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Practice variation in the diagnosis of acute rejection among pediatric heart transplant centers: An analysis of the pediatric heart transplant society (PHTS) registry

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KEYWORDS:
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practice variation;
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BACKGROUND: Freedom from rejection in pediatric heart transplant recipients is highly variable across centers. This study aimed to assess the center variation in methods used to diagnose rejection in the first-year post-transplant and determine the impact of this variation on patient outcomes.

METHODS: The PHTS registry was queried for all rejection episodes in the first-year post-transplant (2010-2019). The primary method for rejection diagnosis was determined for each event as surveillance biopsy, echo diagnosis, or clinical. The percentage of first-year rejection events diagnosed by

Abbreviations: PHTS, Pediatric Heart Transplant Society; PRA, Panel Reactive Antibodies; SBx, Surveillance Biopsy; VAD, Ventricular Assist Device; xxx, xxxxxxx

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surveillance biopsy was used to approximate the surveillance strategy across centers. Methods of rejection diagnosis were described and patient outcomes were assessed based on surveillance biopsy utilization among centers.

RESULTS: A total of 3985 patients from 56 centers were included. Of this group, 873 (22%) developed rejection within the first-year post-transplant. Surveillance biopsy was the most common method of rejection diagnosis (71.7%), but practices were highly variable across centers. The majority (73.6%) of first rejection events occurred within 3-months of transplantation. Diagnosis modality in the first-year was not independently associated with freedom from rejection, freedom from rejection with hemodynamic compromise, or overall graft survival.

CONCLUSIONS: Rejection in the first-year after pediatric heart transplant occurs in 22% of patients and most commonly in the first 3 months post-transplant. Significant variation exists across centers in the methods used to diagnose rejection in pediatric heart transplant recipients, however, these variable strategies are not independently associated with freedom from rejection, rejection with hemodynamic compromise, or overall graft survival.

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Despite advances in the care of heart transplant recipients, acute rejection remains a barrier to long-term success. Allograft rejection is among the leading causes of death up to 10 years post-transplant in children,[1-3] and treated rejection in the first year is associated with decreased graft and patient survival.[2] Additionally, rejection has been associated with the development of cardiac allograft vasculopathy,[4-6] potentially further impacting graft longevity.

The incidence of rejection has declined over time.[1,7,8] Despite this, between 10% and 30% of pediatric heart transplant recipients are diagnosed with rejection during the first year post-transplant in the most recent era depending on patient risk and induction strategy.[8,9] The continued risk of rejection combined with efforts to optimize long-term patient outcomes has led to the development of various strategies for rejection surveillance. This includes both invasive (surveillance endomyocardial biopsy) and non-invasive (clinical or echocardiogram surveillance) approaches. However, there is significant variability in the protocols for rejection surveillance among pediatric heart transplant centers.[10-12]

Significant practice variation exists among pediatric heart transplant centers. This variability creates a barrier to clinical research and makes identification of best practices challenging if not impossible. PHTS recently developed practice variation working groups focusing on three specific areas: (1) Diagnosis of acute rejection, (2) Management of immunosuppression, and (3) Detection of allograft vasculopathy. Through these working groups, the collaboration aims to minimize practice variation and better standardize pediatric heart transplant recipients' care. While practice variation will always exist, creating standardized protocols will facilitate clinical research and help to further advance the care of pediatric heart transplant recipients.

This study aims to describe the overall variation in freedom from rejection among pediatric heart transplant centers, describe the methods used to diagnose rejection, and assess the impact of rejection diagnosis strategies on post-transplant outcomes including the freedom from rejection, freedom from rejection with hemodynamic compromise, and post-transplant graft survival.

Methods

This study utilized data from the Pediatric Heart Transplant Society (PHTS), a multi-center, event-driven database of pediatric heart transplant candidates and recipients. Details of PHTS organization and data collection have been previously described (Participating centers are listed in Supplemental Table 1).[13] All participating centers are required to maintain institutional review board approval to participate in PHTS and confirmation of institutional review board approval for each institution is kept on file at the PHTS data collection center.

The PHTS database was queried for all subjects who underwent their first heart transplant between 2010 and 2019. These dates were chosen based on modification of the PHTS data collection forms that took place in 2010, allowing identification of the primary methods of rejection diagnosis (Supplemental File: PHTS Form 5: Rejection). Acute rejection is defined by PHTS as any event leading to an increase in immunosuppression to treat a biopsy or clinically diagnosed episode of rejection. Overall freedom from rejection in the first-year post-transplant was compared across centers using the Kaplan-Meier method. All first acute rejection episodes occurring within the first year post-transplant were identified and categorized as (1) surveillance biopsy (SBx), (2) echocardiogram diagnosis, or (3) clinical diagnosis. Categorization of rejection events was accomplished using a composite of variables indicating the basis for diagnosis (echo, clinical, or biopsy) and the indication for biopsy (routine protocol, objective evidence of graft dysfunction, or symptoms). The general approach to the categorization of rejection events is presented in Figure 1 with additional details presented in Supplemental Table 2.

