

Association of Left Ventricular Dilation at Listing for Heart Transplant With Postlisting and Early Posttransplant Mortality in Children With Dilated Cardiomyopathy

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Background—In patients with dilated cardiomyopathy, the magnitude of cardiac remodeling often correlates with the clinical severity of heart failure. We sought to determine whether measures of left ventricular (LV) dilation and systolic dysfunction in children with dilated cardiomyopathy at the time of listing for cardiac transplantation are associated with survival while waiting for and early after transplant.

Methods and Results—We analyzed echocardiographic data obtained within 6 months of listing for heart transplant and clinical data from 261 children with dilated cardiomyopathy who were included in both the Pediatric Cardiomyopathy Registry and the Pediatric Heart Transplant Study. Median time to listing after diagnosis was 1.9 months and to transplant after listing was 0.8 months. There were 42 deaths (29 waiting and 13 within 6 months after transplant). We found a significant age-dependent association of LV end-diastolic dimension z score ($n=204$, 31 deaths) with death controlling for race, transplant status, and medical insurance. The association was strongest for infants younger than 6 months at diagnosis (hazard ratio 1.47, $P=0.008$) and was not significant in children older than 5 years at diagnosis. A similar interaction was identified between age and LV end-systolic dimension z score ($P=0.04$). Neither LV function nor mass was associated with death, overall, or in subgroups.

Conclusions—The severity of LV dilation at listing for heart transplant is associated with outcome in infants and young children with dilated cardiomyopathy, whereas the severity of LV systolic dysfunction is not. These findings should be considered in risk stratification of these children at listing. (*Circ Heart Fail.* 2009;2:591-598.)

Key Words: pediatrics ■ cardiomyopathy ■ echocardiography ■ transplantation ■ heart failure

After the initial myocardial injury that results in ischemic or dilated cardiomyopathy (DCM), the subsequent myocardial changes at the genomic, molecular, cellular, and interstitial levels are referred to as cardiac remodeling.¹⁻⁵ In DCM, remodeling manifests as progressive dilation of the left ventricle (LV) that becomes more spherical and hypertrophied with time. Among adults with ischemic or DCM, those with lower LV ejection fraction or more severe LV dilation are at higher risk for clinical events and mortality.⁶⁻¹⁰ Previous studies in children with DCM have also reported that those with more severe LV systolic dysfunction (lower fractional shortening) at diagnosis were at higher risk of death or heart transplant.¹¹⁻¹³ Because only a subset of all children with DCM are listed for cardiac transplant, whether the severity of LV dilation or systolic dysfunction in children with DCM listed for transplant is associated with their

outcome after listing is a critical issue. The merger of the Pediatric Cardiomyopathy Registry (PCMR)¹⁴ and the Pediatric Heart Transplant Study (PHTS)¹⁵ databases (described in Methods section) allowed us to evaluate this association.

Clinical Perspective on p 598

The purpose of this analysis was to determine whether measures of LV dilation and systolic dysfunction in children with DCM at the time of listing for heart transplant are associated with an adverse outcome while waiting for, or early after, transplant. We hypothesized that children with DCM with the most severe LV dilation and systolic dysfunction at transplant listing will have more severe or more rapidly progressive heart failure, resulting in higher mortality risk while awaiting heart transplant. Furthermore, these children will also have a higher risk of early posttransplant

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mortality due to increased risk of early graft failure or posttransplant multiorgan failure (due to marginal end-organ function at time of transplant).¹⁶ To test these hypotheses, we created a merged dataset from the PCMR and the PHTS to examine the association of LV dilation and systolic dysfunction at the time of listing for heart transplant with mortality in the listing or early posttransplant period. We defined early posttransplant mortality as deaths within 6 months after transplant to capture all posttransplant deaths that could be related to pretransplant recipient factors.

