Accepted: 24 February 2017

DOI: 10.1111/petr.12923

ORIGINAL ARTICLE

WILEY

Cancer recurrence and mortality after pediatric heart transplantation for anthracycline cardiomyopathy: A report from the Pediatric Heart Transplant Study (PHTS) group

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Abstract

We aimed to determine whether malignancy after pediatric HTx for ACM affects overall post-HTx survival. Patients <18y listed for HTx for ACM in the PHTS database between 1993 and 2014 were compared to those with DCM. A 2:1 matched DCM cohort was also compared. Wait-list and post-HTx survival, along with freedom from common HTx complications, were compared. Eighty subjects were listed due to ACM, whereas 1985 were listed for DCM. Although wait-list survival was higher in the ACM group, post-HTx survival was lower for the ACM cohort. Neither difference persisted in the matched cohort analysis. Primary cause of death in the ACM group was infection, which was higher than the DCM group. Malignancy rates were not different. All ACM malignancies were due to PTLD without primary cancer recurrence or SMN. Long-term graft survival after pediatric HTx for ACM is no different than for matched DCM peers, nor is there an increased risk of any malignancy. However, risk of infection and death from infection after HTx are higher in the ACM group. Further studies are needed to assess the effects of prior chemotherapy on susceptibility to infection in this group.

KEYWORDS

anthracycline cardiomyopathy, cancer recurrence, chemotherapy-induced cardiomyopathy, database review, pediatric heart transplantation

1 | INTRODUCTION

Treatment of childhood cancer frequently includes the use of cardiotoxic chemotherapeutic agents, such as anthracyclines.[1–3] With an increased number of individuals surviving childhood cancer, the incidence of ACM is expected to increase.[4,5] HTx is often the only long-term option for children with progressive heart failure from ACM;[6–12] however, few studies have evaluated the outcomes after HTx for ACM in the pediatric population.

Two small multicenter studies reported the outcomes of 18 (US, 2004)[6] and 43 (UK database, 2009)[7] listed subjects with ACM, respectively. A larger, more recent study evaluated outcomes of all US pediatric HTx due to ACM using the OPTN database.[8] Although this study found lower long-term survival in the ACM cohort, compared to all pediatric idiopathic DCM recipients, factors accounting for this difference could not be identified due to the limits of this database.

Abbreviations: ACM, anthracycline cardiomyopathy; CAV, cardiac allograft vasculopathy; DCM, dilated cardiomyopathy; ECMO, extracorporeal membrane oxygenation; HTX, heart transplantation; OPTN, Organ Procurement and Transplant Network; PHTS, Pediatric Heart Transplant Study; PRA, panel reactive antibodies; PTLD, post-transplant lymphoproliferative disorder; SMN, second malignant neoplasms; VAD, ventricular assist device.

Lower survival may relate to the fact that heart transplant recipients are at increased risk for malignancy related to long-term immunosuppression, most commonly PTLD.[3] Little is known, however, about the risks of other malignancies, including primary tumor recurrence and SMN, in patients transplanted for ACM. We hypothesized that malignancy after pediatric HTx for ACM is rare and does not affect overall post-HTx survival.

2 | METHODS

2.1 | Study design

We conducted a retrospective review of the PHTS database, based on data as of December 31, 2014. The PHTS collects information on all children listed for HTx at 45 institutions in three countries, while currently capturing data on approximately 80% of pediatric heart transplant candidates worldwide. The PHTS database is curated by the University of Alabama at Birmingham, Birmingham, AL.

2.2 | Patient population

All children (0-17 years) listed for primary HTx due to a diagnosis of DCM secondary to ACM between January 1, 1993, and December 31, 2014, were identified in the PHTS database and were included in the analysis. Patients with a primarily restrictive phenotype and those listed for multi-organ and/or retransplantation were excluded from analysis.

2.3 | Control population

All children (0-17 years) listed for primary HTx due to a diagnosis of DCM without congenital heart disease during the same study period were identified in the PHTS database and were analyzed separately for comparison.