The timing of rejection diagnoses was described over the first post-transplant year and then assessed based on the method of rejection diagnosis. The various methods used to diagnose rejection were then described across participating transplant centers. The percentage of rejection episodes diagnosed by SBx at each center was used as a surrogate marker of rejection surveillance strategy. While prior surveys have described SBx practices, responses may differ from actual practice patterns and SBx practices have changed over time.[10,11] For this reason, our analysis leveraged PHTS data to approximate SBx approaches instead of relying on past survey data. Centers were divided into four groups based on the percentage of their rejection episodes diagnosed using SBx. Cutoffs for groups were chosen based on the overall distribution across centers to approximate quartiles. The groups

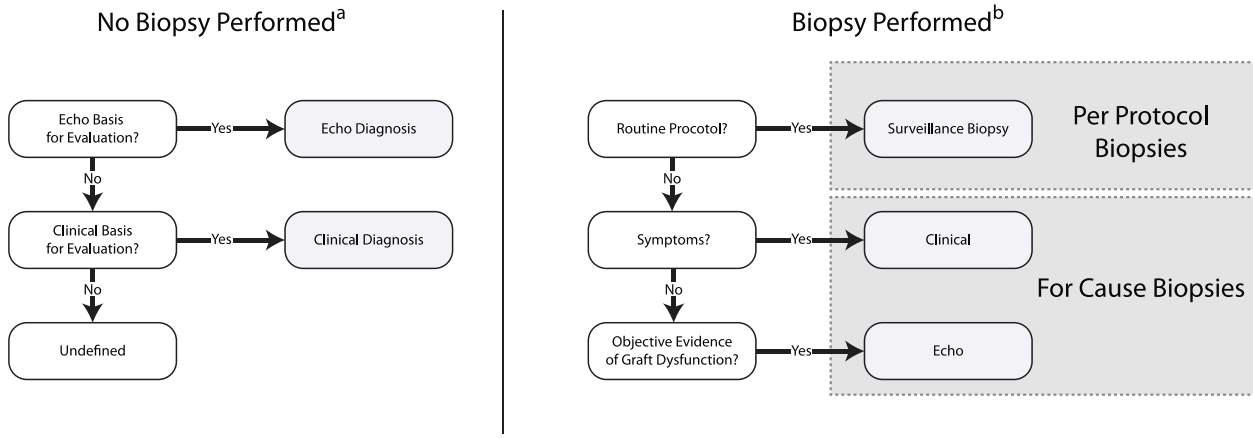

Figure 1 General approach to categorizing rejection events based on whether or not a biopsy was performed based on PHTS rejection form questions (A) 4a and (B) 4b.i (See supplemental material).

were defined based on the SBx percentage as; Q1: <50%, Q2: 50% - 72%, Q3: 73% - 84%, and Q4: ≥85%. Centers with 3 or fewer rejection events throughout the entire study timeframe were excluded a priori as the small number of events precluded confident grouping based on the center methods of rejection diagnosis. Validation of SBx groupings was performed using a previously conducted survey of biopsy practices (Supplemental Figure 1).[11] Patient demographics were compared across SBx groups. Categorical variables were compared using the chi square test and continuous variables were compared using the Kruskal-Wallis test. The Kaplan-Meier method was used to assess the impact of SBx percentage on freedom from rejection, freedom from rejection with hemodynamic compromise, and post-transplant graft survival. Survival curves were compared using the log-rank test. For outcomes that demonstrated significance on univariate analysis ($p < 0.05$), the association of patient characteristics with time to rejection was evaluated using Cox proportional hazard regression. Potential covariates were determined a priori and included age, diagnosis, race, inotrope use, ventricular assist device use, extracorporeal membrane oxygenation use, panel of reactive antibodies percentage, induction therapy, maintenance steroid use, and the center percentage of rejection events diagnosed by SBx. Variables included in the final model were determined using stepwise selection (entry = 0.05, stay = 0.05).

All analyses were performed in SAS version 9.4 (Cary, NC) with two-sided $p < 0.05$ considered statistically significant.

Results

Patient characteristics

A total of 3,985 patients were identified from 56 different centers for inclusion in the analysis. Of the included patients, 873 (21.9%) experienced acute rejection within the first-year post-transplant.

Variability in timing and diagnosis of first rejection

There was significant variability across centers in the freedom from rejection in the first-year post-transplant (Figure 2). A total of 16 (1.8%) rejection events could not be categorized as SBx, echocardiographic, or clinical diagnosis based on the available data (Supplemental Table 2). Of the remaining 857 first rejection episodes, 614 (71.7%) were diagnosed by SBx, 98 (11.4%) were diagnosed primarily using echocardiography, and 145 (16.9%) were diagnosed primarily based upon clinical presentation. Characteristics of rejection episodes based on diagnosis method are presented in Table 1a. Confirmatory biopsy was performed in 109 (75.2%) patients with clinically diagnosed rejection and 46 (46.9%) patients diagnosed using echocardiography. Hemodynamic compromise was less common in patients diagnosed using SBx compared to clinical or echocardiographic diagnosis (18.6% vs. 46.2% and 43.9% respectively, $p < 0.001$).

