Clinical Investigation

Mortality, Resource Utilization, and Inpatient Costs Vary Among Pediatric Heart Transplant Indications: A Merged Data Set Analysis From the United Network for Organ Sharing and Pediatric Health Information Systems Databases

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ABSTRACT

Background: Merging United Network for Organ Sharing (UNOS) and Pediatric Health Information Systems databases has enabled a more granular analysis of pediatric heart transplant outcomes and resource utilization. We evaluated whether transplant indication at time of transplantation was associated with mortality, resource utilization, and inpatient costs during the first year after transplantation.

Methods and Results: We analyzed transplant outcomes and resource utilization from 2004 to 2015. Patients were categorized as congenital (CHD), myocarditis, or cardiomyopathy based on UNOS-defined primary indication. CHD complexity subgroup analyses (single-ventricle, complex, and simple biventricular CHD) were also performed. Of 2251 transplants (49% CHD, 5% myocarditis, 46% cardiomyopathy), CHD recipients were younger (2 [IQR 0−10], 6 [IQR 0−12], and 7 [IQR 1−14] years, respectively; $P < .001$) and less likely to have a ventricular assist device (VAD) at transplantation (3%, 27%, and 13%, respectively; $P < .001$). Patients with single-ventricle CHD had the longest time on the waitlist and were least likely to receive a VAD before transplantation. After adjusting for patient-level factors, transplant recipients with single-ventricle CHD had the greatest mortality during transplantation admission and within 1 year (odds ratio [OR] 11.8 [95% confidence interval (CI) 5.9−23.6] and OR 6.0 [95% CI 3.6−10.2], respectively, vs cardiomyopathy). Mortality was similar between patients with myocarditis and cardiomyopathy. Post-transplantation length of stay (LOS) was longer in transplant recipients with CHD than myocarditis or cardiomyopathy (25 [interquartile range [IQR] 15−45] vs 21 [IQR 12−35] vs 16 [IQR 12−25] days; $P < .001$), related in part to longer duration of intensive care unit−level care (ICU LOS 8 [IQR 4−20] vs 6 [IQR 4−13] vs 5 [IQR 3−8] days; $P < .001$). Similarly, patients with CHD had higher median post-transplantation costs than myocarditis or cardiomyopathy ($415K [IQR $201K−503K] vs $354K [IQR $179K−390K] vs $284K [IQR $145K−319K]; $P < .001$) that persisted after adjusting for patient-level factors (adjusted cost ratio 1.4 [95% CI 1.4−1.5], CHD vs cardiomyopathy) and was primarily driven by longer LOS. More than 50% were readmitted during the first year after transplantation, although readmission rates were similar across transplant indications ($P = .42$).

Conclusions: Children with CHD, particularly single-ventricle patients, require substantially greater hospital resource utilization and have significantly worse outcomes during the first year after heart transplantation compared with other indications. Further work is aimed at identifying modifiable pre-transplantation risk factors, such as pre-transplantation conditioning with VAD support and cardiac rehabilitation, to improve post-transplantation outcomes and reduce resource utilization in this complex population. (*J Cardiac Fail 2019;25:27−35*)

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Pediatric heart transplantation is considered to be a standard therapy for end-stage heart failure refractory to medical and surgical therapy.[1] Since its inception in 1967, heart transplant use has continually increased with expansion to more complex populations.[2,3] A recent International Society of Heart and Lung Transplantation report evaluated post-transplantation outcomes among different transplant indications and found that despite ongoing improvement in overall pediatric transplant survival, there remains a persistent survival advantage for dilated cardiomyopathy compared to congenital heart disease (CHD) and retransplantation.[3,4] This has been corroborated by other studies that have shown CHD, particularly complex or single-ventricle palliated CHD, is associated with increased mortality primarily related to early postoperative morbidity and mortality.[5,6] These mortality data are based on data collected at 30-day and 1-year time points but lack the granular data on inpatient outcomes available from the Pediatric Health Information Systems (PHIS) database.

Furthermore, multi-institutional data comparing inpatient resource utilization in pediatric heart transplantation are limited. Some data have been reported on single-center resource utilization, but large multi-institutional reporting has been limited primarily to outcomes, including mortality and graft failure. Recently, a novel data set has been developed that merged the United Network of Organ Sharing (UNOS) database, which includes extensive individual recipient and donor transplant data, with the PHIS database, an administrative hospital database that includes detailed information on pre-transplantation characteristics as well as in-hospital outcomes, resource utilization, and costs.[7] This merged database contains data on more than 2,200 pediatric heart transplantations and provides an opportunity to evaluate outcomes, including those related to index hospitalization and pre-transplantation recipient characteristics across multiple institutions which is not otherwise possible with either database alone. Because the greatest mortality risk occurs during the first year after transplantation, this time period was chosen for the purposes of the present analysis.[3] The purpose of the present study was to evaluate whether transplant indication at time of transplantation was associated with mortality, resource utilization, and inpatient costs during the first year after transplantation. We hypothesized that CHD has poorer outcomes despite increased resource utilization and costs owing to greater acuity compared with other transplant indications, specifically cardiomyopathy and myocarditis.

