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Cardiomyopathy Phenotypes and Outcomes for Children with Left Ventricular Myocardial Noncompaction: Results from the Pediatric Cardiomyopathy Registry

John L. Jefferies, M.D., M.P.H.^a, James D. Wilkinson, M.D., M.P.H.^{b,c}, Lynn A. Sleeper, Sc.D.^d, Steven D. Colan, M.D.^e, Minmin Lu, M.S.^d, Elfriede Pahl, M.D.^f, Paul F. Kantor, M.B.B.Ch.^g, Melanie D. Everitt, M.D.^h, Steven A. Webber, M.B.Ch.B.ⁱ, Beth D. Kaufman, M.D.^j, Jacqueline M. Lamour, M.D.^k, Charles E. Canter, M.D.^l, Daphne T. Hsu, M.D.^k, Linda J. Addonizio, M.D.^m, Steven E. Lipshultz, M.D.^{c,n}, Jeffrey A. Towbin, M.D.^{a,o}, and the Pediatric Cardiomyopathy Registry Investigators

^aHeart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

^bDepartment of Pediatrics, Wayne State University School of Medicine, Detroit, MI, USA

^cDepartment of Pediatrics, University of Miami Miller School of Medicine and Holtz Children's Hospital, Miami, FL, USA

^dNew England Research Institutes, Watertown, MA, USA

^eDepartment of Cardiology, Boston Children's Hospital, Boston, MA, USA

^fCardiology, Ann and Robert Lurie Children's Hospital, Chicago, IL, USA

^gStollery Children's Hospital, University of Alberta, Edmonton, AB, Canada

^hPediatric Cardiology, Primary Children's Hospital, Salt Lake City, UT, USA

ⁱMonroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, TN, USA

^jChildren's Hospital of Philadelphia, Philadelphia, PA, USA

^kMontefiore Children's Hospital, New York, USA

^lSt. Louis Children's Hospital, St. Louis, MO, USA

^mMorgan Stanley Children's Hospital, New York, USA

ⁿWayne State University School of Medicine and Children's Hospital of Michigan, Detroit, MI, USA

Address for Correspondence: John Lynn Jefferies, MD, MPH, FAAP, FACC, Associate Professor, Pediatric Cardiology, Director, Advanced Heart Failure & Cardiomyopathy, The Heart Institute at Cincinnati Children's Hospital, 3333 Burnet Ave. ML 2003, Cincinnati, OH 45229, Tel: 513-803-1675, Fax: 513-803-3315, John.Jefferies@cchmc.org.

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^oHeart Institute, Le Bonheur Children's Hospital, University of Tennessee Health Science Center, Memphis, Tennessee, USA.

Abstract

Background—Left ventricular noncompaction (LVNC) is a distinct form of cardiomyopathy characterized by hypertrabeculation of the left ventricle. The LVNC phenotype may occur in isolation or with other cardiomyopathy phenotypes. Prognosis is incompletely characterized in children.

Methods and Results—Using diagnoses from the National Heart, Lung, and Blood Institute-funded Pediatric Cardiomyopathy Registry from 1990-2008, 155 of 3219 children (4.8%) had LVNC. Each LVNC patient was also classified as having an associated echocardiographically diagnosed cardiomyopathy phenotype (dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), isolated, or indeterminate). The time to death or transplant differed among the phenotypic groups ($P = 0.035$). Time to listing for cardiac transplantation significantly differed by phenotype ($P < 0.001$), as did time to transplantation ($P = 0.015$). The hazard ratio for death/transplant (with isolated LVNC as the reference group) was 4.26 (95% confidence interval [CI], 0.78 to 23.3) for HCM, 6.35 (95% CI, 1.52 to 26.6) for DCM, and 5.66 (95% CI, 1.04 to 30.9) for the indeterminate phenotype. Most events occurred in the first year after diagnosis.

Conclusion—LVNC is present in at least 5% of children with cardiomyopathy. The specific LVNC-associated cardiomyopathy phenotype predicts the risk of death/transplant and should inform clinical management.