The majority (73.6%) of first rejection episodes were diagnosed in the first 3-months post-transplant and following this time-period there was a low number of initial rejection episodes out to 1-year post-transplant (Figure 3). A similar pattern was seen when including all rejection events (i.e., recurrent rejection) with >80% (1456 out of 1801 total events) of all first year rejection events occurring within 6 months of transplantation (Supplemental Figure 2). The methods of rejection diagnosis were highly variable across centers. Figure 4 shows the frequency of methods used to diagnose rejection in centers with >3 patients experiencing at least one episode in the first year post-transplant.

Quartiles based on center SBx percentage

Centers were divided into quartiles according to the percent of rejection episodes diagnosed by SBx (Q1 <50%, Q2 50%-72%, Q3 73%-84%, Q4 85%-100%). A total of 9 centers (accounting for 141 patients) were excluded from the SBx grouping analysis due to having 3 or fewer patients with first year rejection throughout the 10-year study period, details of which are presented in Supplemental Table 3. A total of 8 centers (743 patients) were in the Q1 SBx group, 15 centers (832 patients) were in Q2, 13 centers

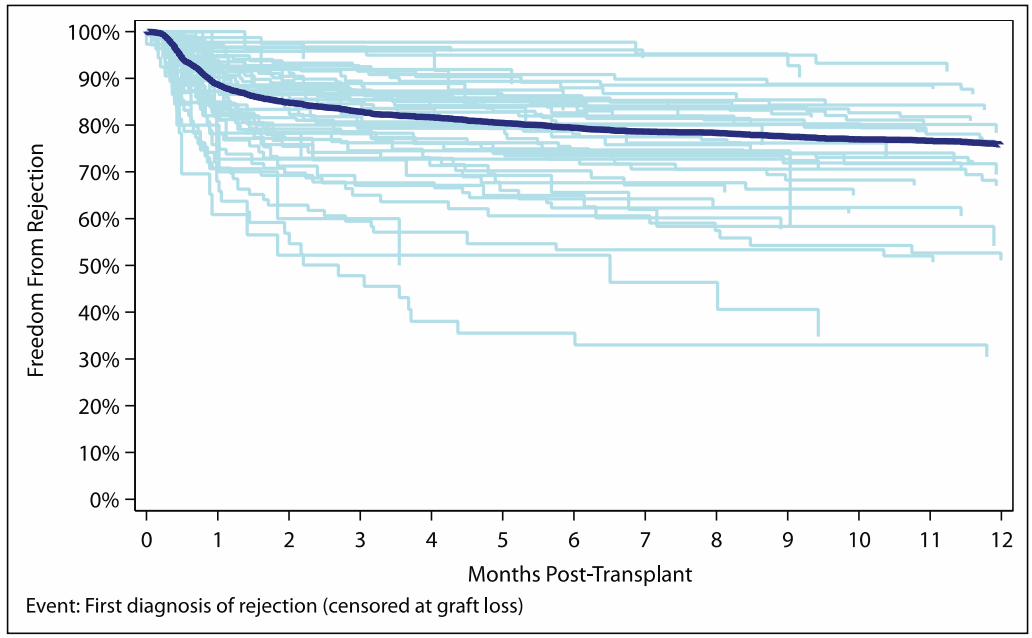

Figure 2 Freedom from rejection by PHTS center. The dark blue line is the overall freedom from rejection when all centers are combined.

(1188 patients) were in Q3, and 11 centers (1081 patients) were in Q4. Characteristics of rejection episodes and demographics of included patients based on SBx groups are shown in Table 1b and Table 2, respectively. Centers with the highest utilization of SBx performed a biopsy in nearly all episodes of rejection (97.8%), more frequently than all other groups. While there were statistical differences in the histologic grade of rejection based on SBx grouping, there was no clear trend demonstrating lower grade rejection in the high-SBx group. Patients from centers with the highest frequency of rejection diagnosed by SBx were older, more likely to be supported with VAD, and less likely to be supported with inotropes in the pre-transplant period compared to other groups. Patients from these centers also demonstrated the highest proportion of patients with sensitization (PRA>10%). There was no difference in the overall number of rejection events based on SBx groups ($p = 0.51$). Data pertaining to the treatment of rejection episodes based on SBx group and diagnosis method are presented in Supplemental Tables 4a and 4b, respectively.

Outcomes based on SBx groups

There was no difference in freedom from rejection in the first-year post-transplant across SBx groups (Figure 5, log-rank $p = 0.313$). However, centers with a greater proportion of rejection episodes diagnosed by SBx (Q4) demonstrated greater freedom from rejection with hemodynamic compromise (Figure 6, log-rank $p = 0.036$). Pairwise comparisons demonstrated that Q4 had significantly greater freedom from rejection with hemodynamic compromise compared to both Q2 and Q3 (pairwise log-rank $p = 0.02$ and 0.01, respectively), but not compared to Q1 (pairwise log-rank $p = 0.1$). After adjusting for covariates in a multivariable Cox proportional hazard regression, SBx grouping was not independently associated with freedom from rejection with hemodynamic compromise (Supplemental Table 5). In our multivariable model, factors independently associated with the occurrence of rejection with hemodynamic compromise include older age, congenital heart disease, mechanical support at transplant, greater sensitization, the use of induction therapy, and the use of maintenance steroids. There was no difference in overall graft survival based on SBx percentage (Figure 7, log-rank $p = 0.582$). Kaplan-Meier curves depicting freedom from rejection, freedom from rejection with hemodynamic compromise, and overall graft survival with a separate group for excluded patients are presented in Supplemental Figures 3a, 3b, and 3c, respectively.

