

ORIGINAL RESEARCH

Progressive Left Ventricular Remodeling for Predicting Mortality in Children With Dilated Cardiomyopathy: The Pediatric Cardiomyopathy Registry

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BACKGROUND: Pediatric dilated cardiomyopathy often leads to death or cardiac transplantation. We sought to determine whether changes in left ventricular (LV) end-diastolic dimension (LVEDD), LV end-diastolic posterior wall thickness, and LV fractional shortening (LVFS) over time may help predict adverse outcomes.

METHODS AND RESULTS: We studied children up to 18 years old with dilated cardiomyopathy, enrolled between 1990 and 2009 in the Pediatric Cardiomyopathy Registry. Changes in LVFS, LVEDD, LV end-diastolic posterior wall thickness, and the LV end-diastolic posterior wall thickness:LVEDD ratio between baseline and follow-up echocardiograms acquired \approx 1 year after diagnosis were determined for children who, at the 1-year follow-up had died, received a heart transplant, or were alive and transplant-free. Within 1 year after diagnosis, 40 (5.0%) of the 794 eligible children had died, 117 (14.7%) had undergone cardiac transplantation, and 585 (73.7%) had survived without transplantation. At diagnosis, survivors had higher median LVFS and lower median LVEDD Z scores. Median LVFS and LVEDD Z scores improved among survivors (Z score changes of +2.6 and -1.1, respectively) but remained stable or worsened in the other 2 groups. The LV end-diastolic posterior wall thickness:LVEDD ratio increased in survivors only, suggesting beneficial reverse LV remodeling. The risk for death or cardiac transplantation up to 7 years later was lower when LVFS was improved at 1 year (hazard ratio [HR], 0.83; $P=0.004$) but was higher in those with progressive LV dilation (HR, 1.45; $P<0.001$).

CONCLUSIONS: Progressive deterioration in LV contractile function and increasing LV dilation are associated with both early and continuing mortality in children with dilated cardiomyopathy. Serial echocardiographic monitoring of these children is therefore indicated.

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Key Words: cardiac transplantation ■ dilated cardiomyopathy ■ heart failure ■ pediatrics ■ remodeling

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CLINICAL PERSPECTIVE

What Is New?

- This study demonstrates the value of serial echocardiographic changes in the prediction of risk in pediatric dilated cardiomyopathy.

What Are the Clinical Implications?

- Serial echocardiographic assessment of left ventricular remodeling in children with dilated cardiomyopathy is able to predict death or cardiac transplantation both in the first year after diagnosis, and later in their course.
- LV dilation and contractile performance are important and persistent markers of disease prognosis during and beyond the first year following pediatric dilated cardiomyopathy diagnosis.
- Serial echocardiography is a valuable means of tracking individual patient progress in pediatric dilated cardiomyopathy and should be routinely performed and endorsed by published appropriate use criteria.

Nonstandard Abbreviations and Acronyms

DCM	dilated cardiomyopathy
LVFS	left ventricular fractional shortening
LVEDD	left ventricular end-diastolic dimension
LVPWT	left ventricular end-diastolic posterior wall thickness
PCMR	Pediatric Cardiomyopathy Registry

Dilated cardiomyopathy (DCM) in children is a heterogeneous group of disorders identified by the echocardiographic characteristics of left ventricular (LV) dilation and LV systolic dysfunction.¹ Although DCM phenotypes are determined by these characteristics, it is now clear that the same echocardiographic appearance may have many underlying causes and therefore differences in prognoses.^{2–5} Identifying patients at highest risk for clinical deterioration and death is challenging as the cause of DCM is undefined or idiopathic in at least 40% of children.⁶

Echocardiographic LV remodeling in children with DCM at presentation has prognostic value, but only the presenting characteristics of remodeling have been studied.^{4,7} Larger LV dimension at presentation of myocarditis, a well-recognized cause of DCM in children, is associated with poor recovery; however, some children with DCM without evident myocarditis may

also eventually recover and regain normal echocardiographic values.^{5,8} Therefore, we sought to determine whether the degree of LV remodeling, as measured on serial echocardiograms in the first 12-months following DCM diagnosis, in the absence of myocarditis, was associated with mortality in these children.

METHODS

Data were abstracted from the PCMR (Pediatric Cardiomyopathy Registry), a National Heart, Lung, and Blood Institute-funded research registry that enrolled more than 3500 children with various phenotypic forms of cardiomyopathy from 98 North American centers between 1990 and 2009. Entry criteria for the PCMR include a diagnosis of familial and certain metabolic, genetic (including dystrophinopathy), and idiopathic causes of DCM. [1] For this investigation, we included all children evaluated between 1990 and 2009 who met PCMR phenotypic criteria for DCM, except for those with a coexisting non-DCM phenotype or with myocarditis as an underlying cause of DCM. We have relied on clinical diagnosis and supportive investigations as determined by the center providing care to make the distinction between myocarditis and nonmyocarditis causes. The diagnosis of myocarditis was therefore based on clinical presentation, endomyocardial biopsy, or core myocardial sample at ventricular assist device placement; viral polymerase chain reaction studies; and cardiac magnetic resonance imaging assessment when available. We have shown previously that acute myocarditis, whether biopsy confirmed or clinically suspected, has a more fulminant course in childhood. Although the outcome of death or cardiac transplant is uncommon, when it occurs, it is attained more rapidly than in cases of pediatric DCM.^{4,5} Familial DCM was defined to be present if 1 or more additional family members were confirmed to have a diagnosis of cardiomyopathy. Children with cardiomyopathies from systemic diseases or in association with malformation syndromes were also excluded. Children with mixed phenotypes, such as LV noncompaction cardiomyopathy with dilation, were excluded, because remodeling in LV noncompaction cardiomyopathy can pose challenges in assessment by serial echocardiography. We have previously described the outcomes of LV noncompaction cardiomyopathy, which is modified by phenotypic overlap with LV dilation or hypertrophy, and others have alluded to the propensity for both progressive and reverse remodeling to occur in some patients with LV noncompaction cardiomyopathy.^{9,10} The authors declare that all supporting data are available within the article (and its online supplementary files).

The designation of DCM in the PCMR requires both an LV end-diastolic dimension (LVEDD) Z score >2

(referenced to means of a healthy population for body surface area) and an LV fractional shortening (LVFS) Z score <-2.0 on baseline echocardiogram. We applied both of these parameters as well as LV posterior wall thickness (LVPWT) and its relationship to LV diastolic dimension (LVPWT:LVEDD) as indicative of remodeling, because there is conflicting evidence as to how closely related these may be over time and whether LVFS change is related to baseline LVEDD or not.^{11,12} The baseline echocardiogram may have been acquired on, or within 3 months before, the date of diagnosis. Our analysis was then restricted to children in whom at least both baseline and 1-year follow-up echocardiograms were available.