Methods

Patients

The PCMR has been sponsored by the National Heart, Lung, and Blood Institute since 1994. Two cohorts of children (younger than 18 years of age at diagnosis) were established: (1) a population-based, prospective cohort of children diagnosed after January 1, 1996, by pediatric cardiologists at 98 pediatric cardiac centers in 2 geographically distinct regions of the United States (New England and the Central Southwest) that was used to estimate the incidence of pediatric cardiomyopathy, and (2) a retrospective cohort of children, seen primarily at 39 tertiary care centers in North America, who were diagnosed between January 1, 1990, and December 31, 1995, and identified by chart review that was used to characterize the national experience with pediatric cardiomyopathy.¹⁴ Exclusion criteria included the presence of congenital heart defects, endocrine disorders, or immunologic diseases known to cause heart muscle disease, treatment with doxorubicin, and inflammation caused by HIV infection (or birth to an HIV-positive mother) or by Kawasaki disease. Annual chart review for both PCMR groups has continued until their last follow-up or on reaching study end-points which are death or heart transplant.

The PHTS is an event-driven multi-institutional database established in January 1993 that collects morbidity and mortality data for all children listed for heart transplantation at participating institutions.¹⁵ Combining data for children included in both the PCMR and the PHTS thus allows longitudinal follow-up of these patients starting with their diagnosis, continuing through their listing and transplant to long-term posttransplant follow-up. All participating PCMR and PHTS centers obtained Institutional Review Board approval for the studies and for merging the databases.

We identified 261 children from 16 pediatric cardiology centers with pure DCM who were listed for transplant at these centers during 1993 to 2004 and whose records were included in both databases (see Appendix for merger sites). Follow-up for the merged database is through December 31, 2005. These patients formed the analytic cohort for this report. We excluded children with mixed functional DCM, including a combination of DCM with hypertrophic, restrictive, or arrhythmogenic cardiomyopathy.

Echocardiographic Measurements

The participating institutions used 2-dimensional echocardiography to obtain LV end-diastolic dimension (LVEDD), LV end-systolic dimension (LVESD), LV posterior wall thickness, and septal thickness. Left ventricular mass was calculated from LVEDD and both wall thickness measures. These measurements were expressed as *z* scores adjusted for body surface area as compared with a normal US pediatric population.^{17,18} Left ventricular fractional shortening, a measure of LV systolic performance, was defined as the ratio of the difference between LVEDD and LVESD to the LVEDD, expressed as a percentage and then as a *z* score adjusted for age. LV volumes and ejection fraction were not part of the original data collection protocol, and because of their small sample size they were not included in this analysis. Right ventricular structure and function data were not systematically collected and likewise are not included in the analysis.

Echocardiographic measurements closest to the time of listing for transplant were used in this analysis, with an allowable window of 6

months before or after listing; all measurements used were obtained before transplant. Echocardiographic measurements were obtained within (\pm) 3 months of listing in 90% of children for whom data were available. The median (interquartile range, 25th to 75th percentile) interval between the echocardiographic study and listing for heart transplant was 11 (3 to 47) days for LVEDD, 11 (4 to 53) days for LVESD, and 11.5 (4 to 45.5) days for fractional shortening.

Statistical Methods

The outcome measure was a composite of all-cause mortality while awaiting heart transplant or within 6 months after heart transplant. The distribution of time to death was estimated using the Kaplan-Meier method, with censoring at 6 months after transplant. We used a multivariate Cox proportional hazards model to assess the relationship between echocardiographic variables and mortality. The multivariate model was constructed by evaluating all variables that had a univariate $P < 0.2$. We included type of medical insurance and race in all models as adjustment factors (regardless of statistical significance in this particular dataset) because of their association with outcomes in previous studies.^{19–21} Age at diagnosis of DCM was also evaluated as a predictor.¹² A time-dependent transplant status indicator was incorporated in the model to allow for the altered hazard of death associated with transplant. Interaction terms between echocardiographic *z* scores and age at diagnosis and transplant status were also explored. All tests were 2 sided. The data were analyzed using statistical software SAS version 9.1 (SAS Institute Inc, Cary, NC).

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Study Cohort

The study population consisted of 261 children with DCM listed for transplant in the combined PCMR-PHTS database. Median age at the time of diagnosis of DCM was 2.5 years and 51% were boys. There were 59% white, 22% black, 11% hispanic, and 8% other children. The cause of DCM was idiopathic in 76%, myocarditis in 12%, familial isolated cardiomyopathy in 7%, neuromuscular disorder in 3%, metabolic in 1%, and present in conjunction with a recognized malformation syndrome in 1%. A family history of cardiomyopathy was present in 26% and of sudden cardiac death in 13%.