Discussion

This analysis provides novel data on the variation in methods used to diagnose rejection across pediatric heart transplant centers. The majority of first-year rejection episodes are diagnosed by SBx and are most common during the first three-months following transplant. Despite considerable variation across centers in overall freedom from rejection and in the methods used to diagnose rejection, we found no difference in freedom from rejection, freedom from rejection with hemodynamic compromise, or overall graft survival based on SBx groups after accounting for relevant covariates. This suggests that although centers utilize varying methods to diagnose rejection, patient outcomes do not appear to be impacted by these differences.

The etiology for the wide variation in freedom from rejection across PHTS centers is unclear. However, the current analysis suggests that variation in rejection diagnosis methods may not contribute significantly to these

Table 1 Characteristics of Rejection Events Based on (a) Diagnosis Method and (b) SBx Percentage

	a. Based on diagnosis method (N = 857)				b. Based on SBx percentage (N = 848)[a]				
	Clinical Diagnosis (*n* = 145)	Echo Surveillance (*n* = 98)	Surveillance Biopsy (*n* = 614)	*p*-value	Q1. 0% - 49% (*n* = 164)	Q2. 50% - 72% (*n* = 190)	Q3. 73% - 84% (*n* = 269)	Q4. 85% - 100% (*n* = 225)	*p*-value
Biopsy performed	109 (75.2)	46 (46.9)	614 (100)	<0.001	116 (70.7)	174 (91.6)	244 (90.7)	220 (97.8)	<0.001
ACR grading				<0.001					<0.001
0R	25 (27.8)	3 (13.6)	54 (9.6)		12 (12.9)	30 (20.0)	22 (10.3)	18 (8.6)	
1R	24 (26.7)	6 (27.3)	190 (33.7)		17 (18.3)	56 (37.3)	68 (31.8)	75 (35.7)	
2R	34 (37.8)	10 (45.5)	295 (52.3)		58 (62.4)	53 (35.3)	116 (54.2)	107 (51.0)	
3R	7 (7.8)	3 (13.6)	25 (4.4)		6 (6.5)	11 (7.3)	8 (3.7)	10 (4.8)	
Biopsy evidence of AMR				<0.001					<0.001
Yes	37 (25.5)	9 (9.2)	182 (29.6)		21 (12.8)	53 (27.9)	98 (36.4)	52 (23.1)	
No	106 (73.1)	89 (90.8)	427 (69.5)		141 (86.0)	137 (72.1)	167 (62.1)	172 (76.4)	
Not evaluated	2 (1.4)		5 (0.8)		2 (1.2)		4 (1.5)	1 (0.4)	
AMR grade				0.002					<0.001
0	109 (75.2)	89 (90.8)	437 (71.2)		143 (87.2)	139 (73.2)	174 (64.7)	174 (77.3)	
1h	8 (5.5)	2 (2.0)	11 (1.8)		4 (2.4)	6 (3.2)	4 (1.5)	6 (2.7)	
1i	3 (2.1)	1 (1.0)	28 (4.6)		3 (1.8)	10 (5.3)	12 (4.5)	5 (2.2)	
2	22 (15.2)	5 (5.1)	117 (19.1)		13 (7.9)	31 (16.3)	72 (26.8)	27 (12.0)	
3	1 (0.7)		2 (0.3)			2 (1.1)		1 (0.4)	
Positive/grade unknown	2 (1.4)	1 (1.0)	19 (3.1)		1 (0.6)	2 (1.1)	7 (2.6)	12 (5.3)	
DSA present				0.592					0.047
Yes	32 (50.8)	11 (39.3)	105 (46.5)		17 (39.5)	41 (44.1)	52 (59.1)	36 (40.4)	
No	31 (49.2)	17 (60.7)	121 (53.5)		26 (60.5)	52 (55.9)	36 (40.9)	53 (59.6)	
Hemodynamic Compromise	67 (46.2)	43 (43.9)	114 (18.6)	<0.001	42 (25.6)	56 (29.5)	76 (28.3)	47 (20.9)	0.175

Abbreviations: ACR, Acute Cellular Rejection; AMR, Antibody-mediated Rejection; DSA, Donor-specific Antibody.

[a]Excluding centers with ≤3 events and rejection events unable to be classified.

