Ref	
Hospital non-ICU	0.97	.845	1.21	.343
Home	0.78	.043	1.17	.331
Inotrope support	1.17	.139	0.99	.958
VAD support	1.00	.982	0.64	.252
ECMO	2.49	<.001	0.69	.277
Mechanical ventilation	1.48	.001	0.93	.698
Positive DSXM	1.24	.118	1.10	.613
Prior sternotomy/surgery for CHD	1.11	.494	1.07	.736
Prior univentricular repair	0.99	.947	0.85	.497

HR, Hazard ratio; Ref, reference category; ICU, intensive care unit; VAD, ventricular assist device; ECMO, extracorporeal membrane oxygenation; DSXM, donor-specific cross-match; CHD, congenital heart disease.

TABLE E7. Multivariate stratified Cox model for survival estimates

Survival			6-mo conditional survival		
Covariate term	Adjusted hazard ratio	Adjusted P value	Covariate term	Adjusted hazard ratio	Adjusted P value
Heterotaxy	1.58	.002	Heterotaxy	1.86	.021
Year	0.97	.038	Race: AA	NA*	
Race: AA	NA*		Age	NA*	
ECMO	NA*				

No significant interactions between terms in the final model were identified (data not shown). AA, African American; NA, not applicable; ECMO, extracorporeal membrane oxygenation. *Hazard ratio estimates not available because these terms were stratified in the Cox model because they violated the proportional hazards assumption (data not shown).

TABLE E8. Univariate logistic regression comparisons for model building

	Cardiac surgery		Post-HT infection		Post-HT dialysis		Post-HT mechanical ventilation >1 wk	
	Univariate		Univariate		Univariate		Univariate	
	OR	P value	OR	P value	OR	P value	OR	P value
Heterotaxy	2.12	.002	1.50	.028	2.16	.002	1.42	.032
Age	0.99	.51	0.97	.003	1.02	.007	0.93	<.001
Female gender	0.88	.501	1.07	.583	0.54	.007	0.97	.821
Race								
White	Ref							
AA	1.69	.039	1.09	.636	0.84	.581	0.98	.895
Asian	4.69	.001	2.21	.081	0.95	.94	2.23	.032
Hispanic	1.28	.365	0.84	.368	1.12	.672	0.89	.453
Other	0.32	.27	1.16	.704	0.76	.706	0.89	.752
Year	1.01	.635	0.96	.012	1.01	.836	0.98	.105
Listing status								
1A	Ref							
1B	0.52	.07	0.68	.065	0.90	.732	0.40	<.001
2	1.21	.586	0.69	.183	0.83	.69	0.39	<.001
Location								
ICU	Ref							
Hospital non-ICU	0.85	.557	0.56	.002	0.27	.001	0.62	.007
Home	0.70	.112	0.44	<.001	0.48	.003	0.69	.147
Inotrope support	1.12	.567	1.04	.782	1.38	.124	1.14	.226
VAD	2.23	.009	1.34	.248	1.96	.039	1.33	.182
ECMO	2.22	.005	2.61	<.001	4.32	<.001	7.51	<.001
Pre-HT mechanical ventilation	2.28	<.001	2.46	<.001	2.70	<.001	5.18	<.001
DSXM positive	1.14	.591	1.46	.02	0.94	.832	NA*	
Prior sternotomy/CHD surgery	1.09	.712	1.28	.11	1.15	.579	NA*	
H/O univentricular repair	1.04	.882	1.33	.06	1.23	.418	NA*	
Total Ischemic time >3.5 h	NA*				1.58	.095	NA*	
eGFR <40	NA*				3.19	<.001	NA*	
Pre-HT dialysis	NA*				13.95	<.001	NA*	

HT, Heart transplant; OR, odds ratio; Ref, reference category to which others are compared; AA, African American; ICU, intensive care unit; VAD, ventricular assist device; ECMO, extracorporeal membrane oxygenation; DSXM, donor-specific cross-match; NA, not applicable; CHD, congenital heart disease; H/O, history of; eGFR, estimated glomerular filtration rate. *Univariate comparison not performed.