2.4 | Matched cohort

A 2:1 propensity-matched DCM cohort was identified and analyzed separately to control for age at listing, sex, race (white or non-white), status at listing, and year of listing. Variables for propensity matching were chosen a priori, based on differences presented in the OPTN database review.[8]

2.5 | Data collection and definitions

Demographic and clinical variables were defined and matching was performed at the most clinically relevant time point (at listing). Demographic, wait-list, and post-HTx variables were examined and compared between the two study groups. Wait-list, short-term (1-year), and long-term (5-year) mortalities were compared between the study groups as well. The primary wait-list survival end-point was death or removal from the wait-list. The primary long-term survival end-point was death or retransplantation (graft survival). Freedom from common post-transplant morbidities, including malignancy, first treated rejection episode, first serious infection, and CAV was compared between the cohorts. As defined by the PHTS data forms, treated rejection is "any episode leading to an increased immunotherapy to treat a biopsy or clinically diagnosed episode of rejection" Serious infection is defined as "evidence of an infectious process requiring IV therapy or a life threatening infection requiring oral therapy."[13]

2.6 | Statistical analysis

Baseline characteristics were compared between groups using summary statistics (mean and standard deviation [SD], number and percentage [%]). The chi-square test was used as appropriate for categorical variables and the two-sample *t* test was used for continuous variables. Wait-list and long-term survival differences, along with freedom from common post-transplant morbidities, between the two groups were assessed via the Kaplan–Meier method and compared using the log-rank test. Univariate relationships between graft survival and several patient characteristics were assessed using the log-rank test for categorical variables and the Cox proportional hazards model for continuous variables. The Cox proportional hazards model with a step-wise selection approach was used to assess independently significant risk factors. Missing values were assigned the mean. Variables with more than 20% missing values were excluded. The analyses were performed for the entire cohort and were repeated with the matched cohort to control for differences in patient demographics. *P*-values <.05 were considered significant. SAS version 9.4 was used to perform statistical calculations. Institutional review board approval was obtained at each participating center.

3 | RESULTS

3.1 | Study population

Eighty children with ACM were listed for HTx in the PHTS database during the study period and were included in the analysis (Figure 1). A total of 1985 subjects with DCM were listed during the same period and were included for comparison. Seventy-nine subjects with ACM had matched peers identified with DCM (158 DCM subjects via 2:1 matching) and were included in the propensity-matched cohort analysis. One ACM subject had no matched peer and was excluded from that analysis.

3.2 | Demographic data

Baseline characteristics for the unmatched and matched groups are summarized in Table 1. Subjects listed for ACM were older than their unmatched DCM peers (12.3±3.8 years [range 3.0-17.9] vs 6.9±6.3 years [range 0-18.4], respectively [*P*-value<.01]), less likely to be listed status 1 (67.1% vs 83.1%, respectively [*P*-value<.01]), and less likely to require ECMO support at listing (1% vs 7%, respectively [*P*-value <.05]). Gender, race, year of listing, inotropic support at listing, VAD at listing, and presensitization (panel reactive antibodies [PRA]

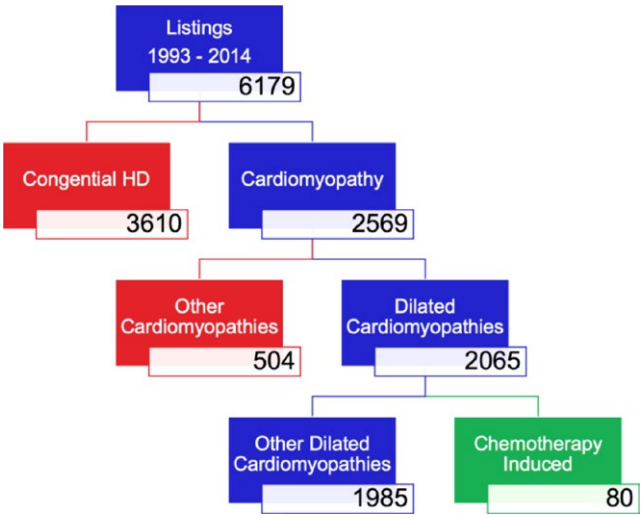

FIGURE 1 Cohort selection

>10% at listing) did not differ between the groups (all *P*-values>.05). As expected, differences in baseline characteristics were no longer seen between the matched cohorts. Data on VAD while listed and induction therapy are included in Table 2.