Methods

Data Source

Data were obtained from a merged UNOS-PHIS cohort of pediatric transplant recipients at participating centers from 2004 to 2015. UNOS is a nonprofit organization that collects data on every organ transplantation since 1987 in the United States. Information collected in UNOS includes detailed pre- and post-transplantation demographic and clinical information for donors and recipients, such as primary diagnosis, severity status, and follow-up information regarding mortality. PHIS is an administrative database that contains inpatient, emergency department, ambulatory surgery, and observation data from 43 not-for-profit tertiary-care pediatric hospitals in the United States.[8] Participating PHIS hospitals provide data including demographics, diagnoses, medications, supportive care, procedures, and charges. Based on our probabilistic merge based on center, date of birth, recipient sex, and transplant date, more than 90% of eligible patients from UNOS were successfully matched in PHIS, as previously described by our group.[7] Despite the robustness of the UNOS data set, specific elements regarding CHD diagnoses as well as patient-level information regarding post-transplantation outcomes, resource utilization, and treatment costs are not captured, but they are available through daily-level PHIS data. The data sources for our study variables are presented in Supplemental Table S1. Regarding missing data in our merged data set, we provided percentage of nonmissingness for each variable used in the study, as presented in Supplemental Table S1, which ranged from 91.5% to 100%.

Study Cohort and End Points

Patients were included if they underwent their first transplant from January 1, 2004, and March 31, 2015, and were aged 21 years or younger at the time of transplantation. Patients were categorized as congenital (CHD), myocarditis, or cardiomyopathy based on the UNOS-defined primary indication for first transplant. Retransplantation as an index event was excluded from the analysis. CHD was further divided into subgroups (simple biventricular CHD, complex biventricular CHD, or single-ventricle disease) based on CHD complexity and International Classification of Disease, 9th Edition, Clinical Modification (ICD-9-CM), diagnostic codes from PHIS (Supplemental Table S2).

Primary outcomes included mortality, inpatient resource utilization, and cost. Transplantion admission mortality was based on PHIS data and 30-day and 1-year mortality were derived from UNOS. Secondary outcomes included readmission within 1-year after transplantation collected from PHIS as well as retransplantation within 1-year after transplantation collected from UNOS. Post-transplantation resource utilization data was collected from PHIS, including transplantation admission and intensive care unit (ICU) length of stay (LOS; with day 0 being the day of transplantation), cumulative LOS within 1 year (including readmissions), duration of inotropic support and mechanical ventilation, use of extracorporeal membrane oxygenation (ECMO), and quantity of inpatient cardiac imaging studies within 1 year after transplantation. ICU was defined by the occurrence of specific ICD-9-CM procedure codes or clinical resources considered to be a marker of ICU care rather than by physical location.[9] Inpatient costs were estimated from PHIS-adjusted charges multiplied by the cost-to-charge ratio for each hospital, then further inflated to 2016 US dollars with the use of the Consumer Price Index. Both total cost

during 1-year after transplantation and cost per hospital day were estimated.

Covariates Definition

Covariate data on pre-transplantation donor and recipient characteristics as well as participating transplant center characteristics were collected from UNOS. Creatinine levels at time of transplantation were summarized only for those not requiring dialysis. Obesity or underweight status were defined by body mass index with the use of the Centers for Disease Control and Prevention 2000 growth chart for patients 2−20 years old and World Health Organization 2006 criteria for patients <2 years old.[10] ICU support score was defined as the sum of the number of the ICU level interventions given, including use of ECMO, mechanical ventilation, or inotropic support, at transplantation. For example, a patient on ECMO at time of transplantation would have an ICU support score of 2, including 1 point for ECMO support and 1 point for mechanical ventilation, with 1 additional point if inotropic support was also present.

Statistical Methods

Descriptive statistics including median and interquartile range (IQR) for continuous variables and proportions for categoric variables were reported. Clinical outcomes, resource utilizations, and costs were compared across indications as well as CHD complexity with the use of chi-square tests (for binary outcomes, such as mortality) or Wilcoxon tests (for continuous outcomes, such as cost). For selected outcomes, regression models (logistic regression for mortality and any readmission within 1 year, and general linear model with gamma distribution for LOS and cost) were constructed to estimate both unadjusted and adjusted associations with the indication groups (using cardiomyopathy as the reference group). Because of potential confounding effect of pre-transplantation patient-level factors on outcomes, we considered adjustment for confounders with the use of multivariable regression analyses. First, a conceptual model was used to elicit potential confounders among a variety of recipient and donor pre-transplantation demographics (Supplemental Fig. S1). Second, each potential confounder identified from the conceptual model was further evaluated regarding its associations with the exposure (indication groups) and each outcome (mortality, readmission, etc). Third, the variables that demonstrated significant associations with both exposure and outcome were included in the final multivariable regression models. All of the analyses were performed in SAS 9.3, and a 2-sided P value of <.05 was considered to be statistically significant.

Results

Patient and Center Characteristics

A total of 2251 pediatric heart transplantations (49% CHD, 5% myocarditis, 46% cardiomyopathy) from 26 US centers were included in the analysis. Among recipients with CHD, 22% had single-ventricle disease and 55% simple biventricular CHD. The majority (86%) of transplantations occurred in medium- to high-volume centers, defined as >10 transplants per year, owing to center volume homogeneity among participating PHIS institutions. Pre-transplantation characteristics of the recipients and donors are presented in Table 1 and Supplemental Table S3. Overall, patients with CHD, myocarditis, and cardiomyopathy were transplanted at similar rates in the earlier (2004−2009) and later (2010−2015) eras, although among patients with CHD, those with single-ventricle and simple biventricular diseases received transplants more often in the later era. Recipients with CHD, particularly simple biventricular CHD, were younger compared with other indications.