The baseline echocardiogram was that performed at or most recently before registration in PCMR and is equivalent to the date of diagnosis assigned. Follow-up echocardiographic measures were derived from annual repeat echocardiograms indexed annually to the date of diagnosis and must have been obtained within 6 months of that anniversary date. If death or cardiac transplantation occurred before the anniversary date, the most proximate echocardiogram obtained within 3 months before the outcome event was assessed. Therefore, all outcomes were indexed to the original baseline echocardiogram. We restricted this analysis to children who remained in follow-up, died, or who underwent cardiac transplantation and echocardiography at or beyond 6 months after their baseline echocardiogram.

Demographic, family history, and clinical data relevant to cardiomyopathy, including vital status and cardiac transplant status and echocardiographic values, were all evaluated. We determined whether symptomatic heart failure (HF) was evident at original presentation. Medical therapies for HF, including angiotensin-converting enzyme inhibitors, calcium channel blockers, beta blockers, digoxin, antiarrhythmics, and diuretics were recorded. Children were grouped by the outcomes of all-cause mortality, cardiac transplantation, or cardiac transplant-free survival. Death and cardiac transplantation were considered censoring events for further analysis. All participating centers obtained institutional review board approval to enroll children in the PCMR. In all cases, a waiver of the requirement for informed consent was granted.

Statistical Analysis

Echocardiographic measurements were converted to Z scores based on normative pediatric reference ranges, to adjust for differences related to age or body surface area. Categorical baseline patient characteristics were compared among the 3 groups using chi-square tests. The Z scores for baseline LVFS, LVEDD, and LVPWT at end-diastole, and the LVPWT:LVEDD were

compared among groups with the Kruskal–Wallis test. Changes in serial echocardiographic measures within these groups were also assessed with these tests. Increasing LV dilation or decreasing LV thickness-to-dimension ratio was interpreted as indicating pathologic LV remodeling.

Secondary analyses used outcome data following the baseline echocardiogram. The Kaplan–Meier method was used to determine the probability of death, cardiac transplantation (whichever occurred first), or transplantation-free survival from baseline as mutually exclusive outcomes. In event-free children followed beyond the first year after diagnosis, Cox proportional hazard modeling was used to determine whether any baseline echocardiographic value or change in any echocardiographic value during the first year of follow-up predicted death or cardiac transplantation after the first year and up to 17 years thereafter. Echocardiographic values significant in the unadjusted analysis were combined into a final model based on a bivariate *P* value of <0.05 . Interactions between patient age and changes in the echocardiographic values were evaluated by treating age as a continuous variable and as dichotomous variables of <1 year and 1 year or more. The variable LVPWT:LVEDD ratio was removed from the model because it was colinear with other independent echocardiographic values.

In addition to the risk assessment, logistic regression was used to fit models for probability of death or cardiac transplantation versus survival, while receiver-operator characteristic curves were used to determine the sensitivity and specificity of baseline LVEDD and LVFS Z scores for the outcome of death or cardiac transplantation versus survival. Outcome was assessed at both 1 and 7 years after baseline. Alpha was set at 0.05, and all tests were 2 tailed. Data were analyzed using statistical analysis software SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Of the eligible 1450 children, 619 (43%) did not have follow-up echocardiograms available in the PCMR database (Figure 1). This number includes 230 children (37%) who died or required cardiac transplantation within 6 months following baseline assessment. The analysis was based on the remaining 794 children with baseline and follow-up echocardiograms.

Baseline Characteristics

The clinical features of the cohort subjected to analysis are shown in Table 1. Baseline echocardiograms were acquired on the actual day of diagnosis for 67% of children. Median age at diagnosis ranged from 1 to 2 years (Table 1). Race or ethnicity and cause of

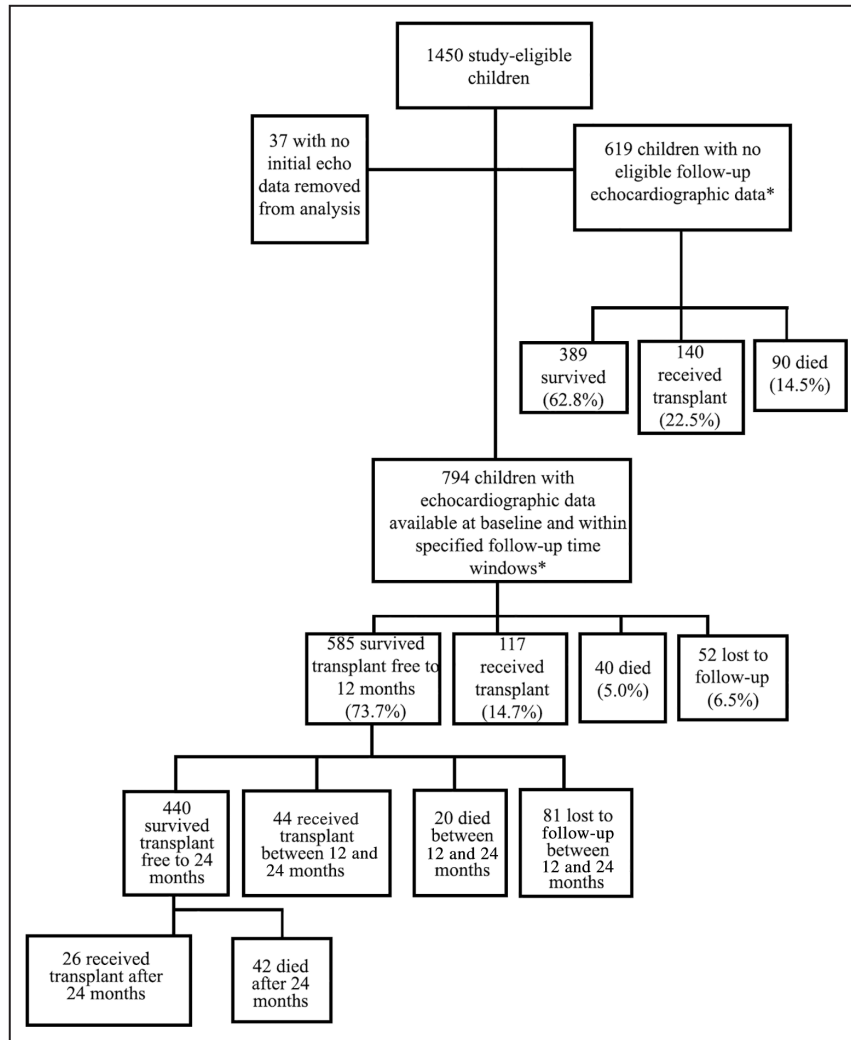


Figure 1. Cohort study flow chart.