Keywords

Cardiomyopathy; Pediatrics; Heart Failure

INTRODUCTION

Left ventricular noncompaction (LVNC) was classified as a distinct form of cardiomyopathy in 2006.¹ LVNC is characterized by the presence of prominent trabeculae, intertrabecular recesses, and myocardium that is characterized by two distinct layers composed of compacted and noncompacted myocardium.² The disease may represent disrupted embryologic development; however the exact mechanism remains unclear given the wide age range in which the phenotype presents.⁴⁻⁷

Patients may present clinically along a spectrum from asymptomatic to heart failure, life-threatening arrhythmias or sudden death, or stroke.⁸⁻¹⁰ Although LVNC was originally described in association with congenital heart disease, it is often seen as an isolated phenotype when no other structural or myocardial disease is present and may constitute up to 9% of pediatric cardiomyopathies.^{9,11-16} The natural history of LVNC in both children and adults is poorly understood, although the absence of systolic dysfunction or serious arrhythmias may be associated with better outcomes.^{11,17-21} We report results from the multicenter National Heart, Lung, and Blood Institute-funded Pediatric Cardiomyopathy

Registry (PCMR) on the prevalence of the different cardiomyopathy phenotypes observed in children with LVNC and, their associated clinical outcomes.

METHODS

This analysis includes PCMR patients diagnosed with cardiomyopathy and/or LVNC between January 1990 and August 2008 (followed through 2011) at 98 participating pediatric cardiology centers in the United States and Canada. The design of the PCMR is described elsewhere.^{22,23} Briefly, patients less than 18 years of age in whom recent diagnosis of cardiomyopathy was made at participating centers were eligible for inclusion. Children with secondary etiologies of cardiomyopathy such as pulmonary disease, endocrine disease, rheumatic disease, immunologic disease, cardiotoxic exposures, systemic hypertension, or congenital cardiovascular malformations were excluded.

The diagnosis of LVNC was made by the managing physician based on interpretation of echocardiographic data. LVNC was recorded as present if the local diagnosis reflected the PCMR imaging-based definition, “very trabeculated spongiform left ventricular myocardium with multiple interstices”. Children with LVNC were divided into 5 phenotypic groups: 1) isolated LVNC with normal LV function; 2) LVNC and the dilated cardiomyopathy (DCM) phenotype; 3) LVNC and the hypertrophic cardiomyopathy (HCM) phenotype; 4) LVNC and the restrictive cardiomyopathy (RCM) phenotype and 5) LVNC without further specification (indeterminate) due to missing structural measurements.²⁴ This indeterminate group's treating cardiologists indicated in the medical record that the patient had LVNC but the echocardiographic measurements needed to determine whether these were isolated cases or whether the patient had another accompanying cardiomyopathy phenotype were missing. For the purposes of this analysis, DCM was echocardiographically defined as a combination of abnormal LV function (LV fractional shortening [LVFS] Z score or LV ejection fraction [LVEF] Z score <-2) and LV dilation (LV end-diastolic dimension [EDD] Z score >2); or the presence of at least moderately depressed LV function, defined as LV fractional shortening Z score <-3 , or LV ejection fraction Z score <-3 , regardless of LV size. HCM was defined as either echocardiographic evidence of localized ventricular hypertrophy or a posterior wall or septal thickness Z score >3 . RCM was defined as one or both atria enlarged relative to ventricles of normal or small size with evidence of impaired diastolic filling and in the absence of significant valvular heart disease.

Demographic and clinical data, including echocardiographic measurements, family history, and clinical data, were collected at diagnosis and annually thereafter by a team of trained data collectors. Heart failure was defined either by its notation in the medical record by the treating cardiologist and/or NYHA or Ross classifications if present in the record. Data regarding etiology were also collected. If no clear etiology could be assigned based on the medical record, the enrolling centers were instructed to assign the etiology as idiopathic. Sudden cardiac death was defined as an unexpected death occurring < 1 hour after the onset of a symptomatic cardiac event. All deaths in the PCMR dataset were adjudicated by up to 3 of the investigators after a review of the circumstances of death abstracted from the medical record and autopsy reports if available. All deaths were classified as either sudden cardiac, non-sudden cardiac, or unknown.