The waitlist time was significantly longer for patients with CHD compared with cardiomyopathy or myocarditis, and that was largely due to patients with single-ventricle disease. Myocarditis was more likely to require mechanical ventilation and inotropic support at the time of transplantation. Mechanical circulatory support (MCS) at time of transplantation was used in 15% of the cohort, with 9% supported by ventricular assist devices (VAD) and 6% by ECMO. VADs were used significantly less often in CHD compared with other indications, particularly in single-ventricle disease and simple biventricular CHD, likely owing to young age.

Post-transplantation Clinical Outcomes

Outcomes and resource utilization by transplant indication are described in Table 2 and by CHD complexity subgroup in Supplemental Table S4. For selected outcomes, regression models (both unadjusted and adjusted) were constructed; the results are presented in Table 3. Mortality during transplantation admission, at 30 days, and at 1 year was significantly greater in CHD but not myocarditis compared with cardiomyopathy. Among CHD recipients, after adjusting for patient-level factors, single-ventricle disease had the highest mortality after transplantation. Of those that died during the first year after transplantation, patients with CHD had greater mortality during the transplantation admission and those with cardiomyopathy were more likely to die after transplantation hospitalization discharge. Use of ECMO within the first year after heart transplantation was greater in patients with CHD and myocarditis compared with cardiomyopathy, and it was used most often in single-ventricle disease transplant recipients. However, there were no significant differences in re-transplantation rates during the first year after transplantation among transplant indications.

Resource Utilization and Inpatient Costs

Post-transplantation LOS was longer for CHD, regardless of CHD complexity, compared with cardiomyopathy, and myocarditis had LOS similar to cardiomyopathy (Tables 2

Table 1. Pre-transplantation Patient Factors

Factor	CHD (n = 1106)	Myocarditis (n = 106)	Cardiomyopathy (n = 1039)	*P* Value
Male	650 (59%)	52 (49%)	537 (52%)	.002
Nonwhite	401 (36%)	58 (55%)	523 (50%)	<.001
Non-Hispanic	927 (84%)	90 (85%)	832 (81%)	.058
Insurance				<.001
Private	548 (50%)	53 (50%)	512 (49%)	
Public	547 (49%)	42 (40%)	484 (47%)	
Other	10 (1%)	11 (10%)	42 (4%)	
Transplantation era				.973
2004−2009	520 (47%)	49 (46%)	484 (47%)	
2010−2015	586 (53%)	57 (54%)	555 (53%)	
Age at transplantation, y	2 (0−10)	6 (0−12)	7 (1−14)	<.001
Age at transplantation				<.001
<1 y	447 (40%)	27 (25%)	232 (22%)	
1−12 y	448 (41%)	53 (50%)	486 (47%)	
>12 y	221 (19%)	26 (25%)	321 (31%)	
Weight at transplantation, kg	11 (6−28)	19 (9−48)	23 (9−50)	<.001
Body mass index at transplantation				.034
Normal	624 (57%)	61 (57%)	599 (58%)	
Obese	110 (10%)	13 (12%)	125 (12%)	
Overweight	91 (8%)	14 (13%)	109 (11%)	
Underweight	262 (24%)	18 (17%)	196 (19%)	
Donor-recipient weight ratio				.006
<0.8	610 (55%)	47 (44%)	507 (48%)	
0.8−1.5	491 (44%)	58 (55%)	528 (51%)	
>1.6	1 (0.1%)	1 (1%)	3 (0.3%)	
Status at transplantation				<.001
1a	904 (82%)	103 (97%)	893 (86%)	
1b	150 (14%)	3 (3%)	94 (9%)	
2	52 (4%)	0 (0%)	52 (5%)	
Waitlist time, d	51 (18−111)	24 (10−59)	41 (16−97)	<.001
Time at status 1a, d	26 (5−64)	22 (8−49)	22 (6−58)	.747
Ratio of time at status 1a to total waitlist time	1 (0.4−1)	1 (1−1)	1 (0.6−1)	<.001
ECMO at time of transplantation	87 (8%)	11 (10%)	36 (3%)	<.001
VAD at time of transplantation	36 (3%)	29 (27%)	133 (13%)	<.001
Mechanical ventilation at time of transplantation	229 (21%)	30 (28%)	136 (13%)	<.001
Inotropic support at time of transplantation	544 (49%)	61 (58%)	518 (50%)	.259
Pulmonary hypertension treatment at time of transplantation	9 (0.8%)	1 (0.9%)	3 (0.3%)	.128
Total bilirubin at time of transplantation	0.7 (0.4−1.3)	0.6 (0.4−1.1)	0.6 (0.3−1.1)	.003
Creatinine at time of transplantation	0.4 (0.3−0.6)	0.4 (0.3−0.7)	0.5 (0.3−0.7)	<.001
Any dialysis from admission to transplantation	60 (5%)	16 (15%)	41 (4%)	<.001
Donor CMV positive	580 (51%)	59 (56%)	565 (54%)	.180
With recipient CMV negative	343 (33%)	28 (27%)	313 (31%)	
Recipient CMV positive	358 (34%)	58 (56%)	419 (42%)	<.001
ICU support score at time of transplantation				<.001
0	489 (44%)	38 (35%)	480 (46%)	
1	422 (38%)	40 (37%)	443 (43%)	
2	147 (13%)	22 (21%)	101 (10%)	
3	48 (4%)	6 (6%)	15 (1%)	