The median age at listing was 3.7 years and at the time of transplant 5.4 years. The median (interquartile range) time to listing after DCM diagnosis was 1.9 months (0.24 to 7.7 months). Eighty percent of the listed children ($n=208$) underwent heart transplant at a median (interquartile range) time of 0.8 months (0.4 to 2.0 months) after listing. The median time to listing after DCM diagnosis was significantly longer for nonwhite than for white children (3.2 versus 1.0 months, $P=0.03$).

Clinical and Echocardiographic Data

At the time of listing for transplant, 92% of the 261 children were hospitalized, 71% were receiving intravenous inotropes, 30% were on assisted ventilation, 9% were on extracorporeal membrane oxygenation, and 4% (11 children) were supported with a ventricular assist device.

Two-dimensional echocardiographic data within 6 months before or after listing (157 before listing, 47 after listing but before transplant) were available for LVEDD in 204 patients (z score= 5.78 ± 2.40 SD), for LVESD in 196 patients (z score= 7.61 ± 2.41 SD) and for LV fractional shortening in

Table 1. Causes of Death in the Overall Study Cohort

Cause of Death	No. of Deaths
Deaths on the waiting list	29
Multiorgan failure	14
Congestive heart failure	7
Cause of death missing	8
Posttransplant deaths	13
Cardiac arrest in the OR	2
Early graft failure with multiorgan failure	5
Sudden death	3
Acute rejection	2
Pneumonia/sepsis	1

216 patients (median z score = -10.07 SD). The z scores for LVEDD and LVESD were highly correlated ($r=0.91$, $P<0.001$). At listing, the mean (\pm SD) LVEDD z score was significantly larger in nonwhite children (6.4 ± 2.5 versus 5.4 ± 2.3 , $P=0.004$) as was that for LVESD (8.2 ± 2.4 versus 7.2 ± 2.4 , $P=0.003$); LV fractional shortening, however, did not significantly differ between these 2 groups.

Medical Insurance

Of the 261 children, 50% had private insurance, 25% had public insurance (Medicaid), 21% were insured but the type of insurance was unknown, and 4% were uninsured. For these groups, the median time to listing after DCM diagnosis was 1.0, 4.0, 2.4, and 2.9 months, respectively. White children were significantly more likely to have private insurance (59% versus 37% of nonwhite children, $P<0.001$).

Outcomes After Listing

There were 42 deaths in the entire cohort: 29 during the listing period and 13 within 6 months after transplant (Table 1). Of the 29 children who died awaiting heart transplant, 21 children died during their inpatient stay. Of the 13 posttransplant deaths, 11 were early deaths in the hospital. Of these, 2 were patients who had a cardiac arrest minutes before being placed on cardiopulmonary bypass for heart transplant, were resuscitated, and underwent heart transplant but had irreversible neurological injury.

There were 31 deaths among the 204 children with LVEDD data. Patient characteristics at the time of cardiomyopathy diagnosis and listing in those who survived and those who died among children with LVEDD data are compared in Table 2. In univariate analyses, no demographic characteristics or echocardiographic parameters at the time of listing were associated with vital status in the overall cohort ($n=204$). However, among subjects who were listed for transplant at less than 6 months of age, mean LVEDD z score was 8.0 ± 2.3 versus 6.0 ± 2.8 for those who died and those who survived, respectively.

Multivariate Model for Postlisting Mortality

The multivariate model for postlisting mortality (mortality while listed or within 6 months posttransplant) included 4 factors (Table 3): race (not significant), type of medical insurance ($P=0.03$), transplant status ($P<0.001$), and an

interaction between age at cardiomyopathy diagnosis and LVEDD z score at the time of listing ($P=0.05$). Both private insurance and heart transplantation were protective against postlisting mortality. Other echocardiographic variables (see Methods) were not significant when added to this model.