Patient confidentiality was assured through the use of coded patient identifiers. All participating centers obtained Institutional Review Board approval for data collection and analysis.

Statistical Analysis

Normally distributed data are summarized with means and standard deviations, and skewed data with medians and interquartile range. The distributions of categorical variables by phenotype group were compared with a Fisher exact test. Means across phenotype groups were compared using analysis of variance, and medians with the Kruskal-Wallis test.

Echocardiographic Z scores relative to body surface area were calculated for LV EDD, posterior wall thickness, interventricular septal thickness in diastole, and LV mass from distributions of healthy children.^{25,26} Echocardiographic Z scores relative to age were calculated for LVFS and LVEF. A Z score is the number of standard deviations from the mean relative to the BSA (structural variables) or age (functional variables).

Outcomes were death, cardiac transplant, listing for cardiac transplant and the composite endpoints of death or transplant and death or listing for transplant. Event-free rates were calculated using the Kaplan-Meier method, and the distributions of time to event by phenotype group were compared using the logrank test. Follow-up time was censored at the time of transplant when analyzing time to death. Cox proportional hazards regression modeling was used to obtain hazard ratios for the composite endpoints by phenotype group, adjusted for age at diagnosis. In this analysis, additional multivariable modeling was not conducted using echocardiographic measurements as candidate predictors, because the phenotype groups were defined based on these echocardiographic measurements. All analyses were conducted using the Statistical Analysis System version 9.3 (Statistical Analysis System, SAS Institute, Inc., Cary, NC) and S-Plus 6.1 (Insightful Corp., Seattle, WA).

RESULTS

Demographics and Clinical Characteristics

Of the total PCMR cohort of 3549 cases, 9.3% (330) did not have sufficient information in the medical record to definitively state the presence or absence of a LVNC pattern and were excluded from the analysis. Of the 3219 remaining patients, 155 (4.8%) were diagnosed with LVNC; 49 were diagnosed between 1990 and 1999, and 106 were diagnosed between 2000 and 2008. All patients were diagnosed with LVNC at the initial clinical presentation. The distribution of phenotypes was: 35 (22.6%) isolated LVNC; 91 (58.7%) LVNC with the DCM phenotype; 17 (11.0%) LVNC with the HCM phenotype; and 12 (7.7%) with LVNC with an indeterminate cardiomyopathy phenotype (Table 1). Upon review of serial echocardiograms, one patient's phenotype changed from DCM at baseline to HCM on a subsequent echocardiogram, and one other patient's phenotype change from DCM at baseline to a combined HCM and RCM phenotype on a later echocardiogram. There were only 3 patients with LVNC with the RCM phenotype so this group was not included in the analysis. Nearly all (86%) had idiopathic disease. Of the non-idiopathic diagnoses, 3 (14%)

were due to metabolic disease, 4 (18%) were due to a malformation syndrome, 2 (9%) were due to myocarditis, and 13 (59%) were determined as familial cases. Registry children with LVNC were significantly more likely to have these etiologies identified compared to the non-LVNC children (all P 's < 0.001).

Children with isolated LVNC were significantly older at diagnosis (median 9.8 years) than the children who had LVNC combined with a cardiomyopathy phenotype (medians 0.4 to 0.6 years, P < 0.001). Gender and ethnicity did not differ significantly among LVNC phenotypes. At the time of diagnosis, heart failure was present in 58% of the children with LVNC combined with DCM, and 35% with LVNC and HCM (P < 0.001).

