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Hospital readmission following pediatric heart transplantation

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Abstract

The frequency, indications, and outcomes for readmission following pediatric heart transplantation are poorly characterized. A better understanding of this phenomenon will help guide strategies to address the causes of readmission. Data from the Clinical Trials in Organ Transplantation for Children (CTOTC-04) multi-institutional collaborative study were utilized to determine incidence of, and risk factors for, hospital readmission within 30 days and 1 year from initial hospital discharge. Among 240 transplants at 8 centers, 227 subjects were discharged and had follow-up.

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AUTHORS' CONTRIBUTION

All contributing authors met all of the following 4 criteria: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and Drafting the work or revising it critically for important intellectual content; and Final approval of the version to be published; and Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

129 subjects (56.8%) were readmitted within one year; 71 had two or more readmissions. The 30-day and 1-year freedom from readmission were 70.5% (CI: 64.1%, 76.0%) and 42.2% (CI: 35.7%, 48.7%), respectively. The most common indications for readmissions were infection followed by rejection and fever without confirmed infection, accounting for 25.0%, 10.6%, and 6.2% of readmissions, respectively. Factors independently associated with increased risk of first readmission within 1 year (Cox proportional hazard model) were as follows: transplant in infancy ($P = .05$), longer transplant hospitalization ($P = .04$), lower UNOS urgency status (2/IB vs 1A) at transplant ($P = .04$), and Hispanic ethnicity ($P = .05$). Hospital readmission occurs frequently in the first year following discharge after heart transplantation with highest risk in the first 30 days. Infection is more common than rejection as cause for readmission, with death during readmission being rare. A number of patient factors are associated with higher risk of readmission. A fuller understanding of these risk factors may help tailor strategies to reduce unnecessary hospital readmission.

Keywords

pediatric heart transplantation; readmission

1 | INTRODUCTION

Heart transplantation is a life-saving therapy for children with advanced heart failure. Fortunately, the last several decades have witnessed a dramatic improvement in survival following pediatric heart transplantation.¹ Data from the Society of Thoracic Surgeons indicate that 96% of all children who receive a heart transplant are successfully discharged to home from the hospital.² In spite of these improving results, children who receive a heart transplant will often require readmission to the hospital, especially in the first month or year following the transplant.

Hospital readmission represents a significant utilization of resources.³ Accordingly, there have been numerous efforts in recent years to reduce hospital readmission.⁴ The US Center for Medicare and Medicaid Services has emphasized that lower hospital readmissions within 30 days are an important benchmark for quality.⁵ To date, little is known about the hospital readmission following pediatric heart transplantation. Such an analysis will be helpful in counseling patients and families. Moreover, by identifying risk factors for readmission, it may be possible to devise strategies to lower the readmission rate. The Clinical Trials in Organ Transplantation for Children (CTOTC) collaborative provides a unique platform to examine this issue and provide important insights into the factors associated with hospital readmission so that future quality improvement initiatives can focus on identifying those children at highest risk for readmission.

2 | PATIENTS AND METHODS/MATERIALS AND METHODS

This is a sub-analysis of the National Institutes of Health (NIH)-sponsored Clinical Trials in Organ Transplantation in Children (CTOTC) “Alloantibodies in Pediatric Heart Transplantation” (www.ctotc.org). Full details of study design are provided in detail elsewhere.⁶ These details include overall study design, organization and duration, study

sites, inclusion and exclusion criteria, subject population, study definitions including presensitizing events, primary and secondary endpoints, rejection surveillance, study visits with “schedule of events,” and details of the various study core laboratories.

The subjects were enrolled beginning 2/1/11 with the last transplant occurring by 12/31/13. The study enrolled 91.5% of all subjects undergoing transplantation at the participating centers during the study period. The standardized immunosuppression protocol has also been described elsewhere.⁶ In brief, all patients received thymoglobulin induction therapy (total cumulative dose of 7.5 mg/kg) and maintenance immunosuppression with tacrolimus and mycophenolate mofetil. CDC-crossmatch-positive subjects also received maintenance corticosteroids for at least six months, along with a course of intravenous immunoglobulin and perioperative antibody removal.⁶ Rejection surveillance was by endomyocardial biopsy interpreted according to the guidelines of the International Society for Heart and Lung Transplantation (ISHLT).⁷ Tacrolimus goal trough levels were as follows: 0–3 months (8–12 ng/mL) and 3–12 months (6–10 ng/mL).