The association of LVEDD z score with mortality decreased linearly with age at diagnosis of DCM. For children diagnosed with DCM at age 3 months, every unit increase in LVEDD z score was associated with a 41% higher risk of death (hazard ratio, 1.41; 95% CI 1.12 to 1.79, $P=0.004$). For children diagnosed at age 1 year, every unit increase in LVEDD z score was associated with a 38% higher risk of death (hazard ratio, 1.38; 95% CI 1.11 to 1.71, $P=0.004$) and for those diagnosed at age 5 years, every unit increase in LVEDD z score was associated with a 19% increase in risk of death (hazard ratio, 1.19; 95% CI 1.00 to 1.42, $P=0.048$). In children aged 10 years or older, the association between LVEDD z score and mortality was not statistically significant (hazard ratio at 10 years = 1.0, 95% CI 0.77 to 1.29, $P=0.99$). Of note, we found no significant interaction between transplant status and LVEDD z score, indicating that for outcomes up to 6 months after transplant, the association between LVEDD z score and mortality was present whether or not transplantation occurred.

To assess the association of age and LVEDD on mortality without assuming linearity, we also fitted the final multivariate model with age at DCM diagnosis treated as a categorical variable based on tertiles. The interaction of age with LVEDD z score at listing was again noted ($P=0.02$; Table 4). In children diagnosed with cardiomyopathy before the age of 6 months, the adjusted hazard ratio was 1.47 (95% CI 1.11 to 1.95, $P=0.008$), but LVEDD z score was not a risk factor for death in older age groups. For illustrative purposes, we dichotomized LVEDD z score at the median score of 5.8. Among children with DCM diagnosed before 6 months of age, postlisting survival was significantly better among those with a LVEDD z score below 5.8 than in those with a z score ≥ 5.8 (5% versus 19% mortality at 6 months postlisting; Figure 1). This association between LVEDD and postlisting mortality was not present in children diagnosed at older ages (Figure 2).

Additional Analyses

We compared children with ($n=204$) and without LVEDD data ($n=57$) for the distribution of their demographic and clinical variables and found these to be similar. To determine whether the association between LV dilation and mortality was mediated by a higher level of hemodynamic support at listing, we compared mean LVEDD z scores for children with and without various medical support measures. The mean LVEDD z score for children on IV inotropes at listing did not differ from those who were not receiving inotropes. Similarly, mean LVEDD z scores did not differ between children who were or were not supported by LV assist device, extracorporeal membrane oxygenation, or mechanical ventilation at listing.

We also confirmed that the age-dependent nature of the LVEDD z -score association with mortality was not a result of differential timing of the echocardiographic study by age: the

Table 2. Clinical Characteristics of 204 Patients With Pure DCM Listed for Heart Transplant by Vital Status

Variable	All (N=204)	Alive (n=173)	Dead* (n=31)	P**
Median (IQR) age at diagnosis, y	3.2 (0.3, 12.5)	1.6 (0.3, 12.2)	6.3 (0.4, 13.2)	0.398
Age <1 y at diagnosis, %	43.1	44.5	35.5	0.432
Age at diagnosis, category, %				
<6 mo	33.8	34.1	32.3	0.444
6 mo to <10 y	30.4	31.8	22.6	
≥10 y to ≤18 y	35.8	34.1	45.2	
Median (IQR) age at listing, y	4.5 (0.7, 12.8)	3.1 (0.6, 12.6)	7.6 (1.3, 13.2)	0.196
Median (IQR) time to listing postdiagnosis, mo	1.74 (0.28, 6.54)	1.35 (0.26, 6.01)	2.40 (0.39, 7.89)	0.421
Median (IQR) duration between echo and listing, mo	0.16 (0, 0.62)	0.16 (0, 0.69)	0.10 (0, 0.49)	
Male, %	49.5	49.1	51.6	0.847
Race, %				
White	61.4	65.1	41.9	0.038
Black	20.3	19.3	25.8	
Hispanic	12.7	11.5	19.4	
Other/unknown	5.6	4.2	12.9	
Retrospective cohort, %	27.9	27.2	32.3	0.664
CHF at diagnosis, %	87.2	85.5	96.8	0.139
Echo z scores closest to listing				
EDD	5.78±2.40	5.73±2.39	6.04±2.47	0.510
ESD (N=196/166/30)	7.61±2.41	7.59±2.40	7.71±2.49	0.795
Median fractional shortening (N=200/169/31)	-9.94	-9.91	-10.03	0.853
Median posterior wall thickness (N=147/125/22)	-0.85	-0.86	-0.68	0.914
Median mass (N=147/125/22)	2.88	2.92	2.59	0.549
Median posterior wall thickness to EDD ratio (N=147/125/22)	0.10	0.10	0.10	0.987
Cardiac transplant	157	150	7	
Median (IQR) age at transplant, y	6.5 (1.0, 13.3)	6.4 (1.0, 13.5)	7.8 (1.3, 13.2)	0.792
Median (IQR) time to transplant post-diagnosis, mo	4.67 (1.71, 10.97)	4.63 (1.61, 10.48)	8.31 (2.46, 16.65)	0.354
Median (IQR) time to transplant post-listing, mo	0.95 (0.43, 2.30)	0.94 (0.43, 2.30)	1.18 (0.49, 2.46)	0.721