3.3 | Wait-list statistics and mortality

The average waiting times were 110.9±196.1 and 73.79±164.3 days for the ACM and matched DCM cohorts, respectively (*P*-value .10). Sixty-two (78%) ACM and 136 (86.1%) matched DCM subjects were transplanted during the study period (*P*-value .09). Mortality while waiting for transplant was lower in the ACM group (Figure 2A-C), although this difference was no longer seen after propensity matching (6-month wait-list mortalities of 2.6% vs. 8.0% for the ACM and matched DCM cohorts, respectively [log-rank test *P*-value .40]) (Figure 2D-F). Wait-list cause of death could not be accurately compared due to high numbers of missing data in each group.

3.4 | Post-transplant statistics and mortality

Actuarial graft survival after transplant was slightly lower in ACM cohort (Figure 3A), while this difference was no longer seen after propensity matching (1- and 5-year matched survivals of 92% and 74% vs 92% and 80%, for the ACM and matched DCM cohorts, respectively [log-rank test *P*-value .37]) (Figure 3B). The most common cause of post-transplant death was infection in the ACM cohort, which was higher than in the DCM group (30% in the ACM cohort vs 3.3% in the matched DCM cohort [*P*-value<.01]). There were no deaths due to malignancy or CAV in the ACM group, while two deaths (20%) occurred due to acute rejection.

3.5 | Freedom from post-transplant malignancy

Five post-transplant malignancies were documented in four individuals with ACM. All post-transplant malignancies in this group were

TABLE 1 A, Patient characteristics at listing for heart transplant in the unmatched cohort. B, Patient characteristics at listing for heart transplant in the 2:1 matched cohort

A			
Variable	**ACM[b] (n=80)**	**DCM[c] (n=1985)**	***P*-value[a]**
Gender—Male	40 (50%)	997 (50%)	.95
Race—White	56 (70%)	1,254 (63%)	.21
Listing Status 1	53 (67%)	1,627 (83%)	.0003
Inotrope Use	50 (63%)	1,385 (70%)	.17
PRA[d] >10%	8 (15%)	216 (16%)	.89
VAD[e] at Listing	5 (6%)	147 (7%)	.70
ECMO[f] at Listing	1 (1%)	136 (7%)	.05
Age Group			
<5 Y	3 (4%)	1,002 (50%)	<.0001
6-11 Y	24 (30%)	290 (15%)	
12-15 Y	30 (38%)	401 (20%)	
>15 Y	23 (28%)	292 (15%)	
Age (Years)	12.3±3.8	6.9±6.3	<.0001
Listing Year	2005.8±7.1	2005.9±6.1	.85
Listing Era			
1993-1999	23 (29%)	381 (19%)	.03
2000-2005	8 (10%)	385 (19%)	
2006-2010	20 (25%)	606 (31%)	
2011-2014	29 (36%)	613 (31%)	
B			
Variable	**ACM (n=79)**	**DCM (n=158)**	***P*-value**
Gender—Male	40 (51%)	76 (48%)	.71
Race—White	55 (70%)	111 (70%)	.92
Listing Status 1	53 (67%)	110 (70%)	.69
Inotrope Use	50 (63%)	89 (56%)	.30
PRA >10%	8 (16%)	10 (10%)	.28
VAD at Listing	5 (6%)	13 (8%)	.60
ECMO at Listing	1 (1%)	6 (4%)	.28
Age Group			
<5 Y	3 (4%)	16 (10%)	.15
6-11 Y	24 (30%)	32 (20%)	
12-15 Y	29 (37%)	56 (35%)	
>15 Y	23 (29%)	54 (34%)	
Age (Years)	12.3+3.9	12.3±4.7	.99
Listing Year	2005.7+7.2	2005.5±6.2	.79
Listing Era			
1993-1999	23 (29%)	32 (20%)	.13
2000-2005	8 (10%)	32 (20%)	
2006-2010	20 (25%)	46 (29%)	
2011-2014	28 (35%)	48 (30%)	

Data are presented as number and percentage (%) or median±standard deviation, as appropriate.