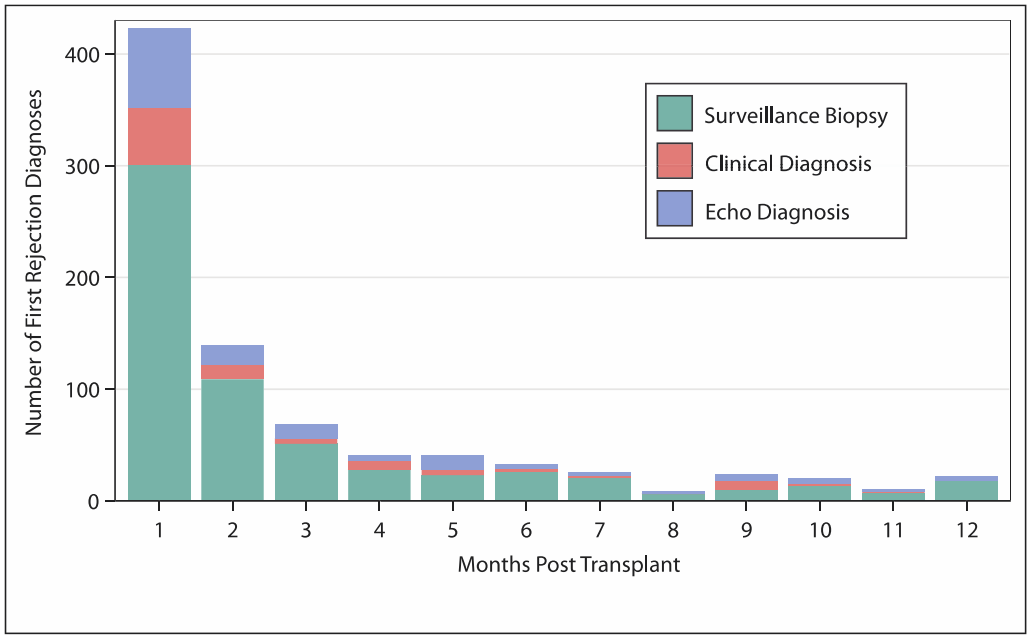

Figure 3 Distribution of first rejection episodes in the 1st post-transplant year with diagnosis method.

differences. Differences in patient populations across centers, including variable patient ages and disease etiologies, may impact this finding but the wide degree of variation is unlikely to be explained by this alone. Centers also vary in their immunosuppression strategies, including the use and choice of agents for induction immunosuppression, use and duration of maintenance steroids, and the choice of medications for long term immunosuppression. It is conceivable that these differences contribute more significantly to the variability in freedom from rejection across centers. This may also be impacted by different thresholds for the treatment of rejection. Because PHTS defines rejection as a change in immunosuppression in response to a biopsy or clinically diagnosed rejection event, centers with a greater number of rejection events may simply be more aggressive when treating patients with low-grade or borderline rejection episodes. Importantly, SBx grouping was not independently associated with freedom from rejection with hemodynamic compromise or overall survival in our analysis. Given the known impact of rejection on long-term

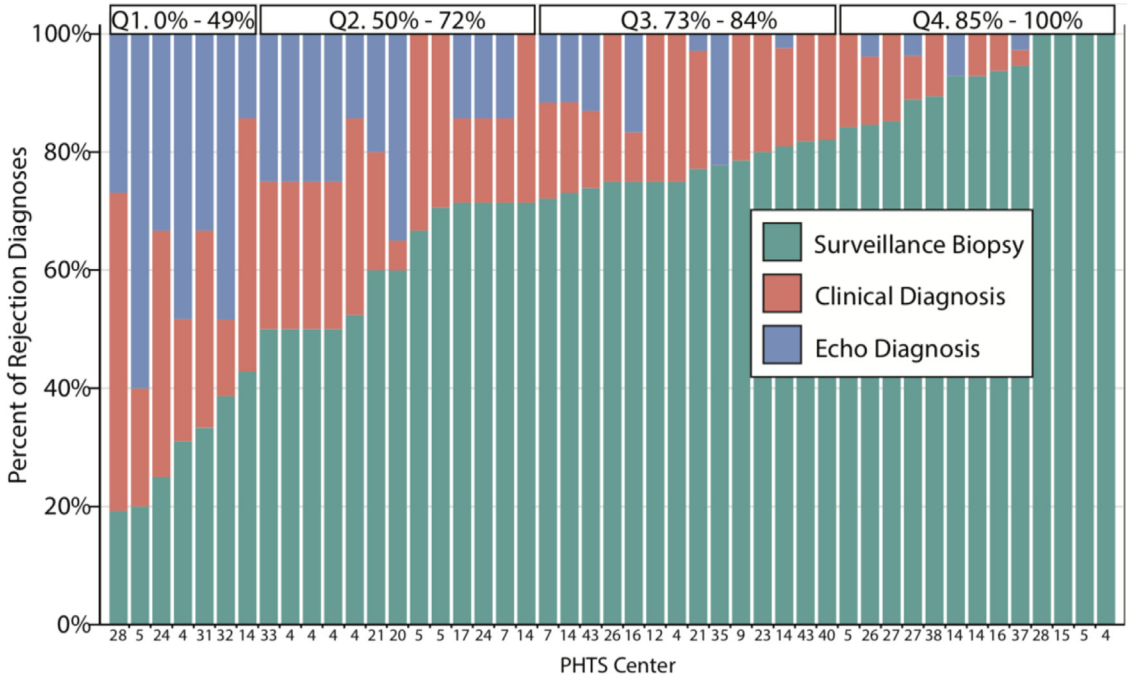

Figure 4 Methods used to diagnose rejection by PHTS center. Numbers along the X-axis represent the total number of rejection events per PHTS center.