Mean±SD or percentage unless otherwise noted.

IQR indicates interquartile range; CHF, congestive heart failure.

*Death while waiting or within 6 mo of heart transplant.

**P value from exact test for categorical variables, *t* test for continuous non-skewed variables where mean is shown, and Wilcoxon rank sum test where median is shown.

median interval between the echocardiographic study and listing was 9 days for infants, 11 days for children between the age of 1 and 9 years and 7 days for children 10 years and older ($P=0.91$).

Age at diagnosis was highly correlated with age at listing ($r=0.98$). When age at diagnosis was replaced by age at listing in the model, the results were similar to those described in Tables 3 and 4 (see online-only Data Supplement for Tables 5 and 6). When LVEDD *z* score was replaced by LVESD *z* score, a similar interaction with age was noted ($P=0.04$), but LVESD was not independently significant. Additional analyses replacing LVEDD with LV fractional shortening or LV mass suggested possible interaction with age ($P=0.13$ and 0.11 , respectively).

Discussion

In this study, we found a significant independent association between the degree of LV dilation (expressed as a *z* score)

close to listing for transplant and the risk of death while waiting or up to 6 months after transplant. This association was strongest in children diagnosed with DCM in early infancy (less than 6 months old) and decreased, but was still statistically significant with increasing age at DCM diagnosis. LVEDD *z* score was not a significant correlate of mortality among children who were older than 5 years of age at DCM diagnosis. Adding a measure of LV systolic dysfunction (fractional shortening *z* score) in the presence of LVEDD *z* score did not improve the predictive ability of the model. We estimate from these data that for infants less than 6 months of age, every 1 cm increase in LVEDD at the time of listing for transplant (a mean *z* score difference of 4.55 SD for that age group) is associated with a 5.8 times higher risk of death while waiting or within 6 months after transplant compared with an infant with an otherwise similar risk profile. The clinical utility of these findings is further illustrated by a nearly 4-fold (19% versus 5%) 6-month postlisting mortality

Table 3. Predictors of Mortality Waiting or Up to 6 mo After Heart Transplant in 204 Children With Age as a Continuous Variable in a Multivariate Model controlling for Race and Medical Insurance

Predictor	Hazard Ratio	95% CI	P
Nonwhite	1.53	(0.70, 3.33)	0.285
Transplant	0.04	(0.02, 0.11)	<0.001
Age at cardiomyopathy diagnosis×LVEDD z score interaction			0.047
LVEDD z score (age 3 mo*)	1.41	(1.12, 1.79)	0.004
LVEDD z score (age 1 y*)	1.38	(1.11, 1.71)	0.004
LVEDD z score (age 5 y*)	1.19	(1.00, 1.42)	0.048
LVEDD z score (age 10 y*)	1.00	(0.77, 1.29)	0.989
Medical insurance			0.027
Medicaid vs private	2.38	(0.91, 6.2)	0.077
None vs private	6.08	(1.14, 32.5)	0.035
Insured (unknown type) vs private	3.61	(1.42, 9.2)	0.007

LVEDD z indicates left ventricular end-diastolic dimension z score obtained within 6 mo before or after listing for transplant.