[a]*P*-values are based on the chi-square or two-sample *t* tests, where appropriate.

[b]anthracycline cardiomyopathy; [c]dilated cardiomyopathy; [d]panel reactive antibodies; [e]ventricular assist device; [f]extracorporeal membrane oxygenation.

TABLE 2 A, Patient characteristics at heart transplant in the unmatched cohort. B, Patient characteristics at heart transplant in the 2:1 matched cohort

A			
Variable	**ACM[b] (n=80)**	**DCM[c] (n=1985)**	***P*-value[a]**
VAD[d] while listed	13 (16%)	380 (19%)	.5
Induction therapy	32 (54%)	1033 (66%)	.06
B			
Variable	**ACM (n=79)**	**DCM (n=158)**	***P*-value**
VAD while listed	13 (16%)	34 (22%)	.4
Induction therapy	31 (53%)	85 (64%)	.2

Data are presented as number and percentage (%).
[a]*P*-values are based on the chi-square or two-sample *t* tests, where appropriate.
[b]anthracycline cardiomyopathy; [c]dilated cardiomyopathy; [d]ventricular assist device.

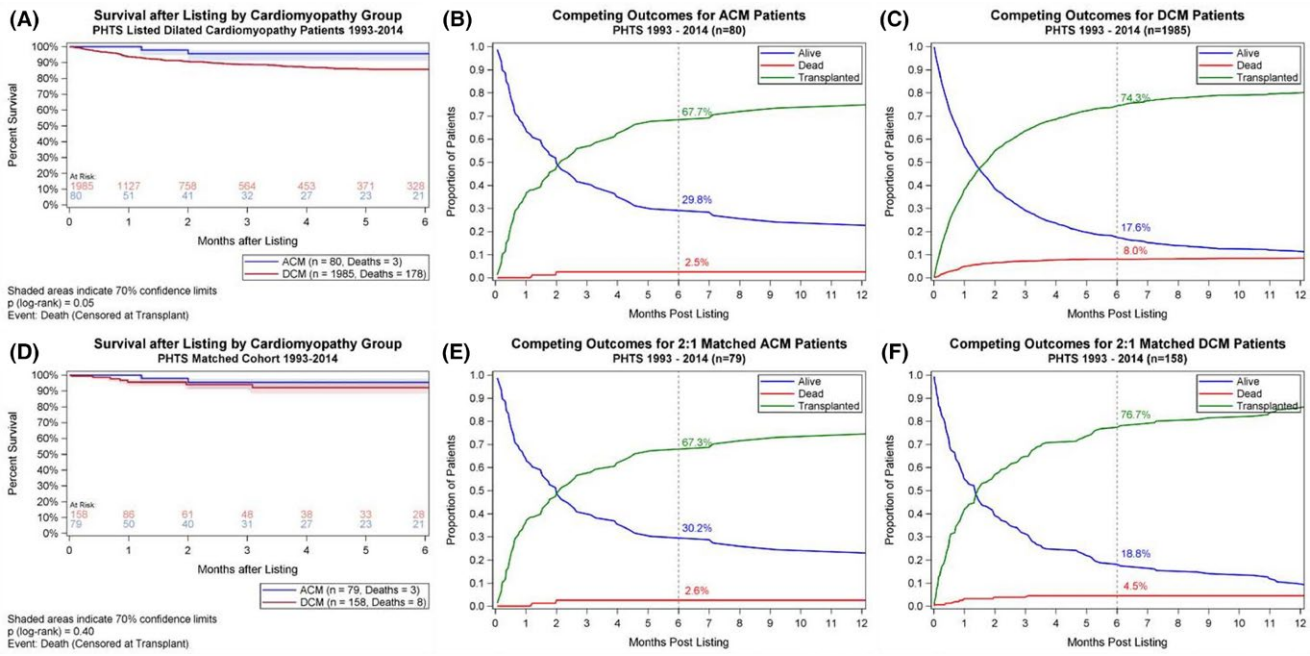

FIGURE 2 Actuarial wait-list survival and competing outcomes for the unmatched (A-C) and matched (D-F) cohorts, respectively

lymphoproliferative in nature (PTLD), without recurrence of pre-transplant malignancy or other SMN. One individual developed PTLD twice. There was no difference in actuarial freedom from malignancy between the cohorts (5-year freedom from malignancy of 93% vs 96 in the ACM and matched DCM groups, respectively [matched log-rank test *P*-value .53]) (Figure 4A).