CHD, congenital heart disease; ECMO, extracorporeal membrane oxygenation; VAD, ventricular assist device; CMV, cytomegalovirus; ICU, intensive care unit. Values are presented as n (%) or median (interquartile range).

and 4; Supplemental Table S4). This difference in LOS persisted after adjusting for pre-transplantation characteristics and was driven by longer need for ICU-level care in CHD transplantations, including longer duration of mechanical ventilation and inotropic support. Among CHD subgroups after adjusting for pre-transplantation patient-level factors, single-ventricle CHD had longer duration of ICU-level care. When evaluating the frequency of post-transplantation imaging, echocardiography and chest x-rays were performed significantly more often in CHD recipients. Notably, the number of readmissions within the first year after transplant was similar among all transplant indications.

Total inpatient costs during the first year after transplantation were significantly greater for patients with CHD compared with myocarditis or cardiomyopathy (Fig. 1; Tables 3−5). However, daily inpatient costs were not significantly different across indications, suggesting that differences in overall post-transplantation hospital costs were primarily driven by hospital LOS. The highest cost categories across all transplant indications were clinical service and room/board charges. As presented in Table 3, after adjusting for pre-transplantation patient characteristics, all CHD recipients regardless of CHD complexity had greater hospital costs after transplantation compared with cardiomyopathy (cost ratio 1.4, 95% confidence interval [CI] 1.4−1.5), and costs

Table 2. Outcomes and Resource Utilizations by Indication Group

Variable	CHD (n = 1106)	Myocarditis (n = 106)	Cardiomyopathy (n = 1039)	*P* Value
Transplantation admission mortality	113 (10%)	5 (5%)	15 (1%)	<.001
30-day mortality	59 (5%)	3 (3%)	11 (1%)	<.001
1-year mortality	156 (14%)	8 (8%)	35 (3%)	<.001
Retransplantation within 1 year	4 (0.4%)	1 (0.9%)	4 (0.4%)	.660
Transplantation admission hospital LOS, d	25 (15−45)	21 (12−35)	16 (12−25)	<.001
Transplantation admission ICU LOS, d	8 (4−19)	6 (4−13)	5 (3−8)	<.001
Total ICU LOS within 1 year after transplantation, d	9 (5−22)	6 (4−15)	5 (3−8)	<.001
Total hospital LOS within 1 year after transplantation, d	34 (20−57)	28 (16−49)	22 (15−36)	<.001
Inotropic support after transplantation, d	7 (5−14)	6 (4−10)	5 (3−8)	<.001
Mechanical ventilation after transplantation, d	7 (3−19)	4 (2−12)	3 (2−6)	<.001
Need for ECMO within 1 year after transplantation	165 (15%)	16 (15%)	62 (6%)	<.001
Any readmission within 1 year after transplantation	641 (58%)	58 (55%)	574 (55%)	.417
No. of readmissions within 1 year after transplantation	1 (0−2)	1 (0−2)	1 (0−2)	.145
No. of inpatient imaging studies within 1 year after transplantation				
Echocardiography	8 (4−14); (range 0−92)	6 (2−9); (range 0−57)	6 (3−10); (range 0−67)	<.001
Chest x-ray	14 (8−28); (range 0−204)	11 (6−21); (range 0−147)	8 (6−14); (range 0−67)	<.001

Values are presented as n (%) or median (interquartile range). LOS, length of stay; other abbreviations as in Table 1.

were similar between myocarditis and cardiomyopathy (cost ratio 1.1, 95% CI 1.0−1.3).

Discussion

This merged UNOS-PHIS data set has enabled a comprehensive evaluation of both pre-transplantation characteristics and post-transplantation outcomes and resource utilization among heart transplant indications in more than 2,200 pediatric heart transplantations in 26 US centers over the past decade. As hypothesized, CHD has greater resource utilization and inpatient costs despite poorer outcomes compared with other transplant indications, even after adjusting for pre-transplantation patient-level factors. Among patients with CHD undergoing transplantation, mortality was similar despite CHD disease complexity, but resource utilization was greater for single-ventricle and simple biventricular disease, largely owing to younger age and comorbidities.

Previous literature has reported using merged data sets to perform more refined analysis of clinical outcomes and resource utilization in multiple contexts. Pasquali et al linked the Society of Thoracic Surgeons and PHIS databases to evaluate the quality-cost relationship in congenital heart surgery.[11] McHugh et al linked the Pediatric Heart Network Single-Ventricle Reconstruction trial clinical database and the Children's Hospital Association Inpatient Essentials database to evaluate center variation in cost of Norwood procedures.[12] And PHIS has been linked to the Children's Oncology Group to evaluate resource utilization and cost in pediatric oncology care.[13] Recently, Godown et al reported a linked data set between PHIS and the Scientific Registry of Transplant Recipients database, which derives data from UNOS, to evaluate care in pediatric heart transplantation.[14] Our study builds on this concept by independently merging the PHIS-UNOS cohort with detailed pre- and post-transplantation patient-level data incorporated to provide a more granular analysis of post-transplantation care among different transplant indications, including transplantation admission outcomes and ICU-level resource utilization.