Cohort selection of children with dilated cardiomyopathy from the Pediatric Cardiomyopathy Registry in a study to determine the prognostic value of serial changes in echocardiographic measurements. *Children not having an echocardiogram within 90 days before death or cardiac transplant in the first year, or within 6 months of their 1-year anniversary of the first echocardiogram, if event free during the first year.

cardiomyopathy we marginally associated with outcomes in the adjusted analysis, with the highest rate of death or transplant occurring in 27.9% of non-Hispanic Black children. Idiopathic cardiomyopathy was the most common diagnosis and was marginally associated with cardiac transplantation. Clinical HF at diagnosis was far more likely in children destined for cardiac transplantation or death within the first year ($P<0.001$). Similarly, a lower LVFS Z score ($P<0.001$), a higher LVEDD Z score ($P<0.001$), and a thinner LVPWT Z score ($P<0.007$) at baseline were all associated with death or cardiac transplantation (Table 2). Median (interquartile range) follow-up duration of the cohort was 2.55 (0.96–5.79) years.

The type and frequency of medications used at the time of diagnosis were similar among the 3 outcome groups, although anticongestive therapy and

angiotensin-converting enzyme inhibitors were more common. Beta blockers were used in a minority of cases at diagnosis.

Left Ventricular Remodeling

Of the 794 children, 585 (74%) survived without transplant, 52 (7%) were lost to follow-up, 40 (5%) had died, and 117 (15%) had received a cardiac transplant by 1 year of follow-up. The 1-year follow-up echocardiograms were acquired at a median 8.6 (interquartile range, 6.0–10.4) months following the baseline study. Changes in the first year after diagnosis differed between groups (Figure 2). Baseline LVEDD Z scores were significantly lower in children who survived for 1 year than for those who died or underwent cardiac

Table 1. Clinical Characteristics of 794 Children With Dilated Cardiomyopathy at Diagnosis by Outcome During the First Year After Diagnosis

Characteristic at diagnosis	Died (N=40)	Cardiac transplant (N=117)	Event-free survival (N=585)	Lost to follow-up (N=52)	P value*
Age at diagnosis, y					
Median (interquartile range)	1.1 (0.4, 11.9)	2.1 (0.4, 11.3)	1.2 (0.3, 11.6)	1.0 (0.3, 5.7)	
Age <1 y at diagnosis, n (%)	18 (45.0)	52 (44.4)	274 (46.8)	28 (53.8)	0.88
Male sex, n (%)	20 (50.0)	65 (55.6)	310 (53.0)	27 (51.9)	0.80
Race or ethnicity, n (% by column)					
White, non-Hispanic	17 (42.5)	60 (51.3)	334 (57.1)	28 (53.8)	
Black, non-Hispanic	10 (25.0)	31 (26.5)	102 (17.4)	4 (7.7)	
Hispanic	6 (15.0)	17 (14.5)	107 (18.3)	14 (26.9)	
Other	7 (17.5)	6 (5.1)	35 (6.0)	5 (9.6)	
Type of DCM, n (% by column)					
Familial	2 (5.0)	4 (3.4)	39 (6.7)	2 (3.8)	
Idiopathic	33 (82.5)	108 (92.3)	463 (79.1)	48 (92.3)	
Other	5 (12.5)	5 (4.3)	83 (14.2)	2 (3.8)	
Congestive heart failure at diagnosis, n (% by column)	33 (82.5)	99 (84.6)	355 (60.7)	36 (69.2)	<0.001
Medication use, n/N (%)†					
Antiarrhythmic	7/23 (30.4)	16/59 (27.1)	69/317 (21.8)	2/14 (14.3)	0.46
Angiotensin-converting enzyme inhibitor	15/23 (65.2)	46/59 (78.0)	226/318 (71.1)	12/14 (85.7)	0.43
Beta blocker	3/23 (13.0)	11/58 (19.0)	31/315 (9.8)	3/14 (21.4)	0.13
Digoxin and diuretics	36/38 (94.7)	106/115 (92.2)	459/542 (84.7)	44/48 (91.7)	0.03

DCM indicates dilated cardiomyopathy.

*Compares death, cardiac transplant, and survival to 1 year after diagnosis.

†n, number of children on the medication; N, group total. Type of DCM "Other" refers to defined diagnoses including dystrophinopathy (Duchenne, Becker, or Emery–Dreifuss muscular dystrophy).

transplant (median Z scores, 4.0, 5.6, and 5.7 respectively; $P<0.001$). This difference was further evident at 1 year when the median LVEDD Z score was reduced by 1.1 (improved and closer to normal) in survivors ($P<0.001$), remained relatively constant in children

undergoing cardiac transplant, and increased by 0.6 ($P<0.001$) in children who died.

In contrast to the progression of LV dilation, changes in LVPWT (Figure 3) differed only slightly among the groups. For the most part, LVPWT was

Table 2. Echocardiographic Characteristics of 794 Children With Dilated Cardiomyopathy at Diagnosis and by Outcome at 12 Months

Characteristic at diagnosis	Died (N=40)	Cardiac transplanted (N=117)	Event-free survival (N=585)	Lost to follow-up (N=52)	P value*
Left ventricular fractional shortening Z score					
Mean (SD)	-9.39 (2.99)	-9.73 (2.62)	-7.84 (3.86)	-8.50 (4.94)	<0.001
Median (IQR)	-10.02 (-11.62 to -7.10)	-9.87 (-11.77 to -8.02)	-8.65 (-10.58 to -5.15)	-9.41 (-11.70 to -6.96)	
LVEDD Z score					<0.001
Mean (SD)	5.68 (2.01)	5.82 (2.00)	4.09 (2.70)	4.88 (2.32)	
Median (IQR)	5.61 (4.47 to 6.83)	5.74 (4.23 to 7.33)	3.97 (2.15 to 5.94)	5.00 (3.14 to 6.59)	
LVPWT Z score					0.07
Mean (SD)	0.28 (1.47)	-0.98 (1.93)	-0.70 (2.33)	-0.12 (1.82)	
Median (IQR)	0.02 (-0.82 to 1.16)	-1.11 (-1.79 to 0.22)	-0.78 (-2.11 to 0.63)	-0.41 (-1.51 to 0.71)	
LVPWT:LVEDD ratio Z score					<0.001
Mean (SD)	-1.83 (1.84)	-2.67 (1.27)	-1.41 (2.17)	-1.47 (1.83)	
Median (IQR)	-1.99 (-3.37 to -0.84)	-2.80 (-3.38 to -2.17)	-1.71 (-2.71 to -0.41)	-1.74 (-2.86 to -0.45)	

IQR indicates interquartile range; LVEDD, left ventricular end-diastolic dimension; and LVPWT, left ventricular end-diastolic posterior wall thickness.