3.6 | Freedom from other post-transplant morbidities

Freedom from first serious infection was lower in the ACM group vs the propensity-matched controls (*P*-value .05) (Figure 4B). Freedom from CAV (*P*-value .11) (Figure 4C) and freedom from first treated rejection (*P*-value .39) (Figure 4D) did not differ between cohorts.

3.7 | Risk factors for post-transplant mortality

In the multivariate analysis, diagnosis, age at listing, gender, VAD at listing, listing status, and era of listing were included in the model. Only those surviving to transplant were included in this analysis (unmatched n=1651, 62 ACM+1589 unmatched DCM; matched n=197, 61 ACM+136 matched DCM). A diagnosis of ACM was not an independently significant predictor of post-transplant survival in the entire cohort (ACM and entire DCM cohort) (hazard ratio [HR] 1.47, 95% confidence limits [CL] 0.88, 2.43, *P*-value .14). In the matched group (ACM and matched DCM cohort), earlier listing era, VAD at listing, and female gender independently predicted worse survival, while diagnosis, age at listing, race, and listing status did not affect survival (Table 3).

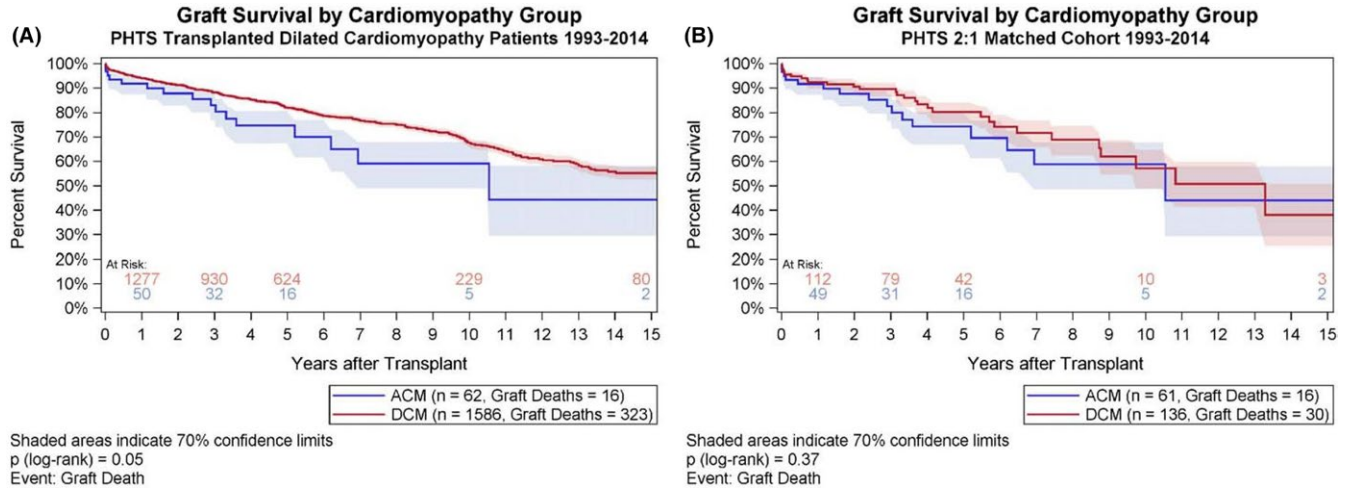

FIGURE 3 Actuarial post-transplant graft survival for the unmatched (A) and matched (B) cohorts, respectively. Conditional on survival to transplant

4 | DISCUSSION

We present the most comprehensive review to date of mortality and cancer recurrence in pediatric patients transplanted for ACM based on a large multicenter pediatric heart transplant registry. This study was aimed at confirming whether long-term survival in these subjects was indeed worse than subjects transplanted for other forms of DCM, as recently reported by an OPTN database review, which did not account for baseline differences in the two populations. The more complete dataset in the PHTS registry allowed us to perform propensity matching for several patient characteristics.[8] Additionally, we sought to determine whether primary cancer recurrence or de novo SMN could account for differences in mortality.