Table 2 Characteristics of Included Patients Based on Surveillance Biopsy Grouping

	Total[a] (N = 3,844)	Q1. 0% - 49% (N = 743)	Q2. 50% - 72% (N = 832)	Q3. 73% - 84% (N = 1188)	Q4. 85% - 100% (N = 1081)	*p*-value
Age(y) at transplant	4.8 (0.7 — 13.1)	4 (0.6 — 12)	4 (0.7 — 13)	5.1 (0.7 — 13.4)	5.4 (1 — 13.1)	0.006
Female sex	1731 (45.0)	336 (45.2)	350 (42.1)	548 (46.1)	497 (46)	0.269
CHD	1864 (48.5)	372 (50.1)	440 (52.9)	568 (47.8)	484 (44.8)	0.004
Race						
White	2514 (65.5)	554 (74.7)	587 (70.6)	741 (62.4)	632 (58.7)	<0.001
Black	637 (16.6)	73 (9.8)	107 (12.9)	293 (24.7)	164 (15.2)	
Other	686 (17.9)	115 (15.5)	138 (16.6)	153 (12.9)	280 (26.0)	
Inotropes at transplant	2295 (60.0)	439 (60.1)	491 (59.1)	819 (69.1)	546 (50.7)	<0.001
VAD at transplant	1026 (26.7)	168 (22.6)	218 (26.2)	281 (23.7)	359 (33.2)	<0.001
ECMO at transplant	163 (4.2)	36 (4.8)	31 (3.7)	61 (5.1)	35 (3.2)	0.10
Ventilator at transplant	648 (16.9)	155 (20.9)	130 (15.6)	198 (16.7)	165 (15.3)	0.01
PRA > 10 at transplant	896 (25.8)	165 (25.8)	174 (22.2)	298 (25.7)	259 (29.0)	0.017
Induction therapy	3272 (85.5)	546 (74.7)	680 (81.8)	1129 (95)	917 (85.3)	<0.001
Planned maintenance steroids	1900 (50.3)	254 (35.3)	385 (46.9)	713 (60.9)	548 (51.6)	<0.001
Number of rejection events	863 (22.5)	171 (23.0)	193 (23.2)	274 (23.1)	225 (20.8)	0.51

Data presented as N(%) for categorical and median (IQR) for continuous data.

p values from the chi square test for categorical and the Kruskal Wallis test for continuous data.

Abbreviations: CHD, Congenital Heart Disease; ECMO, Extracorporeal Membrane Oxygenation; PRA, Panel Reactive Antibodies; VAD, Ventricular Assist Device.

[a]Excluding patients from centers with ≤3 rejection events (N = 141).

outcomes,[14-16] this supports that there may be less variability in clinically relevant rejection across centers.

While our data support that centers diagnose rejection with similar frequency despite varying diagnostic methods, most episodes of rejection in our analysis were diagnosed by SBx. This trend was observed throughout the first post-transplant year. This may suggest that low SBx centers concentrate their routine protocol biopsies during the early post-transplant period, when the overall risk of rejection is greatest.[17,18] Many centers have reduced the frequency of SBx over time.[11] However, given that the majority of rejection in the first year is diagnosed by SBx, it is unclear if further reduction in SBx would be prudent. There is currently insufficient evidence to support superiority of an invasive versus non-invasive surveillance strategy.

It is conceivable that centers which utilize more frequent SBx diagnose rejection earlier compared to centers that rely on non-invasive surveillance. However, this phenomenon is