Outcomes by Cardiomyopathy Phenotype

We observed a significant difference among the 5 phenotypic groups in time to death or transplant (40 events; P = 0.035; Fig. 1a). Children with isolated LVNC had the best outcomes, followed by those with LVNC and HCM. Children with LVNC and the DCM, or indeterminate cardiomyopathy phenotype had the worst outcomes. The hazard ratio for death/transplant (with isolated LVNC as the reference group) was 4.26 (95% confidence interval [CI], 0.78 to 23.3) for HCM, 6.35 (95% CI, 1.52 to 26.6) for DCM, and 5.66 (95% CI, 1.04 to 30.9) for the indeterminate phenotype. Although age at diagnosis differed among the phenotypic groups, it was not an independent predictor of death/transplant after accounting for phenotypic group (continuous age P = 0.742; age <1 year P = 0.865). Accordingly, the age-adjusted hazard ratios for death/transplant were very similar to those from the unadjusted model, although the phenotype group difference was not significant (P = 0.103). The phenotype group difference in time to death or listing (44 events; P = 0.009; Fig. 1b) was marginally significant after adjustment for age (P = 0.061). Time to death did not differ by phenotype (logrank P = 0.35; Fig. 1c). Time to listing for cardiac transplantation significantly differed by phenotype (P < 0.001), as did time to transplantation (P = 0.015; Fig. 1d). Five-year transplant rates were 0% for isolated LVNC or LVNC with HCM, 27% for DCM, and 27% for the indeterminate phenotype group (Table 2). Five-year rates for the combined endpoint of death or transplant (and death or listing) were 33% (35%) for the entire LVNC cohort; phenotype specific rates were 6% (6%) of isolated LVNC, 43% (45%) for DCM, 25% (25%) for HCM, and 33% (42%) for the indeterminate phenotype groups.

We examined the progression of disease in the isolated LVNC group. The majority of patients with isolated LVNC were referred for reasons such as heart murmurs, chest pain, or a family history of cardiomyopathy. Very few isolated LVNC patients developed an associated cardiomyopathy phenotype. Of the 35 cases with isolated LVNC, the 2 deaths observed occurred shortly after diagnosis (Fig. 1c). One of the deceased patients had an associated DCM phenotype on repeat echocardiogram. Of the remaining 33 isolated LVNC cases, a 2-year repeat echocardiogram was available in 24 subjects, with 2 showing characteristics of HCM. Therefore, we estimate that 12% (3 of 25) progressed to an associated cardiomyopathy phenotype within 2 years. One additional case was reported as RCM at 1 year but this was done without an associated supporting echocardiogram. This

patient was alive at 4 years with an LV wall thickness Z score of <-2 , normal LV systolic function, and no evidence of an associated RCM phenotype by echocardiogram at that time.

We compared patients with LVNC and a DCM phenotype to those of children in the PCMR who had DCM without LVNC ($n = 1799$). The time to death or transplant was similar for the two groups (logrank $P = 0.22$; Fig. 2). The five-year composite event rates were 37% for LVNC with DCM phenotype and 47% for children with DCM without LVNC. The distributions of time to transplant and time to death as individual endpoints did not differ ($P = 0.15$ and $P = 0.80$, respectively). In contrast, the survival of children with LVNC and a HCM phenotype was lower (logrank $P = 0.02$) than that of children with idiopathic or familial HCM without LVNC ($n = 778$; Fig. 3). The five-year mortality rates were 25% vs. 10%, respectively. Of the 17 children in the LVNC group with a HCM phenotype, four died, all at less than 9 months of age.

The cause of death and related details for 21 (14%) of the 155 LVNC patients who died during the study are shown in Table 3. All but two patients died less than a year after diagnosis. Only one patient had an adjudicated sudden death cause, while 3 others' adjudication of sudden or not sudden death were unknown. The remaining 17 children were adjudicated as non-sudden deaths. Nearly 60% ($n = 12$) of deaths were classified as cardiac deaths. Non-cardiac causes ($n = 9$) of death included severe sepsis ($n = 2$), multiple organ failure ($n = 2$), severe neurologic compromise ($n = 2$), or parental decisions to limit or withdraw life support based on the individual child's clinical condition and/or prognosis ($n = 3$). Because of the relatively small number of deaths, a comparison of cause of death data across LVNC-cardiomyopathy phenotypes was not statistically feasible