Baseline patient characteristics for both the unmatched ACM and DCM groups were similar to those previously reported.[6–8] Our unmatched analysis confirms the OPTN database findings of higher wait-list and lower long-term survival of ACM subjects vs DCM subjects. However, as the ACM patients were older and more likely to have been transplanted in an earlier era, we performed a propensity match to determine whether these differences were actually due to ACM. After correcting for listing age, listing urgency, era at listing, gender, and race, these differences do not persist. Multivariable analysis confirmed earlier transplant era, VAD at listing, and gender, not etiology of cardiomyopathy, as factors predicting worse post-transplant survival in the matched cohort. Importantly, recurrence of primary cancer and death from malignancy were not seen in any patient in the ACM cohort.

Overall post-transplant malignancy occurrence was not different between cohorts in our study. Additionally, all malignancies were lymphoproliferative disorders, which differ somewhat from the findings of Ward[6] and Levitt.[7] Ward's (2004) US multicenter review of 17 children transplanted for ACM found one primary cancer recurrence of Ewing sarcoma at 15 months after HTx. No PTLD was observed in that cohort. Levitt's (2009) UK registry review of 36 pediatric HTx recipients reported relapses of AML at 2 months and 4 years post-transplant, with one occurrence of PLTD. No malignancy-related post-transplant deaths have been reported in the pediatric HTx population to date. This correlates with Lenneman's[10] finding in his 2013 OPTN database review of all individuals transplanted for ACM, regardless of age. They found no difference in death from cancer between the ACM cohort and those transplanted for other types of cardiomyopathy, although they do not comment on cancer recurrence in survivors.

Interestingly, there was an increased incidence of serious infection in the matched ACM cohort, and mortality from serious infection was higher in this group. No other pediatric HTx studies comment on infection rates or mortality from infection in this population. Exposure to chemotherapy prior to solid organ transplant may have profound long-term effects on immune function.[14] These changes may impact the immune response to various pathogens while receiving immunosuppressive therapy after transplantation, leading to an increased incidence of serious infection, including those from vaccine-preventable diseases.[15] Additional factors, such as induction therapy, may contribute to susceptibility to infection, although no difference in rates of induction therapy was seen between the ACM and DCM groups in the matched cohort (*P*-value .2) (Table 2). Our findings suggest that further studies are needed to more fully evaluate immune function and the effects of immunosuppressive therapy after HTx in patients with prior chemotherapy exposure. Clinical information including underlying oncologic diagnosis, timing of prior chemotherapy exposure related to transplant, intensity and duration of prior chemotherapy exposure, history of allogeneic bone marrow transplant, splenectomy, or radiation therapy may strongly influence immune reconstitution and therefore influence risk of infection following solid organ transplantation; however, these data were not captured in the PHTS database. Increased infection surveillance, changes to post-transplant maintenance immunotherapy, and/or antibiotic prophylaxis may be needed for some subjects with ACM due to this increased risk.