Hospital readmission was defined as rehospitalization for longer than 24 hours. Readmissions for planned elective procedures were not included in the analysis. The primary outcome measure for the analysis was hospital readmission within 1 year of initial post-transplant hospital discharge. We also analyzed separately hospital readmission within 30 days of initial post-transplant hospital discharge as this is a quality metric as defined the US Centers for Medicare and Medicaid. Additionally, we analyzed the cumulative number of hospital readmissions. Per study protocol, all hospital readmissions required completion of a case report form. The primary indication for hospital readmission was recorded for each event as well as the clinical outcome for the readmission. Definitions of all outcomes for CTOTC-04 are provided elsewhere.⁶

2.1 | Statistical considerations

Data are summarized using descriptive statistics for categorical (counts and percentages) and continuous (medians and IQRs) variables. Univariate comparisons were made using Fisher’s exact test and Wilcoxon rank-sum test, as appropriate, with statistical significance set at two-sided $\alpha = 0.05$. Survival curves were estimated using the Kaplan-Meier method with corresponding 95% confidence intervals. The hazard function was plotted with Kernel-smoothed estimates. To determine clinical factors associated with readmission, Cox proportional hazards models were developed to model the time to first readmission within the first 30 days and first year following transplant discharge, separately. Risk factors were identified using a forward selection strategy with $\alpha = 0.10$ threshold for entry into the model. The hazard ratios and corresponding 95% confidence intervals are displayed. Variables considered for the model included age at transplant, sex, ethnicity, race, diagnosis, ABO incompatibility, UNOS status at transplant, prior sensitizing event, waitlist duration, length of transplant hospital stay, number of medications at time of transplant hospital discharge, mechanical support at transplant, and sensitization status at transplant. Log-negative-log plots and plots of Schoenfeld residuals were inspected to assure the proportionality assumption was met. A Poisson regression model was developed to model the incidence of hospital readmission within the first year since more than one readmission

was possible. Risk factors (considered from the same variables listed above) were identified using a forward selection strategy with $\alpha = 0.10$ threshold for entry into the model. The risk ratios and corresponding 95% confidence intervals are displayed. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc).

3 | RESULTS

During the study, 240 subjects underwent transplantation. Of these, 12 died following transplantation prior to discharge to home and one subject withdrew, leaving 227 subjects eligible for analysis. The median length of initial hospital stay was 19 days (IQR 13–34) (Figure 1). The baseline characteristics are summarized in Table 1.

3.1 | Readmission within the first 30 days after initial hospital discharge

There were 67 subjects (29.5%) readmitted within 30 days of transplant hospitalization discharge (Table 2). While the majority of these subjects had only a single readmission within 30 days, there were four subjects that were admitted twice in that timeframe.

3.2 | Readmission within 1 year of initial hospital discharge

The majority of subjects (56.8%) had at least one hospital admission within 1 year of initial hospital discharge. The number of readmissions per subject varied with just less than half of these subjects having only a single readmission. There were twelve subjects with 5 or more readmissions within the 1 year timeframe. The median length of stay was relatively short, 4 days (IQR 3–8). Hospitalization resulting in death was relatively uncommon, occurring in 4 of 129 (3.1%) of those readmitted. The most common indications for readmission were infection followed by rejection and fever without confirmed infection, which accounted for 25.0%, 10.6%, and 6.2% of readmission events, respectively (Table 2).

The freedom from readmission within the first year is shown in Figure 2A. The instantaneous hazard rate for first readmission was greatest immediately following transplant hospitalization discharge. This is shown graphically in Figure 2B. Of note, the risk of readmission continued to decrease throughout the entire year follow-up period.