DISCUSSION

Analysis of data from more than 3000 children with primary cardiomyopathy in the PCMR database, identified 155 (5%) children with LVNC as an isolated phenotype or in combination with a DCM, HCM, or RCM phenotype. The prevalence of LVNC in our database was consistent with other reports.^{15,16} However, we observed more than a doubling of LVNC diagnoses between the 1990s and the following decade. This suggests that the 5% estimate may be an underestimate due to cases before 2000 being diagnosed with cardiomyopathy, but going undetected with respect to LVNC features specifically. This increase also likely reflects an increasing awareness of LVNC as well as improved imaging techniques which allow for greater resolution of LV trabeculations.

Our findings indicate that 6% of children with the isolated form of LVNC die or undergo cardiac transplantation in the first 5 years after diagnosis. We did not have arrhythmia data on more than 60% of this cohort; furthermore, patients with chronic arrhythmia were excluded from the PCMR. Based on a recent retrospective single institution report, arrhythmias appear to be a significant factor in predicting poor patient outcomes.²¹ These findings suggest that consideration of implantable cardioverter-defibrillators (ICD) may impact outcome. In the current report, data regarding ICD placement were not available on the majority of patients. Future studies are needed to clarify the potential benefit in children with LVNC.

Few studies have described LVNC in children. Wald et al. reported the experience of a single center over 15 years which consisted of 22 children with LVNC with a median age at diagnosis of 3.9 years (range 0.1 to 16 years) and a median follow-up of 3 years.²⁷ Seventeen (77%) also had LV dilation at presentation. A poor outcome (death or listing for transplant) occurred in 6 (27%) of the group with LVNC and LV dilation. A more recent retrospective review of 50 children with LVNC found 23 (46%) also had DCM.²⁸ Death or transplant occurred in 16 (59%) of the children with LVNC and DCM; half of the entire group of 50 children died within 1.2 years of presentation. Time to death or transplant was not reported for the LVNC with DCM subgroup. The combined end-point of death or transplant was met by 26% of our cohort at 5 years, most commonly among children with the DCM phenotype. Congenital heart disease was an exclusion criterion in our analysis. Ichida et al. reported on a retrospective group of 27 children with LVNC and ages at presentation ranging from 1 week to 15 years.²⁹ A significant number of patients had asymptomatic disease. They also documented a 44% incidence of familial recurrence. Importantly, elevation of LV end-diastolic pressures was found on cardiac catheterization in most of their cases. Brescia et al. recently reported on 242 patients with isolated LVNC which was defined as LVNC in the absence of associated congenital heart disease or known metabolic syndromes.²¹ Of these, 31 (12.8%) died and 13 (5.4%) underwent cardiac transplant. Evidence of preceding cardiac systolic dysfunction or the presence of ventricular arrhythmias was associated with increased mortality.

Numerous genetic disorders have been associated with LVNC, including sarcomeric and Z-disk gene mutations, mitochondrial disorders, and α -dystrobrevin mutations.³⁰⁻³⁴ Sarcomeric gene defects are known to result in diverse cardiomyopathy phenotypes within family members sharing the same mutation suggesting a shared molecular etiology.³⁰ Recent reports indicate that LVNC may also occur with other clinical syndromes.^{35,36} Furthermore, LVNC may be seen commonly in children with congenital heart disease.³⁷ Familial occurrence of LVNC has been reported and may be as high as 30%.¹⁰ Family history data were limited in our database; however, a family history of sudden death was reported in 18% of children with isolated LVNC. Although genotyping is frequently used in the current assessment of LVNC and other cardiomyopathy phenotypes such as HCM, clinical genetic testing was not available during the initial enrollment period of the PCMR. As a result, we cannot report genotype data on any of the existing subjects in the PCMR nor can we make genotype-phenotype correlations for this study.