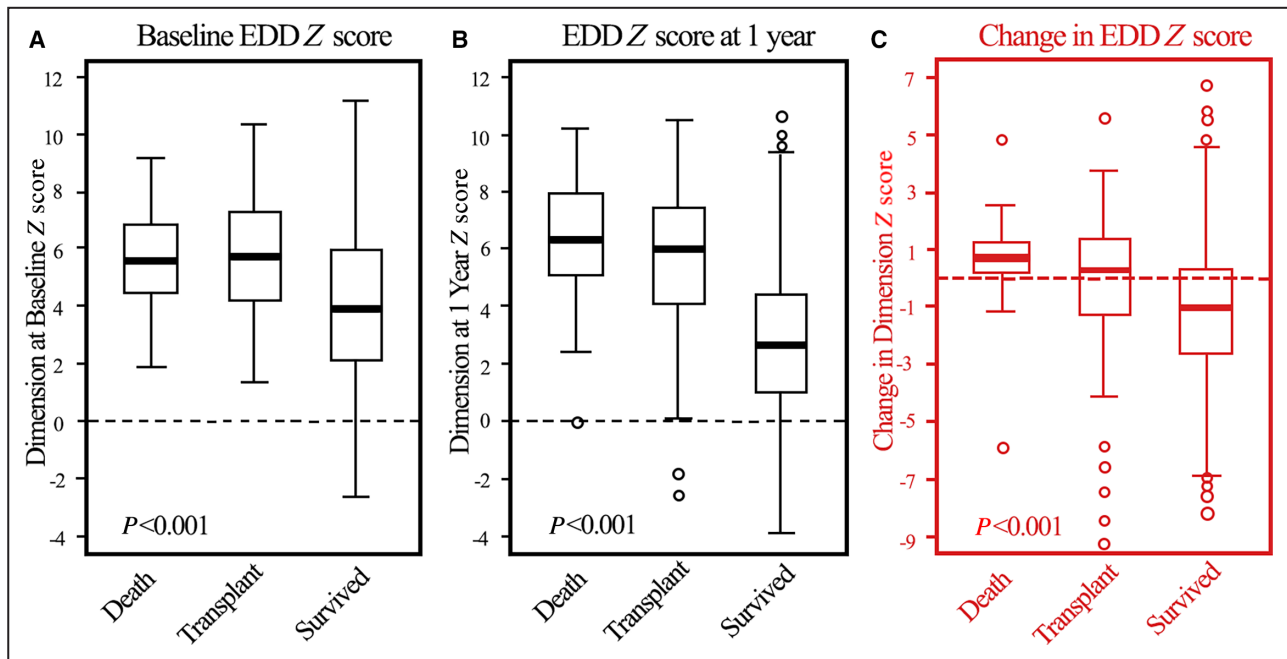


Figure 2. Progression of LV dimension Z score.

Left ventricular end-diastolic dimension Z scores at (A) diagnosis, (B) 1 year later, and (C) changes between baseline and 1 year for children with dilated cardiomyopathy who died, underwent heart transplant, or survived during the first year after diagnosis. Data in the box-and-whisker plots are medians, interquartile ranges, minimum and maximum within median \pm 1.5 interquartile range and outliers. Survivors differed significantly from both other groups at time points A and B. The changes in left ventricular end-diastolic dimension Z scores between survivors, those transplanted, and nonsurvivors (C) were also significant. EDD indicates end-diastolic dimension; and LV, left ventricular.

normal for all groups, both at baseline and at 1 year (median Z scores ranged between 0 and -2). However, baseline LVPWT was higher in the children who later died. The LVPWT:LVEDD ratio Z score differed significantly among groups, both at baseline and at follow-up, with the Z score marginally higher in survivors at both times than in children in the other groups (Figure 4). Changes in the LVPWT:LVEDD ratio from baseline over the first year did not differ significantly among the 3 groups.

Baseline LV systolic function, as measured by LVFS (Figure 5), was depressed in all groups but significantly less so in survivors, in whom LVFS improved substantially (change in LVFS Z score of $+2.6$, $P<0.001$). LVFS remained unchanged in the other 2 groups.

Survival Beyond 12 Months After DCM Diagnosis

We determined whether the progressive changes in LVEDD, LVPWT, LVPWT:LVEDD ratio, and LVFS were associated with survival beyond 1 year for the 585 children who did not undergo early cardiac transplantation. Of these children, 440 (75.2%) survived beyond 24 months, after which 42 (9.5%) died and 26 (5.9%) received a cardiac transplant (Figure 6B). We determined the hazard function for death or cardiac transplantation after survival to 1 year, both at baseline

and at follow-up assessment (Table 3). Changes in LVEDD ($P<0.001$) and LVFS ($P=0.004$) measured in the first year were important determinants of the time to death or cardiac transplant beyond 1 year after diagnosis. In this multivariable model, baseline LVEDD and progressive dilation during the first year after diagnosis were associated with an increased hazard for death or cardiac transplantation. Conversely, a higher baseline LVFS and an increase in interval LVFS were associated with better cardiac transplant-free survival. We assessed for any interaction with age at presentation (<1 year of age versus base case >1 year of age) in the multivariable model and found no significant interaction with age at presentation.

Prognostic Value of Echocardiographic Changes

The area under the receiver-operator characteristic curve (AUC) for a particular baseline LVEDD z-score was relatively low for 1-year survival (0.67), and even lower for 7-year survival (0.60; data not shown). However, specificity for a 1-year outcome of death or cardiac transplantation was 77.8% at a baseline LVEDD Z score of 6.4 or greater (Table 4). The prognostic value of LVEDD was improved somewhat by measuring the change in LVEDD Z score during the first year, both for death or cardiac transplantation at 1 year (area under