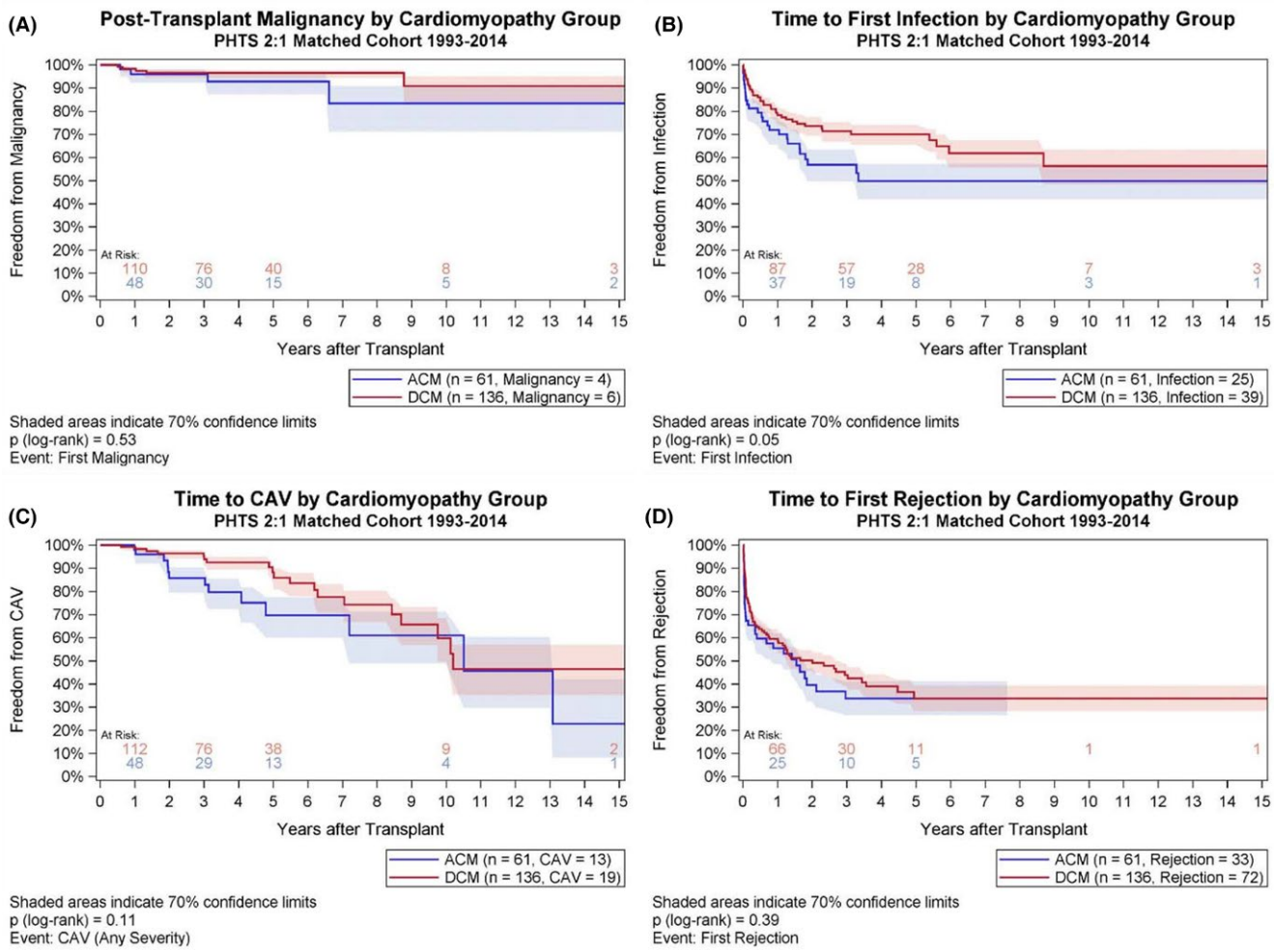

FIGURE 4 Actuarial freedoms from post-transplant malignancy (A), serious infection (B), cardiac allograft vasculopathy (CAV) (C), and first treated rejection episode (D) in the matched cohort. Conditional on survival to transplant

TABLE 3 Multivariate analysis of matched cohort (ACM[b]+matched DCM[c])

Variable	Hazard Ratio	95% CL[d]	*P*-value[a]
Diagnosis of ACM	1.51	0.80, 2.88	.21
Older age at listing	1.08	0.99, 1.18	.09
Female gender	1.88	1.01, 3.53	.05
VAD[e] at listing	3.59	1.14, 11.26	.03
Status 1 at listing	0.61	0.32, 1.16	.13
Earlier era of listing	1.83	1.29, 2.59	<.0001

[a]*P*-values are based on the Cox proportional hazards model with a stepwise selection approach.
[b]anthracycline cardiomyopathy; [c]dilated cardiomyopathy; [d]95% hazard ratio confidence limits; eventricular assist device.
n=197+; Events=52; +—conditional on survival to transplant.