Previous registry analyses have focused on comparing outcomes between patients with CHD and cardiomyopathy, whereas the present analysis identified myocarditis and CHD complexity subgroups, including single-ventricle disease, as separate populations through use of diagnostic codes from PHIS. These subgroups were chosen based on the unique clinical risk profiles associated with these transplant indication groups which may affect outcomes and resource utilization and thus warranting further investigation.[15] In our population, there was a 12-fold increase in risk of hospital mortality in single-ventricle compared with cardiomyopathy patients. A study using the UNOS database to evaluate graft survival over 20 years identified adolescents with myocarditis as having worse graft survival compared with other myocarditis age groups, whereas CHD had similar graft survivals regardless of age, suggesting that there may be disease-specific factors related to myocarditis that affect outcomes.[16] In the present population, although the use of technologies such as ECMO and mechanical ventilation before transplantation was higher in recipients with myocarditis than with cardiomyopathy, 1-year post-transplantation outcomes were quite similar.

Additional analyses of pre-transplantation patient-level factors, particularly among the CHD subgroups, highlighted important differences that may influence post-transplantation outcomes. Specifically, rates of transplantation for single-ventricle disease have increased over the past decade. However, single-ventricle CHD has significantly longer waitlist times compared with other transplant indications. Although 9% of the cohort were supported with VADs at the time of transplantation, VADs were rarely used in CHD,

Table 3. Univariate and Multivariable Regression Models by Transplant Indication

Indication	Univariate		Multivariate	
	Unadjusted OR (95% CI)	Unadjusted *P* Value	Adjusted OR (95% CI)	Adjusted *P* Value
Transplant-admission mortality				
All CHD	7.7 (4.5−13.4)	<.001	6.8 (3.8−12.1)	<.001
Single-ventricle	10.7 (5.6−20.3)	<.001	11.6 (5.8−23.2)	<.001
Complex BV	7.1 (3.7−14.0)	<.001	7.1 (3.6−14.2)	<.001
Simple BV	7.8 (4.4−14.0)	<.001	6.0 (3.2−11.1)	<.001
Myocarditis	3.4 (1.2−9.4)	.021	2.6 (0.9−7.6)	.090
Cardiomyopathy	Reference	–	Reference	–
30-day mortality				
All CHD	5.3 (2.8−10.1)	<.001	5.2 (2.6−10.5)	<.001
Single-ventricle	6.5 (2.9−14.6)	<.001	6.6 (2.8−15.4)	<.001
Complex BV	6.4 (3.0−13.8)	<.001	6.8 (3.0−15.4)	<.001
Simple BV	4.6 (2.3−9.4)	<.001	4.0 (1.9−8.7)	<.001
Myocarditis	2.7 (0.7−9.9)	.129	2.1 (0.5−8.3)	.258
Cardiomyopathy	Reference	–	Reference	–
1-year mortality				
All CHD	4.7 (3.2−6.9)	<.001	4.3 (2.9−6.3)	<.001
Single-ventricle	5.8 (3.5−9.5)	<.001	6.0 (3.6−10.0)	<.001
Complex BV	4.1 (3.2−8.2)	<.001	5.1 (3.1−8.3)	<.001
Simple BV	4.6 (3.0−6.9)	<.001	3.7 (2.4−5.7)	<.001
Myocarditis	2.3 (1.1−5.2)	.036	1.9 (0.8−4.3)	.139
Cardiomyopathy	Reference	–	Reference	–
Any readmission within 1 year				
All CHD	1.1 (0.9−1.3)	.205	1.0 (0.9−1.2)	.754
Single-ventricle	0.9 (0.7−1.3)	.687	0.9 (0.7−1.2)	.419
Complex BV	1.2 (0.9−1.5)	.242	1.1 (0.8−1.4)	.603
Simple BV	1.2 (0.9−1.4)	.129	1.1 (0.9−1.3)	.520
Myocarditis	1.0 (0.5−1.5)	.917	1.1 (0.7−1.7)	.644
Cardiomyopathy	Reference	–	Reference	–
	Unadjusted Mean Ratio (95% CI)	Unadjusted *P* Value	Adjusted Mean Ratio (95% CI)	Adjusted *P* Value
Transplant-admission hospital LOS				
All CHD	1.6 (1.5−1.7)	<.001	1.5 (1.4−1.6)	<.001
Single-ventricle	1.6 (1.4−1.7)	<.001	1.6 (1.5−1.8)	<.001
Complex BV	1.5 (1.4−1.7)	<.001	1.5 (1.3−1.6)	<.001
Simple BV	1.7 (1.6−1.8)	<.001	1.5 (1.4−1.6)	<.001
Myocarditis	1.4 (1.2−1.6)	<.001	1.1 (1.0−1.3)	.141
Cardiomyopathy	Reference	–	Reference	–
Transplant-admission ICU LOS				
All CHD	2.3 (2.1−2.4)	<.001	2.1 (1.9−2.3)	<.001
Single-ventricle	2.3 (2.0−2.6)	<.001	2.5 (2.2−2.9)	<.001
Complex BV	2.1 (1.8−2.4)	<.001	2.0 (1.7−2.3)	<.001
Simple BV	2.4 (2.1−2.6)	<.001	2.0 (1.8−2.2)	<.001
Myocarditis	1.6 (1.4−2.1)	.015	1.2 (1.0−1.4)	.138
Cardiomyopathy	Reference	–	Reference	–
Total hospital costs				
All CHD	1.4 (1.2−1.5)	<.001	1.4 (1.4−1.5)	<.001
Single-ventricle	1.5 (1.3−1.6)	<.001	1.5 (1.4−1.7)	<.001
Complex BV	1.4 (1.3−1.5)	<.001	1.4 (1.3−1.5)	<.001
Simple BV	1.5 (1.4−1.7)	<.001	1.5 (1.3−1.6)	<.001
Myocarditis	1.3 (1.1−1.4)	<.001	1.1 (1.0−1.3)	.116
Cardiomyopathy	Reference	–	Reference	–
Daily hospital costs				
All CHD	1.1 (1.0−1.2)	.113	1.0 (1.0−1.1)	.242
Single-ventricle	1.2 (1.1−1.3)	.002	1.1 (1.0−1.3)	.011
Complex BV	1.1 (1.0−1.2)	.098	1.1 (1.0−1.2)	.038
Simple BV	0.9 (0.9−1.0)	.127	1.0 (0.9−1.1)	.616
Myocarditis	1.1 (1.0−1.3)	.058	1.2 (1.0−1.4)	.024
Cardiomyopathy	Reference	–	Reference	–