*Hazard ratios at selected ages are shown to illustrate differential risk associated with EDD z score by age.

for those with a z score above median versus those with a z score below median in this age group (Figure 1). Because children with more severe LV dilation did not seem to be on a higher level of hemodynamic support at listing, these findings suggest that among infants and young children with DCM, those with more severe LV dilation at listing had a more rapid progression to end-organ dysfunction than those with less severe LV dilation.

These findings are novel for pediatric patients with DCM with advanced heart failure and should be considered in

Table 4. Predictors of Mortality Waiting or Up to 6 mo After Heart Transplant in 204 children With Age as a Categorical Variable in a Multivariate Model Controlling for Race and Insurance Status

Predictor	Hazard Ratio	95% CI	P
Nonwhite	1.35	(0.61, 3.30)	0.463
Transplant	0.04	(0.02, 0.11)	<0.001
Age at cardiomyopathy diagnosis×LVEDD z score interaction			0.02
LVEDD z score (age <6 mo*)	1.47	(1.11, 1.95)	0.008
LVEDD z score (age 6 mo to <10 y*)	1.14	(0.87, 1.48)	0.353
LVEDD z score (age >10 y*)	0.64	(0.37, 1.08)	0.095
Medical insurance			0.015
Medicaid vs private	2.55	(0.96, 3.01)	0.061
None vs private	8.31	(1.52, 45.4)	0.015
Insured (unknown type) vs private	4.20	(1.58, 11.2)	0.004

LVEDD z left ventricular end-diastolic dimension z score, obtained ±6 mo of listing for transplant.

*Hazard ratios in selected age groups are shown to illustrate differential risk associated with EDD z score by age.

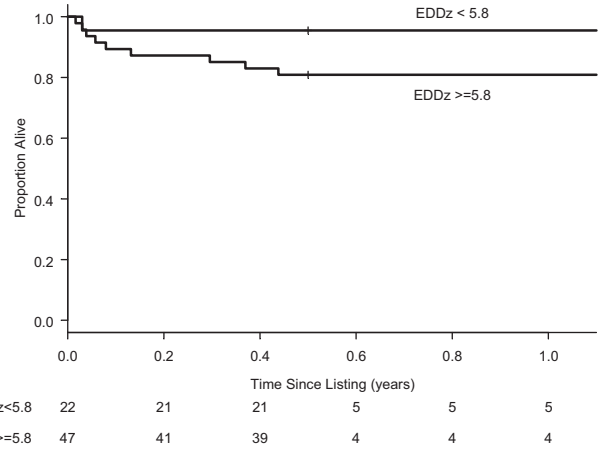


Figure 1. Survival of children diagnosed with DCM before age 6 months, comparing those with left ventricular end-diastolic dimension z score (EDDz) at diagnosis of DCM below the median z score of 5.8 to those with z scores at or above the median (P=0.008). Curves are truncated at 1 year. Mortality by 6-months postlisting was 19% in those with z scores above and 5% in those with z scores below the median.

schemata used to risk stratify these children at listing for transplant. A previous report from the PCMR that described risk factors for outcomes in all children with DCM demonstrated an association of lower LV fractional shortening z score at DCM diagnosis with increased risk of death or transplant on follow-up.¹² Similar reports from Australia and the United Kingdom in children with DCM have also described lower initial fractional shortening at presentation and failure to increase fractional shortening during follow-up to be associated with higher risk of death or transplant.^{11,22} However, these reports attempted to risk stratify the entire pediatric DCM population at diagnosis and thus did not focus on children listed for transplant who were in advanced heart failure. Because only 30% to 35% of children with DCM in these cohorts were in advanced heart failure and died or underwent transplant within 1 year after diagnosis, the heterogeneity in fractional shortening values in these cohorts