4.1 | Limitations

This study has the limitations encountered with most retrospective database analyses. The reliability and completeness of entries is dependent upon the contributing institution. Several criteria important in this analysis were not available in the database, including age at malignancy diagnosis, time from chemotherapy completion to listing, cumulative anthracycline dose, and radiation treatment. Matching and analyses based on variables obtained at listing were performed to allow for comparison of wait-list and post-transplant outcomes and was the most clinically relevant time point. Matching and analyses performed based on clinical variables obtained after listing (VAD, induction therapy, maintenance immunosuppression) may have resulted in differing post-transplant outcomes than those reported here. Despite the "significant" *P*-values, small cohort size and few events (ie, death from infection) in the matched cohort create challenges in drawing inferences from this analysis. However, given the multi-institutional nature and long time span of the study, this sample size is as large as one could reasonably expect.

5 | CONCLUSIONS

Long-term graft survival after pediatric HTx for ACM is no different than for matched peers with DCM, nor is there an increased risk of

primary cancer recurrence, SMN, or PTLD. However, the risk of infection and death from infection after HTx is higher in the ACM group. Further studies are needed to assess the effects of prior chemotherapy on susceptibility to infection in this group.

ACKNOWLEDGMENTS AND DISCLOSURE STATEMENT

We would like to thank the centers participating in the Pediatric Heart Transplant Study (Appendix 1). None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented article or other conflict of interest to disclose.

AUTHORS' CONTRIBUTIONS

Matthew J. Bock: Took part in research design, interpretation of data, drafting of manuscript, and approval of the submitted and final versions; and Elfriede Pahl, Paolo G. Rusconi, Gerard J. Boyle, John J. Parent, Clare J. Twist, James K. Kirklin, Elizabeth Pruitt and Daniel Bernstein: Participated in research design, interpretation of data, critically revising paper, approval of the submitted and final versions.

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How to cite this article: Bock MJ, Pahl E, Rusconi PG, et al. Cancer recurrence and mortality after pediatric heart transplantation for anthracycline cardiomyopathy: A report from the Pediatric Heart Transplant Study (PHTS) group. *Pediatr Transplant*. 2017;21:e12923. https://doi.org/10.1111/petr.12923

APPENDIX 1

Participating Centers for the Matched Analysis

Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois.
Arkansas Children's Hospital, Little Rock, Arkansas.
Boston Children's Hospital, Boston, Massachusetts.
Children's Healthcare of Atlanta, Atlanta, Georgia.
Children's Hospital Colorado Heart Institute, Denver, Colorado.
Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania.
Children's Hospital of Wisconsin, Milwaukee, Wisconsin.
Children's National Medical Center, Washington DC.
Children's of Alabama, Birmingham, Alabama.
Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio.
Cleveland Clinic Children's, Cleveland, Ohio.
Columbia University-Morgan Stanley Children's Hospital of New York Presbyterian, New York, NY.
Duke Children's Hospital, Durham, North Carolina.
Great Ormond Street Hospital for Children, London, United Kingdom.
Joe DiMaggio Children's Hospital, Hollywood, Florida.
Johns Hopkins All Children's Heart Institute, St. Petersburg, Florida.
Johns Hopkins Hospital, Baltimore, Maryland.
Loma Linda University Medical Center, Loma Linda, California.
Lucile Packard Children's Hospital at Stanford, Stanford, California.
Medical University of South Carolina, Charleston, South Carolina.
Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, Tennessee.
Nationwide Children's Hospital, Columbus, Ohio.
Phoenix Children's Hospital, Phoenix, Arizona.
Primary Children's Hospital, Salt Lake City, Utah.
Riley Hospital for Children, Indianapolis, Indiana.
Seattle Children's, Seattle, Washington.
St. Louis Children's Hospital, St. Louis, Missouri.
Texas Children's Hospital, Houston, Texas.
The Children's Hospital at Montefiore, New York, New York.
The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania.
University of Alberta, Edmonton, Canada.

University of Florida, Shands Hospital, Gainesville, Florida.
University of Iowa Children's Hospital, Iowa City, Iowa.
University of Miami, Jackson Memorial Hospital, Miami, Florida.
University of Michigan, CS Mott Children's Hospital, Ann Arbor, Michigan.
University of Minnesota, Amplatz Children's Hospital, Minneapolis, Minnesota.
University of North Carolina, Chapel Hill, North Carolina.
University of Texas, Children's Medical Center, Dallas, Texas.