BV, biventricular; other abbreviations as in Tables 1 and 2.

particularly in single-ventricle disease and infants with simple biventricular CHD. These differences in waitlist time and MCS support as bridge to transplant among transplant indications highlight important variation in pre-transplantation management that may provide opportunities to identify modifiable risk factors in pediatric heart transplant recipients. Specifically, pre-transplantation interventions, including increased VAD utilization and cardiac rehabilitation in recipients with CHD, could potentially improve post-transplantation outcomes and reduce resource utilization and costs by reducing end-organ injury and improve musculoskeletal conditioning during the waitlist period. For example, improved musculoskeletal conditioning may decrease duration of mechanical ventilation and time to ambulation and ultimately

Table 4. Total Costs During First Year After Transplantation by Indication, US$ (2016), Median (Interquartile Range)

Cost	CHD	Myocarditis	Cardiomyopathy	*P* Value
Total	415,465 (201,634–503,798)	354,088 (179,521–390,315)	284,944 (145,787- 318,474)	<.001
Clinical	168,727 (66,554–220,034)	118,163 (66,214–208,384)	149,205 (50,299–178,945)	<.001
Imaging	12,333 (3585–15,116)	8500 (2316–10,373)	6607 (2019–8216)	<.001
Laboratory	37,661 (14,529–43,138)	27,231 (10,774- 32,497)	19,120 (9314–21,878)	<.001
Room and board	123,425 (46,650–141,275)	91,264 (34,856- 109,341)	71,199 (35,936–80,674)	<.001
Pharmacy	54,978 (15,254–62,369)	34,322 (11,671–40,306)	27,399 (10,423–30,443)	<.001
Supply	18,341 (4638–20,679)	11,147 (3316–13,980)	11,414 (2535–12,105)	<.001

CHD, congenital heart disease.

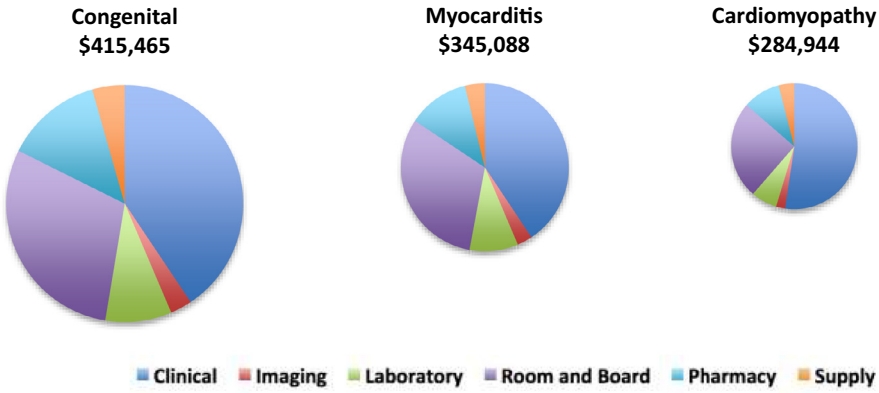

Fig. 1. Total inpatient costs during 1 year after transplantation. The diameters of the indication-specific pie graphs are proportional to the total inpatient costs.

post-transplantation LOS, which is the main driver of increasing hospital costs. Thus, such interventions warrant further investigation within the pediatric population.