3.3 | Risk factors for readmission

Independent risk factors associated with *increased risk of first readmission within 30 days* of initial transplant discharge (Cox proportional hazards model) included lack of a prior sensitizing event ($P = .01$) and diagnosis of congenital heart disease ($P = .06$; Figure 3A). Independent risk factors associated with *increased risk of first readmission within 1 year* (Cox proportional hazards model) were lower UNOS urgency status (2/IB vs 1A) at transplant ($P = .04$), longer hospital stay for transplant admission ($P = .04$), transplant in infancy ($P = .05$), Hispanic ethnicity ($P = .05$), and lack of prior sensitizing event ($P = .10$; Figure 3B).

Analysis for the *incidence of readmission within 1 year* (Poisson regression model) demonstrated similar risk factors, namely lower UNOS status at transplant (2/IB vs 1A;

$P < .01$), longer hospital stay for heart transplant admission ($P < .01$), transplant in infancy ($P < .01$), Hispanic ethnicity ($P = .04$), and female gender ($P = .05$; Table 3).

Sensitization status, mechanical support before transplant, and pretransplant diagnosis were not associated with the risk of first readmission within 1 year or the incidence of readmission within 1 year.

4 | DISCUSSION

Readmission is common following pediatric heart transplantation. Our analysis from the eight centers participating in the CTOTC-04 prospective cohort study found that over half the pediatric heart transplant recipients were readmitted at least once in the year following transplant. Many of these children had multiple admissions.

In recent years, there has been great interest in hospital readmissions particularly for common conditions in adults. The US Centers for Medicare and Medicaid estimates that nearly one in five of all hospital patients covered by Medicare are readmitted within 30 days, accounting for \$15 billion a year.⁸ As CMS has oversight of solid-organ transplantation, 30-day hospital readmission is also a metric included in heart transplant measures including pediatric heart transplant programs. It has been suggested that through better predischarge teaching and close outpatient follow-up, many hospital readmissions could be avoided. We did find that the first 30 days represented the greatest risk for readmission. However, we did not find patient- or procedure-related characteristics that could easily identify those at risk of early readmission.

There were few factors associated with readmission within 30 days. Curiously, prior sensitizing events were associated with a lower risk of early readmission. There is not an obvious explanation for this association. Interestingly, in a prior analysis from our study we found that ventricular assist device (VAD) implantation was associated with a lower risk of developing newly detected donor-specific anti-HLA antibodies, suggesting the relationship of sensitizing events to outcomes in children may differ from that reported in adults.⁹ When one examines readmission within 1 year of initial hospital discharge, there are several factors that are strongly associated with the incidence of readmission. A longer duration of initial hospital admission is associated with a higher readmission rate. It is likely that the factors that might lead to particularly long transplantation hospitalization such as comorbidities or deconditioning might also impact the health of the child in the first year following discharge. The use of rehabilitation services was not routinely captured in this study as there is considerable variability in how such services are administered. In future studies, it would be beneficial to better understand how a dedicated rehabilitation stay might impact hospital readmission rates following pediatric heart transplantation. Studies in adults have found that rehabilitation programs reduce the rate of hospital readmission following heart transplantation.¹⁰ We also found that transplantation in infancy was strongly associated with higher incidence of readmission. This is likely a reflection of an increased burden of infections and concern for infections in this population. Interestingly, subjects with Hispanic ethnicity had a higher readmission rate. This same phenomenon has been reported in children undergoing heart surgery for congenital heart disease.¹¹ This would

seem likely to be a social rather than biological mediator. For many children of Hispanic ethnicity living in the United States, English is not the primary language used at home. One could speculate that language barriers could create barriers to communication with the transplant team either in the discharge teaching process or in the follow-up assessment. While we did not collect extensive data on social support as part of this study, it is possible that these factors may contribute to a higher readmission rate.¹² We also noted that those subjects listed at a lower UNOS status were more likely to have hospital readmission events. The factors underpinning such an association are not entirely clear. One could speculate that children listed status 1A are complicated pre-operatively and the parents/caregivers may have more experience with medication regimens or clinical assessment. Of note, when we analyzed risk factors for any readmission using a Cox proportional hazards model, the risk factors were comparable.