The survival rate of children with LVNC and the HCM phenotype was lower than that of published reports of children with pure HCM. In the PCMR, children with idiopathic HCM, compared to those with HCM due to a known cause, had the poorest outcome if diagnosed before 1 year of age.³⁸ Consistent with that finding, in our current report all four deaths among the 17 children with the HCM phenotype occurred in infancy. Similarly, the rates of death and transplantation in children with LVNC and the DCM phenotype paralleled, although were somewhat better, than those with pure DCM at all time points up to 10 years after diagnosis. This finding suggests that the underlying echocardiographic abnormalities of LV wall thickness, dimension, or function are the primary determinants of the risk of death or the need for cardiac transplant rather than the presence of LVNC. These findings further

underscore the suggestion that the outcomes of children with LVNC can generally be predicted by their associated cardiomyopathy phenotype or lack thereof.

Strengths and Limitations of the Study

The strengths of this study are its relatively large sample size, standardized definitions of cardiomyopathy phenotypes and robust follow-up regarding clinical outcomes. The enrollment period of 18 years may include fluctuating interpretations of the LVNC phenotype given potential changes in personnel and the subjective nature of the diagnosis. Since there is a subjective component to the echocardiographic diagnosis of LVNC, the lack of a central core echocardiogram laboratory, not typically available for this and other registry studies, is a limitation. This may have also resulted in the under- or over-diagnosis of LVNC in our cohort. Our analysis is also limited by missing data in a majority of cases for electrocardiographic evidence of arrhythmias, which could be a risk factor for negative clinical outcomes. We recognize that cardiac magnetic resonance imaging (cMRI) is potentially a more effective modality for diagnosis of LVNC.³⁹⁻⁴¹ However, cMRI was not routinely used clinically during most years of PCMR enrollment, and was not collected. Therefore, we cannot comment on the relative merits of cMRI vs. echocardiogram in diagnosing LVNC, or whether our reported prevalence of LVNC would be different if cMRI were utilized. Finally, we recognize the potential impact of genetic testing in this cohort. However, this was not in the initial design of the PCMR data collection and samples are not available on the subjects in this report. This precludes any possibility of genotype-phenotype correlations in our study.

We conclude that the specific cardiomyopathy phenotype that is associated with LVNC predicts the risk of adverse clinical outcomes in children. More than 20% of our LVNC cases had no evidence of a cardiomyopathy phenotype or congestive heart failure. Outcomes for children with isolated LVNC were generally better than the other LVNC patients who had an associated cardiomyopathy phenotype. Therefore, limiting their competitive or recreational activities may be unnecessary. However, the fact that 2 of 35 children with the isolated LVNC phenotype died suggests that it is incorrect to conclude that this phenotype is always benign. Although LVNC is a diagnosis that is increasingly recognized by pediatric cardiologists, it remains an uncommon diagnosis in children. Given that 20% of cases may be familial, family screening is recommended when the diagnosis of LVNC is made in a child.

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Highlights

- LVNC is present in at least 5% of children with cardiomyopathy
- The concurrent phenotype seen in association with LVNC predicts outcome
- The survival rate of children with LVNC and the HCM phenotype was lower than that of published reports of children with pure HCM
- In children with the isolated form of LVNC, 6% die or undergo cardiac transplantation in the first 5 years after diagnosis

a

No. at risk		Years Since Diagnosis						
		0	1	2	3	4	5	6
Isolated LVNC:	35	26	21	14	8	7	3	
Dilated LVNC:	91	54	44	35	27	22	20	
Hypertrophic LVNC:	17	9	9	7	6	6	4	
LVNC w/unk Pheno:	12	9	8	8	6	3	3	

b

No. at risk		Years Since Diagnosis						
		0	1	2	3	4	5	6
Isolated LVNC:	35	26	21	14	8	7	3	
Dilated LVNC:	91	49	42	34	26	20	19	
Hypertrophic LVNC:	17	9	9	7	6	6	4	
LVNC w/unk Pheno:	12	8	7	7	5	2	2	

c

No. at risk		Years Since Diagnosis						
		0	1	2	3	4	5	6
Isolated LVNC:	35	26	21	14	8	7	3	
Dilated LVNC:	91	54	44	35	27	22	20	
Hypertrophic LVNC:	17	9	9	7	6	6	4	
LVNC w/unk Pheno:	12	9	8	8	6	3	3	

d

Figure 1. Kaplan-Meier estimates of time to death, listing for cardiac transplant or cardiac transplant in children with left ventricular noncompaction by associated cardiomyopathy phenotype

LVNC = left ventricular noncompaction; Unk Pheno = unknown phenotype.