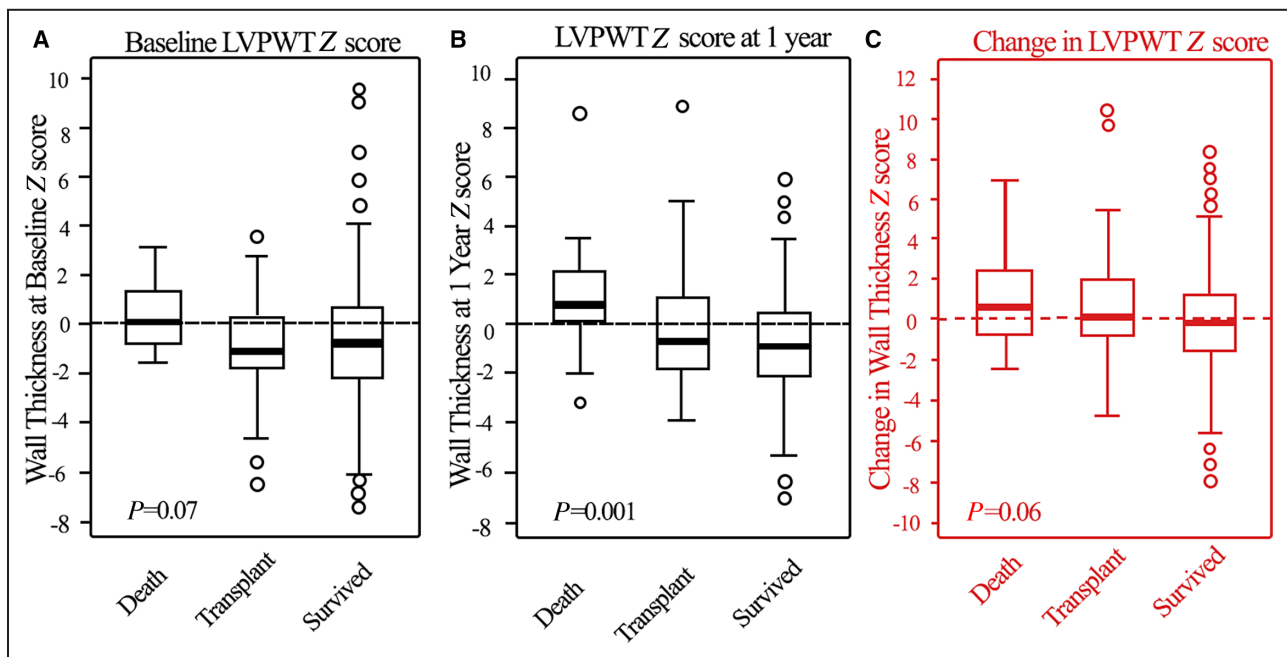


Figure 3. Progression of LV posterior wall thickness Z score.

LVPWT Z scores at (A) diagnosis, (B) 1 year later, and (C) changes between diagnosis and 1 year for children with dilated cardiomyopathy who died, underwent heart transplant, or survived during the first year after diagnosis. Data in the box-and-whisker plots are medians, interquartile ranges, minimum and maximum within median \pm 1.5 interquartile range and outliers. Differences were only marginally significant at baseline but were more evident at 1 year. Changes in left ventricular wall thickness (C) were similar in all 3 groups, with no clear between-group differences from baseline. LVPWT indicates left ventricular end-diastolic posterior wall thickness.

the curve, 0.69) and at 7 years (area under the curve, 0.74). Progressive dilation, signified by an increase in the LVEDD Z score of only 0.49 (the 75th percentile of the changes we observed), was \approx 79% specific for the outcome of death or cardiac transplantation at 1 year and $>$ 83% specific for death or transplantation at 7 years (Table 4).

Baseline LVFS Z scores (a lower Z score indicates worse LV function) did not discriminate well (32% sensitivity and 78% specificity) for values at or below the 25th percentile: $z \leq -10.9$ (Table 5). However, again, a decline in LVFS Z score of only -0.18 during the first year (the 25th percentile observed) was more specific for death or cardiac transplantation (79% at 1 year and 81% at 7 years) (Table 5).

DISCUSSION

We found important echocardiographic milestones of disease progression or recovery for children with DCM in the first year after diagnosis, which should help clinicians define the evolution of risk in specific patients. In describing the relationship of serial changes in LVFS, LVEDD, and LVPWT to the outcomes of survival, death, or cardiac transplantation in a large cohort of children with DCM, the risk for death or cardiac transplantation was associated with severity of LV dilation and LV systolic dysfunction at diagnosis. Furthermore,

the progression of these abnormalities was associated with reduced survival at 1 year and beyond. Serial changes in LV dimension and function predicted later outcomes of survival versus death or cardiac transplant better than a single assessment at diagnosis. To date, the field of risk prediction in adult nonischemic HF has relied on multiple clinical attributes to create a single point risk estimate, exemplified by the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) calculator for HF risk score and others. Although these have fair discriminant value, it is worth noting that no risk score has yet been deployed that leverages the degree of progressive or reverse remodeling that is accruing over time as a risk modifier.^{13,14}

Dilation of the systemic ventricle is considered to be a signal event in LV remodeling.¹⁵ In nonischemic DCM, the mechanisms leading to LV remodeling are multifactorial and have been linked to changes in the expression or function of structural sarcomeric proteins or the interstitial matrix, ultimately leading to myocardial cell death with associated interstitial fibrosis.^{16–19} Although children with HF had different patterns of LV remodeling, the children we studied by definition had LV dilation and diminished LV systolic function.¹⁹

In such children, LV mass, sphericity index, and LV stroke volume are all closely associated, and a reduction in the LV ejection fraction $<$ 20% is associated with an even more pronounced reduction in LV

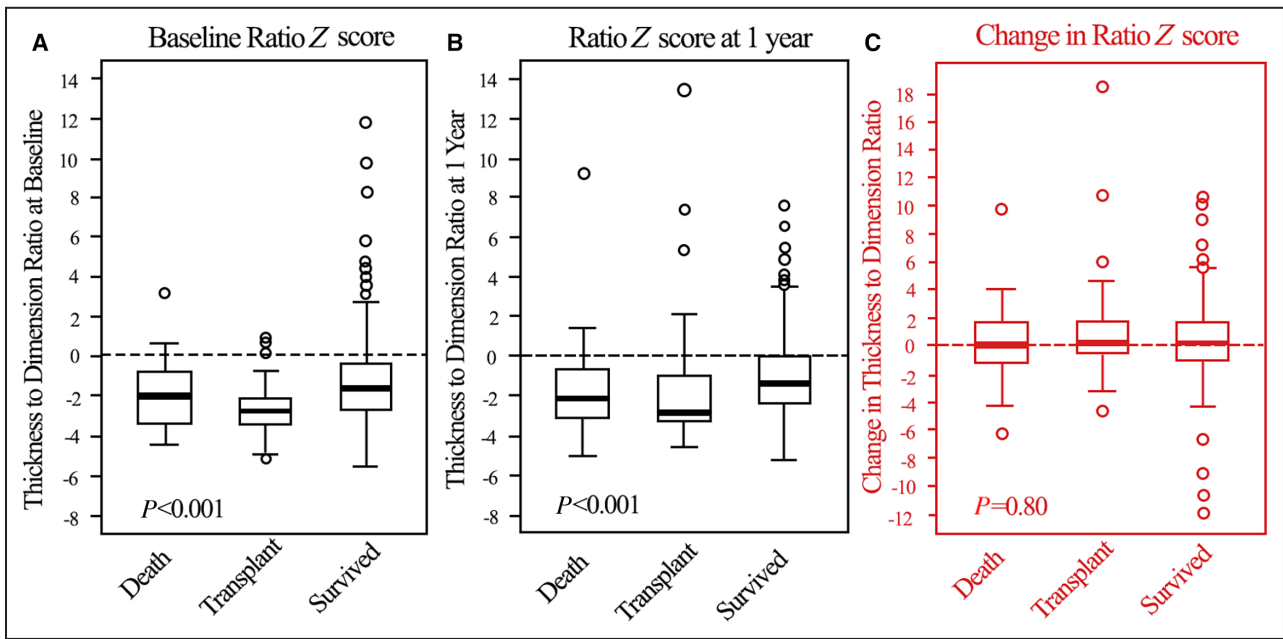


Figure 4. Progression of LV wall thickness to dimension ratio Z score.