Based on the inpatient data collected from the PHIS database that supplemented the UNOS data in our merged cohort, more detailed mortality analysis was performed at several time points. UNOS has previously reported 30-day and 1-year mortality rates, but multicenter data on outcomes besides these 2 time points have been scarce. Through the use of this UNOS-PHIS merged data set, we were able to evaluate multicenter inpatient outcomes throughout the first year after transplantation. Specifically, this study compared inpatient mortality during the transplantation admission across transplant indications and across 26 US centers. Consistent with previous reports, CHD had the highest mortality at 30 days and 1 year as well as during the transplantation hospitalization. Interestingly, of those that died within the first year after transplantation, those with CHD and myocarditis were more likely to die during the transplantation admission whereas those with cardiomyopathy were more likely to die after discharge. Furthermore, we were able to perform more granular analyses of CHD disease complexity and found that CHD had greater post-transplantation mortality regardless of disease complexity compared with other indications. These data provide important information for practicing providers when counseling families about post-transplantation outcomes by quantifying the transplantation admission mortality risk in relation to overall 1-year mortality.

In addition to higher mortality, CHD had greater resource utilization after transplantation. The post-transplantation LOS was longer for patients with CHD, and post-transplantation LOS was similar for those with cardiomyopathy and

Table 5. Cost per Inpatient Day During 1 Year After Transplantation, US$ (2016), Median (Interquartile Range)

Cost	CHD	Myocarditis	Cardiomyopathy	*P* Value
Total	8747 (6063–12,966)	8236 (5917–15,415)	8853 (6201–14,181)	.626
Clinical	3257 (1548–6867)	3508 (1806–9793)	3993 (1843–8812)	.002
Imaging	225 (129–337)	177 (94–299)	188 (109–291)	<.001
Laboratory	721 (498–1025)	662 (483–940)	634 (449–849)	<.001
Room and board	2449 (1931–3058)	2344 (1834–2980)	2329 (1867–2854)	<.001
Pharmacy	908 (577–1458)	910 (583–1235)	774 (511–1203)	<.001
Supply	313 (134–578)	298 (120–556)	274 (109–535)	.024

CHD, congenital heart disease.

myocarditis. This was driven in part by longer duration of ICU-level care, including longer inotropic support and mechanical ventilation after transplantation among single-ventricle disease and young simple biventricular heart disease recipients. In addition, CHD recipients had more thoracic imaging, including echocardiography and chest x-rays, during the post-transplantation period compared with other indications. The increased resource utilization after transplantation for patients with CHD compared with myocarditis and cardiomyopathy is likely multifactorial and related to significant comorbidities and deconditioning in CHD recipients before transplantation, as well as anatomic variations in some CHD-related systemic and pulmonary venous connections that may affect the transplantation surgery itself.

Interestingly, despite the association between pre-transplantation indication and post-transplantation LOS, underlying disease was not associated with readmission rates within the first year after transplantation. More than 50% of transplant recipients were readmitted an average of 1 time within the first year after transplantation, regardless of underlying disease. A previous single-center report found that rehospitalization in children after transplant was common, with an average of 2 readmissions within the first year, which is greater than our cohort and may indicate that there is center variation in post-transplantation outpatient management across US institutions.[17] However, that study evaluated all transplants without differentiating among pre-transplantation indications. Further study is needed to determine whether post-transplantation practice patterns, such as transplantation admission LOS, were associated with rates of readmission.

The present study also provides insight into understanding the cost for post-transplantation care in this complex population. Even after adjusting for pre-transplantation patient-level factors, including age and severity of illness, transplantation for CHD regardless of disease complexity was associated with greater post-transplantation hospital costs compared with cardiomyopathy. Although there were differences in post-transplantation resource utilization across transplant indications, including frequency of cardiac imaging and duration of ICU-level care including mechanical ventilation and medication use, the primary driver of increased post-transplantation costs in CHD recipients was post-transplantation LOS. The association between LOS and hospital costs has been reported in congenital heart surgery and heart transplantation but has not evaluated among different indications for pediatric heart transplantation.[18–20] Further analyses are needed to evaluate the drivers of this increased LOS after transplantation to try to identify ways to improve outcomes and reduce hospital resource utilization and costs.[20] Evaluation of center variation in post-transplantation care among different transplant indications may provide insight into optimal management and high-value care delivery in this resource-intense population; it has been helpful in in identifying ways to deliver high-value care in congenital heart disease.[12,21] Future analyses of our data set will focus on better understanding how individual pre-transplantation patient- and center-level factors influence post-transplantation resource utilization and costs with the ultimate goal being the development of a risk model for post-transplantation outcomes, resource utilization, and costs. This risk model development will potentially be an important next step to help improve care for this complex population.

Study Limitations

This study has several limitations. It is a retrospective observational analysis from a large multicenter cohort. Although patient-level factors were adjusted for in our analyses, there may be factors that were not captured and thus could not be included in our analysis. We identified that most transplantations in our cohort occurred at moderate- to large-volume transplant centers based on the represented centers participating in PHIS. We think that our findings are valid for centers of similar volume but may have limitations regarding their generalizability to smaller centers. The 26 merged centers in our UNOS-PHIS cohort account for ~85% of free-standing children's hospitals, so these data reflect a multicenter practice experience from a significant portion of academic US centers. Finally, the PHIS database, which is an administrative database, relies on the input of accurate information regarding diagnostic coding. To address this potential limitation, PHIS data quality and reliability metrics are assured through a joint effort between the Children's Hospital Association and participating hospitals, with data subject to a number of reliability and validity checks before being included in the database.