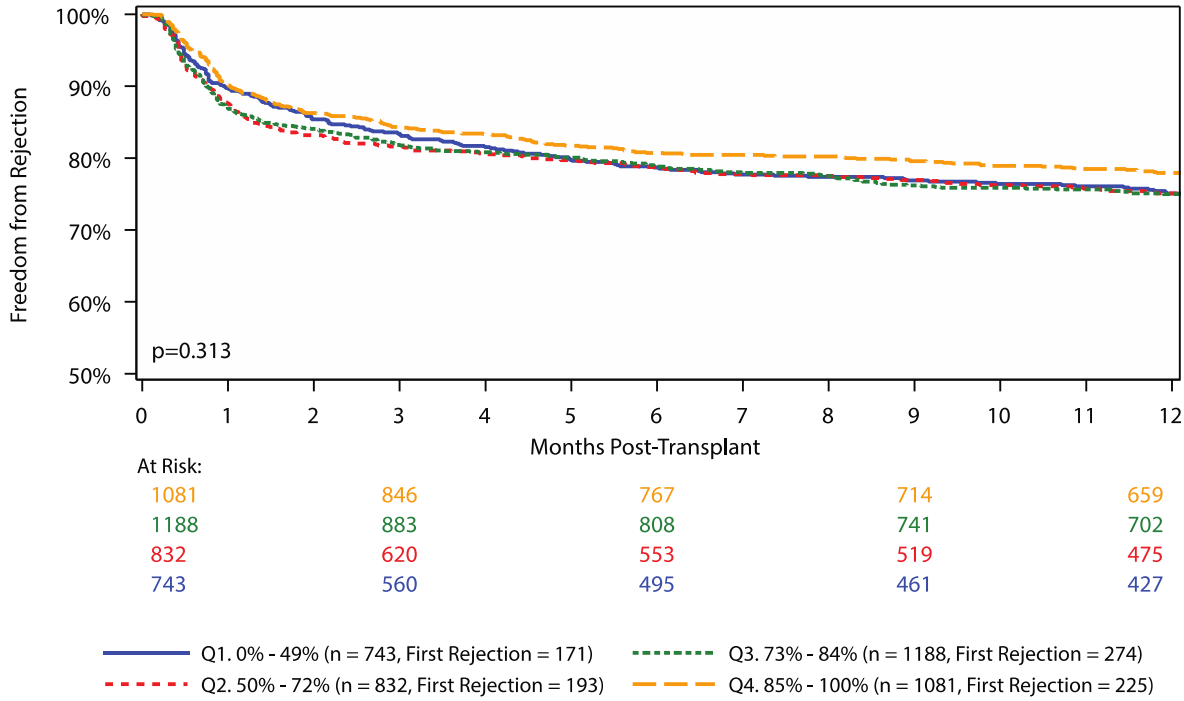

Figure 5 Freedom from rejection by surveillance biopsy group.

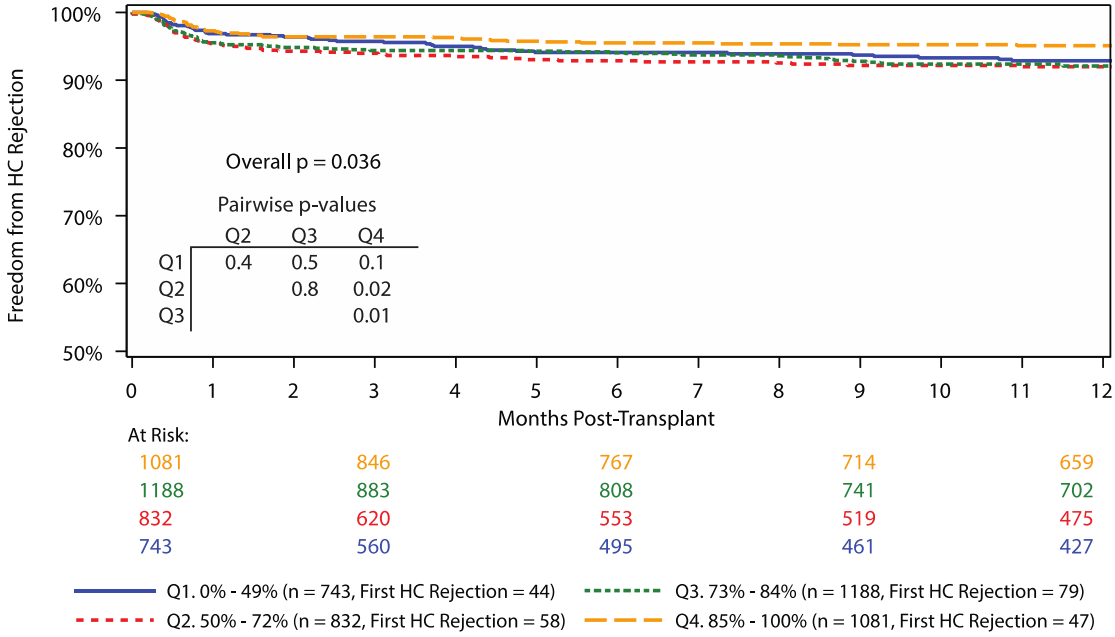

Figure 6 Freedom from rejection with hemodynamic compromise by surveillance biopsy group.

not evident in our analysis. While there was no clear trend in histopathologic grading of rejection across SBx groups, centers with the greatest proportion of events diagnosed by SBx demonstrated less rejection with hemodynamic compromise on univariate analysis. However, this difference did not persist when adjusting for patient-specific factors. While this may indicate that varying SBx protocols do not influence the occurrence of rejection with hemodynamic compromise, it could also reflect a lower-risk patient population at high-SBx centers. Therefore, it remains important to consider patient risk when assessing the utility of varying surveillance strategies and acknowledge that the optimal approach to SBx may vary across centers. Despite this, our results suggest that SBx frequency does not independently influence the risk of rejection with hemodynamic compromise and is not independently associated with graft survival. Similar to our results, a separate study which also utilized the PHTS database demonstrated that a higher frequency of SBx did not result in earlier detection of acute cellular rejection and was not associated with a decrease in 4-year mortality.[10]

Prior studies on this topic support the results of our analysis. Levi and colleagues reported an overall low yield of SBx in pediatric heart transplant recipients but noted that rejection diagnosed by SBx was most common in the early post-transplant period.[19] Multiple other studies have