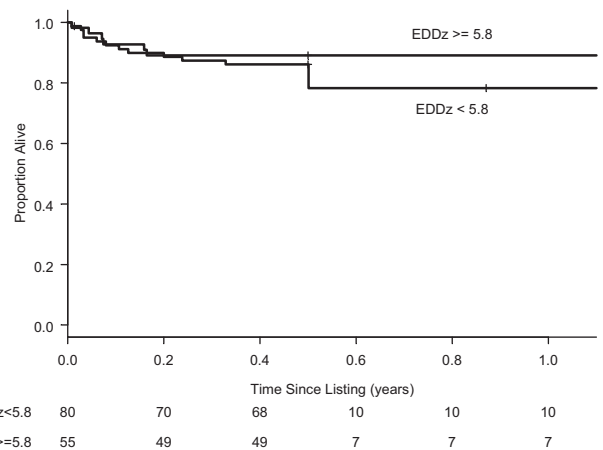


Figure 2. Survival of children diagnosed with DCM at age 6 months or older, comparing those with left ventricular end-diastolic dimension z score (EDDz) at diagnosis of DCM below the median z score of 5.8 to those with z scores at or above the median (P=NS). Curves are truncated at 1 year.

was large enough to demonstrate the association of low values with worse outcomes. In children with severe LV dilation and advanced heart failure, fractional shortening values are clustered in a narrow range at the lower end, making fractional shortening a less useful predictor of differences in clinical course in those listed for heart transplant. In addition, the small differences in end-diastolic and end-systolic dimensions that are seen in these children augment the relative magnitude of error in the fractional shortening calculation secondary to any measurement error in the dimension data.

The prognostic value of LV remodeling has been more extensively studied in large controlled trials of adults with heart failure secondary to dilated or ischemic cardiomyopathy.^{6–9,23} Among 382 adults with advanced heart failure referred for transplant evaluation, Lee et al²⁴ reported significantly lower survival in those with an indexed LVEDD greater than 4 cm/m². The association of LV remodeling with survival is also indirectly supported by data showing that therapies that improve survival in adults with heart failure (angiotensin-converting enzyme inhibitors, β -blockers, and aldosterone antagonists) also stop, reduce, or reverse the remodeling process.^{25–29}

These findings have important clinical implications. Advances in the care of heart transplant recipients during the past 15 years have greatly improved outcomes; the current 1-year posttransplant survival rate in children approaches 90%.³⁰ However, because donor hearts remain scarce, heart transplant should be offered only to those patients in whom it offers a clinically important survival advantage over survival with medical management. Risk factors that predict 1-year survival in adults with advanced heart failure have been used to determine the optimum timing for heart transplant listing in adults for almost 2 decades.^{31–35} Current guidelines for heart transplant listing in children are based mostly on expert consensus rather than on evidence-based, clearly defined risk factors for mortality on contemporary heart failure management in children.³⁶ Our analysis identifies LV dilation (LVEDD *z* score) at listing as one of the potential predictors of outcome in the youngest children (infants) with heart failure, the age group with the highest wait-list mortality of all patients waiting for heart transplant.³⁷ Other potential risk factors that may contribute to such prediction models for children may include cause of heart failure, levels of serum sodium and biomarkers (such as B-type natriuretic peptide), hemodynamic measures, and exercise performance in older children.^{38,39} Prospective data collection of potential risk factors in large cohorts of children with heart failure may help determine their relative contribution in predicting adverse outcomes by multivariate modeling.

The importance of the type of medical insurance as a determinant of outcome may indicate that socioeconomic disparities affect medical care. However, we could not ascertain the relative contribution of social factors such as parental resources, travel distance from transplant centers, and parental preference for advanced therapies (such as mechanical support and transplant) that could have put lower socioeconomic position patients at higher risk for death at the time of listing for transplant.

Study Limitations

The results of this study should be interpreted in the context of its potential limitations. First, the echocardiographic measurements reported in this study were not performed at a core laboratory but at individual participating centers. However, because these centers were all academic tertiary care centers where these measurements are routinely made in clinical practice, we considered the reported measurements to be reliable for the purpose of this analysis. Furthermore, because the participating centers used these data to make clinical decisions for their patients, one may argue that this is not a limitation of this study, and our findings have already demonstrated their clinical utility in the study cohort. Second, echocardiographic data within 6 months of listing were missing for several patients, so their values could not be included in the modeling of outcome variables. However, the adverse outcomes were not different in those with or without echocardiographic data, and thus the missing data were unlikely to affect the risk estimates.