Conclusion

Children with CHD, particularly single-ventricle disease, have poorer outcomes despite increased resource utilization and costs during the first year after transplantation compared with children with cardiomyopathy and myocarditis. Data from this merged database—UNOS combined with PHIS, an administrative hospital database—have enabled more granular pre- and post-transplantation analysis of patient- and center-level factors in children. Further work is aimed at identifying modifiable pre-transplantation risk factors, such as pre-transplantation conditioning with VAD support and cardiac rehabilitation, to improve post-transplantation outcomes and reduce resource utilization in this complex population.

Disclosures

None.

Previous Presentation

This study was presented at the 67th Annual Meeting and Scientific Session of the American College of Cardiology, Orlando, Florida, March 10–12, 2018, and the 38th Annual Meeting and Scientific Sessions of the International Society for Heart and Lung Transplantation, Nice, France, April 11–14, 2018.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2018.11.014.

References

1. Canter CE, Shaddy RE, Bernstein D, et al. Indications for heart transplantation in pediatric heart disease: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young; the Councils on Clinical Cardiology, Cardiovascular Nursing, and Cardiovascular Surgery and Anesthesia; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation 2007;115:658–76.
2. Kantrowitz A, Haller JD, Joos H, Cerruti MM, Carstensen HE. Transplantation of the heart in an infant and an adult. Am J Cardiol 1968;22:782–90.
3. Rossano JW, Dipchand AI, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: nineteenth pediatric heart transplantation report—2016; focus theme: primary diagnostic indications for transplant. J Heart Lung Transplant 2016;35:1185–95.
4. Kirk R, Dipchand AI, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: fifteenth pediatric heart transplantation report—2012. J Heart Lung Transplant 2012;31:1065–72.
5. Lamour JM, Kanter KR, Naftel DC, et al. The effect of age, diagnosis, and previous surgery in children and adults undergoing heart transplantation for congenital heart disease. J Am Coll Cardiol 2009;54:160–5.
6. Murtuza B, Fenton M, Burch M, et al. Pediatric heart transplantation for congenital and restrictive cardiomyopathy. Ann Thorac Surg 2013;95:1675–84.
7. Getz KHC, He C, Burstein DS, Rossano JW, Aplenc R. Successful merging of data from the United Network for Organ Sharing (UNOS) and the Pediatric Health Information Systems (PHIS) databases. Pediatr Transplant 2018;22:e13168.
8. Braggion-Santos MF, Lossnitzer D, Buss S, et al. Late gadolinium enhancement assessed by cardiac magnetic resonance imaging in heart transplant recipients with different stages of cardiac allograft vasculopathy. Eur Heart J Cardiovas Imaging 2014;15:1125–32.
9. Maude SL, Fitzgerald JC, Fisher BT, et al. Outcome of pediatric acute myeloid leukemia patients receiving intensive care in the United States. Pediatr Crit Care Med 2014;15:112–20.
10. Division of Nutrition PA, and Obesity, National Center for Chronic Disease Prevention and Health Promotion. Growth Chart Training 2016.
11. Pasquali SK, Jacobs JP, Bove EL, et al. Quality-cost relationship in congenital heart surgery. Ann Thorac Surg 2015;100:1416–21.
12. McHugh KE, Pasquali SK, Hall MA, Scheurer MA. Cost variation across centers for the Norwood operation. Ann Thorac Surg 2017.
13. Getz KD, Li Y, Alonzo TA, et al. Comparison of in-patient costs for children treated on the AAML0531 clinical trial: a report from the Children's Oncology Group. Pediatr Blood Cancer 2015;62:1775–81.
14. Godown J, Thurm C, Dodd DA, et al. A unique linkage of administrative and clinical registry databases to expand analytic possibilities in pediatric heart transplantation research. Am Heart J 2017;194:9–15.
15. Schumacher KR, Almond C, Singh TP, et al. Predicting graft loss by 1 year in pediatric heart transplantation candidates: an analysis of the Pediatric Heart Transplant Study database. Circulation 2015;131:890–8.
16. Savla J, Lin KY, Lefkowitz DS, et al. Adolescent age and heart transplantation outcomes in myocarditis or congenital heart disease. J Heart Lung Transplant 2014;33:943–9.
17. Hollander SA, McElhinney DB, Almond CS, et al. Rehospitalization after pediatric heart transplantation: Incidence, indications, and outcomes. Pediatr Transplant 2017;21.
18. Law SP, Kim JJ, Decker JA, et al. Hospital charges for pediatric heart transplant hospitalizations in the United States from 1997 to 2006. J Heart Lung Transplant 2012;31:485–91.
19. Oostenbrink JB, Kok ET, Verheul RM. A comparative study of resource use and costs of renal, liver and heart transplantation. Transpl Int 2005;18:437–43.
20. Pasquali SK, He X, Jacobs ML, et al. Excess costs associated with complications and prolonged length of stay after congenital heart surgery. Ann Thorac Surg 2014;98:1660–6.
21. Pasquali SK, Sun JL, d'Almada P, et al. Center variation in hospital costs for patients undergoing congenital heart surgery. Circ Cardiovasc Qual Outcomes 2011;4:306–12.