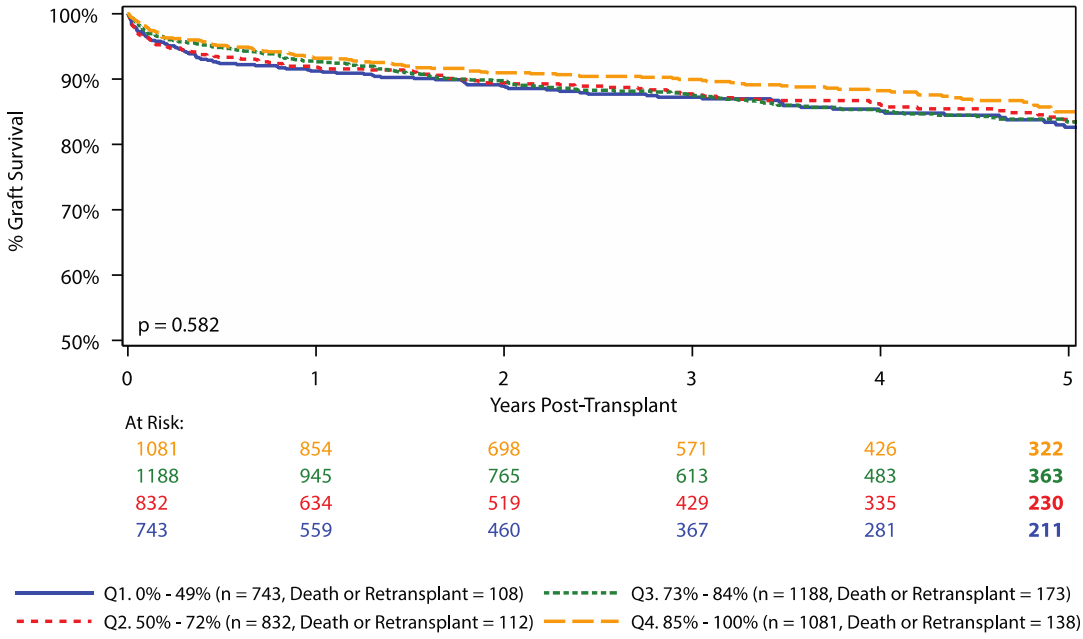

Figure 7 Graft survival (freedom from death or retransplantation) by surveillance biopsy group.

demonstrated a greater yield of SBx within the first 6 months post-transplant and have suggested that routine SBx beyond this timeframe may be of limited clinical utility.[17,18] The timing of first-year rejection in our analysis provides important data to inform surveillance practices. Rejection is most common in the first 3-months and the occurrence of a first rejection event beyond this timeframe is less common. For patients with at least one episode of early rejection, the majority of first-year rejection events occur within 6-months of transplantation. Despite this, at least one study has demonstrated the detection of moderate rejection in asymptomatic patients' years from transplant, suggesting there may be a role for SBx long-term.[20]

Limitations

Our analysis has inherent limitations. Rejection within the PHTS database is defined based on augmentation of immunosuppression. Therefore, we are unable to account for varying thresholds for the treatment of rejection and there are a number of rejection events in our analysis that either did not undergo biopsy or were associated with low-grade histologic rejection. However, detailed information regarding the timing of biopsy in relation to rejection therapies is unavailable in the PHTS database, potentially impacting the histopathologic grading of rejection events. The PHTS database does not clearly document the primary method used to diagnose rejection. Therefore, the current analysis inferred this from a combination of variables, potentially resulting in misclassification. However, we believe that biopsies indicated as being, "routine protocol" are likely to accurately capture SBx and thus served as the basis for our primary analysis. Additionally, using the percentage of rejection events diagnosed using SBx as a surrogate for overall center surveillance strategy has inherent limitations. However, validation of the SBx grouping using a previously conducted survey supports this methodology as a reasonable approximation. Regardless, the results should be interpreted with caution given the inherent measurement errors in our methodology, potentially biasing our results towards a non-significant finding (type II error). Our approach necessitated exclusion of centers with few rejection events to enable grouping by SBx percentage. While this may result in exclusion of centers with the lowest rates of rejection, the excluded centers represented relatively small volume programs, helping to explain the limited number of rejection events. Excluded patients also demonstrated less ventilator use at transplant and less sensitization, suggesting that this group may have lower risk at baseline. Additionally, centers likely utilize a combination of modalities to monitor for rejection, therefore diagnostic modalities may not be independent of other surveillance approaches. Surveillance strategies have also changed over time and may be variable within a center depending on age and immunologic risk.[11] However, the limited timeframe included in our study may help to minimize this limitation. Given that PHTS does not collect data from negative biopsies, we are unable to assess the yield of varying surveillance strategies. The association of induction therapy and maintenance steroids with rejection with hemodynamic compromise may indicate and underlying selection bias within the PHTS data, whereby higher risk patients are more likely to receive these therapies. Data pertaining to the timing of rejection events is likely also influenced by current surveillance practice patterns focusing on detection of rejection in the early post-transplant period. Lastly, as with any large database, erroneous or missing data can be problematic. While PHTS performs routine data integrity checks to flag inconsistent data, there is no formal audit process to assess how accurately data are collected.

Conclusions

There is significant variation in the methods used to diagnose rejection across pediatric heart transplant centers in the first-year post-transplant. The majority of acute rejection episodes occur within the first 3 months post-transplant and are diagnosed using SBx. There are significant differences in overall freedom from rejection across centers, but varying methods of rejection diagnosis do not appear to contribute significantly to this finding. Minimizing practice variation and creation of standardized surveillance protocols may help to further define best practices in this population.

Author contributions

Project conceptualization, data analysis, manuscript preparation: J. Godown, D. Hsu, J. Kirklin, R. Cantor, D. Koehl, E. Cummings, J. Vo.

Participation in working group meeting, critical review and revision of manuscript, acceptance of final submitted version: All authors

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Supplementary materials

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