Conclusions

In conclusion, after controlling for race, type of insurance, and transplant status, the degree of LV dilation at listing is significantly associated with the risk of death while waiting or within 6 months posttransplant in children diagnosed with DCM at 5 years of age or younger. This association between LV size and the risk of death is strongest in those diagnosed with DCM during the first 6 months of life. Adding LV fractional shortening to the model did not improve its predictive ability. Thus, the severity of LV dilation at listing is a potential predictor of outcome in infants and young children listed for heart transplant. These findings should be considered in risk stratification of these children at transplant listing.

Appendix

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CLINICAL PERSPECTIVE

Previous studies in children with dilated cardiomyopathy (DCM) have reported that those with more severe left ventricle (LV) systolic dysfunction at diagnosis are at higher risk of death or heart transplant. Because only a minority of children with DCM are listed for heart transplant, whether the severity of LV dilation or systolic dysfunction in this sicker subset of children with DCM is associated with their outcome after listing is unknown. In this multicenter study, using merged dataset from the Pediatric Cardiomyopathy Registry and the Pediatric Heart Transplant Study, the authors evaluated echocardiographic data obtained in children with DCM listed for heart transplant close to the time of listing and related these data to risk of death on the waiting list or early (6 months) posttransplant. A significant age-dependent association of LV end-diastolic dimension z score was found with death controlling for race, transplant status, and medical insurance. The association was strongest for infants younger than 6 months at diagnosis (47% higher risk of death for each z score increment) and was not significant in children older than 5 years at diagnosis. A similar interaction was identified between age and LV end-systolic dimension z score. Neither LV function nor mass was associated with death. These data demonstrate that the severity of LV dilation at listing for heart transplant is associated with outcome in infants and young children with DCM with advanced heart failure. These findings may be useful in risk stratification of these children at the time of listing for transplant.

Association of Left Ventricular Dilation at Listing for Heart Transplant With Postlisting and Early Posttransplant Mortality in Children With Dilated Cardiomyopathy

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SUPPLEMENTAL MATERIAL

Supplemental Tables

Table 5: Predictors of Mortality Waiting and up to 6 months after Heart Transplant with Age at Listing as a Continuous Variable in a Multivariate Model controlling for Race and Medical Insurance

Predictor	Hazard Ratio	95% CI	P-value
Non-white	1.46	(0.67, 3.20)	0.339
Transplant	0.04	(0.02, 0.11)	<.001
Age at Listing x LVEDD z-score			0.064
Interaction			
LVEDD z-score (age 6 mo*)	1.42	(1.11, 1.82)	0.006
LVEDD z-score (age 1 yr*)	1.40	(1.10, 1.77)	0.005
LVEDD z-score (age 5 yr*)	1.22	(1.02, 1.46)	0.027
LVEDD z-score (age 10 yr*)	1.03	0.81, 1.31	0.792
Medical Insurance			0.028
Medicaid vs. Private	2.42	(0.92, 6.40)	0.074
None vs. Private	5.74	(1.08, 30.48)	0.040
Insured (Unknown type) vs. Private	3.72	(1.45, 9.55)	0.006

*Hazard ratios in selected age groups are shown to illustrate differential risk associated with EDD z-score by age

Table 6: Predictors of Mortality Waiting and up to 6 months after Heart Transplant with Age at Listing as a Categorical Variable in a Multivariate Model controlling for Race and Medical Insurance

Predictor	Hazard Ratio	95% CI	P-value
Non-white	1.91	(0.88, 4.14)	0.103
Transplant	0.03	(0.01, 0.09)	<.001
Age at Listing x LVEDD z-score			0.043
Interaction			
LVEDD z-score (age < 4 years*)	1.66	(1.18, 2.34)	0.004
LVEDD z-score (age \geq 4 yrs*)	1.10	(0.89, 1.36)	0.361
Medical Insurance			0.028
Medicaid vs. Private	1.81	(0.69, 4.74)	0.229
None vs. Private	3.78	(1.42, 10.03)	0.008
Insured (Unknown type) vs. Private	0=.59	(1.18, 36.70)	0.031

*Hazard ratios in selected age groups are shown to illustrate differential risk associated with EDD z-score by age