Figure 1a. Kaplan-Meier estimates of time to death or cardiac transplant in 155 children with left ventricular noncompaction, by associated cardiomyopathy phenotype (logrank $P = 0.035$). The curves are truncated at 6 years

Figure 1b. Kaplan-Meier estimates of time of listing-free survival in 155 children with left ventricular noncompaction by associated cardiomyopathy phenotype (logrank $P = 0.009$). The curves are truncated at 6 years.

Figure 1c. Kaplan-Meier estimates of time to death in 155 children with left ventricular noncompaction, by associated cardiomyopathy phenotype (logrank $P = 0.347$). The curves are truncated at 6 years.

Figure 1d. Kaplan-Meier estimates of time to cardiac transplant in 155 children with left ventricular noncompaction, by associated cardiomyopathy phenotype (logrank $P = 0.015$). The curves are truncated at 6 years.

Figure 2. Kaplan- Meier estimates of time to death or cardiac transplant in children with DCM vs. children with LVNC and an associated DCM phenotype

Kaplan-Meier estimates of time to death or cardiac transplant in 1799 children with dilated cardiomyopathy (DCM) vs. 91 children with left ventricular noncompaction (LVNC) and a DCM phenotype (logrank $P = 0.223$). The curves are truncated at 6 years. The DCM without LVNC comparison group was comprised of all PCMR patients with that phenotype at baseline.

No. at risk							
LVNC HCM :							
	17	9	9	7	6	6	4
Pure HCM :							
	778	549	473	387	304	241	185

Figure 3. Kaplan-Meier estimates of time to death or cardiac transplant in children with HCM vs. children with LVNC and an associated HCM phenotype

Kaplan-Meier estimates of time to death or cardiac transplant in 778 children with idiopathic or familial isolated hypertrophic cardiomyopathy (HCM) vs. 17 children with left ventricular noncompaction (LVNC) and an HCM phenotype (logrank $P = 0.018$). The curves are truncated at 6 years. The HCM without LVNC comparison group was comprised of all PCMR patients with that phenotype at baseline.

Table 1

Characteristics of 155 Children with Left Ventricular Noncompaction at the Time of Diagnosis, by Associated Cardiomyopathy Phenotype.

Characteristic	Cardiomyopathy Phenotype				P
	Isolated n = 35	Dilated n = 91	Hypertrophic n = 17	Indeterminate n = 12	
Age at diagnosis, yr, Mean $\pm$ SD	8.1 $\pm$ 6.4	3.7 $\pm$ 5.8	5.2 $\pm$ 6.7	1.4 $\pm$ 2.4	<0.001
median (IQR)	9.8 (1.3-14.3)	0.4 (0.1-5.3)	0.6 (0.05-11.6)	0.5 (0.04-1.5)	<0.001
Age < 1 yr at diagnosis, %	22.9	61.5	52.9	66.7	<0.001
Male, %	68.6	63.7	47.1	75.0	0.41
Race/ethnicity, %					0.59
White, non-Hispanic	62.9	52.7	47.1	58.3	
Black, non-Hispanic	22.9	17.6	35.3	25.0	
Hispanic, %	11.4	22.0	17.6	16.7	
Other, %	2.9	7.7	0.0	0.0	
Year of Diagnosis, %					0.53
1990-1999	25.7	36.3	23.5	25.0	
2000-2008	74.3	63.7	76.5	75.0	
CHF present at diagnosis, %	0.0	58.2	35.3	41.7	<0.001
Family history of sudden death, %	18.2	1.9	8.3	0.0	0.07
LV end-diastolic dimension Z score	0.19 $\pm$ 1.30	3.21 $\pm$ 2.38	0.66 $\pm$ 2.50	1.19 $\pm$ 1.01	<0.001
LV end-systolic dimension Z score	0.27 $\pm$ 1.63	4.98 $\pm$ 2.54	-0.78 $\pm$ 2.47	NA	<0.001
LV fractional shortening Z score	-0.21 $\pm$ 2.35	-7.86 $\pm$ 3.18	1.44 $\pm$ 4.92	NA	<0.001
LV end-diastolic posterior wall thickness Z score	-0.18 $\pm$ 1.99	0.43 $\pm$ 2.40	2.87 $\pm$ 2.58	1.51 $\pm$ 1.56	0.001
LV end-diastolic septal thickness Z score	0.05 $\pm$ 1.75	-0.19 $\pm$ 2.03	1.82 $\pm$ 2.00	-1.41 $\pm$ 1.18	0.004
LV mass Z score	0.16 $\pm$ 1.67	2.10 $\pm$ 2.51	2.68 $\pm$ 2.59	0.69 $\pm$ 0.60	<0.001