The ratio of left ventricular posterior wall thickness:left ventricular end diastolic dimension Z scores at (A) diagnosis, (B) 1 year later, and (C) changes between baseline and 1 year for children with dilated cardiomyopathy who died, underwent heart transplant, or survived during the first year after diagnosis. Data in the box-and-whisker plots are medians, interquartile ranges, minimum and maximum within median \pm 1.5 interquartile range and outliers. Differences between the 3 groups were significant at both time points but not with regard to the magnitude of change during the first year shown in panel (C). LV indicates left ventricular.

stroke volume.²⁰ In children, reduced LV ejection fraction or LVFS at presentation are important risk factors for death.^{4,21,22} The degree of LV dilation and reduced

LV function are additive in increasing the hazards of death in these children.^{22,23} We found here that serial changes in LVFS, LVEDD, and in the LVPWT:LVEDD

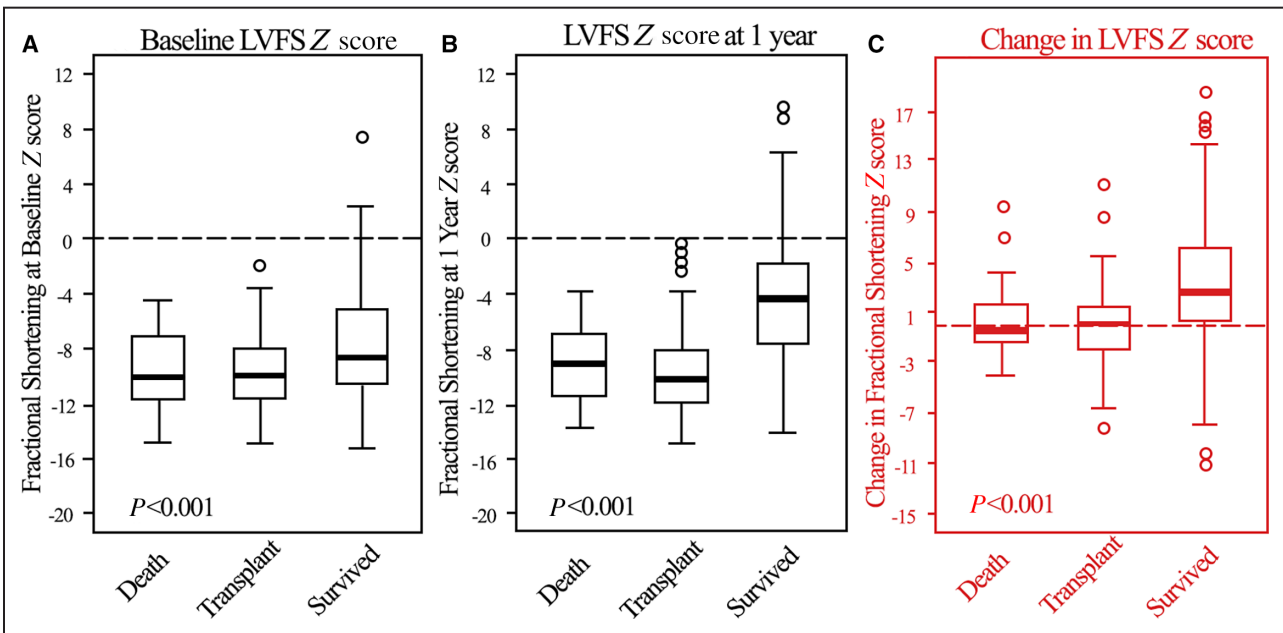


Figure 5. Progression of LV fractional shortening Z score.

Left ventricular fractional shortening Z scores at (A) diagnosis/(baseline), (B) 1 year later, and (C) changes between baseline and 1 year for children with dilated cardiomyopathy who died, underwent heart transplant, or survived during the first year after diagnosis. Data in the box-and-whisker plots are medians, interquartile ranges, minimum and maximum within median \pm 1.5 interquartile range and outliers. The groups differed significantly at both time points, as well as in respect of the improvement in LVFS from 0 to 1 year (C). LVFS indicates left ventricular fractional shortening.

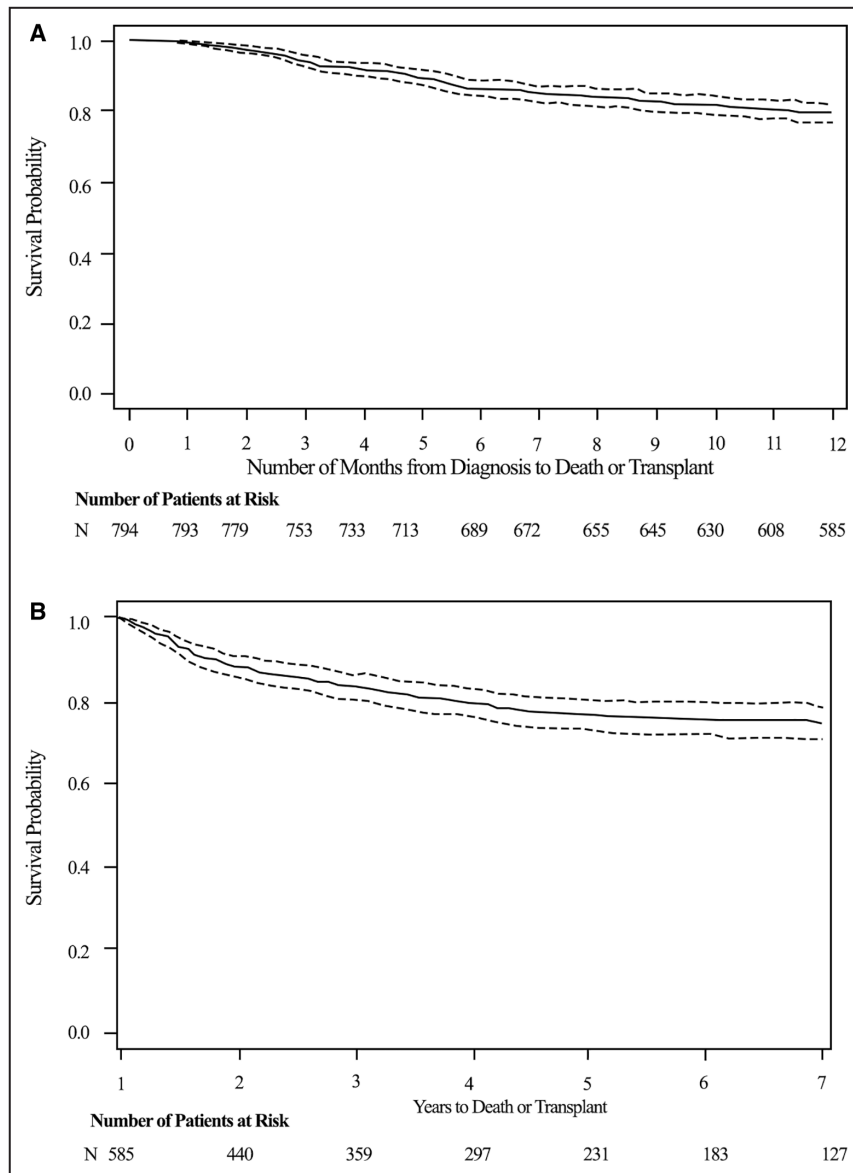


Figure 6. Transplant-free survival probability distribution in children with dilated cardiomyopathy.