The most common indication for hospital readmission was infection or concern for infection. This is in keeping with previous analyses of adult heart transplant series and other pediatric solid-organ transplant series.^{13,14} Infections are common in pediatrics, especially in young children. Certainly, immunosuppression may increase the risk of infection. Moreover, clinicians are vigilant for infections in the pediatric solid-organ transplant community perhaps leading to a lower threshold for hospital admission. While bacterial infections have a risk for serious complications, such life-threatening bacterial complications tend to occur immediately following the transplant.¹⁵ Viral infections are more common and tend to have a benign course. Notably, none of the 4 deaths that occurred during hospital readmissions in the first year were attributed primarily to an infection. Evaluation for fever was also a common reason for admission underscoring the circumspect approach to potential infections in children. Interestingly, fever associated with neutropenia was also a common cause for hospital readmission. Recent literature suggests that neutropenia following pediatric heart transplantation is common and not associated with adverse outcomes.¹⁶ With further analyses, it is conceivable that clinicians might use the data from this and other sources to develop and test prediction models that determine the need for hospital readmission in some pediatric heart transplant patients with suspected infection, with or without neutropenia. Similar strategies have been developed following chemotherapy for childhood cancer, with promising results.¹⁷ Rejection was a less common cause of hospital readmission in our cohort. This parallels observations after pediatric renal transplantation, which also show that infection now exceeds acute rejection as the dominant cause for readmission.¹⁸ Importantly, there were no hospital deaths associated with the 31 rejection-related readmission events. One of the more common treatment approaches to acute rejection is intravenous pulsed corticosteroids, almost always performed during inpatient hospitalization. However, it should be noted that there is institutional variation regarding treatment for acute rejection, with many cases being managed with outpatient administration of oral corticosteroids in some centers. These latter cases would not have been captured during this analysis. A future analysis will focus on efficacy of inpatient versus outpatient management of acute rejection in the absence of hemodynamic compromise.

As important as the factors associated with hospital readmission are the factors not associated with hospital readmission. The CTOTC-04 study particularly focused on the

impact of allosensitization on transplant outcomes.⁶ The immunosuppression protocol mandated added immunosuppressive therapies for those with a positive crossmatch. In the present analysis, we found no association between hospital readmission rates and allosensitization with or without donor-specific antibody. This would suggest that clinicians can mitigate the risks of allosensitization without increasing comorbidities that might result in hospital readmission. The total number of immunosuppressant medications at transplant hospitalization discharge was not associated with readmission.

The analysis has several limitations. Detailed data regarding management during readmission, such as needed for intensive care unit admission, were not collected. In addition, there were no formal criteria for readmission among participating centers so that threshold for admission might have varied by site. While we noted an association between Hispanic ethnicity and outcomes, we did not collect data regarding the level of fluency in English in order to fully understand whether the aforementioned association was likely due to language barriers. Lastly, data regarding socioeconomic status were not collected, which is relevant as it has been associated with hospital readmission rates in some studies.

Hospital readmission is common in the first year following heart transplantation, particularly in the first month. A number of patient-related factors are associated with readmission and may be used to design strategies to reduce preventable admissions in this population.

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Abbreviations:

CDC	Centers for Disease Control
CMS	Centers for Medicare & Medicaid Services
CTOTC	Clinical Trials in Organ Transplantation for Children
NIH	National Institutes of Health
VAD	ventricular assist device

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FIGURE 1.
Histogram showing the distribution of the length of the initial transplant hospital stay

FIGURE 2.

Probability of freedom from hospital readmission in the first year following the initial transplant hospital discharge with 95% confidence interval (A) and corresponding hazard function (B). The number of participants at risk is presented at select time points along the x-axis. Censored data are shown as circles

FIGURE 3.

Risk factors for first hospital readmission within 30 days (A) and 1 year (B) of initial transplant hospital discharge using Cox proportional hazards model

TABLE 1
Baseline characteristics comparing subjects hospitalized and not hospitalized within 30 d and 1 y of transplant discharge