IQR denotes interquartile range, and CHF congestive heart failure.

Table 2

Outcomes of 155 Children with Left Ventricular Noncompaction, by Associated Cardiomyopathy Phenotype.

Outcome	Cardiomyopathy phenotype			
	Isolated n = 35	Dilated n = 91	Hypertrophic * n = 17	Indeterminate n = 12
Median follow-up in event-free subjects, yrs	3.3	4.2	4.3	5.5
Total no. of deaths	2	14	4	1
5-year death rate (95% CI)	6% (2-22%)	22% (13-37%)	25% (10-53%)	9% (1-49%)
Total no. of transplants	0	16	0	3
5-year transplant rate (95% CI)	0%	27% (17-41%)	0%	27% (9-62%)
Total no. of transplant listings [†]	0	23	0	5
5-year listing rate (95% CI)	0%	38% (25-55%)	0%	42% (20-73%)
Total no. with death or transplant	2	30	4	4
5-year death/transplant rate (95% CI)	6% (2-22%)	43% (31-57%)	25% (10-53%)	33% (14-66%)
Total no. with death or listing	2	33	4	5
5-year death/listing rate (95% CI)	6% (2-22%)	45% (34-59%)	25% (10-53%)	42% (20-73%)

CI denotes confidence interval.

* Idiopathic or familial isolated hypertrophic cardiomyopathy.

[†] 24 of 28 initial listings were Status 1A. One of the remaining 4 was upgraded to Status 1A.

Table 3

Cause of Death for 21 Children of the Study Cohort of 155 Children with Left Ventricular Noncompaction.

Age at Diagnosis (years)	Time from Diagnosis to Death (years)	Age at Death (years)	Cause of Death (cardiac or non-cardiac)*	Adjudicated Sudden Death
0.57	0.17	0.74	Cardiac	No
15.56	0.03	15.59	Non-cardiac	No
0.002	0.02	0.03	Non-cardiac	No
0.06	0.05	0.12	Cardiac	No
14.28	0.10	14.39	Cardiac	Unknown
0.00	0.03	0.03	Cardiac	No
15.11	0.03	15.15	Cardiac	No
0.15	0.28	0.43	Cardiac	Unknown
15.59	0.11	15.70	Non-cardiac	No
5.67	0.43	6.10	Cardiac	No
17.76	4.42	22.18	Cardiac	No
0.26	0.53	0.79	Non-cardiac	Unknown
0.18	5.60	5.78	Non-cardiac	No
1.63	0.27	1.90	Non-cardiac	No
5.99	0.08	6.07	Cardiac	No
1.34	0.00	1.34	Cardiac	Yes
0.64	0.07	0.71	Non-cardiac	No
0.03	0.24	0.27	Non-cardiac	No
0.002	0.21	0.21	Cardiac	No
0.12	0.23	0.35	Non-cardiac	No
0.17	0.10	0.27	Cardiac	No

* Non-cardiac causes of death include: sepsis, multiple organ failure, severe neurologic compromise, or withdrawal or limitation of ventilator support.