A, From diagnosis to 12 months after baseline echocardiogram. **B**, For those surviving beyond 1 year after diagnosis (x axis is in years). Dotted lines are 95% confidence limits.

ratio were associated with survival at 1 year after diagnosis and relevant to longer-term survival.

A higher baseline LVFS Z score and improvement of LVFS Z scores during the first year predicted improved survival beyond the first year. In this respect, our findings are similar to those of the Australian Childhood Cardiomyopathy study, in that a low baseline LVFS and a failure of improvement in LVFS during follow-up were associated with higher risk for death or transplantation.¹¹ Similarly, in the first year, a progressive Z score reduction (improvement) of LV dilation was associated with survival, whereas a progressive increase in LV dilation was associated with death or

cardiac transplantation. Simultaneously, an increase in the LVPWT:LVEDD ratio, consistent with LV reverse remodeling, in the first year, was associated with improved survival. Moreover, a lower LVEDD at baseline and at 1 year, and a reduction in LVEDD between diagnosis and 1 year had similar favorable prognostic values.

Overall, in our population with pediatric DCM, marked LV remodeling seems to have occurred by the time of diagnosis, with LVPWT:LVEDD ratio Z scores ≤ -2 . A failure to compensate with LV hypertrophy in the presence of chronic LV volume loading is associated with progressive contractile dysfunction and HF

Table 3. Hazard Ratios From Multivariable Modeling of Incremental Risk of Death or Cardiac Transplant Per 1-SD Change in Z Score for 585 Children With Dilated Cardiomyopathy Surviving 1 Year After Diagnosis

Characteristic	Separate bivariate models (baseline and change)		Multivariable model	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Baseline LVEDD Z score	1.57 (1.40–1.75)	<0.001	1.22 (1.01–1.49)	0.04
Change in LVEDD Z score	1.73 (1.54–1.94)	<0.001	1.45 (1.21–1.75)	<0.001
Baseline LVPWT Z score	0.96 (0.82–1.12)	0.61		
Change in LVPWT Z score	1.15 (1.01–1.32)	0.03	1.10 (1.00–1.21)	0.06
Baseline LVFS Z score	0.77 (0.71–0.83)	<0.001	0.86 (0.75–0.99)	0.04
Change in LVFS Z score	0.79 (0.74–0.84)	<0.001	0.83 (0.73–0.94)	0.004
Baseline LVPWT:LVEDD ratio Z score	0.72 (0.60–0.87)	<0.001		
Change in LVPWT:LVEDD ratio Z score	0.78 (0.66–0.92)	0.004		

All analyses are adjusted for age and sex. LVEDD indicates left ventricular end-diastolic dimension; LVFS, left ventricular fractional shortening; and LVPWT, left ventricular end-diastolic posterior wall thickness.

in valvular heart disease and is also a hallmark of pediatric DCM.^{15,24} Poorer survival in the first year after diagnosis was associated with a lower LVPWT:LVEDD ratio, which is consistent with pathologic LV remodeling in other populations. However, this effect was not evident in the multivariable hazard analysis after

1 year, suggesting that the effect of this LV remodeling may be exerted early in the disease course. In addition, children with greater LV dilation and a lower LVPWT:LVEDD ratio Z score early in the clinical course (Table 1) may have been listed for cardiac transplantation more often, as we have noted.²³

Table 4. Baseline LVEDD Z Scores and Changes in Z Score in Children With Dilated Cardiomyopathy by Percentile and by Outcome

EDD percentile	EDD-Z	Death/Transplant		Survived		Sensitivity %	Specificity %
		Baseline ≥EDD-Z (true +)	Baseline <EDD-Z (false -)	Baseline <EDD-Z z (true -)	Baseline ≥EDD-Z (false +)		
Outcome at 1 y							
(n=135)				(n=496)			
25th	2.51	128	7	153	343	94.8	30.8
50th	4.69	92	43	275	221	68.1	55.4
75th	6.35	46	89	386	110	34.1	77.8
Outcome at 7 y							
(n=135)				(n=103)			
25th	2.51	206	26	30	73	88.8	29.1
50th	4.69	142	90	49	54	61.2	47.6
75th	6.35	71	161	79	24	30.6	76.7
Change in EDD percentile	Change in EDD-Z score	Change ≥EDD-Z (true +)	Change <EDD-Z (false -)	Change <EDD-Z (true -)	Change ≥EDD-Z (false +)	Sensitivity %	Specificity %
Outcome at 1 y							
(n=118)				(n=440)			
25th	-2.52	104	14	114	326	88.1	25.9
50th	-0.81	90	28	236	204	76.3	53.6
75th	0.49	53	65	347	93	44.9	78.9
Outcome at 7 y							
(n=200)				(n=95)			
25th	-2.52	181	19	27	68	90.5	28.4
50th	-0.81	156	44	61	34	78.0	64.2
75th	0.49	88	112	79	16	44.0	83.2

Sensitivity and specificity of baseline echocardiographic LVEDD Z score and change in baseline LVEDD Z at follow-up assessment for the prediction of death or cardiac transplant vs survival at 1 year and at 7 years in children with dilated cardiomyopathy for whom echocardiographic values were available. Values at the 25th, 50th, and 75th percentile of the range are shown. EDD indicates end-diastolic dimension; and LVEDD, left ventricular end-diastolic dimension.