	First 30 d after transplant discharge		First year after transplant discharge		P-value	Total (N = 227)
	At least 1 readmission (N = 67)	No readmissions (N = 160)	At least 1 readmission (N = 129)	No readmissions (N = 98)		
Median age (y) at listing (IQR)	8 (1–14)	6 (1–14)	3 (1–12)	11 (3–15)	<.01	6 (1–14)
Median age (y) at transplant (IQR)	8 (1–14)	6 (0–14)	3 (0–12)	11 (2–15)	<.01	6 (1–14)
Median weight (kg) at listing (IQR)	22.1 (9.6–46.9)	18.0 (8.2–50.4)	12.8 (7.1–36.2)	32.2 (13.0–54.8)	<.01	18.1 (8.5–49.5)
Median weight (kg) at transplant (IQR)	23.4 (10.0–46.3)	19.8 (8.8–51.3)	13.7 (8.0–40.1)	34.9 (14.1–55.0)	<.01	20.6 (9.2–50.0)
Diagnosis						
Cardiomyopathy	36 (53.7)	89 (55.6)	64 (49.6)	61 (62.2)	0.14	125 (55.1)
Congenital Heart Disease	31 (46.3)	67 (41.9)	62 (48.1)	36 (36.7)		98 (43.2)
Other	0	4 (2.5)	3 (2.3)	1 (1.0)		4 (1.8)
Race						
White	38 (56.7)	89 (55.6)	73 (56.6)	54 (55.1)	.18	127 (55.9)
Black or African American	12 (17.9)	40 (25.0)	23 (17.8)	29 (29.6)		52 (22.9)
Non-White/Non-Black	7 (10.4)	0310 (6.3)	11 (8.5)	6 (6.1)		17 (7.5)
Unknown or Not Reported	10 (14.9)	21 (13.1)	22 (17.1)	9 (9.2)		31 (13.7)
Ethnicity						
Hispanic or Latino	10 (14.9)	19 (11.9)	22 (17.1)	7 (7.1)	.05	29 (12.8)
Not Hispanic or Latino	48 (71.6)	104 (65.0)	85 (65.9)	67 (68.4)		152 (67.0)
Unknown or Not Reported	9 (13.4)	37 (23.1)	22 (17.1)	24 (24.5)		46 (20.3)
Male	33 (49.3)	91 (56.9)	70 (54.3)	54 (55.1)	.90	124 (54.6)
UNOS Status at Transplant						
1A	57 (85.1)	139 (86.9)	107 (82.9)	89 (90.8)	.16	196 (86.3)
1B	6 (9.0)	15 (9.4)	16 (12.4)	5 (5.1)		21 (9.3)
2	4 (6.0)	6 (3.8)	6 (4.7)	4 (4.1)		10 (4.4)

TABLE 2

Characteristics of readmission events within 30 d and 1 y of transplant discharge

	Readmission within 30 d	Readmission within 1 y
Total number of readmissions	71	292
Number of subjects with readmission, n (%)	67 (29.5)	129 (56.8)
Number of readmissions per subject, n (%)		
0	160 (70.5)	98 (43.2)
1	63 (27.8)	58 (25.6)
2	4 (1.8)	34 (15.0)
3	0	14 (6.2)
4	0	11 (4.8)
5+	0	12 (5.3)
Reason for readmission, n (%) [subject count]		
Diabetes	0	3 (1.0) [3]
Infection	11 (15.5) [11]	73 (25.0) [49]
Rejection	12 (16.9) [11]	31 (10.6) [26]
PTLD	0	9 (3.1) [2]
Other	48 (67.6) [46]	176 (60.3) [99]
Days to first readmission, median (IQR)	8 (5–15)	26 (8–134)
Length of stay in days, median (IQR)	4 (3–8)	4 (3–8)
Cumulative length of stay per subject in days, median (IQR)	5 (3–11)	10 (4–20)
Hospitalization resulted in death, n (%)	0	4 (1.4)

Factors associated with increased incidence of readmission within 1 y of transplant discharge using Poisson regression model

TABLE 3

Parameter	Incidence rate ratio	95% confidence limit	P-value
Age at transplant			
Infant vs Not	1.61	(1.26, 2.07)	<.01
Length of transplant hospitalization stay (per 30 d)	1.30	(1.16, 1.44)	<.01
UNOS Status			
IB/2 vs 1A	1.67	(1.21, 2.30)	<.01
Sex			
Male vs Female	0.78	(0.61, 1.00)	.05
Ethnicity			
Hispanic or Latino vs Not Hispanic or Latino	1.45	(1.06, 1.98)	.04
Unknown/Not Reported vs Not Hispanic or Latino	0.90	(0.66, 1.24)	