TABLE E9. Final multivariate logistic regression models

Covariate term	Adjusted OR	Adjusted <i>P</i> value
Cardiac surgery		
Heterotaxy	1.98	.006
Race: White	0.70	.075
VAD	1.92	.038
Pre-HT mechanical ventilation	2.24	<.001
Post-HT infection		
Heterotaxy	1.55	.023
Year of HT	0.96	.022
ECMO	1.59	.059
Pre-HT mechanical ventilation	1.81	.001
Location: home	0.67	.013
Positive DSXM	1.40	.044
Prior univentricular repair	1.32	.086
Post-HT dialysis		
Heterotaxy	2.58	.001
Pre-HT dialysis	8.62	<.001
Female gender	0.51	.006
ECMO	2.17	.018
Location: ICU	1.65	.045
Total ischemic time >3.5 h	1.72	.058
eGFR <40	2.55	.003
Post-HT mechanical ventilation >1 wk		
Heterotaxy	1.70	.003
ECMO	4.11	<.001
Pre-HT mechanical ventilation	3.61	<.001
Age (y)	0.96	<.001

OR, Odds ratio; VAD, ventricular assist device; HT, heart transplant; ECMO: extracorporeal membrane oxygenation; DSXM, donor specific cross-match; ICU, intensive care unit; eGFR, estimated glomerular filtration rate.

TABLE E10. Linear regression model of total ischemic time

Covariate	Coefficient	95% CI	<i>P</i> value
Heterotaxy	19.17	(10.89 to 27.46)	<.001
Year of transplant	1.16	(0.46 to 1.86)	.001
Hispanic race	8.13	(0.53 to 15.73)	.036
Location: home	13.42	(7.46 to 19.38)	<.001
Distance between OPOs (miles)	0.13	(0.12 to 0.14)	<.001
Prior univentricular repair	6.07	(−0.93 to 13.07)	.089
Constant	−2165.27	(−3571.95 to −758.60)	.003

CI, Confidence interval; OPO, Organ Procurement Organization.

TABLE E11. Hospitalization cost and cost breakdown

	Nonheterotaxy CHD		Heterotaxy		P value
Total cost after HT	378,495	(261,770-576,221)	449,011	(320,080-710,692)	.001
Pharmacy costs	30,008	(18,011-62,295)	45,767	(23,588-87,732)	.000
Lab costs	26,136	(16,374-47,399)	33,320	(18,273-71,766)	.004
Imaging costs	8148	(3739-15,625)	10,855	(4358-19,884)	.001
Supplies costs	13,535	(7347-26,703)	16,370	(8074-31,916)	.090
Clinical costs	187,931	(119,210-266,740)	205,137	(139,825-283816)	.048
Other costs	82,245	(53,870-141,743)	100,512	(62,045-201,019)	.002

Costs are in adjusted to 2016 inflation, presented as median cost (interquartile range). Other costs constitutes predominately rooming and nursing charges. CHD, Congenital heart disease; HT, heart transplant.

TABLE E12. Hospitalization cost and cost breakdown, conditional on survival to discharge

	Nonheterotaxy CHD		Heterotaxy		P value
Total cost after HT	360,211	(251,672-527,349)	421,040	(298,588-666,392)	.001
Pharmacy costs	27,877	(1754-54,045)	43,025	(19,927-80,849)	.000
Lab costs	23,740	(15,652-40,543)	28,507	(17,178-55,377)	.010
Imaging costs	7800	(3629-14,736)	10,521	(4743-18,890)	.001
Supplies costs	11,830	(6957-24,540)	14,889	(7065-29,305)	.190
Clinical costs	180,428	(116,189-257,664)	197,117	(136,997-270,880)	.076
Other costs	79,614	(53,041-134,655)	100,962	(62,045-194,149)	.001

Costs are adjusted to 2016 inflation, presented as median cost (interquartile range). Other costs constitutes predominately rooming and nursing charges. CHD, Congenital heart disease; HT, heart transplant.