Table 5. Baseline Fractional Shortening Z Scores and Changes in Z Score in Children With Dilated Cardiomyopathy by Percentile and by Outcome

FS Percentile	FS-z	Death/Transplant		Survived		Sensitivity %	Specificity %
		Baseline <FS-Z (true +)	Baseline ≥FS-Z (false -)	Baseline ≥FS-Z (true -)	Baseline <FS-Z (false +)		
Outcome at 1 y							
(n=137)				(n=518)			
25th	-10.94	44	93	402	116	32.1	77.6
50th	-9.04	83	54	277	241	60.6	53.5
75th	-5.94	119	18	153	365	86.9	29.5
Outcome at 7 y							
(n=241)				(n=112)			
25th	-10.94	67	174	82	30	27.8	73.2
50th	-9.04	132	109	53	59	54.8	47.3
75th	-5.94	200	41	29	83	83.0	25.9
Change in FS percentile	Change in FS Z score	Change<FS-Z (true +)	Change≥FS-Z (false -)	Change≥FS-Z (true -)	Change<FS-Z (false +)	Sensitivity %	Specificity %
Outcome at 1 y							
(n=117)				(n=479)			
25th	-0.18	50	67	380	99	42.7	79.3
50th	1.95	95	22	267	212	81.2	55.7
75th	5.50	111	6	134	345	94.9	28.0
Outcome at 7 y							
(n=210)				(n=105)			
25th	-0.18	85	125	85	20	40.5	81.0
50th	1.95	160	50	64	41	76.2	61.0
75th	5.50	197	13	33	72	93.8	31.4

Sensitivity and specificity of baseline echocardiographic LV fractional shortening Z score and change in baseline LV fractional shortening Z score at follow-up assessment for the prediction of death or cardiac transplant vs survival at 1 year and at 7 years in children with dilated cardiomyopathy for whom echocardiographic values were available. Values at the 25th, 50th, and 75th percentile of the range are shown. FS indicates fractional shortening; and LV, left ventricular.

The clinical utility of changes in LVEDD and LVFS over time relative to absolute values is indicated by the receiver-operator characteristic analysis that, without setting specific cutoff values, indicates the improved predictive value of changes in LV dimension and contractility over baseline values. The specificity of death or transplant for a hypothetical patient whose LVEDD is greater than the 75th percentile at diagnosis is 77.8% by 1 year and 76.7% by 7 years. Serial assessment increases that specificity to 78.9% in year 1 and to more than 83% specificity by year 7. For LVFS, the specificity for death or transplant was 77.6% at 1 year and 73.2% at 7 years, if baseline LVFS is below the 25th percentile (Table 5). By accounting for changes in the first year, a slight reduction in Z score (further reduced LV function) increases that specificity to 79.3% and 81% for such an outcome at years 1 and 7, respectively. These changing values may be important in treatment planning and reinforce the evidence that adverse ventricular remodeling in children portends a poor outcome.

In response to the perceived misuse or overuse and increasing expenses of echocardiography,

appropriate use criteria were developed in 2011.^{25–28} For adults with systolic or diastolic HF, these criteria state that serial echocardiography is *inappropriate* in patients at risk for HF, or even in those with established HF, at <1 year intervals unless clinical cardiac status changes.^{29–32} Yet, several studies of adults with HF have suggested that early improvement, indicated by serial echocardiograms, predicts better long-term survival and that changes in New York Heart Association functional class do not always correlate with ventricular function.^{32–34} Although the goal of optimizing clinical testing is laudable, our data do not support eliminating serial diagnostic echocardiography in children with HF. In the developing child, ventricular anatomy and function may substantially change soon after diagnosis of cardiomyopathy.⁸ Indeed, the careful mapping of echocardiographic remodeling in children with DCM is likely to prove both clinically valuable and cost effective if it guides early and appropriate intervention. Conversely, if appropriate use criteria are rigidly applied without clinical judgment, disease progression may be overlooked and outcomes may be affected.

Our data support the benefit of serial assessment at relevant intervals for children regardless of any change in symptoms.

Finally, our results suggest that the clinical course and risk factors in children with DCM, most of whom have systolic HF, may differ from that of adults with the same phenotype: in fact, progression in several forms of systolic HF in children appears to be closely associated with echocardiographic evidence of remodeling.^{35,36} This observation is consistent with data showing differential gene expression and remodeling pathways in adults and children with HF.^{37–39} These findings indicate that disease causation, outcomes, and management of HF differ substantially between children and adults, differences that should be acknowledged in future pediatric HF guidelines.^{40,41}

Study Limitations

The results of the study cannot be generalized to patients presenting with DCM who expired or received a transplant within 6 months of presentation and to those with a clinical diagnosis of myocarditis. Ascertainment bias for the degree and extent of remodeling is also possible, because the time of onset is usually unknown in DCM and is assigned as the date of first echocardiographic diagnosis in the PCMR. The observed rate and extent of LV remodeling may be influenced by the duration of unrecognized disease and may differ by the cause of disease. Nonetheless, the value of echocardiographic assessment described here was independent of any specific diagnosis. Similarly, our assessment assumes a constant trajectory of remodeling, but whether the actual changes in LV dimensions over time are more complex (with early improvement followed by deterioration) is unknown.

The low interobserver and intertest reliability of echocardiographic measurements is a limitation to any serial assessment of changes in LV dimensions. However, our echocardiographic measurements were acquired in real-world settings, which indicates their pragmatic value. Overall, the most important changes were in LVEDD values whose variability (2%–4%) is the lowest among echocardiographic measures.⁴² It is important to note that small changes in LVPWT can result in a large change in the LVEDD:LVPWT ratio, which is an inherent limitation in the echocardiographic measurement of LVPWT. Therefore, the impact of changes we observed in LVEDD:LVPWT ratio may well have been driven mainly by LVEDD.

Outcomes of cardiac transplantation are likely to be somewhat skewed by the subjective nature of cardiac transplantation listing decisions. Nevertheless, this subjectivity represents an important realistic end point and should be considered. A study from the Netherlands illustrates that, in more recent cohorts,

cardiac transplantation rate may be lower than in our experience.⁴³ The Netherlands series, however, is from a later era and included patients with myocarditis and other causes not represented in our DCM cohort, which may have reduced the likelihood for cardiac transplantation as an outcome in that series.

Finally, we did not formally address the effect of medical therapy on the trajectory of LV remodeling. Although no clear association of medical therapy with any outcome-defined group was shown, we were unable to examine this in detail, given our registry design.

CONCLUSIONS

Although children with DCM are collectively at high risk for death in the first 2 years after diagnosis, the risk profile can be refined according to whether LV dilation is progressive or not. Serial changes in both LVEDD and LVFS are more sensitive and specific for predicting an adverse event by 1 year or later than are the initial echocardiographic values. Thus, serial monitoring of echocardiographic remodeling in pediatric DCM in the first year after diagnosis is important in determining prognosis. Furthermore, because changes in LVEDD and LVFS in the first year following diagnosis affect long-term survival, therapy that limits this progressive LV remodeling is likely to improve later cardiac transplant-free survival.

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Disclosures

Dr Lipshultz is on the medical advisory board of Secretome Therapeutics, which is a paid position. He is also chairman of the medical advisory board of the Children's Cardiomyopathy Foundation, which is an unpaid position.

Supplemental Material

Data S1

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